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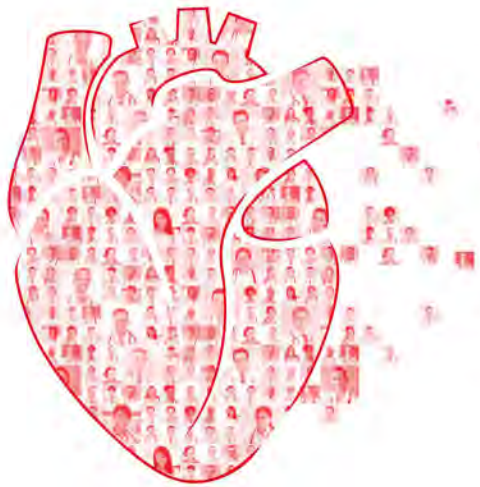
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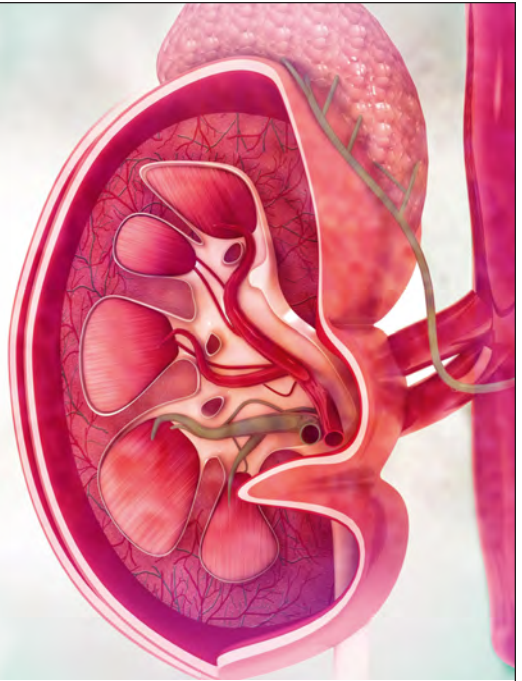
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Second and third trimesters of pregnancy. Biliary obstructive disorders. Severe hepatic impairment. The concomitant use of Telmisartan with aliskiren containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 m²). **Warnings And Precautions - Fetal Toxicity:** Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible. **Hypotension:** In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan, or start treatment under close medical supervision with a reduced dose. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized. **Hyperkalemia:** may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Periodic determinations of serum electrolytes to detect possible electrolyte imbalances should be considered particularly in patients at risk. **Impaired Hepatic Function:** As the majority of Telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Telmisartan should be initiated at low doses and titrated slowly in these patients. **Impaired Renal Function:** as a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function should be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with Telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. **Dual Blockade of the Renin-Angiotensin-Aldosterone System:** Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, combined use of drugs from different classes of RAS inhibitors should be avoided. Blood pressure, renal function and electrolytes in patients on Telmisartan and other agents that affect the RAS should be closely monitored. Aliskiren must not be co-administered with Telmisartan in patients with diabetes. Concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR <60 mL/min/1.73 m²) must be avoided. **Nonclinical Toxicology:** Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of carcinogenicity when Telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m² basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of Telmisartan. These same doses have been shown to provide average systemic exposures to Telmisartan > 100 times and > 25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day). Genotoxicity assays did not reveal any Telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test. No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m² basis, the MRHD of Telmisartan. This dose in the rat resulted in an average systemic exposure (Telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day). **Use In Specific Populations: Nursing Mothers:** It is not known whether Telmisartan is excreted in human milk, but Telmisartan was shown to be present in the milk of lactating rats. **Pediatric Use:** Safety and effectiveness of Telmisartan in pediatrics has not been established. Thus, the drug is not recommended in pediatrics. **Geriatric Use:** No dose adjustment is needed in elderly patients.



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The dose may be up-titrated if necessary. **CONTRAINDICATIONS** The fixed dose combination of Telmisartan and Cilnidipine is contraindicated in : • Patients with known hypersensitivity to Telmisartan, Cilnidipine or any other component of this product. • Patients with diabetes who are co-administered aliskiren. • Conditions like cardiogenic shock; recent MI or acute unstable angina and severe aortic stenosis. • The concomitant use of fixed dose combination of Cilnidipine, Telmisartan and Chlorthalidone tablets with aliskiren-2 containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR<60ml/min/1.73m²). • Biliary obstructive disorders • Severe hepatic impairment • Pregnant Women **WARNINGS AND PRECAUTIONS - TELMISARTAN Fetal Toxicity** Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. 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This dose in the rat resulted in an average systemic exposure (Telmisartan AUC as determined on day of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day). **CILNIDIPINE Pregnancy:** Cilnidipine should not be administered to pregnant women as it has been reported that Cilnidipine prolongs the gestation period and delivery time in animal experiments (in rats). **Impaired Hepatic Function:** Close observation should be made and if any abnormality is observed appropriate measures, such as discontinuation of Cilnidipine, should be taken. **Elderly Patients:** Cilnidipine should be administered carefully under close observation of the patient's condition, start with low dose (5 mg) **Sudden Withdrawal:** It has been reported that sudden withdrawal of a calcium antagonist caused aggravation of certain symptoms. Therefore, if the discontinuation of Cilnidipine is necessary, appropriate measures, such as replacement with other antihypertensive agents, should be taken. **Effects on Ability to Drive and Operate Machine:** The symptoms, such as dizziness may occur because of the hypotensive action from this drug. It is hazardous to engage in activities which require alertness, such as working at a height, operating machinery or driving motor vehicles. **Others:** Precaution should also be exercised in patients with angina, chronic renal insufficiency, congestive heart failure, hypotension, liver dysfunction, or elevated liver enzymes, peripheral edema (confounding physical findings in congestive failure) and in patients with a history of serious adverse reactions to calcium antagonists. **USE IN SPECIFIC POPULATIONS Pregnancy:** Use of drugs that act on the renin-angiotensin system like Telmisartan, during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Cilnidipine has been reported to prolong the gestation period and delivery time in animal experiments (in rats). Therefore, the fixed dose combination of Telmisartan and Cilnidipine should be discontinued when pregnancy is detected, as soon as possible. **Nursing Mothers:** It is not known whether Telmisartan is excreted in human milk, but Telmisartan was shown to be present in the milk of lactating rats. Transfer of Cilnidipine to mother's milk has been reported in animal experiments (in rats). Therefore it is advisable to avoid the administration of the fixed dose combination of Telmisartan and Cilnidipine to nursing mothers. **Pediatric Use:** Safety and effectiveness of both Telmisartan and Cilnidipine in pediatrics has not been established. Thus, the fixed dose combination of Telmisartan and Cilnidipine is not recommended in pediatrics. **Geriatric Use:** The fixed dose combination of Telmisartan and Cilnidipine should be administered carefully under close observation of the patient's condition. No dose adjustment is needed in elderly patients

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Abbreviations: ARB, angiotensin II receptor blocker, ACE, angiotensin-converting enzyme, BP, blood pressure, MACE, major adverse cardiovascular events

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Dr Yash Pal Munjal

MD, FICP, MAMS, FRCP (EDIN), FACP (USA), FIACM, FIAMS, FIMSA

02.01.1942 * 25.07.2024

***"A truly great mentor is hard to find,
difficult to part with, and impossible to forget"***

A legend in his own right, a physician with exemplary abilities, a team leader who knew how to get the best from the team members. Dr Yash Pal Munjal was a graduate from Maulana Azad Medical College, New Delhi (1964), and did postgraduation from PGI Chandigarh.

Dr Y P Munjal had the distinction of serving in various capacities holding prime positions at the Association of Physicians of India (API), Delhi Medical Association, and Indian Medical Association. In the last five decades, he served as an able administrator as Medical Director of Jessa Ram Hospital, Jaipur Golden Hospital, Banarsidas Chandiwalla Institute of Medical Sciences in the capital city of Delhi. Besides this, he kept himself actively involved in patient care at St Stephen's and Sunder Lal Jain Hospitals in Delhi as well as Artemis and St Stephen's Hospitals, Gurugram. He established 'Diabetes and Lifestyle Diseases Center' at Banarsidas Chandiwalla Institute, which is one its kind in North India catering to all types of diabetes, hypertension, obesity and other Lifestyle Diseases.

Dr Y P Munjal was a clinician par excellence, a great team leader, a mentor in the true sense of the term and a wonderful human being. He worked tirelessly for the Association of Physicians of India for the last 35 years in various capacities—President, API 1999, Dean, ICP 2007, Director, Physicians Research Foundation 2016 and Editor-in-Chief of 9th and 10th editions of the prestigious API Textbook of Medicine. He also served as President of the Hypertension Society of India in 2001 and Convenor of 11th National Conference of Hypertension Society of India in 2002. He contributed more than 80 publications in journals and chapters in various books. He was recipient of many prestigious awards, to name a few—Distinguished Alumnus Award of Maulana Azad Medical College & LNJP Hospital 1991, API Distinguished Member Award 2002, and the prestigious Dr Jivraj Mehta Award of API in 2023.

Dr Munjal was an exceptionally sincere, honest and dedicated human being, who worked with unmatched zeal for the betterment of the internists. He was a role model for innumerable physicians from all over the country. Indian medical fraternity shall remain indebted to him for his inspirational leadership and visionary foresight. His legacy of excellence and kindness will be remembered fondly by all who had the privilege of knowing him. I am really fortunate that I started my professional journey in 1982 with Dr Munjal and for the last 42 years, he has been my mentor, *guru* and guide in my professional career. He was the catalyst for my induction in the API and all that I have been able to achieve was possible only with his guidance, constant support and encouragement. I have no words to express my deepest gratitude to him for always being there as a pillar of support for me.

My heart is filled with great sorrow as I express my heartfelt condolences to his wife Dr (Mrs) Rama Munjal, son Dr Akshay, daughter Ms Jaya, and daughter-in-law Dr (Mrs) Yashika. May God give them strength and courage to bear this irreparable loss.

Dr Munjal's legacy of professional and moral integrity and selfless service will continue to inspire and guide all of us forever. His life was a blessing, his memory a treasure, he was loved beyond words and missed beyond measure.

***"Though you are far away, but still close to our hearts.
Your memory like the fragrance is spread all over our lives".***

Long Live API, Long Live Sir!

Dr R K Singal
Dean, ICP

Principal Director and Head, Dept. of Internal Medicine
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Nonarteritic Anterior Ischemic Optic Neuropathy and Semaglutide: What is This All About?

Awadhesh Kumar Singh^{1*}, Jothydev Kesavadev², Mangesh Tiwaskar³

Nonarteritic anterior ischemic optic neuropathy (NAION) was first documented by a French physician Jean-Pierre Saint-Yves in 1817 (19th century). The clinical description of NAION was not known until 1935 when C. Miller Fischer thoroughly described it. Briefly, NAION is a rare (2.5–11.8 per 1,00,000 cases in men above 50 years) but serious condition that causes sudden painless loss of vision due to ischemia of the optic nerve.¹ It is more common in Caucasians compared with Asians and is associated with various risk factors such as hypertension, type 2 diabetes (T2D), smoking, hyperlipidemia, obesity, obstructive sleep apnea, small optic nerve cup (“disk at risk”), optic nerve drusen, and certain drugs, especially phosphodiesterase type 5 inhibitors (PDE-5I), amiodarone, and cabergoline.² Although the clinical development programs and real-world studies of semaglutide [a glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for the treatment of T2D and obesity] did not report any significant increase in the risk of NAION, a recent retrospective cohort study suggested a possible link between NAION and semaglutide.³ This editorial briefly summarizes the current knowledge about NAION and its relation to metabolic disorders, cardiovascular, and antidiabetes drugs and puts a perspective concerning semaglutide.

Nonarteritic anterior ischemic optic neuropathy is a rare condition characterized by sudden painless vision loss due to ischemia affecting the anterior optic nerve without evidence of arteritis. While NAION and arteritic ischemic optic neuropathy (AION)

are related, their causes, affected locations, optic disc appearances, visual field defects, and treatments differ. The precise cause of NAION remains unclear, though it is believed to be associated with vascular risk factors. In contrast, AION can have multiple causes depending on its type. The ischemic location within the optic nerve varies between NAION and other forms of AION. NAION affects the anterior portion of the optic nerve, typically presenting with optic disc edema, while other types of AION can impact any part of the optic nerve—anterior, posterior, or the entire nerve—resulting in different optic disc appearances depending on the ischemia’s type and severity. NAION usually leads to altitudinal (horizontal) or arcuate visual field defects, while AION can cause various visual field defects based on the ischemia’s location and extent. Currently, there is no effective treatment for NAION, and the vision loss is generally permanent, though some studies suggest corticosteroids may be beneficial in certain cases. The treatment for AION depends on its underlying cause.²

Risk factors associated with NAION have been summarized in Table 1. These conditions may increase the risk of NAION by causing vascular dysfunction, inflammation, or oxidative stress, which can lead to optic nerve damage.^{4,5} Some other conditions that may be associated with NAION are hyperhomocysteinemia, migraine, Raynaud’s phenomenon, sickle cell disease, history of myocardial infarction or stroke, Factor V Leiden heterozygotes, and vasculitis.^{2,5} Several drugs have also been linked with NAION. PDE-5I such as sildenafil and tadalafil exhibited some

association with NAION.⁶ Studies consistently indicate a small yet significant increased risk of NAION linked to PDE-5I use, particularly among individuals with preexisting vascular risk factors. It has been hypothesized that these medications might exaggerate the physiological nocturnal hypotension, resulting in ischemia to the optic nerve head and compartment syndrome in susceptible patients with a small cup-to-disk ratio (“disk at risk”). Additionally, these medications might interfere with the autoregulation of blood flow, thereby decreasing perfusion to the optic nerve head.⁶ Although the association of PDE-5I to NAION remains controversial, multiple prospective studies have shown an increased risk of NAION development in patients exposed to PDE-5I.^{7–9} Interestingly, some of the commonly used cardiovascular drugs have also been linked to NAION and are summarized in Table 2.⁴ Studies show that hormone replacement therapy (HRT) use is associated with an increased incidence of NAION in postmenopausal women [hazard ratio (HR), 1.268; 95% confidence interval (CI), 1.197–1.344].¹⁰

Hathaway et al.³ conducted a retrospective cohort study to assess the association between semaglutide use and the development of NAION over 6 years.

Table 2: Cardiovascular drugs and NAION⁵

Drugs	OR/RR (95% CI)	p-value
Antithrombotic	2.30 (1.86–2.84)	<0.00001
Statins	1.32 (1.18–1.48)	<0.00001
β-blockers	1.48 (1.05–2.08)	0.02

Table 1: Conditions associated with NAION^{4,5}

Risk factor	Kim et al. ⁴			Liu et al. ⁵		
	OR	95% CI	p-value	OR/RR	95% CI	p-value
Hypertension	2.29	0.97–5.36	0.056	1.28	1.20–1.37	<0.00001
Diabetes mellitus	3.61	1.17–11.11	0.020	1.53 ¹	1.36–1.73	<0.00001
Dyslipidemia	5.20	1.84–14.73	0.001	1.43 ¹	1.26–1.62	<0.00001
Smoking	3.59	1.25–10.29	0.014	–	–	–
CHD	–	–	–	1.68 ¹	1.24–2.27	0.0008
Sleep apnea	–	–	–	3.28 ¹	2.08–5.17	<0.00001
Factor V Leiden heterozygous	–	–	–	2.21 ¹	1.19–4.09	0.01
Small cup	17.20	3.71–78.82	<0.001	35.20	4.45–278.25	0.007

OR: odds ratio; RR: risk ratio

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Published in *JAMA Ophthalmology* on July 3, 2024, the study utilized a centralized clinical data registry comprising patients with no prior NAION events. GLP-1RA users were identified through prescribing and dispensing data. Propensity-matched analysis in the T2D cohort indicated a higher risk of NAION for patients receiving semaglutide (HR, 4.28; 95% CI, 1.62–11.29; $p < 0.001$). Similarly, in the obesity cohort, there was an elevated risk of NAION for patients prescribed semaglutide (HR, 7.64; 95% CI, 2.21–26.36; $p < 0.001$). These findings translate to an increased absolute risk of NAION by 7.5% in people with T2D and by 7.0% in obesity. The number needed to harm (NNH) with NAION with semaglutide in T2D and obesity was calculated to be 13 and 14, respectively, at 3 years. If it is true, this could have serious implications. It should be noted that once-weekly semaglutide for T2D was approved by the United States Food and Drug Administration on October 18, 2017, and with its widespread use thus far, such adverse events would have come to notice by now. Notwithstanding, several methodological limitations must be considered while interpreting the findings from this retrospective study. These include: (1) *Single-center study*: The study was conducted at a single tertiary care institution likely to introduce a high risk of selection bias. (2) *Retrospective design*: The study design is not ideal for assessing causal relationships between exposure and outcome. (3) *Measurement of exposure*: Exposure to semaglutide was measured through prescription and dispensing information, not direct measures of adherence, which is a common issue. (4) *Confounding factors*: The rationale for semaglutide prescription was not provided, potentially leading to confounding variables. Important confounders such as smoking, duration of diabetes, and optic disc morphology were not considered in the analysis. Similarly, baseline glycated hemoglobin (HbA1c) and body mass index (BMI) were not propensity-matched in both T2D and/or obesity cohorts respectively, which are potential confounders. (5) *Outcome definition*: Due to the lack of an ICD-10 (International Classification of Diseases, 10th Revision) code for NAION, the outcome was not properly defined. Approximately 40% of cases coded as ischemic optic neuropathy were not NAION but rather AION. (6) *Sample size*: The number of patients exposed to semaglutide in the T2D and obesity cohorts ($n = 169$ and $n = 254$, respectively) was very small compared to

the exposed population in semaglutide clinical trials and real-world evidence, and the proportion of the population who had T2D and obesity does not match the country-specific prevalence of these conditions, indicating that the study population was not representative of the general population. (7) *Statistical precision*: The retrospective nature of the data and the fewer outcome events (NAION events: $n = 17$ and $n = 20$ in the T2D and obesity cohorts, respectively) resulted in wide 95% CI, depicting less statistical precision. (8) *Immortal time bias*: The cohorts have not been matched for background nonsemaglutide antidiabetic medications, which they have been on for a much longer period compared with semaglutide being used only in the recent past, indicating the potential of introducing immortal bias.

Nevertheless, the moot question is why semaglutide has received more attention regarding NAION while several other cardiovascular drugs were also linked to NAION in the past. The reason could be multiple which include: (1) *Recent approval*: Semaglutide was recently approved (2021) for weight loss, whereas other drugs linked to NAION have been on the market for a very long time. (2) *High-profile marketing*: Semaglutide has been heavily marketed, which has led to increased awareness and scrutiny. (3) *Previous link to retinopathy*: Semaglutide was linked to an increased risk of diabetic retinopathy exacerbation in SUSTAIN-6. (4) *High-risk population*: Semaglutide is used in patients with T2D and obesity, who already have a higher risk of NAION. (5) *Intense media coverage*: Semaglutide's association with NAION has been widely reported in the media, creating public awareness and concern. While other drugs such as PDE-5I, amiodarone, and cabergoline have also been linked to NAION, semaglutide's recent approval and high-profile marketing have contributed to the increased attention and "noise" surrounding its association with NAION.

So, what is the way forward? NAION is not a known adverse drug reaction for marketed formulations of semaglutide (Ozempic®, Wegovy®, Rybelsus®) as per the approved label.^{11–13} Semaglutide has been extensively studied in various formulations globally with large numbers of study participants exposed to semaglutide for durations up to 5 years in clinical trials (SUSTAIN, PIONEER, STEP, SELECT, OASIS) as well as in real-world studies. The totality of data provides reassurance

regarding the safety profile of semaglutide.^{11–13} Semaglutide is currently under examination in the FOCUS trial to assess its long-term effects on diabetic retinopathy in patients with T2D, with an expected completion date in 2027.¹⁴ Considering the extensive number of participants involved in randomized clinical trials and the large global population using GLP-1RAs, any confirmed absolute risk of developing NAION due to semaglutide use is likely very low. Therefore, the potential risk of NAION should not currently discourage the prescribed use of GLP-1RAs in managing T2D or obesity. This situation underscores the need for additional data-driven research to verify or disprove the association's robustness and mechanistic studies to explore biological plausibility.

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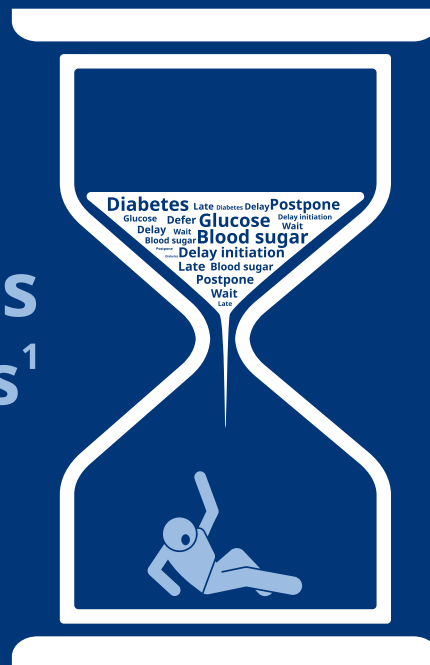
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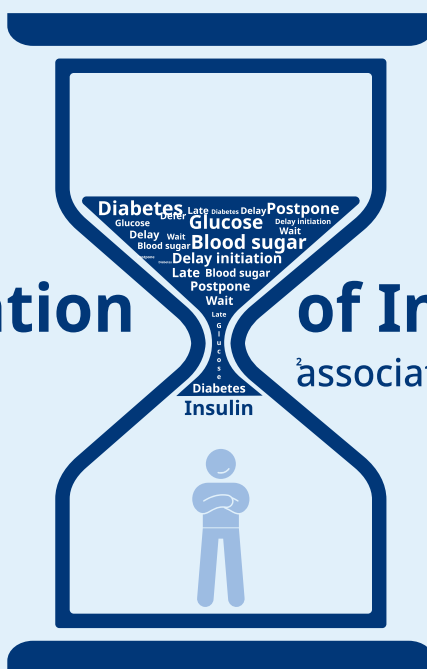


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Blockades in the Pathway of Specialty Care in Rheumatoid Arthritis: A Report Based on Indian Rheumatology Association Database

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ABSTRACT

Aim: The study aims to identify factors influencing referral patterns and delays in rheumatoid arthritis (RA) patients across clinical settings in India.

Materials and methods: A prospective, multicenter, observational study collected data from eight centers using the Indian Rheumatology Association (IRA) database. Patient-related factors and referral factors were determined based on patient narration. The modified PRASAD scale categorized patients' socioeconomic status.

Results: The study included 4,643 RA patients from eight centers. Data from 35 patients were excluded due to inconsistent reporting of diagnosis and delay. Lack of awareness was the predominant factor causing the delay in referral. Approximately, 39% of patients were referred to the rheumatology specialty within 6 months of disease onset, while 26% reported later, and 34% reported over 2 years. Referral delays were linked to socioeconomic factors in Madhya Pradesh (21.43%) and West Bengal (28.57%). Lack of awareness about the disease and rheumatology specialty was highest in West Bengal (100%), followed by Delhi and Rajasthan (93.70%). Misconceptions about modern medicine, reluctance to refer patients to the rheumatologist, and previous treatment by other specialties were other factors influencing referral delay. Primary care clinicians' unawareness of the rheumatology specialty was the primary reason for referral delay in Gujarat (33.56%) and Delhi and Rajasthan (25.18%).

Conclusion: Both patient and healthcare professional-related factors contribute to referral delays in RA patients. Major factors causing referral delays include reluctance to refer and inadequate knowledge about rheumatology among primary care physicians and the general public. Patients' education and occupation also influence the timing of referrals to specialty care.

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INTRODUCTION

Rheumatoid arthritis (RA) poses a significant burden on individuals and healthcare systems in India, with an estimated prevalence of 0.75% affecting 5–7 million individuals. RA not only impairs the physical health and quality of life of the affected individuals but also has substantial socioeconomic implications.^{1,2}

The disability caused by RA is largely preventable, especially with the early introduction of disease-modifying antirheumatic drugs (DMARDs). The delayed introduction is a major challenge in RA management and leads to increased disease burden and suboptimal outcomes.³ In 2010, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised the diagnostic criteria to facilitate early identification of the disease and prompt initiation of effective therapy. However, despite these efforts, there exist several challenges in the early introduction of DMARDs.⁴

Rheumatologists play a crucial role in the prompt diagnosis, management, and

initiation of DMARD therapy for RA. Delayed referral of patients to specialty care has been identified as one of the key factors contributing to the delayed introduction of DMARDs in Indian settings. Delays in referral can occur due to various reasons, such as limited access to rheumatology care, lack of awareness among primary care physicians about early signs and symptoms, or patients themselves not seeking medical attention promptly.^{5,6} Numerous studies have investigated the challenges confronted by patients in accessing specialty care, and they include underestimation of symptoms by patients, limited knowledge of autoimmune diseases by primary care physicians, lengthy wait times, travel distances, and shortage of rheumatologists. The delay in seeking medical care is also influenced by several patient-related factors and variables like fear, lack of health literacy, and patients' misbeliefs about the healthcare system.⁷ Some patients might neglect their symptoms or think they have other causes for them, thereby delaying their decision to seek medical attention.

Addressing the delay in accessing optimal care in RA patients requires a comprehensive approach involving the implementation of an effective referral system, increased physician awareness, and patient empowerment.⁷ Based on multiple factors, the present study has arbitrarily chosen 6 months as the delay in accessing specialty care. The present study aims to determine the factors influencing referral patterns and delays in RA patients across different regions of India by analyzing the data collected through the database created by the Indian Rheumatology

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Association (IRA). To ensure a comprehensive analysis, the centers were selected from different zones of India, representing all five zones, namely northern, western, central, southern, and eastern states.

MATERIALS AND METHODS

Registry/Database Design and Study Population

The independent prospective, multicenter, observational study collected data from eight centers, with each center specifically providing data for patients with RA. The selection of centers was based on their geographic locations and the availability of patients diagnosed with six autoimmune diseases, namely RA, spondyloarthritis, psoriatic arthritis, systemic lupus erythematosus (SLE), scleroderma, and primary Sjogren's syndrome (pSS). The present study considered data of adult patients fulfilling the ACR/EULAR criteria for RA 2010.⁴ These referral centers had a footfall of patients from the entire state where they belong to and from neighboring states. The study database, initiated in April 2020, included both newly diagnosed patients and those undergoing follow-up at the participating centers. Data collection was done using a predefined proforma specifically designed for each disease. Two separate structured forms were used: one for collecting general demographic and socioeconomic information, functional impairment, obstetric history, and overall health-related parameters, and another form for capturing disease-specific details. All participating centers obtained clearance from their respective institutional ethical committees (list enclosed as supplementary file), and written informed consent was obtained from all selected patients prior to their participation, following the recommendations of their respective institutions.

Sample Size Calculation for Registry

The minimum number of subjects to be recruited was determined based on the primary objective of evaluating the clinical and laboratory profiles of the autoimmune rheumatic diseases under consideration based on the reported prevalence of the individual diseases. A total of 6,500 patients were estimated to be recruited for the study.⁸

Data Collection and Definitions Specific to Delay

To investigate the factors contributing to delayed access, the study considered the time taken to access tertiary care from the onset of the first attributable symptom or sign related to the primary diagnosis. A referral delay or delay in accessing tertiary care was defined

as a period exceeding 6 months. Rather than considering the diagnostic conclusion before referral or in the rheumatology department, the study focused on the patient's initial encounter with specialty care.

Each patient was interviewed and assessed by the research team to better understand the factors associated with the delay. The patient-related factors considered were their belief in modern medical care, unawareness of the rheumatology specialty, socioeconomic reasons, and the notion that modern medical care carries an elevated risk for adverse events. The key referral factors considered based on the patient narration are briefed below: the primary care provider did not refer to a rheumatologist or was reluctant to do so; despite being diagnosed correctly, the patients were referred to different specialties like nephrology, dermatology, orthopedics etc.; the primary care physician was unaware of the rheumatology specialty; and the patient was unaware of the primary diagnosis, or there was no document ascertaining it. If the researcher was unable to ascertain the reason, despite considering all these factors, it was recorded as not ascertainable. The modified PRASAD scale was used for socioeconomic classification, which includes the patient's income, education status and profession.⁹ Clinical presentation and system involvement were also considered for the analysis.

Statistical Analysis

Microsoft Excel was used to perform the descriptive analysis. The data of SLE, pSS, and scleroderma patients were analyzed separately. To compare the causes, analysis of variance (ANOVA) was employed for continuous variables, while the Chi-squared test and Fisher's exact test were used for categorical variables.^{10,11} Missing data, particularly those lacking identifiable reasons, were excluded from the analysis as they were presumed to be unrelated to the expected cause. Subjects within each disease group were divided into two categories—those referred to the rheumatology specialty within 6 months and those referred after >6 months. The differences among different centers were compared to understand the influence of different population demographics.

RESULTS

A total of 4,643 patients diagnosed with RA were enrolled in the study from eight centers. However, the data of 35 patients with inconsistent reporting of delay in diagnosis and cause for delay, collected from three different centers, were excluded from the analysis. The mean age of the patients was

49.23 ± 12.18 years with a male-to-female ratio of 1:7.1. Approximately, 39% of patients were referred to rheumatology within 6 months of disease onset, while 26% reported later, with 34% reporting over 2 years. Lack of awareness emerged as the prominent factor for referral delay, with 32% of participants reporting being unaware of their condition and their specialty. About 7, 6, and 7% of the subjects reported late to the rheumatology specialty since they had no belief in modern medicine, socioeconomic reasons, and the perception of modern care drugs having adverse events, respectively. The delay caused by patients being managed by specialties other than rheumatology (41.97%) has been identified as the prominent referral factor responsible for delay in accessing rheumatology specialty care. Other factors were reluctance to refer to rheumatology (17.09%), primary care physicians not being aware of the rheumatology specialty (12.36%), and not being diagnosed as a rheumatic disease (13.15%). A total of 84% of patients delayed their visit as they opted for alternative methods and treatment (the category of the alternative system used to manage was not certain) (Table 1).

Comparison between the groups (referred within 6 months and after 6 months) revealed that the mean age of patients was 49.23 ± 12.18 years for those reported within 6 months and 49.96 ± 11.85 for those reported after 6 months to the specialty ($p = 0.001$). Patients with symmetric arthritis, pattern additive, episodic, and relapsing arthritis were referred early to the specialty group compared to those with atypical presentations. Patients with typical signs of inflammation had an increased likelihood of early referral to rheumatology specialty (31.90 vs 28.35%), whereas a higher proportion of patients with deformities were referred after 6 months of disease onset (9.95 vs 15.69%) (Table 2).

The study also compared variables related to education, occupation, monthly income, and a composite score called the "total score" of the earning person within a family between the two groups. However, due to the lack of socioeconomic data, the data of 11 patients in the <6 months group and 17 patients in the >6 months group were not considered for further analysis (Table 3). The education levels were categorized into five groups, each with an associated score (7, 6, 5/4/3, 2, and 1) representing increasing levels of education. The overall education status of the patients did not influence their referral to tertiary centers. However, there was a significant referral delay in patients whose education level was below graduation (intermediate/high school/middle school), whereas the referral was better for

Table 1: Probable reasons, referral factors, and anticipated length of time for diagnosis delay

Variables	Mean $\pm$ SD (range)
Age (years)	49.23 $\pm$ 12.18 (16–97)\$
Gender M (F)	567 (4,041)
Estimated time of delay in diagnosis from first symptom to diagnosis (<i>n</i> = 4608)	
<6 months	1818 (39.45%)
6–24 months	1214 (26.34%)
$\geq$ 24 months	1576 (34.20%)
Probable causes of delay	
Patient factors (<i>n</i> = 2790)	
No belief in modern medicine	197 (7.06%)
Lack of awareness on disease condition and rheumatology specialty	898 (32.18%)
Socioeconomic reason	175 (6.27%)
Perception of modern care drugs having adverse events	188 (6.73%)
Referral factors (<i>n</i> = 2790)	
Reluctance to refer to rheumatology	477 (17.09%)
Managed by another specialty	1171 (41.97%)
Lack of awareness about rheumatology specialty among primary care physicians	345 (12.36%)
Not diagnosed as rheumatic disease	367 (13.15%)
Others (<i>n</i> = 899)	
Ayurveda	50 (8.44%)
Medicines purchased from local shop	6 (1.01%)
Homeopathy	7 (1.18%)
Both homeopathy and Ayurveda	24 (4.05%)
Uncertain, but used alternative methods	498 (84.12%)
Other alternative medicines like Siddha, Chinese Tibetan etc.	7 (1.18%)

\$, analysis of variance

Table 2: Demographic distribution according to less than or >6 months

Variables	<6 months (<i>n</i> = 1818)	>6 months (<i>n</i> = 2790)	<i>p</i> -value
Age (years)			
Mean $\pm$ SD (range)	49.23 $\pm$ 12.18 (16–97)	49.96 $\pm$ 11.85 (18–96)	0.001\$
Gender			
M (F)	247 (1,571)	320 (2,470)	0.036*
Musculoskeletal manifestations			
Arthralgia/arthritis	1788 (98.35%)	2760 (98.92%)	0.12*
Symmetry	1019 (56.05%)	1387 (49.71%)	<0.001*
Pattern additive	804 (44.22%)	1108 (39.71%)	0.0026*
Relapsing	113 (6.21%)	116 (4.15%)	0.002*
Episodic	52 (2.86%)	30 (1.07%)	<0.0001*
Swelling			
Hand	5 (0.27%)	0	0.02*
Discoloration of joints	74 (4.07%)	158 (5.66%)	0.02*
Limitation of movements			
Hand	2 (0.11%)	0	0.30*
Deformities	181 (9.95%)	438 (15.69%)	<0.0001*
Early morning stiffness	1091 (60.01%)	1610 (57.70%)	0.13*
Signs of inflammation	580 (31.90%)	791 (28.35%)	0.01*
Aggravating or relieving factors			
Work			
Increase	758 (41.69%)	1201 (43.04%)	0.4*
Decrease	765 (42.08%)	1191 (42.68%)	0.70*
Cold			
Increase	1097 (60.34%)	1819 (65.19%)	0.0009*
Decrease	326 (17.93%)	462 (16.56%)	0.24*
Rest			
Increase	348 (19.14%)	551 (19.74%)	0.64*
Decrease	1008 (55.44%)	1624 (58.20%)	0.06*

*, Chi-squared test; \$, analysis of variance

those who graduated and above (Table 3). A higher proportion of skilled workers had delayed referrals to the specialty (46.59 vs 51.72%; $p = 0.001$), while a significantly higher proportion of professionals reached specialty care within 6 months (15.98 vs 12.74%; $p = 0.003$). The referral to tertiary care was not significantly impacted by family income, with the exception of patients whose earnings were $>₹41,430$.

The study also compared the age, gender, patient factors, referral factors and other reasons for referral delay across the participating centers. Since the center from Rajasthan had recruited only a small number of participants, it was combined with Delhi for analytical purposes, representing northern India according to the suggested geographic distribution. The patient's age varied across different locations, ranging from 40 to 51 years, and each facility received more female patients than male subjects. There was a significant difference in patients reporting to the centers >6 months and ≥ 24 months ($p < 0.0001$ for each, respectively). A significant proportion of patients (72.53%) recruited from Telangana referred to the specialty within 6 months, followed by centers in Madhya Pradesh (45.45%) and Kerala (43.85%). A notable proportion of patients from West Bengal (37.41%) were reported between 6 and 24 months, while patients reported to the Telangana center had a lower proportion (21.97%) (Table 4).

The proportion of patients with no belief in modern medicine was higher in Gujarat (34.92%) and Madhya Pradesh (21.43%). Lack of awareness about the RA disease condition and rheumatology specialty was highest in West Bengal (100%), followed by Delhi and Rajasthan (93.70%), Gujarat (76.87%), and Madhya Pradesh (66.66%). Socioeconomic reasons were attributed to referral delays in West Bengal and Madhya Pradesh (28.57% and 21.43%). Patients with misconceptions regarding modern care medicine were more in Gujarat and Madhya Pradesh (31.06 and 26.19%). The proportion of patients who were reluctant to refer to rheumatology specialty was higher (47.61%) in Madhya Pradesh, followed by Karnataka (24.22%). Besides, the majority of the patients who were referred to Delhi and Rajasthan (88.14%) and Gujarat (78.00%) were previously managed by other specialties. Moreover, referral delays in Gujarat (33.56%), Delhi, and Rajasthan (25.18%) centers were primarily attributed to primary care physicians not being aware of the rheumatology specialty. Around 51% of patients from Gujarat were not initially diagnosed with rheumatic disease by their physician.

Table 3: Demographic distribution of socioeconomic data according to less or more than 6 months

Variables		<6 months (n = 1745)	>6 months (n = 2668)	p-value
Age	Mean $\pm$ SD (range)	48.13 $\pm$ 12.63 (16–97)	49.91 $\pm$ 11.82 (18–96)	0.002 [§]
Gender	M (F)	242 (1,503)	299 (2,369)	0.01*
Education of earning person of the family	Profession or honors (score = 7)	106 (6.07%)	131 (4.91%)	0.11*
	Graduate or postgraduate (score = 6)	564 (32.32%)	701 (26.27%)	<0.0001*
	Intermediate/high school/ middle school (score = 5/4/3)	828 (47.45%)	1413 (52.96%)	0.0004*
	Primary school (score = 2)	122 (6.99%)	165 (6.18%)	0.32*
	Literate (score = 1)	125 (7.16%)	258 (9.67%)	0.005*
Occupation of earning person of the family	Professionals (score = 10)	279 (15.98%)	340 (12.74%)	0.003*
	Semi-professionals (score = 6)	214 (12.26%)	272 (10.19%)	0.03*
	Clerks, shop-owners (score = 5)	180 (10.31%)	296 (11.09%)	0.44*
	Skilled workers (score = 4)	813 (46.59%)	1380 (51.72%)	0.001*
	Semi-skilled workers (score = 3)	98 (5.61%)	145 (5.43%)	0.84*
	Unskilled workers (score = 2)	85 (4.87%)	135 (5.06%)	0.84*
	Unemployed (score = 1)	76 (4.35%)	100 (3.75%)	0.35*
Monthly income of earning person of the family in rupees (₹)	>₹41,430 (score = 12)	202 (11.57%)	202 (7.57%)	<0.0001*
	₹20,715–₹41,429 (score = 10)	344 (19.71%)	473 (17.73%)	0.105*
	₹15,536–₹20,714 (score = 6)	611 (35.01%)	999 (37.44%)	0.2*
	₹10,357–₹15,535 (score = 4)	410 (23.49%)	681 (25.52%)	0.13*
	₹6,214–₹10,356 (score = 3)	121 (6.93%)	221 (8.28%)	0.11*
	₹2,092–₹6,213 (score = 2)	47 (2.69%)	74 (2.77%)	1.00*
	<₹2,091 (score = 1)	10 (0.57%)	18 (0.67%)	0.82*
Based on total score	Upper (score = 26–29)	229 (13.12%)	239 (8.96%)	<0.0001*
	Upper middle (score = 16–25)	560 (32.09%)	788 (29.53%)	0.07*
	Lower middle (score = 11–15)	695 (39.82%)	1221 (45.76%)	0.0001*
	Upper lower (score = 5–10)	245 (14.04%)	403 (15.10%)	0.35*
	Lower (score = <5)	16 (0.91%)	17 (0.64%)	0.4*

*, Chi-squared test; [§], analysis of variance

A higher proportion of patients from Kerala (12.43%) opted for Ayurveda as a treatment modality for RA, and 5% from West Bengal used Homeopathy. Approximately, 7% of the patients from West Bengal had obtained RA medication from a nearby pharmacy without a prescription, and around 5% of patients from the same state resorted to Homeopathy for the treatment of RA ($p = 0.0008$). Moreover, approximately 32% of the patients recruited from Karnataka reported using alternative methods for managing RA. In contrast, a smaller percentage of patients from Telangana used other traditional medicines, including Siddha, Chinese, and Tibetan (4%) (Table 4). However, these findings were not statistically significant.

DISCUSSION

In the current study, approximately 60% of patients reported late to rheumatology with a delay of >6 months between the onset of the disease and their referral to a rheumatologist. The factors influencing such delays are multifaceted, encompassing both patient- and referral-related aspects. The

study has identified reluctance to refer to rheumatology care, inadequate knowledge of the rheumatology field, and failure to recognize RA as a rheumatic condition as significant barriers to timely referrals. Additionally, patient-related factors, such as education and occupation, also impact the timing of referrals.

A United Kingdom-based study by Kumar et al. observed a median duration of 23 weeks between the onset of RA symptoms and the assessment by a rheumatologist in about 57% of patients.¹² In a Europe-based study of 482 RA patients from 10 centers, the median delay between the onset of disease symptoms and the rheumatologist visit was 24 weeks, with a range of 8–42% for patients who were seen within 12 weeks of symptom onset.¹³ A Netherlands-based study noted a median total delay of 13.7 weeks, with a delay of 8 weeks in referral by the general practitioner and a patient delay of 2.4 weeks. Among 598 patients, 31% of them reported consulting rheumatologist <12 weeks after the disease onset.¹⁴ A Poland-based study reported a delay in 28% of patients who sought medical

attention after 4 months or longer post onset of symptoms, while 36% waited for the same duration for a referral to a rheumatologist.⁵

A comparison of the data between European and developing countries like India indicates that the proportion of patients who were referred early to rheumatology care was better in developed nations. This could be attributed to greater awareness of rheumatology among healthcare providers and the public, well-established healthcare systems, and better access to specialized clinics in developed countries. In contrast, limited awareness, resource constraints, and socioeconomic factors impair the recognition of RA symptoms and referrals to specialists in developing countries. The Danish nationwide DANBIO registry-based study observed that improved awareness regarding the significance of early diagnosis reduced diagnostic delay since 2000.¹⁵

In line with these findings, the current study identified the lack of awareness about the disease condition and patients being managed by healthcare providers of other specialities as the primary reasons for the

Table 4: Diagnosis, patients, and referral factors responsible for referral delay in Indian rheumatology centers

Variables	Delhi, Rajasthan (n = 414)	Kerala (n = 659)	Karnataka (n = 2553)	Telangana (n = 91)	West Bengal (n = 147)	Madhya Pradesh (n = 77)	Gujarat (n = 699)	p-value
Age	43.76 ± 11.29 (22–76)	50.52 ± 10.80 (20–84)	51.16 ± 12.16 (17–97)	44.76 ± 11.40 (16–81)	42.61 ± 10.97 (19–75)	44.07 ± 12.90 (18–80)	47.89 ± 12.25 (18–87)	0 [§]
Gender	57 (355)	60 (599)	325 (2198)	9 (82)	24 (123)	12 (65)	80 (619)	0.06*
<6 months	142 (34.46%)	289 (43.85%)	975 (38.64%)	66 (72.53%)	53 (36.05%)	35 (45.45%)	258 (36.90%)	<0.0001*
6–24 months	137 (33.25%)	177 (26.85%)	607 (24.05%)	20 (21.97%)	55 (37.41%)	21 (27.27%)	197 (28.18%)	<0.0001*
≥24 months	133 (32.28%)	193 (29.28%)	941 (37.29%)	5 (5.49%)	39 (26.53%)	21 (27.27%)	244 (34.91%)	<0.0001*
Patient factor	n = 270	n = 370	n = 1548	n = 25	n = 94	n = 42	n = 441	
No belief in modern medicine	5 (1.85%)	17 (4.86%)	10 (0.64%)	1 (4.00%)	1 (1.06%)	9 (21.43%)	154 (34.92%)	NS
Lack of awareness on disease condition and rheumatology specialty	253 (93.70%)	144 (38.91%)	33 (2.13%)	7 (28.00%)	94 (100.00%)	28 (66.66%)	339 (76.87%)	NS
Socioeconomic reason	18 (6.66%)	17 (4.59%)	3 (0.19%)	2 (8.00%)	0	9 (21.43%)	126 (28.57%)	NS
Misconception that modern care drug has lot of adverse events	1 (0.37%)	37 (10.00%)	1 (0.06%)	1 (4.00%)	0	11 (26.19%)	137 (31.06%)	NS
Referral factor	n = 270	n = 370	n = 1548	n = 25	n = 94	n = 42	n = 441	
Reluctance to refer to rheumatology	8 (2.96%)	16 (4.32%)	375 (24.22%)	3 (12.00%)	0	20 (47.61%)	55 (12.47%)	NS
Managed by another specialty	238 (88.14%)	169 (45.67%)	351 (22.67%)	15 (60.00%)	23 (24.47%)	31 (73.80%)	344 (78.00%)	NS
Primary care physician not aware of rheumatology	68 (25.18%)	41 (11.08%)	30 (1.93%)	5 (20.00%)	48 (51.06%)	5 (11.90%)	148 (33.56%)	NS
Not diagnosed as rheumatic disease	7 (2.59%)	90 (24.32%)	28 (1.80%)	5 (20.00%)	8 (8.51%)	3 (7.14%)	226 (51.24%)	NS
Others	n = 270	n = 370	n = 1548	n = 25	n = 94	n = 42	n = 441	
Ayurveda	0	46 (12.43%)	3 (0.19%)	0	0	1 (2.38%)	0	NS
Medicines from local shop	0	0	0	0	7 (7.44%)	0	0	NS
Homeopathy	0	1 (0.27%)	0	0	5 (5.32%)	0	0	0.0008 [#]
Both Homeopathy and Ayurveda	0	0	24 (1.55%)	0	0	0	0	NS
Uncertain, but used alternative methods	0	0	498 (32.17%)	0	0	0	0	NS
Others alternative medicines like Siddha, Chinese Tibetan etc.	0	0	4 (0.26%)	1 (4.00%)	2 (2.12%)	0	0	0.23

NS, nonsignificant; *, Chi-squared test; [§], analysis of variance; [#], Cramer's V test

delay in referral to rheumatology specialties. Atypical presentations and low inflammatory features also contributed to delayed referral. A qualitative study by Jain et al. reported that lack of knowledge, self-diagnosis, self-management at home, and stigma associated with disease largely contribute to delay in seeking rheumatology care.⁷ Jain et al. also noted that the understanding of RA symptoms varied among RA patients, resulting in diagnostic delay.⁷ Due to the lack of medical knowledge, the patients often attribute their symptoms to a wide range of causes, including nutrition, stress, excessive work, and lifestyle, among many others. Therefore, the long journey to diagnosis

in Indian settings is primarily caused by a lack of knowledge about the disease and the "rheumatology branch," in addition to the scarcity of rheumatologists across the country. This scenario is comparable to other developing nations. A nonsystematic comprehensive review conducted by the researchers of Portugal has also reported that the general population's dearth of knowledge regarding inflammatory arthritis is frequently recognized as a significant barrier to seeking medical attention.¹⁶

Another major factor contributing to the delay in accessing rheumatology specialty care is the management of patients by healthcare providers from other specialties.

Additionally, a cross-sectional study by Naeem et al. observed that a significant proportion of patients initially sought care from orthopedic surgeons (39.2%) and general practitioners (26.5%), thereby highlighting the lack of an appropriate referral system at the primary level.¹⁷ A retrospective multicenter questionnaire survey study conducted in Poland found that only 34% of patients diagnosed with inflammatory rheumatic diseases or undergoing the diagnostic process seek medical attention and are referred directly to a rheumatologist.⁵ Hence, early diagnosis of RA disease is possible when the patient is referred directly to the rheumatologist, avoiding referral delay due to

accessing rheumatology specialty care. Jain et al. also noted the primary causes for delays as rationalization of the symptoms, a lack of proper medical guidance, family influence and/or education, adherence to conventional beliefs, poor referral, and a shortage of rheumatologists, among other factors.⁷

The key causes found in the current study for referral delays include misinterpretation of the symptoms, ignorance of the disease, clinical presentation and effect of symptoms, difficulty for general practitioners to diagnose arthritis, lack of confidence, inadequate provider teamwork, and a shortage of rheumatologists. A cross-sectional study by Diamant et al. reported that 33% of the subjects reported delay in seeking medical care in the previous 12 months, and 25% of them reported that their needs were unmet due to competing priorities.¹⁸ Improved rheumatology treatment delivery, a strong referral system, and more local and national government involvement are required to reduce the time gap in RA Indian patients seeking medical attention in Indian settings.⁷

According to the recommendations put forth by the EULAR in 2016, every patient experiencing persistent swelling in at least one joint should be promptly referred to and assessed by a rheumatologist within six weeks of symptom onset. In addition, effective treatment should be initiated by the end of the 12th week.¹⁹ The present study findings noted that patients with certain specific arthritis patterns and typical signs of inflammation were more likely to be referred early to the rheumatology specialty compared to those with atypical presentations. Patients with symmetric arthritis, pattern additive, episodic, and relapsing arthritis were more promptly referred to the specialty.

The current study underscores the need for primary care clinicians to be vigilant in recognizing typical signs of inflammatory rheumatic disease, such as joint pain, swelling, and morning stiffness, to ensure timely referral and appropriate management. Patients treated for <6 months for swelling reported hand swelling and joint discoloration in the current study. Raciborski et al. reported joint pain (94%) and joint swelling (78%) as the most prevalent early signs of inflammatory rheumatic disease, followed by morning stiffness (77%), exhaustion (76%), and sleep disruption due to joint discomfort (74%) as symptoms of RA in stable patients.⁵ The same number of participants (76%) who reported morning weariness also reported joint stiffness.⁵ The duration of symptoms, discomfort in the shoulders and hands, and back pain were the most frequent contributors

to reduced quality of life resulting from musculoskeletal pain, as reported in a rural community-based study in South India.²⁰ The study revealed a significant difference in referral timing based on the type of occupation. Professionals were more likely to receive a referral to the specialty within 6 months, while individuals with other occupations were frequently referred after 6 months. This indicates that professionals may have better access to healthcare or are more proactive in seeking specialized care for their arthritis compared to people in other occupations.

Overall, the study suggests that education level and occupation may play crucial roles in determining the timing of referrals to specialty care, while family income appears to have a more limited impact, suggesting a possible socioeconomic barrier to receiving early specialty care. A retrospective cohort study conducted in Taiwan involving 581,770 male subjects noted that those with lower median household income (<\$45,200) had a reduced likelihood of receiving a rheumatologist referral, an annual physical assessment or annual laboratory testing.²¹ A Korean-based study on the prevalence and socioeconomic status of RA patients found that delayed diagnosis was associated with lower income.²² Furthermore, a Swedish longitudinal study noted that RA patients' fear-avoidance behaviors were associated with lower income levels than the national norm.²³ The current study found considerable variations in referral patterns across the different participating centers, including the proportion of individuals referred between 6 and 24 months and after 24 months after the disease onset. These regional variations raise the possibility of discrepancies in healthcare infrastructure, knowledge, or referral procedures, which subsequently contribute to delayed access to specialty care.

Socioeconomic factors significantly influence the timing of seeking specialty care. Upon comparison of different zones, it was evident that West Bengal and Madhya Pradesh had a higher percentage of the population facing delays in reaching specialty care due to socioeconomic reasons. These findings corroborate the fact that a higher proportion of poverty was noted in these two states compared to the other five zones.²⁴ However, the comparison of the entire patient population showed that there was no significant influence of family earnings on seeking specialty care, except in higher-income groups. The selected centers included both public healthcare facilities and private institutions, where private institutions

may have higher out-of-pocket expenses. However, the access to care may be biased since the survey was conducted with patients who reached the institutions rather than the general population. Overall, healthcare has become expensive, leading to potential barriers to accessing specialty care for certain socioeconomic groups.

Referral delays are a result of patient decisions (delay in seeking medical attention, self-treatment, etc.) as well as systemic variables (prolonged wait times for appointments).⁵ The current study findings corroborate the collective role of patient-related factors, referral factors, and alternative treatment-seeking behaviors in delaying diagnosis and subsequent management of autoimmune rheumatic diseases. Improved access to rheumatology care, an efficient and well-structured referral system, increasing awareness and education about rheumatic diseases among primary care physicians and the general public, and increased involvement from local to national governments to enhance the overall healthcare infrastructure are warranted to improve the quality of care and outcomes for patients with rheumatic conditions.^{7,25}

Comprehensive data collection through the IRA database, encompassing multiple centers across different regions, a larger sample size, and consideration of both patient-related and referral factors are the major strengths of the study. However, uneven recruitment from different centers, lack of geographic representation, and potential recall bias may limit the generalizability of the study findings.

CONCLUSION

Both patient-related and referral factors contribute to referral delay in RA patients. Refusal to refer to rheumatology, inadequate knowledge of rheumatology among primary care physicians and the general public, and failure to recognize the illness as a rheumatic condition were identified as major contributors to referral delays. Education level and occupation are also crucial in determining the timing of referrals to specialty care.

AUTHOR CONTRIBUTIONS

All the authors have contributed equally to the conceptualization, data capturing, and content development. Dr Rudra Prosad Goswami served as coinvestigator, and Dr Debashish Danda served as overall in charge of the IRA database. All other authors served as principal investigators from respective centers.

AVAILABILITY OF DATA AND MATERIALS

Data will be provided on request.

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Impact of Immunoglobulin M-enriched Immunoglobulins on the Outcomes of Severe Coronavirus Disease 2019



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ABSTRACT

Background and aim: Coronavirus disease 2019 (COVID-19) led to a major global health crisis, leading to a worldwide pandemic. Several therapeutic interventions have been tried with varied results. The purpose of this academic work was to assess the efficacy of immunoglobulin M (IgM)-enriched Ig in the management of patients with severe COVID-19 pneumonia.

Materials and methods: In this retrospective cohort study, severe COVID-19 pneumonia patients who received IgM-enriched immunoglobulin, in addition to standard-of-care treatment, were retrospectively enrolled. Levels of inflammatory biomarkers, oxygenation status, and organ dysfunction were evaluated, and differences were noted after giving IgM-supplemented IgM.

Results: Data from 32 consecutive severe COVID-19 patients admitted to medical intensive care units (ICUs) were analyzed. After giving IgM-enriched Ig, there was an improvement in oxygenation indices as shown by saturation of oxygen/fraction of inspired oxygen (SpO_2/FiO_2) on days 3 and 7, but it was not statistically significant. Oxygen support could be de-escalated in 13 (40.6%) patients on day 3 and in 8 (25%) patients on day 7, after giving IgM-enriched Ig. After giving IgM-enriched Ig, there was a reduction in the levels of all the studied inflammatory markers [interleukin-6 (IL-6), D-dimer, and ferritin) on days 3 and 7, but it was statistically significant only for IL-6. The overall ICU mortality was 53.1%.

Conclusion: Outcomes of patients with severe COVID-19 requiring ICU care remain dismal. IgM-enriched Ig may be helpful in improving oxygenation and combating cytokine storm in these patients. However, in the present study, the improvement in oxygenation indices (SpO_2/FiO_2) and reduction in inflammatory markers like D-dimer and ferritin were not statistically significant. Hence, larger randomized controlled trials are required to get more definitive evidence to support this therapy and show significant clinical and mortality benefits.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic caused by a novel β -coronavirus spread out in December 2019 in Wuhan City, Hubei Province, China. The years 2020–2022 witnessed a worldwide pandemic resulting in millions of deaths and an unprecedented global crisis due to COVID-19 infection. Even though a great majority had an asymptomatic or mild infection, a significant proportion required hospitalization and even ICU stay.

Treatment strategies have also changed over time, and several therapeutic modalities have been tried to improve outcomes in these patients. In spite of steroids, outcomes of patients with severe disease remain poor. In severe COVID-19 infection, patients needing invasive mechanical ventilation (IMV) have been shown to have high mortality. Drugs like remdesivir, which have shown mortality benefit in other patients, are not recommended for use in patients on IMV.¹

Several therapeutic modalities, including immunomodulators like high-dose pulse steroid therapy, cytokine filtration, IL-6 inhibitors, IL-1 inhibitors, kinase inhibitors, granulocyte-macrophage colony-stimulating

factor (GM-CSF) inhibitors, and use of Ig, have been suggested and tried in these patients with refractory hypoxemia as salvage therapy to improve outcomes. However, none of these therapies have shown consistent results.

The benefit of therapy with intravenous immunoglobulins (IVIg) has been demonstrated in several autoimmune and inflammatory conditions. IgM-enriched Ig are also commercially available, which may have the added advantage of providing immediate immunity due to the presence of IgM. In patients with severe sepsis and septic shock, IgM-enriched Ig have shown encouraging results as adjuvant therapy.^{2,3} However, there is a lack of data regarding its efficacy in managing COVID-19 patients with refractory hypoxemia. Hence, we aimed to conduct this retrospective analysis of patients with severe COVID-19 who had received IgM-enriched Ig.

MATERIALS AND METHODS

Study Design and Treatment Protocol

This retrospective cohort study was conducted in a tertiary care hospital in patients with severe COVID-19 pneumonia.

Institutional Scientific (TS/MSSH/MHIL/ISC/CCM/22-48) and Ethical Committee (BHR/RS/MSSH/MHIL/SKT-1/MHEC/CCM/22-09) approvals were obtained in advance.

Eligibility criteria for the study included patients above 18 years of age who were diagnosed with severe COVID-19 pneumonia with a positive reverse transcription polymerase chain reaction (RT-PCR) nasopharyngeal swab requiring ICU admission. Patient demographics such as age, sex, and chronic comorbidities were collected. Clinical data, including baseline laboratory parameters, levels of inflammatory markers, oxygen support, ICU course, need for organ support, and ICU outcomes, were obtained from the clinical records.

Inclusion and Exclusion Criteria

All consecutive COVID-19 patients admitted to the ICU who received IgM-enriched immunoglobulin were included. Patients who received IgM-enriched Ig for <24 hours, and those who received IgM-enriched Ig for indications other than COVID-19 disease, were excluded from the analysis.

Patients were managed with standard of care treatment according to regional and institutional COVID-19 guidelines, along with IVIg supplemented with IgM (Pentaglobin, Biotest AG, Dreieich, Germany), at the physician's discretion. Injection pentaglobin was administered at a dose of 0.75 gm/kg/day for 3 consecutive days as an IV infusion. Clinical, laboratory, and radiological monitoring were conducted daily during the ICU stay for all patients. Hospital records were also reviewed for any safety issues and unfavorable outcomes throughout their hospitalization.

Patients were provided supplemental oxygen therapy to target SpO_2 around

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92–96%. If there was evidence of secondary bacterial infection, antibiotics were initiated at the physician's discretion. Dexamethasone phosphate at a dose of 8 mg (equivalent to 6.66 mg dexamethasone) was administered daily for 10 days. Vitamin C supplementation at a dose of 1 gm daily and low molecular weight heparin (dose adjusted based on patient's body weight and kidney function) for venous thromboprophylaxis were given to all patients, unless contraindicated. IV remdesivir was initiated whenever indicated, with a loading dose of 200 mg on the 1st day, followed by a maintenance dose of 100 mg daily for 4 days. Mechanical ventilation support was considered in patients exhibiting respiratory distress using accessory respiratory muscles, requiring FiO_2 of 80% or more to maintain a SaO_2 level of 90%, or having a partial pressure of oxygen (PaO_2)/ FiO_2 ratio below 200 mm Hg.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was used to evaluate the severity of disease, while the Glasgow Coma Score was applied to assess cognitive, affective, and behavioral states for all patients. Patients were monitored for inflammatory laboratory markers, SpO_2 / FiO_2 ratio, and organ dysfunction. Relevant data were compared before and after administering IgM-enriched immunoglobulin on days 3 and 7.

The primary objective was to evaluate the effect of IgM-enriched Ig on oxygen

parameters (SpO_2 / FiO_2 ratio), while the secondary objectives were to assess the impact of IgM-enriched Ig on inflammatory biomarkers, reduction in ventilatory support, and ICU mortality.

Statistical Analysis

The collected data were recorded in an Excel sheet. For the statistical analysis, Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, Illinois) was used. Student's *t*-test was employed to compare means of continuous variables, and the Chi-squared test or Fisher's exact test was used to compare categorical variables, as appropriate. Analysis was considered significant when the *p*-value was <0.05 .

RESULTS

In this single-center retrospective study, we collected data from 32 severe COVID-19 patients admitted to the medical ICU who received IgM-enriched IVIG in addition to standard therapy. The baseline patient parameters are provided in Table 1. After receiving IgM-enriched Ig, there was improvement in oxygenation on days 3 and 7, but it was not statistically significant (Table 2). Furthermore, there was a marked reduction in levels of inflammatory markers (IL-6, D-dimer) on days 3 and 7, with statistical significance observed only for IL-6 on both days.

On day 3 after receiving IgM-enriched Ig, 13 patients required de-escalation of oxygenation support, 15 patients required escalation of support, and four patients required no change in oxygenation support.

On day 7 after receiving IgM-enriched Ig, eight patients required de-escalation of oxygenation support, eleven patients required escalation of support, and nine patients required no change in oxygenation support. However, four patients who required increased oxygenation support on day 3 deteriorated further and expired. Out of 32 patients, only fifteen survived, resulting in an overall mortality rate of 53.1%.

DISCUSSION

To address the "cytokine storm" responsible for refractory hypoxemia and multi-organ failure, several therapeutic strategies have been attempted with varying clinical efficacy. In this retrospective analysis, we aimed to assess the efficacy of IgM-enriched IVIG in severe COVID-19 pneumonia patients. Statistically, there was no significant change in respiratory variables, including the SpO_2 / FiO_2 ratio, after administration of IgM-enriched IVIG, although there was a trend toward improvement. There was a reduction in levels of inflammatory biomarkers, with a statistically significant decrease in IL-6 levels on days 3 and 7 following administration of

Table 1: Baseline patient parameters at the time of ICU admission

Patient parameter	Overall (N = 32)	Survivors (N = 15)	Nonsurvivors (N = 17)	p-value
Age, mean ($\pm$ SD)	64.50 ($\pm$ 9.27) years	61.53 ($\pm$ 10.19) years	67.12 ($\pm$ 7.75) years	0.375
Sex, males (%)	27	14	13	0.338
SPO_2 / FiO_2 , mean ($\pm$ SD)	128.69 ($\pm$ 50.87)	202.0527 ($\pm$ 137.51)	146.51 ($\pm$ 95.43)	0.69
IL-6, mean ($\pm$ SD)	214.14 ($\pm$ 622.25) pg/mL	107.73 ($\pm$ 130.35) pg/mL	307.25 ($\pm$ 845.01) pg/mL	0.133
D-dimer, mean ($\pm$ SD)	2429.88 ($\pm$ 7644.22)	3053.85 ($\pm$ 10299.99)	1883.913 ($\pm$ 4510.73)	0.228
Ferritin, mean ($\pm$ SD)	517.19 ($\pm$ 7)	492.22 ($\pm$ 271.13)	539.22 ($\pm$ 560.41)	0.016*
CRP, mean ($\pm$ SD)	85.37 ($\pm$ 89.23)	85.55 ($\pm$ 96.65)	85.24 ($\pm$ 87.65)	0.832
APACHE, mean ($\pm$ SD)	16.59 ($\pm$ 5.29)	13.93 ($\pm$ 4.16)	18.94 ($\pm$ 5.15)	0.384
Comorbidity	23	12	11	0.444

*Statistically significant; APACHE, Acute physiology and chronic health evaluation; CRP, C-reactive protein; FiO_2 , fraction of inspired oxygen; IL, interleukin; SD, standard deviation; SPO_2 , oxygen saturation

Table 2: Change in respiratory parameters and inflammatory markers after administration of IgM-enriched IVIG

Patient parameter	Before administration	3rd day	Δ Change	p-value	7th day	Δ Change	p-value
SPO_2 / FiO_2 , mean ($\pm$ SD)	130.43 ($\pm$ 50.74)	157.36 ($\pm$ 92.98)	26.93	0.314	167.93 ($\pm$ 128.82)	37.5	0.922
IL-6, mean ($\pm$ SD)	473.39 ($\pm$ 1053.97) pg/mL	452.63 ($\pm$ 941.76) pg/mL	-20.76 pg/mL	0.001	297.81 ($\pm$ 951.27) pg/mL	-175.81 pg/mL	<0.001
D-dimer, mean ($\pm$ SD)	3465.36 ($\pm$ 8320.36) ng/mL	1842.25 ($\pm$ 1983.77) ng/mL	-1623.11 ng/mL	0.899	1212.35 ($\pm$ 237.76) ng/mL	-2253.01 ng/mL	0.524
Ferritin, mean ($\pm$ SD)	590.75 ($\pm$ 423.88) ng/mL	814.01 ($\pm$ 741.83) ng/mL	223.26 ng/mL	0.957	599.63 ($\pm$ 426.85) ng/mL	8.88 ng/mL	0.339

FiO_2 , Fraction of inspired oxygen; IL, interleukin; SD, standard deviation; SPO_2 , oxygen saturation

IgM-enriched IVIG. However, ICU mortality remained high in these patients.

Coronavirus disease 2019 patients present with variable symptoms and an unpredictable course. Clinical manifestations can range from asymptomatic to life-threatening disease. The respiratory system is particularly affected, with many patients developing severe and refractory hypoxemia. Those with severe COVID-19 infection often require IMV and experience significant mortality. Even though up to 75% of infected individuals remain asymptomatic,⁴ 15% of patients may develop severe pneumonia associated with multisystem failure, which may eventually result in death.⁵

Protracted and fluctuating disease progression, with multiple pathophysiological processes due to viral activity and host immune reaction, makes it difficult to develop a single specific therapy.⁶ In severe COVID-19 pneumonia, the "cytokine storm" is a characteristic feature caused by an exaggeration of the host's immune system and hyperinflammation. The release of several inflammatory mediators resulting in the "cytokine storm" has been shown to be the chief pathophysiology behind refractory hypoxemia and multi-organ failure. This phenomenon is not unique to COVID-19 but has also been observed in other inflammatory conditions. The levels of inflammatory markers such as C-reactive protein (CRP) and IL-6 become elevated in these patients.⁵

The benefit of therapy with IVIG has been demonstrated in several autoimmune and inflammatory conditions. Typically, IVIGs are composed of >95% unmodified IgG with intact Fc-dependent effector functions and only a small quantity of IgA or IgM. In contrast, IgM-enriched IVIG (pentaglobulin) contains 76% IgG, along with 12% IgM and 12% IgA antibodies. This composition is more physiologically similar to human plasma. Moreover, higher levels of IgM may provide immediate immunity, which can be particularly useful in the management of severe acute conditions associated with an increased risk of immediate mortality.^{7,8} This provides a logical rationale for initiating therapy with IgM-enriched IVIG in the management of patients with severe pneumonia secondary to SARS-CoV-2.

Compared to specific IgG preparations, polyvalent Ig containing IgG, IgA, and IgM may offer multiple advantages and potentially improve mortality when used in the management of patients with sepsis and septic shock. Polyvalent Ig possess several pathophysiological functions that can be beneficial in infective and inflammatory conditions. These functions include pathogen

recognition, opsonization, and elimination, as well as neutralization of exotoxins due to their antibodies directed against bacterial lipopolysaccharides. These actions may aid in the removal and inhibition of gene transcription of inflammatory mediators.⁹ Due to its pentameric structure, IgM may prove superior to IgG in neutralizing toxins and agglutinating microorganisms. Furthermore, IgM may have a more pronounced bactericidal effect because it can activate complement 400 times more than IgG and is nearly 1000 times more effective in opsonizing microorganisms.¹⁰

For several years, IgG enriched with IgM and IgA has been used successfully for managing patients with sepsis and septic shock.^{11–15} The hyperinflammatory state present in these patients may benefit from IgM-enriched IVIG due to its ability to decrease proinflammatory cytokines and increase anti-inflammatory cytokines. Other proposed pathophysiological mechanisms of action, such as phagocytosis of pathogens, neutralization of bacterial toxins (endotoxins and exotoxins), and immunomodulation *via* interaction with complement factors, may all enhance its therapeutic efficacy.¹⁶ This may translate to an improved clinical course and outcomes by enhancing the immune defense of the patient.¹³ Patients undergoing hematopoietic stem cell transplantation (HSCT) have also shown a significant reduction in infection-related mortality with the use of IgM and IgA-enriched Ig.¹⁷ A recent meta-analysis also demonstrated a reduction in mortality rates and a decrease in time on IMV in sepsis and septic shock patients treated with IgM- and IgA-enriched Ig.¹³

Previously, IgM-enriched Ig have also been successfully used in the management of steroid-resistant severe SARS-CoV infection.¹⁸ Nonetheless, robust clinical evidence to support the efficacy of IgM-enriched Ig in patients with COVID-19 infection is lacking, as various descriptive observational studies have reported ambiguous findings.^{19–22} These patients with severe disease are prone to develop bacterial coinfections and secondary bacterial infections,^{7,8} and it may be postulated that the use of IgM-enriched Ig which contains antibodies against a variety of pathogens, may be beneficial in preventing such secondary bacterial infections. Early reports in COVID-19 patients suggested that the use of polyclonal preparation of IgM as adjuvant therapy may lead to faster clinical and radiological healing.¹¹ In a case series of fifteen patients with severe COVID-19 pneumonia treated with IgM-enriched immunoglobulin, there was significant radiological recovery as confirmed

by improvement in computed tomography (CT) score.²³

In a retrospective cohort study of 58 severe or critical patients with COVID-19, those who received IVIG within 48 hours showed improved ventilatory function, reduced length of hospital stay, and 28-day mortality.¹³ Another retrospective study comparing severe COVID-19 pneumonia patients receiving IgM- and IgA-enriched Ig with patients receiving only standard therapy and similar baseline characteristics demonstrated significantly lower mortality in the intervention group (37.5 vs 56.5%, $p < 0.01$). Furthermore, at day 7, the probability of dying was three times lower in those who received IgM/IgA-enriched Ig compared to those who received standard therapy alone.²⁴ However, a nonrandomized prospective trial did not show any benefit regarding the duration of hospital stay, requirement for IMV, or mortality in patients with severe COVID-19 receiving IgM-enriched Ig. This study was limited by its small sample size and did not assess the effect of IgM- and IgA-enriched IVIG on oxygenation indices or inflammatory biomarkers.²⁵ A meta-analysis assessing the efficacy of IVIG in the management of COVID-19 disease reported that the use of IVIG may be effective in reducing mortality in a select subgroup of COVID-19 patients with critical disease.²⁶

We also observed a trend toward improvement in oxygenation parameters, with the mean admission SpO₂/FiO₂ ratio increasing from 130.43 to 157.36 on day 3 and 167.93 on day 5. Experience from patients with severe SARS-CoV infection also suggests that the use of pentaglobin may lead to remarkable recovery in radiological scores and oxygenation parameters.^{18,27} Previous studies have also shown a significant reduction in inflammatory biomarkers like IL-6 and IL-10 when IgM-enriched Ig were used in patients with sepsis.²⁸ However, the effect of pentaglobin on inflammatory biomarkers in COVID-19 patients has not been previously evaluated. In our study, there was a reduction in inflammatory markers like IL-6 and D-dimer after pentaglobin administration, but it was statistically significant only for IL-6.

This is the largest retrospective single-center study, with 32 severe COVID-19 pneumonia patients receiving IgM-enriched IVIG. Our study has some limitations, as it was a single-center retrospective study prone to missing data, including PaO₂ values. Additionally, patients were receiving other immunomodulatory therapies such as corticosteroids or the recombinant modified IL-1 receptor antagonist, tocilizumab; therefore, attributing clinical benefits solely to IVIG may be challenging.

CONCLUSION

Outcomes of patients with severe COVID-19 requiring ICU care remain dismal. IgM-enriched Ig may be helpful in improving oxygenation and combating cytokine storm in these patients. However, in the present study, the improvement in oxygenation indices ($\text{SpO}_2/\text{FiO}_2$) and reduction in inflammatory markers like D-dimer and ferritin were not statistically significant. Hence, larger randomized controlled trials are required to obtain more definitive evidence to support this therapy and demonstrate significant clinical and mortality benefits.

Data Availability

The data supporting the findings of this study are available from the corresponding author, Dr Amit Goyal, upon reasonable request.

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Utility of HACOR Score in Patients with Acute Exacerbation of Post-tuberculosis Obstructive Airway Disease: A Retrospective Observational Study



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ABSTRACT

Objective: In this study, we tried to analyze the utility of the HACOR score in the acute exacerbation of post-tuberculosis obstructive airway disease (post-TB-OAD).

Materials and methods: The HACOR score for patients in acute exacerbation of post-TB-OAD who needed noninvasive ventilation (NIV) support was calculated at 1, 12, 24, and 48 hours. The history of NIV success or failure was noted. Using a cutoff score of >5, the sensitivity, specificity, positive predictive value, and negative predictive value were calculated. The receiver operating characteristic (ROC) curve was plotted based on the HACOR score 1 hour after the NIV trial. In subjects requiring NIV for up to 2 days, the trend in the HACOR score was analyzed using a paired t-test.

Results: A total of 38 out of 100 patients belonged to the NIV failure group. The mean HACOR score at 1 hour was 9.47 in the NIV failure group. The sensitivity was 89.47%, and the specificity was 87.09% for a score of >5. The positive predictive value and negative predictive value were 80.95 and 93.10%, respectively. The area under the curve (AUC) for the ROC was 0.853. The mean score showed an upward trend in the NIV failure group and a downward trend in the NIV success group. The change in the score in the NIV success group was statistically significant ($t = -4.290$, p -value = 0.00044).

Conclusion: The HACOR score can predict NIV failure in patients with acute exacerbation of post-TB-OAD.

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INTRODUCTION

Post-tuberculosis obstructive airway disease (post-TB-OAD) is a common sequelae associated with pulmonary TB. It is a common cause of chronic OAD in India after smoking. It is associated with symptoms of chronic airway obstruction such as cough, breathlessness, and obstructive abnormality on spirometry. The mainstay treatment of clinically stable post-TB-OAD is an oral or inhaled bronchodilator and inhaled steroids. Their clinical course is marked by the waxing and waning of symptoms. Acute exacerbation of post-TB-OAD is characterized by acute worsening of symptoms and needs a change in the medications. Hypoxia and respiratory fatigue are indications for hospitalization and are common causes for admission to the intensive care unit (ICU) or high-dependency units. Respiratory muscle fatigue due to acute bronchospasm is commonly seen. This precipitates respiratory acidosis and type II respiratory failure. Patients with acute exacerbation may not always respond to a conservative line of management and may need ventilatory support. Noninvasive ventilation (NIV) is often the first form of mechanical ventilatory support offered to patients in the ICU. It reduces the work

of breathing, corrects hypoxia, and treats respiratory acidosis.

Noninvasive ventilation (NIV) is an important treatment modality in the management of patients with acute respiratory failure. Unlike other low and high-flow oxygen delivery devices, it provides positive pressure. At the same time, it is possible to provide higher and less variable fractional-inspired oxygen. Thus, it treats hypoxia and reduces respiratory pump failure. Face masks, nasal masks, oronasal masks, helmet masks, or nasal pillows are the interfaces used for NIV. As these interfaces do not breach the integrity of the normal airway, NIV is devoid of complications associated with intubation. Its role in the management of airway diseases such as chronic OAD and bronchiolitis is well established. The Global Initiatives for chronic obstructive lung disease have acknowledged the role of NIV in the initial management of acute exacerbation of chronic obstructive pulmonary disease (COPD) as it reduces respiratory acidosis and the need for intubation. Thus making it the intervention of choice for respiratory failure in these patients.

Despite the high success rate, its utility is offset by certain complications such as aerophagia, claustrophobia, and dryness of the mouth. Patient discomfort and

ventilatory patient dyssynchrony can reduce its acceptability. Even in the absence of these complications, the clinical condition continues to deteriorate in a certain subset of patients. This is related to the underlying condition of the patient or the development of new complications. Patients not improving on NIV will need intubation. In such patients, delayed intubation may increase the risk of mortality. Various parameters such as poor Glasgow Coma Scale score, low prealbumin, acute kidney injury, heart rate, and respiratory rate during the NIV period have been linked to NIV failure.^{1,2} Traditionally, clinicians have used increasing fraction of inspired oxygen (FiO_2) requirements, new onset needs for inotropes, hemoptysis, and loss of consciousness during the course of NIV usage as cues for escalation from NIV to invasive ventilation. However, these complications may develop late in the course of the illness and may not provide enough time to salvage the patient.

Duan et al., in 2016, developed the HACOR score to predict NIV failure.³ HACOR is an acronym for heart rate, acidosis, consciousness, oxygenation, and respiratory rate. It is an easy bedside score that requires minimal expertise and can be used in resource-limited settings. A score of >5 is suggestive of impending NIV failure. Since its introduction, this score has been used by many clinicians to predict the risk of NIV failure. However, very few have studied its utility in the acute exacerbation of post-TB-OAD. In this study, we retrospectively used the HACOR score in patients of post-TB-OAD who required NIV support. Our aim was to

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study the predictive capacity of this score in patients with post-TB-OAD. We also tried to study the trend in the HACOR score in patients who required NIV support for >2 days.

MATERIALS AND METHODS

Approval for conducting this study was obtained from the hospital's Institutional Ethics Committee. The medical records of patients with acute exacerbation of post-TB-OAD were selected. For the purpose of the study, we defined acute exacerbation of post-TB-OAD as acute deterioration of the patient's condition requiring NIV support. Clinical and radiological information was noted to confirm the diagnosis of post-TB-OAD. NIV trial failure or success was also noted. For the purpose of the study, NIV success was defined as clinical improvement, correction of respiratory acidosis, and no subsequent need for intubation. The need to shift from NIV to the invasive mode of ventilation was defined as NIV failure. Based on this information, the enrolled subjects were divided into two groups—NIV success and NIV failure. In both groups, the HACOR score was calculated. The clinical information and arterial blood gas reports after 1 hour of NIV application were used for this purpose. A cutoff score of >5 was considered predictive of NIV failure. A truth table was used to calculate the sensitivity and specificity, as well as positive and negative predictive values. Based on the HACOR scores calculated at 1 hour, the receiver operating characteristic (ROC) curve was plotted, and the area under the curve (AUC) was calculated with the help of Microsoft Excel. In patients requiring up to or >2 days of NIV support, the trend in the HACOR score was studied. To do this, the score was calculated at 12, 24, and 48 hours. In these patients, the difference between the score at 1 and 48 hours was compared and statistically analyzed (two-tailed paired *t*-test with a significance level of 0.05).

RESULTS

A total of 100 patients with acute exacerbation of post-TB-OAD were included in this study. They all required NIV support. Infective exacerbation followed by noncompliance with bronchodilator therapy was the common reason for admission into the ICU. A total of 62 patients were successfully weaned off NIV, while the remaining 38 subsequently required invasive ventilation (Flowchart 1). The common causes for escalation to invasive mode of ventilation were deterioration of respiratory acidosis, altered consciousness, and the need for inotropic drugs. The average age in the NIV success group was 53.04 [standard deviation (SD) $\pm$ 13.47], and in the NIV failure group, 56.13 (SD $\pm$ 13.93). A total of 86 patients in the study

had respiratory acidosis. There was a slight female preponderance in the NIV success group (44/62) and male preponderance in the NIV failure group (28/38). The average HACOR score after 1 hour in the NIV success group was 3.88 and 9.47 in the failure group (Table 1). The number of patients with HACOR scores >5 in both groups is as per Table 2. A total of 34 (*N* = 38) patients had HACOR scores >5 in the NIV failure group compared to 8 in the NIV success group. The sensitivity of the score was 89.47%, and specificity was 87.09%. The positive predictive value of the score was 80.95%, and the negative predictive value was 93.10%. The ROC analysis was performed for the HACOR score at 1 hour (Fig. 1). The area under the curve was 0.853.

A total of 25 patients needed NIV support for >2 days. Nineteen of them were successfully weaned off NIV. The mean HACOR scores at 1, 12, 24, and 48 hours in these 27 patients are as per Table 3. The NIV failure group had a higher mean baseline (at 1 hour) score ($\bar{x}$ = 6.5)

Flowchart 1: Flowchart of subject's enrolment

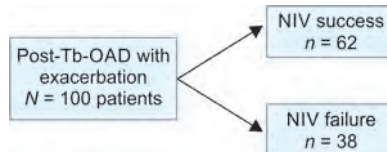


Table 1: Characteristics of the study population

Parameters	NIV success (<i>N</i> = 62)	NIV failure (<i>N</i> = 38)
Gender:		
male	18 (44)	28 (10)
(female)		
Age	53.04 ($\pm$ 13.47)	56.13 ($\pm$ 13.93)
Average HACOR score	3.88 ($\pm$ 1.80)	9.47 ($\pm$ 3.72)
Average NIV days	1.93 ($\pm$ 1.8)	1.73 ($\pm$ 1.9)
Most common comorbidity	Systemic hypertension (11/62)	Diabetes mellitus (12/38)

Table 2: HACOR score at 1-hour in NIV success and failure group

HACOR score	NIV failure	NIV success	Total
>5	34	8	42
≤5	4	54	58
Total	38	62	100

Table 3: Mean HACOR scores in the patients requiring NIV >2 days

Mean HACOR score	At 1 hour	At 12 hours	At 24 hours	At 48 hours
NIV success group (<i>N</i> = 19)	4.16	3.37	2.26	2
NIV failure group (<i>N</i> = 6)	6.5	4	4.33	6.83

compared to the NIV success group ($\bar{x}$ = 4.16). It showed a downward trend in the NIV success group and an uptrend in the NIV failure group (Fig. 2). The change in the score in both groups (at 1 and 48 hours) was analyzed with the help of paired *t*-test (two-tailed). The fall in the HACOR scores in the NIV success group was statistically significant (*t* = −4.290, *p*-value = 0.00044). However, the increase in the HACOR scores in the NIV failure group was found to be statistically not significant (*t*-value = 0.362, *p*-value = 0.731).

DISCUSSION

Pulmonary TB is a leading cause of morbidity and mortality in India. Effective treatment can lead to a complete cure. However, 60–90% of the patients develop post-TB sequelae.⁴ These sequelae result from structural to functional remodeling of the airways and the lung parenchyma. Studies have demonstrated airway obstruction in the large and small airways in these patients.^{5,6} These patients present with symptoms like chronic OAD related to smoking. This condition is known by multiple names, like post-TB-OAD or post-TB chronic OAD. The clinical course in these patients is characterized by multiple

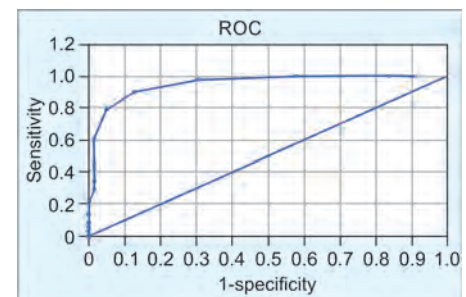


Fig. 1: The ROC for HACOR score at 1 hour after NIV application

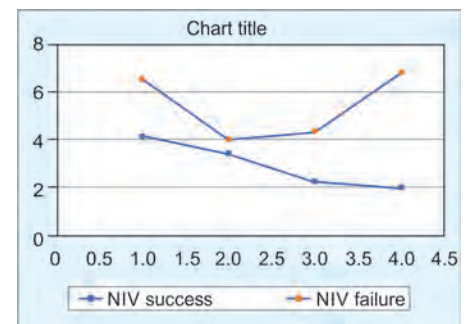


Fig. 2: The trend in the HACOR score in the patients needing NIV for >2 days

Table 4: Sensitivity, specificity, and positive and negative predictive value of HACOR score (>5) at 1, 12, 24, and 48 hours

Timing of HACOR score (>5 cutoffs)	Total number of patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value
1 hour	100	89.47%	87.09%	80.9%	93.10%
12 hours	64	41.66%	98.07%	83.33%	87.3%
24 hours	39	42.85%	100%	100%	88.88%
48 hours	27	66.66%	100%	100%	90.90%

Table 5: Sensitivity, specificity, NIV failure rates, and types of respiratory disorders data of other studies

No.	Authors	Respiratory disorder	NIV failure rate	Sensitivity	Specificity
1	Duan et al. ³	Hypoxic respiratory failure (excluding COPD)	47%	72.6%	90.2%
2	Contreras et al. ¹²	Acute respiratory failure (HACOR score cutoff 4)	29.3	70%	70%
3	Ding et al. ¹¹	Non-COPD causes of respiratory failure	13%	90%	85%
4	Guia et al. ¹³	COVID-19 with hypoxemic respiratory failure	27.3%	62.86%	89.25%
5	This study	Post-TB-OAD	38%	89.47%	87.09%

exacerbations. Some require hospitalization and a mechanical ventilator.

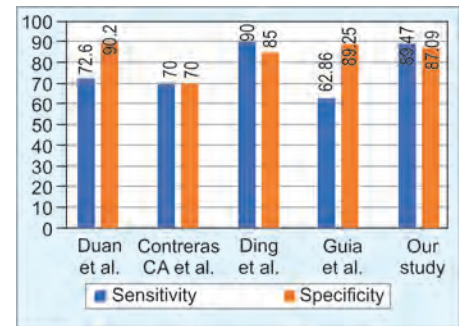
Acute exacerbation of post-TB-OAD is associated with hypoxia, respiratory acidosis, and acute increase in pulmonary artery pressures. Respiratory acidosis results due to respiratory pump failure secondary to respiratory muscle fatigue. In these situations, NIV is often used. In our study, NIV was administered to the patients because of underlying respiratory acidosis or increased work of breathing. Respiratory acidosis results from bronchospasms and respiratory muscle fatigue. Though effective, NIV carries a risk of failure. In a narrative review published in 2014, post-TB changes in the lung and bronchiectasis were associated with NIV failure.⁷

To study its utility in the acute exacerbation of post-TB-OAD, we selected 100 patients. The majority of these patients have hypercapnic respiratory failure (86%). The NIV failure rate in our study was 38% (38/100). Likewise, in a study of 242 patients with hypercapnic respiratory failure, the failure rate of the NIV trial was 20–30%.⁸ NIV usage in hypercapnic respiratory failure retards worsening of respiratory acidosis, risk of intubation, and reduces ICU and hospital stay.⁹ The HACOR scoring system was invented by Duan et al. to predict the likelihood of NIV failure. We observed a lower mean HACOR score (at 1 hour) in the NIV success group (3.88) compared to the failure group (9.47) at 1 hour. High HACOR scores were associated with NIV failure in other studies as well. In a study done on patients with COVID-19, a score >5 was linked

to intubation and hospital mortality.¹⁰ The score was also able to predict the risk of NIV failure in non-COPD causes of type II respiratory failure.¹¹

This score was calculated at 1, 12, 24, and 48 hours (score cutoff >5). We observed a sensitivity of 89.47% and a specificity of 87.09% at 1 hour (Table 4). The sensitivity was the lowest at 12 hours (41.66%). The specificity was 100% at 24 and 48 hours of NIV usage. Duan et al. found a sensitivity of 72.6% and a specificity of 90.2% at 1 hour. The sensitivity and specificity of the score obtained by other authors are given in Table 5. Compared to other studies, the sensitivity of the HACOR score of >5 (at 1 hour) in our study was the highest; however, the specificity was almost equal (Fig. 3). None of these studies used this score in patients of post-TB-OAD. The positive predictive value (80.9%) was lower than that observed by Duan et al. (87.2%) but higher than that obtained by Guia et al. (68.75%). The negative predictive value obtained in this study was the highest among these three studies (Duan et al.: 78.1% and Guia et al.: 86.46%).

A total of 25 patients needed NIV support for >2 days. Nineteen patients could be successfully weaned. In the NIV failure group, the mean HACOR score was more than those in the NIV success group at 1, 12, 24, and 48 hours (Table 3). Duan et al. had a similar observation in their study.³ We compared the HACOR score at 1 and 48 hours in the two groups. We found a decline in the HACOR score in the NIV success group and an increase in the NIV failure group. The decrease in the score in the NIV success

**Fig. 3:** The sensitivity and specificity obtained in various other studies and our study

group was found to be statistically significant. These changes in the score were due to improvements in oxygenation and respiratory acidosis. Of the 38 patients with NIV failure, 26 patients needed intubation after 1 hour of NIV trial. Their mean score was 10.98. NIV failure rate of 100% was seen when the score was ≥ 9 . In a study done by Teh et al. in patients with chronic OAD and acute decompensated heart failure, a score of 8 was associated with a 100% failure rate.¹⁴

CONCLUSION

In our study, we tried to assess the effectiveness of the HACOR score in predicting NIV failure in patients with post-TB-OAD. This score demonstrated a higher specificity and negative predictive value in predicting NIV failure. Thus, the HACOR score can be used to predict failure in post-TB-OAD patients. Patients with scores >5 need more frequent monitoring. Serial monitoring of the score helps to assess the effectiveness of NIV treatment. An increasing score could be considered a harbinger of impending NIV failure.

AUTHORS' CONTRIBUTION

- Dr Siddharth R Waghmare: Study design and analysis of data.
- Dr Swapnil Thorve: Analysis of data and intellectual inputs.
- Dr Sonal Karpe: Intellectual inputs.
- Dr Harshita Mishra: Data collection.
- Dr Amol Shenurkar: Data collection.
- Dr Shivam Gurme: Data collection.
- Dr Jairaj P Nair: Intellectual inputs.

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Diagnostic Signs and Symptoms of Cyanocobalamin Deficiency at Rural Setting in India: Novel Method of Supplementation



Himmatrao Saluba Bawaskar^{1*}, Pramodini Himmatrao Bawaskar², Vikas LB Jadhav³

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ABSTRACT

Background: Cyanocobalamin or B₁₂ deficiency is common in the Indian population, and responsible for anemia. Various clinical manifestations include central nervous system and cardiovascular manifestations, secondary to a rise in serum homocysteine levels.

Method and patients: In a routine outpatient department at Bawaskar Hospital and Clinical Research Centre, Mahad, patients with suspected clinical signs and symptoms suggestive of cyanocobalamin deficiency were studied in detail regarding their dietary habits, serum hemoglobin, B₁₂, and homocysteine levels.

Findings: A total of 1,992 (female 1,009, 50.75%) were clinically examined in detail. Of these, 945 (49.94%), 999 (50.17%), and 48 (2.40%) were strict vegetarians, both vegetarian and nonvegetarian, and strict nonvegetarians, respectively. Common occupations associated with B₁₂ deficiency include 666 (33.4%) housewives, 396 (19.9%) service workers, 316 (15.9%) businesspeople, 180 (9%), and 198 (9.9%) retired and industrial populations, respectively. Clinical manifestations include recurrent scalp hair loss in 268 (13.5%), poor memory in 240 (12%), tingling and numbness in 200 (10%), and generalized weakness in 387 (19.4%) patients. Additionally, 541 (27.15%) patients had pigmentation of the nail bed, knuckles, oral mucosa, and tongue, while 237 (10.81%) suffered from hypertension and ischemic heart disease. During the process of preparation of vegetarian and nonvegetarian food, there is a 30–48% reduction in vitamin content. Supplementation of vitamin by adding table salt to food on a plate at the time of eating improves the vitamin level in the blood.

Conclusion: In the absence of laboratory investigations in rural settings, clinical signs and symptoms are helpful in detecting B₁₂ deficiency. Directly adding vitamin powder, similar to table salt, to cooked food on the plate improved blood vitamin levels.

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INTRODUCTION

Vitamin B₁₂ deficiency is a common condition that can present with nonspecific clinical features and neurological and hematological abnormalities. Vitamin B₁₂ deficiency has been identified as a health concern for nearly 100 years. Vegetarians are at a higher risk of vitamin B₁₂ deficiency. Megaloblastic anemia, a nutritional deficiency either due to B₁₂ or folic acid (vitamin B₉) deficiency, is not uncommon in India. Its prevalence ranges from 2 to 40%.¹ The main dietary sources of vitamin B₁₂ are meat, eggs, and dairy products. Individuals consume about 2–4 µg of vitamin B₁₂ per day.² The liver acts as a depot for vitamin B₁₂, so any reduction in dietary vitamin B₁₂ deficiency takes 5–10 years to manifest clinically.^{3,4} Common clinical effects include weakness, fatigue, glossitis, paresthesias, pigmentation of the tongue, knuckles of fingers and toes, and loss of scalp hairs.^{5,6} Dementia, psychosis, and mental health deficiencies have been reported due to B₁₂ deficiency.⁷ Mental illness, including neuropsychiatric illness, may be accompanied by vitamin B₁₂

deficiency without anemia or macrocytosis. Hypermatured granulocytes are often noted in the peripheral blood film.^{8,9} At times, a poor concentration of vitamin B₁₂ binding protein, as well as the use of antidepressants, anticonvulsants, and benzodiazepines, may give a pseudo serum B₁₂ level.¹⁰ Maximum vitamins are lost during the preparation of food, such as washing and cooking. Vitamin B₁₂ is synthesized by the intestinal microflora. Nonvegetarian diets contain vitamin B₁₂ in trace amounts.¹¹ Gastric parietal and distal ileum cells secrete intrinsic factors, which aid in B₁₂ absorption.¹²

METHOD AND PATIENTS

Written consent for investigations was obtained. Patients with a minimum of two or more signs and symptoms, including weakness, fatigue, pallor, pigmentation of toes, tongue, oral mucosa, knuckles, palm, tongue, loss of memory, recurrent glossitis, headache, transient ischemic attacks, and sagittal sinus thrombosis, as well as macrocytosis with hypermatured or multiplied neutrophils seen in peripheral

blood smear, were investigated in detail regarding their clinical, dietary, and occupational history (Figs 1A to J and Tables 1 and 2). Detailed dietary history included those who were strict vegetarians, whose diet did not include meat, fish, dry fish, eggs, and egg-containing foods, as well as bakery products. Those who consumed nonvegetarian food thrice a week and those who consumed it daily were also noted. In the Indian context, specifically within the Hindu community in Maharashtra, there is a deeply rooted tradition that nonvegetarian diet should only be consumed on specific days, including Tuesday, Wednesday, and Sunday. Fasting blood samples were collected and transferred at room temperature to Mumbai for laboratory investigations for serum B₁₂ and homocysteine levels. These cases complained of recurrent acidity for which they consumed antacid tablets and a proton pump inhibitor, but they were unable to provide the exact duration and dose of consumption of these tablets.

RESULTS

A total of 1,992 cases (male 983, 49.3%; female 1,009, 50.7%) of suspected B₁₂ deficiency were studied and investigated. Of these, 945 (49.94%), 999 (50.17%), and 48 (2.40%) were strict vegetarians, both vegetarian and nonvegetarian, and strict nonvegetarians, respectively (Table 3). Common occupations associated with B₁₂ deficiency include 666 (33.4%) housewives, 396 (19.9%) service workers, 316 (15.9%) businesspeople, 180 (9%) retirees, and 198 (9.9%) industrial workers,

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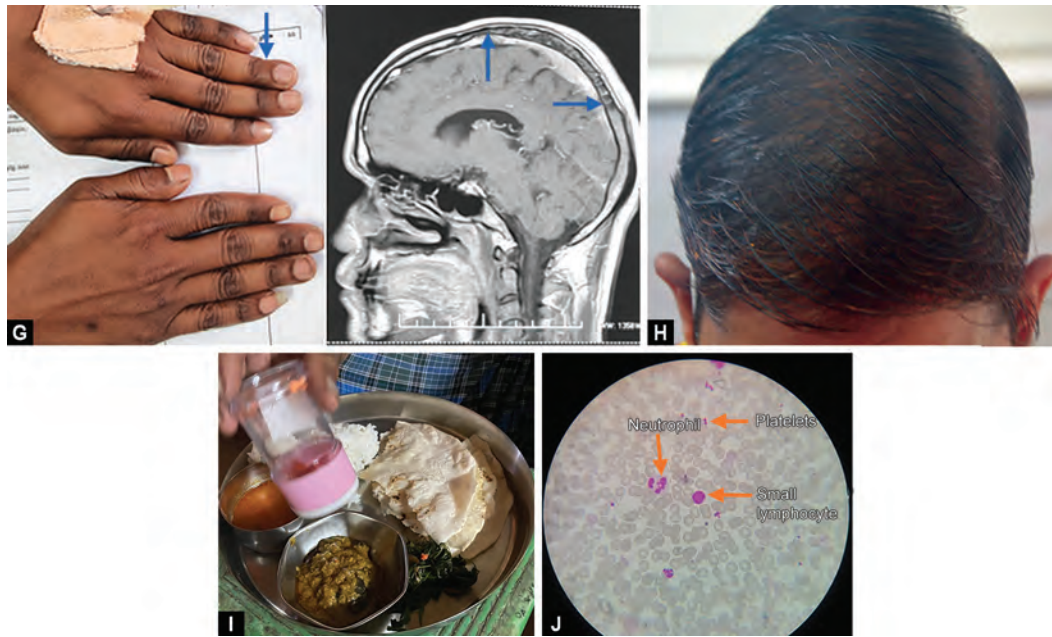
respectively. Clinical manifestations include recurrent scalp hair loss in 268 (13.5%), poor memory in 240 (12%), tingling and numbness in 200 (10%), and generalized weakness in 387 (19.4%) patients. Additionally, 541 (27.15%) patients had pigmentation of the nail bed,

knuckles, oral mucosa, and tongue, while 237 (10.81%) suffered from hypertension and ischemic heart disease (Table 2). A total of 365 cases (18.32%) showed vitamin B₁₂ levels <190 µg/mL (normal >190 µg/mL). Mean corpuscular volume (MCV) was >100 in 31

cases (1.6%). Additionally, 73 cases (3.66%) had serum homocysteine levels greater than 11 (Table 3). After a detailed study of dietary habits, the B₁₂ content of fish, crab (gray-white) and black, unwashed and washed vegetables, commercially packed and



Figs 1A to J: Contd...



Figs 1A to J: (A) Extensive deep pigmentation of knuckles; (B) Pigmentations around eyes; (C) Pigmenting over tongue; (D) Angular stomata's and blepharitis; (E) Aphthous ulcers; (F) Extensive anterior myocardial infarction b- and c-pigmentations; (G) Arrows showing knuckle pigmentation with sagittal sinus thrombosis (homocysteine 48.5 serum B₁₂-123); (H) Sparse hairs over scalp; (I) B₁₂ powder is added to food in plate-like table salt only one or two-stroke; (J) Arrows peripheral blood smear show macrocytosis hyper segmented neutrophils

Table 1: B₁₂ deficiency in relation to occupation (total 1992)

Occupation	Total	%
Housewife	666	33.4%
Service	396	19.9%
Business	316	15.9%
Retired	180	9.0%
Industrial	198	9.9%
Student	126	6.3%
Farmer	45	2.3%
Hotel worker	18	0.9%
Driver	18	0.9%
Carpenter	9	0.5%

homemade curd, as well as three different types of meat precooked and postcooked, were studied (Tables 4 to 6). This investigation was conducted at a specialized laboratory in Mumbai focused specifically on food analysis. Details regarding specific meats and laboratory information are available with the author upon request. External supplementation of B₁₂ powder by adding it to food on the plate, similar to common salt, helps to prevent and improve vitamin B₁₂ deficiency (Table 7 and Fig. 1J).

DISCUSSION

In the present study, various clinical manifestations related to serum B₁₂ deficiency and raised homocysteine levels were examined. Methionine synthetase

Table 2: Clinical manifestations

Clinical presentation	Total	%
Scalp hair loss	268	13.5%
Loss of memory	240	12.0%
Paresthesia's	200	10.0%
Weakness	387	19.4%
Nail bed and knuckle pigmentation	296	14.9%
Oral mucosal pigmentation	138	6.9%
Pigmentation of tongue	107	5.4%
Hypertension	191	9.6%
Ischemic heart disease	46	2.3%
Diabetes mellitus	13	0.7%
Aphthous ulcers	11	0.6%
Hypothyroidism	18	0.9%
TIA	9	0.5%
Recurrent urinary tract infection	22	1.1%
Post COVID-19	13	0.7%
Herpes zoster	2	0.1%
Bulimia	2	0.1%
Parkinsonism	2	0.1%
Loss of taste	6	0.3%
Lacunar infarction	6	0.3%
Hyperlipidemia	15	0.8%

and methylmalonyl-coenzyme A mutase are two enzymes for which vitamin B₁₂ acts as a cofactor. These enzymes prevent the synthesis of homocysteine, which is implicated in atherosclerosis.¹³ B₁₂ is essential for the synthesis, normal functioning, and

maintenance of the myelin sheath for the central and peripheral nervous systems. There is an inverse relationship between the severity of neurological involvement and the severity of megaloblastic anemia.¹⁴ The most common cause of malabsorption of vitamin

Table 3: Details of B₁₂ deficiency

	Total	%
<i>Homocysteine</i>		
No. of samples (data)	100	
<10.99	27	27.0%
11–15.9	31	31.0%
16–20.9	16	16.0%
31–40.9	18	18.0%
>41	8	8.0%
<i>Serum B₁₂</i>		
No. of samples (data)	1992	
<100	48	2.4%
101–140	111	5.6%
141–190	206	10.3%
>190	1504	75.5%
>2000	123	6.2%
<i>Hemoglobin</i>		
No. of samples (data)	1992	
<9.9	145	7.3%
10–12.9	977	49.0%
>13	870	43.7%
<i>MCV</i>		
No. of samples (data)	1992	
<80	673	33.8%
81–100	1288	64.7%
>100	31	1.6%
<i>Age-group</i>		
No. of samples (data)	1992	
<20	262	13.2%
21–40	543	27.3%
41–60	799	40.1%
>60	388	19.5%
<i>Gender</i>		
No. of samples (data)	1992	
Male	983	49.3%
Female	1009	50.7%

Table 4: B₁₂ levels

	B ₁₂ level
Fish	1.29
Crab–gray–white	0.52
Crab–black	2.31

Table 5: B₁₂ levels

	Vitamins Unwashed vegetable	Washed vegetables
B ₆	1.08 mg/100 gm	0.52 mg/100 gm (reduction 48%)
B ₉	132.98 µg/100 gm	39.62 µg/100 gm (reduction of 30%)
B ₁₂	ND <2.0 µg/100 gm	ND <2.0 µg/100 gm
Commercial-packed and homemade curd		
B ₆	0.84	0.52
B ₉	ND <2 µg/100 gm	ND <2 µg/100 gm
B ₁₂	ND <2 µg/100 gm	ND <2 µg/100 gm

ND, Not detected

Table 6: B₁₂ levels

Sample	Vitamin B ₁₂ µg/100 gm raw or precooked	Vitamin B ₁₂ µg/100 gm postcooked
Meat-1	4.37	1.50 (34% reduced)
Meat-2	5.55	0.17 (30.6% reduced)
Meat-3	7.80	0.04 (51.2% reduced)

Table 7: Showing improvement of serum B₁₂ pre- and postsupplementation of B₁₂ like table salt

No.	Age	Sex	Hemoglobin	Serum B ₁₂ before pg/mL	Serum B ₁₂ postsupplement (like table salt)
1	65	M	11.8	50	117
2	33	F	8.2	170	591
3	44	M	11.3	166	228
4	51	M	13.7	136	450
5	31	F	11.9	63	787

B₁₂ from food is the failure to release B₁₂ from ingested food due to proton pump inhibitors or antacids and gastritis. This occurs because of the reduction in gastric acid secretion, thereby resulting in the failure to liberate vitamin B₁₂ from food proteins.¹⁵

The clinical effects of vitamin B₁₂ deficiency include glossitis, hyperhomocysteinemia, thrombosis, dementia, hyperpigmentation of the oral mucosa, tongue, nail beds, knuckles, toes, and fingers, as well as hair loss and weakness (Figs 1A to J).^{16,17} The mechanism of hyperpigmentation is attributed to a reduction in glutathione levels, which is responsible for stimulating the tyrosinase enzyme and facilitating the transfer of melanin to melanosomes. Thus, a defective mechanism due to B₁₂ deficiency interrupts the melanin transfer between melanocytes and keratinocytes, leading to hyperpigmentation.⁹ B₁₂ synthesis bacteria grow over the vegetables, and their vitamin secretion deposits on them. However, washing vegetables and cooking result in the loss of B₁₂. Additionally, routine use of pesticides contributes to this loss. Similarly, there is a remarkable reduction in B₁₂ in cooked meats compared to precooked meats (Table 5). Curd is prepared by adding lactobacillus, and there is a myth that curd is a rich source of B₁₂. However, in the present study, no B₁₂ was detected in routine homemade and commercial curd (Table 5).

There is a remarkable reduction or complete disappearance of waterborne diseases due to the routine use of Euro-filtered, sterile commercial water and increased awareness of hygienic food and water practices. However, cooked food results in the loss of B₁₂ synthesis bacteria and the total loss of B₁₂ availability. Surprisingly, in a recent survey conducted in children and schools, it was noticed that B₁₂ deficiency is rare in poor and tribal

communities. This rarity is attributed to the routine consumption of bore well or open well water and the routine consumption of incompletely cooked crab meat (Table 5) and unwashed vegetables and roots⁹ false positive and false negative values occurring up to 50% B₁₂ chemical analysis. Hence one should more rely on clinical manifestations (Table 2) and response to the B₁₂ supplementation.⁹

In the present study, 68 patients underwent serum homocysteine study, of which 57 (84.5%) had significantly raised levels of homocysteine (>15 mol/L). This result is associated with vascular diseases and thrombosis.

The daily body requirement of vitamin B₁₂ is 2.5 µg.¹⁸ Routine daily consumption of meat and vitamin B₁₂ results in a reduction of methylmalonic acid values, which may require 4–7 µg of vitamin B₁₂. In rural settings where regular intake of injectable vitamin B₁₂ is not possible due to restricted medical resources, nasal sprays or sublingual preparations, or the addition of B₁₂ powder, similar to table salt added to food on the plate, have been found to be useful alternatives (Table 7 and Fig. 1I).¹⁹

In India, irrespective of economic status, deficiencies in vitamin B₁₂, folic acid, vitamin D, and iron often occur together due to various reasons, including dietary practices, lifestyle factors, and cultural beliefs. Myths regarding food, life, and social issues also contribute to these deficiencies. Additionally, in the Hindu community, eating nonvegetarian diet may be considered taboo or sinful, further impacting dietary choices and nutrient intake.

Dementia, psychosis, and mental health issues have been reported as consequences of B₁₂ deficiency. Additionally, mental illness may be accompanied by B₁₂ deficiency without the presence of anemia, macrocytosis, or hypermatured granulocytes (Fig. 1J).^{7,8}

In 1885, Thomas Addison coined the term "pernicious anemia," referring to anemia that is not corrected by iron therapy. In 1926, Minot and Murphy demonstrated improvement in 45 patients with pernicious anemia using liver therapy. Subsequently, Costly WP described the synthesis of intrinsic factor in the stomach and extrinsic factor B₁₂, both of which are necessary to improve pernicious anemia. The chemical structure of the B₁₂ molecule was studied in 1948 by Dorothy Crowfoot and Hodgkin. Later, it was confirmed that bacterial fermentation produces B₁₂.^{20,21} Vitamin B₁₂ is an essential component of DNA synthesis and the maintenance of myelin integrity. A common source of B₁₂ is found in nonvegetarian diets (Tables 4 and 6), strict vegetarian or mixed diet consumers suffered from subclinical B₁₂ deficiency, in the present study 98% suffered from B₁₂ deficiency compared to only 1.35% of nonvegetarian. There is enterohepatic circulation of B₁₂, and severe deficiency occurs in victims of malabsorption such as those with ileal diverticulitis or blind loop syndrome. A common cause of B₁₂ deficiency in India is a faulty diet, which includes foods rich in pulses, potatoes, rice, wheat, maize, and oats. India has a large population of vegetarians, and nonvegetarian diets without deep frying are the primary source of B₁₂. However, even among nonvegetarians, regular consumption of nonvegetarian food is not common. In the present study, 50% of the participants showed B₁₂ deficiency. Fresh fruits and green leafy vegetables, when unwashed and with bacterial growth, are good sources of B₁₂. However, due to pesticide use and routine washing of vegetables, these sources are often devoid of B₁₂.²²

Deep-fried meat is a rich source of the toxin nitrosamines but has a poor content of B₁₂. A total of 10 patients with hypothyroidism were found to have B₁₂ deficiency accidentally, despite having no gastric symptoms or gastrin deficiency. Now, each diabetic patient's prescription includes a B₁₂ tablet, especially common with metformin, which interferes with B₁₂ absorption. Proton pump inhibitors, which are routinely available over the counter without a doctor's prescription, are often self-consumed chronically and are responsible for B₁₂ and iron deficiency anemia. A common reason for B₁₂ deficiency is food-bound cobalamin malabsorption. The daily requirement of B₁₂ is 1–3 µg/day. The Indian diet, which is mostly vegetarian, is a poor source of B₁₂. Chronic intestinal diseases, including inflammation, tuberculosis, pancreatitis, and hepatobiliary dysfunction, are common causes of B₁₂ deficiency in the Indian scenario. Most fruits and vegetables,

when washed and stored in freezers or cooked in high-pressure cookers, result in a total loss of B₁₂. A common clinical manifestation is anemia (Table 2). In the present study, 31% of cases had MCV values greater than 100 fL, hypersegmented neutrophils, which were associated with glossitis and pigmentation of the knuckles (Fig. 1I). B₁₂ deficiency affects the rapidly multiplying mucosal cells, resulting in glossitis, duodenitis, soreness of the mouth, proctalgia, urinary tract infections, and cervical smear dysplasia (Table 1).²³ Paraesthesias, sensory loss, ageusia, spinal cord and cerebellar degeneration, depression, dementia, and mood changes are reversed by B₁₂ correction. B₁₂ and folic acid supplementation during pregnancy prevents neural tube defects.^{14,24,25}

In India, B₁₂ and folic acid deficiency induce raised homocysteine levels, which are a main cause responsible for cardiovascular disease, cerebral thrombosis, pulmonary thromboembolism, peripheral vascular disease, and deep vein thrombosis (Fig. 1G).²⁶ B₁₂ supplementation from early pregnancy until 6 months postpartum did not improve child growth and neurodevelopment.^{27,28} High vitamin B₁₂ levels (>350 pmol/L) are associated with hematological and hepatic disorders, particularly cancer. B₁₂ deficiency results in raised serum homocysteine levels, ischemic heart disease, and type 2 diabetes mellitus. Approximately, 240,000 tablets of antacids are sold each month in Manado, a population of 20,000, and many individuals consume them daily without a diagnosis for their acidity. Metformin prevents B₁₂ absorption, resulting in deficiency and a rise in homocysteine levels, leading to cardiovascular manifestations in diabetes mellitus.²⁹ However, concomitant with vitamin B₁₂ deficiency, irrespective of the rise in homocysteine levels, there is some evidence to confirm that B₁₂ deficiency does not increase the risk of cardiovascular manifestations.³⁰ Macrocytic anemia is indicative of B₁₂ deficiency and is often used to diagnose it. Animal-derived foods are the main sources of vitamin B₁₂. However, in the present study (Tables 4 and 6), malabsorption of food cobalamin is one of the main reasons in 20% of the population with B₁₂ deficiency.³¹ Cellular unrest and cancer manifestations due to chromosomal injury and breaks may occur due to vitamin B₁₂, folic acid, and B₆ deficiency.³² Depression, dementia, stroke, decline in cognitive performance, and delirium are often presentations of raised homocysteine due to B₁₂ deficiency. These changes can be totally recovered with supplementation and correction of B₁₂ deficiency.^{33,34} B₁₂ is synthesized

by microorganisms such as *Paracoccus denitrificans*, *Bacillus megaterium*, *P. shermanii*, and *Salmonella typhimurium*.^{35,36} Thus, similar to the Indian situation with multiple myths regarding nonvegetarian food and routine consumption of heavily cooked food, there is a need for fortification of food products with vitamin B₁₂.²² A novel method involves routinely adding vitamin powder to food on the eating plate, similar to table salt, providing an easy way to correct and prevent vitamin deficiency (Fig. 1I).

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Total Antioxidant Status and Oxidative Stress in Patients with COVID-19 Infection



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ABSTRACT

Introduction: Oxidative stress (OS) may have a role in the pathogenesis and severity of the coronavirus disease 2019 (COVID-19) disease. The present study was conducted to estimate the association of inflammatory markers, total antioxidant status (TAS), and malondialdehyde (MDA) levels with the severity of the disease and to identify their trends after recovery.

Materials and methods: Adult patients admitted with moderate or severe COVID-19 were included after obtaining written informed consent from patient or next of kin. Patients who were critically ill, on ventilator, or in sepsis/septic shock were excluded. Levels of inflammatory markers, TAS, and OS as measured by MDA were estimated within 24 hours of admission and reevaluated at 12 weeks following discharge.

Results: The mean age of the 40 patients (42.5% females) was 55 ± 15 years. TAS values (in trolox equivalents/L) were significantly reduced in severe compared to moderate COVID-19 patients at admission (7.2 ± 4.19 vs 12.3 ± 5.21). These increased at 12 weeks after discharge. The MDA levels (in nmol/mL) were significantly higher in severe in comparison to moderate disease (7.1 ± 2.68 vs 4.1 ± 1.81). These values showed a downward trend 12 weeks after discharge in severe disease group. Admission levels of interleukin-6 (IL-6), D-dimer, and lactate dehydrogenase (LDH) were statistically higher in severe COVID-19 patients in contrast to moderate disease.

Conclusion: Moderate and severe COVID-19 are associated with a state of high OS and a low total antioxidant levels which tend to recover at 3 months following discharge.

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INTRODUCTION

Despite a large volume of data on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the conundrum on the various players in its pathogenesis is yet to be unraveled for developing specific therapeutic plan to diminish the severity of disease and is an opportunity to throw light on similar infectious disease fiascos in the future. Several variables have been observed to be associated with disease progression and death in coronavirus disease 2019 (COVID-19). These include comorbidities, advanced age, lymphopenia, sequential organ failure assessment score at admission, elevated C-reactive protein (CRP), D-dimer $>1 \mu\text{g/mL}$, serum levels of interleukin-6 (IL-6), high-sensitivity cardiac troponin I, and lactate dehydrogenase (LDH).¹ The pathogenesis of severe disease is based on the various models, including cytokine storm or cytokine imbalance, with variable individual immune response to clinical infection.²

High oxidative stress (OS) is one of the putative mechanisms linked with aging as well as the pathogenesis and progression of many acute and chronic diseases with antioxidants playing a potential protective role. The serum antioxidant levels have been observed to be decreased in these diseases.³ In respiratory infections as well, increased

levels of reactive oxygen species (ROS) or reactive nitrogen species (RNS) are linked with severity of the disease since they result in a decreased antioxidant capacity.⁴ The role of OS in the pathogenesis and of antioxidants in therapeutics has been identified in COVID-19 disease as well.^{5,6}

Oxidative stress is a dysregulated state where the ROS production is amplified exceeding the antioxidant capacity. ROS generation is predominantly controlled by antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase (GP-X), and catalase-peroxidase (CAT).⁷ Researchers have demonstrated reduced alveolar levels of SOD in elderly COVID-19 patients that contribute to disease severity.⁸ In another cross-sectional comparative study, decreased levels of SOD, CAT, and GPx were noted in patients infected with SARS-CoV-2.⁹ Another study has also linked increased NADPH oxidase-induced OS to increased disease severity and thrombotic events.¹⁰ Researchers from Iran, however, did not find a significant difference in serum levels of total antioxidant capacity (TAC), total oxidant status (TOS), and TAC/TOS in relation to disease severity in 331 hospitalized patients with COVID-19.¹¹

The current role of antioxidants and possible role of nutraceuticals for the management of the COVID-19 is still a matter of speculation. It is worthwhile to evaluate the

total antioxidant status (TAS) and OS in this disorder in our population and the data will help us evaluate the COVID-19 milieu in Indian patients with reference to OS, providing a basis for treating patients with antioxidant drugs.

MATERIALS AND METHODS

This was a prospective, observational study conducted in the departments of General Medicine and Biochemistry at Government Medical College and Hospital, Chandigarh, which is a tertiary referral hospital. The study commenced after obtaining due clearance from the Institutional Ethics Committee (IEC) vide letter GMCH/IEC/2020/570R/170.

The sample size was derived using a mean TAS of 1.77 (1.69~1.88) in trolox equivalent/L from published data and estimating a predicted 5–10%, that is, 7.5% lower values in the target population, 40 patients were needed for the study, keeping power of 80% and α of 0.05.¹²

Adult patients who tested positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) and were of moderate or severe category were included after obtaining written informed consent from patient or next of kin. Patients who were critically ill, on ventilator, or in sepsis/septic shock were excluded. Moderate disease was defined as pneumonia with no signs of severe disease, that is, an adult with presence of clinical features of dyspnea and/or hypoxia, fever, cough including oxygen saturation (SpO_2) $<94\%$ on room air and respiratory rate >24 per minute. Severe disease: Severe pneumonia, that is, adult with clinical signs of pneumonia plus one of the following: respiratory rate >30 per minute severe respiratory distress and SpO_2 $<90\%$ on room air.

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A blood sample was drawn for routine testing along with specific laboratory parameters that included LDH, CRP, serum ferritin, D-dimer, and IL-6. In addition, TAS and OS, as measured by malondialdehyde (MDA), were assessed within 24 hours of admission. TAS was estimated by spectrophotometric method on a random access chemistry analyzer. MDA was measured in the plasma at 555 nm wavelength using a spectrophotometer. The patients were treated as per protocol in the COVID-19 facility, and at discharge, they were advised to follow up in the post-COVID outpatient department on a monthly basis. Levels of inflammatory markers LDH, ferritin, CRP, D-dimer, IL-6, and oxidant status by TAS and MDA were evaluated again at 12 weeks.

Statistical Analysis

The data acquisition and analysis were done using Microsoft Excel and Statistical Package for Social Sciences (SPSS) software, IBM, Chicago, United States, version 25.0. All categorical variables were analyzed using Chi-squared or Fisher's exact test. The continuous variables were analyzed by using Student's *t*-test. For statistical analysis, $p < 0.05$ was considered statistically significant.

RESULTS

In the present study, 40 admitted patients of COVID-19 were enrolled, of which, 16 had moderate disease and 24 had severe disease. About 42.5% (17) patients were females. All patients received standard treatment as per the existing protocol. All 40 (100%) patients received steroids, 36 (90%) received Low-molecular-weight heparin (LMWH), and 4 (10%) received remdesivir therapy. None of the patients received tocilizumab therapy.

Additionally, 15 (37.5%) reported using oral supplements of zinc and vitamin C tablets before hospitalization. Demographic and anthropometric characteristics of the patient population are presented in Table 1.

Table 2 shows that the inflammatory markers, LDH, D-dimer, and IL-6 were considerably higher in severe compared to moderate COVID-19 at admission ($p < 0.05$). Although the admission ferritin and CRP levels were higher in the population with severe disease compared to those with moderate disease, the difference was not statistically significant. All these markers decreased

remarkably when measured at 12 weeks post discharge. However, no significant difference in their levels was observed between the two groups at 12 weeks.

Table 3 depicts the temporal trends of inflammatory markers at admission and at 12 weeks. In patients with severe disease, there was a marked decrease in inflammatory markers at 12 weeks ($p < 0.05$). Similarly, in patients with moderate disease, LDH, CRP, and ferritin levels were significantly reduced at 12 weeks. Although IL-6 and D-dimer levels were also lower at 12 weeks, the difference was not statistically significant.

Table 1: Characteristics of moderate and severe COVID-19 patients

Characteristics		Moderate COVID-19	Severe COVID-19
Total patients (40)		16	24
Gender	Female	5	12
	Male	11	12
Age (years)	20–40	3	3
	40–60	7	11
	>60	6	10
BMI	18.5–24.9	9	9
	25–29.9	5	8
	>30	2	7
Comorbidities	Diabetes mellitus	7	9
	Hypertension	7	11
	CVD	2	8
	CKD	5	4
	Other	0	2
FBS	Diabetes mellitus	8	12
	Impaired fasting glucose	6	8
	Normal	2	4
ALT	<3ULN	14	22
	>3ULN	2	2

BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; FBS, fasting blood glucose; ULN, upper limit of normal

Table 2: Comparison of inflammatory markers in moderate and severe COVID-19 at baseline and 12 weeks

Disease	Moderate (n = 16)	Severe (n = 24)	
Inflammatory markers	Mean $\pm$ standard deviation (SD) (range, median)	Mean $\pm$ SD (range, median)	p-value (Student's <i>t</i> -test)
At admission			
LDH (units/L)	528 $\pm$ 342 (157–1311, 458)	851 $\pm$ 321 (393–1853, 835)	0.004
Ferritin (μ g/L)	412 $\pm$ 272 (98–901, 327)	547 $\pm$ 416 (98–1489, 457)	0.259
CRP (mg/L)	43 $\pm$ 45 (2–165, 28.7)	79 $\pm$ 81 (1–298, 52)	0.115
D-dimer (mg/L)	0.7 $\pm$ 0.85 (0.14–2.80, 0.35)	1.6 $\pm$ 1.6 (0–5.5, 1.14)	0.034
IL-6 (pg/mL)	24.3 $\pm$ 29 (0–125.3, 18.5)	87.1 $\pm$ 86 (0–379.2, 71.5)	0.008
At 12 weeks			
LDH (units/L)	309 $\pm$ 148 (113–652, 266)	280 $\pm$ 170 (114–896, 244)	0.578
Ferritin (μ g/L)	166 $\pm$ 104 (28–385, 126)	158 $\pm$ 103 (14–401, 146)	0.813
CRP (mg/L)	10 $\pm$ 9 (1–28, 5.5)	9 $\pm$ 12.5 (0.1–45, 4)	0.782
D-dimer (mg/L)	0.6 $\pm$ 0.66 (0.1–2.40, 0.27)	0.8 $\pm$ 0.94 (0.1–2.5, 0.3)	0.548
IL-6 (pg/mL)	8.3 $\pm$ 14 (0–49, 2.8)	14.7 $\pm$ 18.3 (0–85, 12.15)	0.247

Table 3: Temporal comparison of inflammatory markers in moderate and severe COVID-19 at admission and 12 weeks

Inflammatory markers	Admission	12 weeks	<i>p</i> -value (paired t-test)
	Mean ± SD	Mean ± SD	
Moderate COVID-19 (N = 16)			
LDH (units/L)	528 ± 342	309 ± 148	0.026
Ferritin (µg/L)	412 ± 272	166 ± 104	0.007
CRP (mg/L)	43 ± 45	10 ± 9	0.008
D-dimer (mg/L)	0.7 ± 0.85	0.6 ± 0.66	0.67
IL-6 (pg/mL)	24.3 ± 29.3	8.3 ± 14.05	0.064
Severe COVID-19 (N = 24)			
LDH (units/L)	851 ± 321	280 ± 170	<0.001
Ferritin (µg/L)	547 ± 416	158 ± 103	<0.001
CRP (mg/L)	79 ± 80	9 ± 12	<0.001
D-dimer (mg/L)	1.6 ± 1.6	0.8 ± 0.94	0.02
IL-6 (pg/mL)	87.1 ± 86	14.7 ± 18.3	<0.001

Table 4: Malondialdehyde and TAS level in moderate and severe COVID-19 at admission and 12 weeks

Parameter	Admission	12 weeks	<i>p</i> -value (paired <i>t</i> -test)
	Mean ± SD (range, median)	Mean ± SD (range, median)	
MDA (nmol/mL)			
Moderate COVID-19 (<i>n</i> = 16)	4.1 ± 1.82 (1.42–7.17, 4.34)	3.2 ± 2.90 (0.14–10.12, 2.16)	0.175
Severe COVID-19 (<i>n</i> = 24)	7.1 ± 2.68 (3.69–14.48, 6.71)	3.4 ± 2.61 (0.14–9.10, 3.19)	<0.001
<i>p</i> -value (Student's <i>t</i> -test)	<0.001	0.839	
TAS (mmol/L)			
Moderate COVID-19 (<i>n</i> = 16)	12.3 ± 5.21 (4.81–28.12, 11.16)	14.8 ± 5.15 (8.26–28.24, 13.69)	0.263
Severe COVID-19 (<i>n</i> = 24)	7.2 ± 4.19 (0.12–15.17, 7.18)	13.4 ± 7.20 (3.58–34.53, 12.39)	0.001
<i>p</i> -value (Student's <i>t</i> -test)	0.002	0.521	

Table 4 shows that MDA levels were significantly greater in severe COVID-19 in comparison to moderate disease ($p < 0.001$). These values reduced to a significant extent at 12 weeks in severe COVID-19. However, in moderate disease, this difference was not statistically significant. Significantly higher MDA levels were observed in patients with two or more comorbidities as compared to those with no comorbidity (4.85 ± 3.07 vs 1.41 ± 0.7 nmol/mL; $p < 0.001$).

The TAS levels were significantly lower in severe COVID-19 at admission ($p = 0.002$). The values of TAS considerably improved from baseline when measured at 12 weeks in patients with severe COVID-19 ($p < 0.001$). However, the improvement was not substantial in moderate disease. Significantly lower values were observed in patients with two comorbidities vs no comorbidity (11.38 ± 4.7 vs 15.62 ± 5.51 mmol trolox equivalent/L; $p < 0.05$).

DISCUSSION

Coronavirus disease 2019 pandemic spurred scientists and health professionals of various backgrounds to delve into the mysteries of

its pathogenesis so as to develop effective therapeutic agents. One of the key factors studied in pathogenesis is OS. While initially, empiric use of antioxidants was promoted due to lack of viable and effective medication, there is a need to evaluate their role in the disease.

Recent evidence suggests that an augmented OS and depleted antioxidant indices are closely related to the severity of COVID-19 infection. In the present study, TAS values in mmol trolox equivalent/L were found to be markedly lower in severe COVID-19. Çakırca et al. demonstrated that serum levels of thiol and TAS were noticeably lower in patients admitted to intensive care unit (ICU).¹³ On the contrary, TOS and OS index were markedly high. Yaghoubi et al. have shown that TAC levels were considerably lower and depleted in COVID-19 patients compared with healthy individuals.¹⁴ Patients with reduced TAC had greater risk of disease exacerbation and increase in the severity of COVID-19. They attributed the decrease in antioxidant levels in severe disease to increased ROS generation, inflammation, multi-organ dysfunction and declining oxygen saturation. Karkhanei et al. found

an important association between the levels of TOS, glutathione and TAC with oxygen saturation and the prognosis of COVID-19. They concluded that heightened OS and reduced antioxidant indices can worsen disease's severity in COVID-19 patients. On the basis of their findings, they suggested the administration of antioxidant drugs to hospitalized patients.¹⁵

We observed the MDA levels to be particularly higher in patients who had severe disease. Mehri et al. have shown that MDA levels were nearly three times greater in COVID-19 positive patients in comparison to control group.¹⁶ MDA levels in their study were considerably elevated in patients requiring ICU admission contrary to non-ICU patients. In an analysis of 152 patients, Avila-Nava et al. reported that in comparison to controls, COVID-19 patients raised MDA and decreased TAC levels. They observed that higher levels of MDA showed a considerable increase in mortality and reported that a combination of the OS biomarkers (MDA $\pm$ TAC) were important predictors of mortality.¹⁷

We also observed that inflammatory markers like IL-6, D-dimer, and LDH levels

were strikingly elevated in patients with severe disease. Marimuthu et al. in their study documented that IL-6 levels correlated with mortality (43 pg/mL in survivors and 120 pg/mL in nonsurvivors).¹⁸ IL-6 levels correlated with greater odds of developing respiratory failure, mechanical ventilation, and inhospital mortality.¹⁸ In a meta-analysis of nine studies involving 1,426 COVID-19 patients, IL-6 levels were ≥ 3 times greater in patients with complicated disease as in comparison with noncomplicated disease.¹⁹ Similarly, D-dimer is a sensitive predictor of mortality in COVID-19 patients. Dogan et al. showed that the increasing D-dimer levels were associated with worsening disease severity.²⁰ In another study, D-dimer were much lower in survivors as compared to nonsurvivors (0.4 vs 0.85 U/L).¹⁸ Additionally, Dogan et al. also correlated LDH enzyme activities with OS and inflammatory parameters and disease severity in COVID-19 patients and observed that increasing LDH levels were associated with increased disease severity.²⁰

Limitations

The sample size in the present study was limited due to changing trends in COVID-19 case admissions during the period of study and some patients being lost to follow-up. As it was a single-center study, the generalization of findings is limited. Mild cases and critically ill patients were excluded from the study, although their inclusion would have enriched the data. Additionally, there was no comparative group of normal healthy controls.

CONCLUSION

There is paucity of objective data on assessment of oxidant stress and antioxidant status in COVID-19. The present research examined this phenomenon and its direct relationship with disease severity. This is one of the few Indian studies that have analyzed OS and TAS in COVID-19 infection and their temporal trends. It should set the stage for a fresh look at these indicators in acute respiratory infections with new pathogens as well as for identifying their role in pathophysiology as well as potential for rational antioxidant therapeutics in COVID-19.

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Assessment of Thrombotic Complications among Coronavirus Disease 2019 Positive Hospitalized Patients at One of Government Tertiary Care Centres of Gujarat: A Retrospective Observational Study



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ABSTRACT

Objectives: The objectives of the study were to (1) study risk factors of thrombotic complications in coronavirus disease 2019 (COVID-19) pneumonitis, and (2) study progression of thrombotic complications after COVID-19 pneumonitis and its outcome.

Materials and methods: A total of 50 COVID-19-positive admitted patients were studied using a purposive random sampling method. A questionnaire was used to collect data from patients' case records.

Results: Diabetes (42%) and hypertension (40%) were common comorbidities. The most common presentation of patients was thromboembolism, followed by cerebrovascular accident (CVA) and myocardial infarction (MI). Around 32% of patients died during the course of treatment. Deaths were more commonly seen in the age-group of 56 years or above than in those below 56 years. Death rates were higher among the group of patients with diabetes, hypertension, and ischemic heart diseases than the group of patients without those diseases, respectively. Patients in whom intubation was needed had a higher death rate than those without the need for it. The mean C-reactive protein (CRP) value was higher in patients who died than in those who survived. The death rate was lower in patients who were thrombolysed than in those who were not, in both pulmonary embolism and MI cases.

Conclusion: The most common age-group admitted to the hospital was 46–55 years. The two most common underlying risk factors were diabetes and hypertension. Three common presentations of patients were thromboembolism, followed by CVA and MI. Around 32% of patients died during the course of treatment. Deaths were more commonly seen in the age-group of 56 years or above than in those below 56 years. Death rates were higher among the group of patients with diabetes, hypertension, and ischemic heart diseases than the group of patients without those diseases, respectively. Patients in whom intubation was needed had a higher death rate than those without the need for it. The mean CRP value was higher in patients who died than in those who survived.

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INTRODUCTION

Patients infected with coronavirus disease 2019 (COVID-19) develop a wide range of clinical manifestations, typically presenting with fever, cough, myalgia, and fatigue. Severely ill patients may fall victim to acute respiratory distress syndrome, acute heart injuries, neurological manifestations, or complications due to secondary infections. These critically ill patients are also found to have disrupted coagulation function, predisposing them to consumptive coagulopathies and both venous and thromboembolic complications. Common laboratory findings include thrombocytopenia, elevated D-dimer, fibrin degradation products, and fibrinogen, all of which have been associated with greater disease severity. Many cases of pulmonary embolism have been noted, along with deep vein thrombosis, ischemic

stroke, myocardial infarction (MI), and systemic arterial embolism.¹ So our study was conducted with the objectives to (1) study risk factors of thrombotic complications in COVID-19 pneumonitis, and (2) study progression of thrombotic complications after COVID-19 pneumonitis and its outcome.

MATERIALS AND METHODS

- Study design: Retrospective observational study.
- Study place: Pandit Dindayal Upadhyay Medical College, Rajkot, Gujarat, India.
- Study duration: January 2021 to December 2021.
- Study population: Coronavirus disease 2019 positive patients admitted to the study place during the study period.
- Sample size: A total of 50 participants.
- Sampling method: Purposive sampling method.

- Selection of participants: Participants were selected based on inclusion and exclusion criteria.

Inclusion Criteria

- Age: Nearly >18 years.
- Reverse transcription polymerase chain reaction or rapid antigen test confirmed COVID-19.

Exclusion Criteria

- Age: Nearly <18 years.
- A pretested semi-structured questionnaire was used to collect data, including questions related to demographic details of patients, clinical history, laboratory investigations, and treatment. The questionnaire was filled out by the investigator himself using case records of patients. For stroke, clinical findings such as hemiparesis and aphasia were assessed. For pulmonary embolism, worsening of dyspnea, tachycardia, and increased demand for O₂ after significant improvement in O₂ requirement initially were assessed. For deep vein thrombosis, dry gangrene of limbs, new-onset swelling, tenderness, and pain were assessed. Diagnosis was confirmed by computed tomography pulmonary angiography (CTPA), magnetic resonance imaging (MRI) brain, and venous or arterial Doppler studies.

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Consent

As it was a retrospective study, obtaining consent from participants was not possible. Consent from the institutional authority was taken with the condition of maintaining the confidentiality of participants (patients).

Ethical Clearance

It was obtained from the Institutional Ethics Committee before starting the study.

Data Entry and Analysis

Data entry was performed in Microsoft Excel 2007, and data analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 20.0. For the analysis of qualitative data, frequencies and percentages were calculated, and for quantitative data, means and standard deviations were used. Appropriate tests of significance were selected based on the type of data.

RESULTS

It can be seen from Table 1 that the most common (32.0%) age-group involved was of 46–55 years. The two most common underlying risk factors were diabetes (42%) and hypertension (40%). Approximately 38% of patients had a tobacco addiction. The most common presentation of patients was thromboembolism (62%), followed by cerebrovascular accident (CVA) (16%) and MI (14%). Intubation was required in 26% of patients. About 98% of patients developed symptoms within 15 days of becoming COVID-positive. Steroids were used during treatment in 88% of patients, while antivirals were used in 94% of patients.

Table 2 shows that 32% of all patients died, while 68% survived. An independent nationally representative survey of 0.14 million adults indicated that COVID-19 constituted 29% (95% confidence of interval 28–31%) of deaths from June 2020 to July 2021.²

It can be observed from Table 3 that there is a significant difference between age-groups and the outcomes of patients, as indicated by a significance value (p -value) of <0.05 . Deaths were more commonly seen in the age-group of 56 years or above compared to those below 56 years. The death rate was higher among patients with diabetes compared to those without diabetes, and this association was statistically significant (p -value <0.05). Deaths were also more common among patients with hypertension compared to those without it, as this finding was not due to chance (p -value <0.05). Similarly, death was more commonly seen among patients with preexisting ischemic heart disease compared to those without it, with a statistically significant

difference (p -value <0.05). Lastly, death was more common in the group of patients who required intubation compared to those who did not, and this association was supported by a statistical test of significance (p -value <0.05).

As it can be stated from Table 4 there is no statistically significant difference in the outcome of patients regarding variables such as D-dimer at admission, highest D-dimer during COVID-19, serum ferritin, and activated partial thromboplastin time (APTT) highest recorded, as the significance values for all these associations were <0.05 . However, the mean C-reactive protein (CRP) value was higher in the group of patients who died compared to those who survived, and this finding is statistically significant (p -value <0.05). In other words, higher CRP levels can be considered an indicator for higher mortality due to thromboembolic complications.

It can be seen from Table 5 that the death rate was lower in patients who were thrombolysed than in those who were not, in both pulmonary embolism and MI cases.

DISCUSSION

Ours was a retrospective observational study involving 50 COVID-19-positive patients. The mean age of patients in our study was 54.9 years, which is comparable to the mean ages reported in studies by Al-Samkari et al.

Table 2: Distribution of cases according to outcome

Outcome	Frequency	Percentage
Death	16	32.0
Discharge	34	68.0
Total	50	100.0

Table 1: Basic details, clinical history, and treatment history of patients

Variable	Subgroup	Frequency	Percentage
Age-group (years)	36–45	12	24
	46–55	16	32
	56–65	12	24
	>65	10	20
Sex	Male	27	54
	Female	23	46
Underlying risk factors	Diabetes	21	42
	Hypertension	20	40
	IHD	5	10
	Malignancy	1	2
	CKD	1	2
	Hypothyroidism	1	2
Addiction	BAJJAR	1	2.0
	Smoker	8	16.0
	Tobacco	11	22.0
	No	30	60.0
Type of presentation	Thromboembolism	31	62
	Acute limb ischemia	3	6
	Acute mesenteric thrombosis	1	2
	CVA	8	16
	MI	7	14
Presentation of symptoms after days of COVID-19 positive	0–5	19	38
	6–10	25	50
	11–15	5	10
	>15	1	2
Supplemental oxygen use	Room air	2	4
	Nasal cannula	20	40
	BIPAP	15	30
	Intubated	13	26
Use of steroid	Yes	44	88
	No	6	12
Use of antiviral	Yes	47	94
	No	3	6

BAJJAR, chewable tobacco formulation; BIPAP, bilevel positive airway pressure; CKD, chronic kidney disease; IHD, ischemic heart disease

Table 3: Comparison of outcome with different variables (factors) of patients

Variable	Subgroup	Death	Discharge	Total	Statistical test value	p-value
Age-groups (years)	36–45	1 (6.3%)	11 (32.4%)	12 (24.0%)	$\chi^2 = 9.769$	0.0321
	46–55	3 (18.7%)	13 (38.2%)	16 (32.0%)		
	56–65	6 (37.5%)	6 (17.6%)	12 (24.0%)		
	>65	6 (37.5%)	4 (11.8%)	10 (20.0%)		
	Total	16 (100.0%)	34 (100.0%)	50 (100.0%)		
Diabetes	Yes	14 (87.5%)	7 (20.6%)	21 (42.0%)	$\chi^2 = 19.997$	<0.001
	No	2 (12.5%)	27 (79.4%)	29 (58.0%)		
	Total	16 (100.0%)	34 (100.0%)	50 (100.0%)		
Hypertension	Yes	13 (81.3%)	7 (20.6%)	20 (40.0%)	$\chi^2 = 16.682$	<0.001
	No	3 (18.7%)	27 (79.4%)	30 (60.0%)		
	Total	16 (100.0%)	34 (100.0%)	50 (100.0%)		
Ischemic heart diseases (preexisting)	Yes	4 (25.0%)	1 (2.9%)	5 (10.0%)	$\chi^2 = 5.882$	0.015
	No	12 (75.0%)	33 (97.1%)	45 (90.0%)		
	Total	16 (100.0%)	34 (100.0%)	50 (100.0%)		
Intubation done	Yes	13 (81.3%)	0 (0.0%)	13 (26.0%)	$\chi^2 = 37.331$	<0.001
	No	3 (18.7%)	34 (100.0%)	37 (74.0%)		
	Total	16 (100.0%)	34 (100.0%)	50 (100.0%)		

Table 4: Distribution of cases according to blood parameters

Blood parameters	Death	Discharge	p-value
D-dimer at admission ($\mu\text{g/L}$)	2136.9 $\pm$ 1534.3	2487.3 $\pm$ 2075.5	0.551
Highest D-dimer during COVID-19 ($\mu\text{g/L}$)	6369.3 $\pm$ 3749.8	6144.6 $\pm$ 3020.8	0.822
Serum ferritin ($\mu\text{g/L}$)	82.9 $\pm$ 65.3	98.3 $\pm$ 64.8	0.44
CRP (mg/L)	317.8 $\pm$ 105.7	244.7 $\pm$ 113.3	0.035
APTT highest recorded (second)	66.1 $\pm$ 41.7	86.4 $\pm$ 38.4	0.097

Table 5: Comparison of outcome in pulmonary embolism and MI cases with the use of fibrinolytic

Cases	Thrombolysed*	Death	Discharged	Total
Pulmonary embolism	Yes	2 (20%)	8 (80%)	10 (100%)
	No	5 (71.4%)	2 (28.6%)	7 (100%)
MI	Yes	0 (0%)	5 (100%)	5 (100%)
	No	1 (50%)	1 (50%)	2 (100%)

*using alteplase in pulmonary embolism and streptokinase in MI

(60 years) and Artifoni et al. (58 years).^{3,4} The proportions of male patients were 54.3% in the current study, 52.7% in the study by Al-Samkari et al., and 60.6% in the study by Artifoni et al..^{3,4}

Diabetes was present in 31, 20, and 41% of the present study and the studies by Artifoni et al. and Desborough et al., respectively.^{4,5} Hypertension was found in 21, 41, and 45% of the current study and the studies by Artifoni et al. and Desborough et al., respectively.^{4,5} In our study, the presentation of symptoms such as thromboembolism, acute limb ischemia, CVA, and MI occurred within 30 days of COVID-19 pneumonitis positivity, which is comparable to the findings of the study

by Bompard et al., where 68% of patients presented with symptoms within the first month after COVID-19 infection.⁶

Death as the outcome was seen in 32, 57, and 34% patients in the present study and the study by Zhang et al. and Poyiadi et al., respectively.^{7,8} Proportion of death rates among various age-groups 36–45, 46–55, 56–65, and >65 years were 6.3, 18.7, 37.5, and 37.5% in our study while the same was seen in 6, 16, 43, and 35% patients, respectively in a study by Cantador et al.⁹ Death rates among diabetes were 87.5, 72, and 82% in this study and the studies by Nahum et al. and Maatman et al., respectively.^{10,11} Death rate among hypertensive were 81.3, 90, and 64% in the current study and the studies

by Desborough et al. and Fraisse et al. respectively.^{5,12}

CONCLUSION

The commonest age-group of COVID-19-positive patients admitted to the hospital was 46–55 years. The two most common underlying risk factors were diabetes and hypertension. The three most common presentations of patients were thromboembolism, followed by CVA and MI. Around 32% of patients died during the course of treatment. Deaths were more commonly seen in the age-group of 56 years or above compared to those below 56 years. Death rates were higher among patients with diabetes, hypertension, and ischemic heart diseases compared to those without these diseases, respectively. Patients who required intubation had a higher death rate than those who did not. The mean CRP value was higher in patients who died than in those who survived.

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Study of Association of Infection-related Biomarkers and Inflammatory Cytokines with the Severity of Coronavirus Disease 2019: A Prospective Observational Study



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ABSTRACT

Background: Sepsis-linked biomarkers and inflammatory cytokines are markedly associated with potential risks of progression to severity in coronavirus disease 2019 (COVID-19). Clinical studies that find a plausible association between sepsis biomarkers and the inflammatory cytokine response in the Indian community need to be studied with clarity.

Objectives: To study the relationship between sepsis-linked biomarkers and inflammatory cytokines interleukin-6 (IL-6), C-reactive protein (CRP), ferritin, and D-dimer linked to clinical severity resulting from COVID-19 infection.

Materials and methods: The present prospective observational cohort study was conducted between March and December 2021 in the Department of Critical Care Medicine at a tertiary care hospital in Pune, Maharashtra, India, on COVID-19 patients. Upon patient admission, inflammatory biomarkers such as IL-6, CRP, ferritin, and D-dimer were recorded. Oxygen requirements during hospitalization, invasive mechanical ventilation (IMV), high-flow nasal cannula (HFNC), noninvasive mechanical ventilation (NIV), duration of ventilator use, intensive care unit (ICU) stay, and mortality were documented.

Results: The average levels of IL-6, CRP, D-dimer, and serum ferritin protein recorded at the time of patient arrival were notably higher in the severe (S) group compared to the nonsevere (NS) group. The average duration of ventilator use, ICU stay, and hospital stay was significantly longer in the S group than in the NS group. The percentage of patients who required HFNC, NIV, IMV, and mortality was significantly higher in the S group compared to the NS group.

Conclusion: Sepsis-linked biomarkers and inflammatory cytokines such as IL-6, CRP, D-dimer, and serum ferritin levels at the time of admission were markedly associated with severity outcomes in COVID-19 infection.

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INTRODUCTION

The pandemic coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), with the first reported outbreak case in Wuhan, China, in December 2019. COVID-19 has affected a total of 219 countries, resulting in >765,222,932 confirmed positive cases and 6,921,614 recorded deaths as of 3rd May 2023.¹ As per the World Health Organization (WHO), a total of 44,952,996 established cases of COVID-19 and 531,564 losses of human lives in India were reported, as on 3rd May 2023.² In India, the prominent number of cases were seen in states of Delhi, Tamil Nadu, Kerala Maharashtra, Karnataka, and Andhra Pradesh.³

The coronavirus enters the human cell through the functional receptor angiotensin-converting enzyme 2 (ACE2) with its spike protein structures. Pathogenesis involves indirect mechanisms such as an inflammatory response and excessive production of cytokines, which is known as a cytokine storm. SARS-CoV-2 triggers a cascade cycle that

leads to the generation of proinflammatory cytokines, such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor α , contributing to the cytokine storm, which in turn causes lung tissue damage and cell death.⁴⁻⁶

Patients with COVID-19 may suffer from complications such as SARS, acute respiratory distress syndrome (ARDS), cardiac dysfunction, liver dysfunction, and kidney failure, leading to multi-organ failure and loss of life.⁷

The elevated risks of progression to severe COVID-19 may be caused by the presence of inflammatory markers such as serum ferritin, procalcitonin, C-reactive protein (CRP), IL-6, and erythrocyte sedimentation rate (ESR).⁸⁻¹⁰ On the contrary, a few studies did not find any plausible differences in the levels of IL-6, ESR, and CRP.¹¹⁻¹³

Clinical manifestations of COVID-19 include fever, cough, breathing difficulty, myalgia, sore throat, dyspnea, muscle fatigue, and gastroenterological disturbances such as nausea and indigestion. Complications may include thrombocytopenia, impaired

coagulation functions, thrombi formation, and the development of microthrombi in the lungs. COVID-19 can also impact cognitive functions, as well as upper and lower limb circulation, liver function, and renal function, through disseminated intravascular coagulation leading to sepsis.¹⁴⁻¹⁶

Due to the limited study size of COVID-19 progression in the Indian population and their varied responses related to the interplay of sepsis-linked biomarkers and inflammatory cytokine responses, associated with the severity and outcome of COVID-19 inflammation. The primary aim of the present research was to establish a correlation between sepsis-related biomarkers and inflammatory cytokines such as CRP, ferritin, IL-6, and D-dimer with the severity and outcome of COVID-19 infection.

MATERIALS AND METHODS

This prospective observational study was conducted between March and December 2021 after obtaining approval from the registered Institutional Ethics Committee (letter No. KEMHRC/RVM/EC/2346). Prior to enrollment, written informed consent was obtained from all participating patients. The study included subjects of both sexes, aged 18 years and above, with a confirmed positive reverse transcription polymerase

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chain reaction (RT-PCR) test for COVID-19, who were admitted to a tertiary care hospital in Pune, India.

Demographic details, medical history, signs and symptoms, and laboratory examinations were recorded. Laboratory examinations included complete blood count, blood biochemical parameters such as total serum bilirubin, serum glutamic pyruvic transaminase (SGPT)/alanine aminotransferase (ALT), serum glutamic-oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST), total blood urea, total serum creatinine, serum electrolytes, coagulation functions including international normalized ratio (INR) and D-dimer, infection-related biomarkers (CRP, serum ferritin), and inflammatory cytokines (IL-6). Daily clinical assessment was conducted using the National Early Warning Score (NEWS). Inflammatory markers were recorded at the time of admission. COVID-19-positive cases were categorized according to WHO classification into mild, moderate, severe, and critical based on the severity of the disease.¹⁷ These groups were further divided into two groups—group severe (S), consisting of severe and critical COVID-19 patients, and group nonsevere (NS), consisting of NS COVID-19 patients, including those in the mild/moderate disease category.

The oxygen requirement during hospitalization (O₂ mask/nasal cannula, O₂ nonbreather mask), noninvasive mechanical ventilation (NIV), high-flow nasal cannula (HFNC), invasive mechanical ventilation (IMV), number of days on a ventilator, intensive care unit (ICU) stay, and hospital stay were noted.

C-reactive protein (quantitative) test was conducted using particle-enhanced turbidimetric assay, with a normal reference value of 0.00–5.00 mg/L. Serum ferritin was tested by enzyme-linked immunofiltration assay (ELIFA), with a normal reference value of 15.00–300.00 ng/mL. Total IL-6 levels were estimated using enzyme-linked immunosorbent assay (ELISA), with a normal reference value of 0.00–6.50 pg/mL. D-dimer was measured by immunoturbidimetric assay, with a normal reference value of <500 ng/mL. The primary objective was to study mortality, while the secondary objectives were to assess ICU stay duration and requirements.

The aforementioned test data were tabulated in Microsoft Excel Worksheet version 2007, and statistical analysis was performed using Statistical Package for the Social Sciences for Windows, version 20.0 from IBM Corporation, Armonk, New York, United States of America. Categorical variables are presented as *n* (% of cases), while continuous variables are reported as mean and standard deviation (SD). Associations

among categorical variables were assessed using the Chi-squared test or Fisher's exact test. Unpaired *t*-tests were used to compare continuous variables between groups. The significance level was set at 95% with a *p*-value < 0.05.

RESULTS

A total of 94 patients were included in this cohort observational research conducted at the Department of Critical Care Medicine, a tertiary care hospital in Pune, India, between March and December 2021. Mild and moderate COVID-19 patients accounted for 29 (30.9%) subjects each, while severe and critical patients were observed in 32 (34.0%) and 4 (4.2%) subjects, respectively. The mild and moderate subjects were categorized into the NS group, and severe and critical cases were categorized into the S group.

The age-groups, gender distribution, prevalence of ischemic heart disease, and history of smoking were comparable between the NS and S groups. However, the prevalence of diabetes mellitus, hypertension, and chronic kidney disease was significantly higher in group S compared to the NS group (Table 1). The average levels of mean hemoglobin, total white blood count, platelet count, serum sodium, serum creatinine, serum alkaline phosphatase (ALP), and INR were comparable between the NS and S groups. However, serum potassium, blood urea, SGOT, SGPT, CRP, serum ferritin, IL-6, D-dimer, and NEWS score at the time of admission were significantly elevated in the S group compared to the NS group (Table 2). The mean duration of ventilator requirement, mean duration of ICU stay, and mean duration of hospital stay

were significantly higher in group S compared to group NS. Additionally, the average number of COVID-19 patient subjects who required HFNC, NIV, and IMV was significantly higher in group S compared to group NS. The mortality rate was notably higher in group S compared to group NS (Table 3).

DISCUSSION

The present cohort observational study was conducted to investigate the association of sepsis-linked biomarkers and levels of inflammatory cytokines with the severity and outcome of COVID-19 infection. The ongoing study establishes a significant correlation between CRP, serum ferritin, and IL-6 levels at the time of patient admission and the severity and outcome of COVID-19.

Mammen et al. conducted a study on factors associated with mortality in a fixed cohort sample of clinically moderate-to-severe COVID-19 subjects in India. The study found that admission IL-6 levels were significantly elevated (*p*-value < 0.001) in nonsurvivors compared to survivors. The study also reported a strong association of mortality with a total platelet count <100 × 10⁹/L (*p*-value < 0.001), neutrophil-to-lymphocyte ratio (*p*-value < 0.001), D-dimer levels <1 mg/L (*p*-value = 0.002), and ferritin levels ≥500 ng/mL (*p*-value < 0.001), while CRP did not show statistical significance (*p*-value = 0.080).¹⁸ Qin et al. reported that severe COVID-19 cases had higher leukocyte counts (5.6 vs 4.9 × 10⁹ with significant *p*-values < 0.001), higher neutrophil counts (4.3 vs 3.2 × 10⁹ with significant *p*-values < 0.001), lower lymphocyte counts (0.8 vs 1.0 × 10⁹ with significant *p*-values < 0.001),

Table 1: Comparison of baseline characteristics between S and NS groups

Variables	NS group <i>n</i> (%)	S group <i>n</i> (%)	<i>p</i> -value
Age-groups in years			
≤30	4 (6.9)	1 (2.7)	0.053*
31–50	25 (43.1)	10 (27.8)	
51–70	16 (27.6)	21 (58.3)	
>70	13 (22.4)	4 (11.1)	
Gender			
Male	38 (65.5)	23 (63.9)	0.87**
Female	20 (34.5)	13 (36.1)	
Comorbidities/risk factors			
Diabetes mellitus	13 (22.4)	16 (44.4)	0.02**
Hypertension	15 (25.9)	20 (55.6)	0.01**
Ischemic heart disease	1 (1.7)	3 (8.3)	0.12*
Chronic kidney disease	1 (1.7)	6 (16.7)	0.01*
Lung disease	1 (1.7)	0 (0.0)	0.01*
History of smoking	1 (1.7)	1 (2.8)	0.73*

*, Fisher's exact test was used; **, Chi-squared test was used

Table 2: Comparison of laboratory parameters between S and NS groups

Parameters in mean	NS group	S group	p-value
Hematological parameters			
Hemoglobin%	12.8	12.1	0.08
Total leukocyte count	7916.5	9753.2	0.11
Platelets count	2.2	2.0	0.19
Serum electrolytes			
Sodium	134.3	135.0	0.28
Potassium	4.2	4.5	0.02
Biochemical parameters			
Blood urea	31.3	55.9	0.01
Serum creatinine	1.1	1.6	0.06
Serum bilirubin	0.7	1.1	0.02
SGOT	36.3	81.5	0.02
SGPT	31.6	55.7	0.02
ALP	66.5	71.3	0.25
INR	1.1	1.1	0.13
CRP at admission	54.0	105.8	0.01
D-dimer at admission	820.8	1618.4	0.01
Serum ferritin at admission	276.8	858.9	0.01
IL-6 at admission	72.74	259.28	0.01
NEWS score at admission	3.8	4.4	0.01

Unpaired *t*-test was used; ALP, alkaline phosphatase; CRP, C-reactive protein; IL-6, interleukin-6; INR, international normalized ratio; NEWS, national early warning score; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase

Table 3: Comparison of outcome variables between S and NS groups

Parameters	NS group N (%)	S group N (%)	p-value
Mean duration ventilator required in days	0.7	5.7	0.01*
Mean duration of ICU stay in days	3.3	11.5	0.01*
Mean duration of hospital stay in days	10.4	14.5	0.01*
O ₂ requirement			
On room air	21 (36.2)	0 (0.0)	0.01**
On O ₂ nasal/mask	12 (20.7)	0 (0.0)	
On O ₂ reservoir	8 (13.8)	0 (0.0)	
On HFNC	6 (10.3)	3 (8.3)	
Noninvasive ventilation	7 (12.1)	5 (13.9)	
Mechanical invasive ventilation	4 (6.9)	28 (77.8)	
Outcome			
Death	9 (15.5)	22 (61.1)	0.01***
Discharged	49 (84.5)	14 (38.9)	

*, Unpaired *t*-test was used; **, Fisher's exact test was used; ***, Chi-squared test was used

higher neutrophil-to-lymphocyte ratio (5.5 vs 3.2 with significant *p*-value < 0.001), and lower levels of monocyte counts (6.6 vs 8.4% with significant *p*-value < 0.001), eosinophils (0.0 vs 0.2% with *p*-value < 0.001), and basophils (0.1 vs 0.2% with *p*-value = 0.015). The ongoing study categorically proposes that severe COVID-19 patients demonstrate significantly higher levels of infection/sepsis-linked biomarkers compared to NS COVID-19 patients. Specifically, procalcitonin levels (0.1 vs 0.05 ng/mL with *p*-values < 0.001), total serum ferritin protein levels (800.4 vs 523.7 ng/mL with *p*-value < 0.001),

and total CRP levels (57.9 vs 33.2 mg/L with *p*-value < 0.001) were markedly elevated in severe cases. Inflammatory cytokines were also found to be higher in severe cases compared to NS cases, including IL-2R (757.0 vs 663.5 U/mL with *p*-value = 0.001), IL-6 levels (25.2 vs 13.3 pg/mL with *p*-values < 0.001), IL-8 levels (18.4 vs 13.7 pg/mL with *p*-values < 0.001), and IL-10 levels (6.6 vs 5.0 pg/mL with *p*-value < 0.001).¹⁰

A retrospective multicentric study conducted by Ruan et al. to identify clinical prognosticators of death due to COVID-19 observed significant differences in total

bilirubin levels, blood urea nitrogen, total white blood cell (WBC) count, lymphocyte count, total serum albumin levels, blood creatinine, CRP, and IL-6 between patients who did not survive and those who successfully recovered.¹⁹ Gao et al. stated that there were no significant differences in WBC, lymphocyte, neutrophil, mononuclear cell counts, procalcitonin levels, uric acid levels, AST, ALT, serum creatinine levels, cystatin, and activated partial thromboplastin time between the mild and severe groups, which is consistent with the findings of the present study.⁹

Xu et al. reported that D-dimer levels in COVID-19 patients escalate in a cyclical cascade fashion with disease severity, showing statistically significant differences between nonsevere, severe, and critical types (*p*-value < 0.05).²⁰ Higuera-de la Tijera et al. compared the features of patient subjects with stable hospitalization to those who did not require ventilation (positive controls). Comparative assessment between patient subjects and positive controls revealed significantly lower mean blood oxygen saturation (SpO₂) (73.5 ± 12.0% vs standard 83.0 ± 6.8%, *p*-value < 0.0001), higher median ALT levels (128 IU/L vs 33 IU/L, *p*-value = 0.003), higher median AST levels (214 IU/L vs 44 IU/L, *p*-value = 0.001), and elevated median D-dimer values (3463 ng/mL vs 829 ng/mL, *p*-value = 0.003).²¹ Chu et al. reported that median D-dimer levels were significantly higher in severe cases of COVID-19 patients compared to those with mild-to-moderate disease. They found no statistically significant differences in total WBC count, neutrophil count, lymphocyte count, platelet count, ALT/AST levels, total serum bilirubin levels, and CRP levels between patients with mild/moderate disease and severe disease.²²

Han et al. reported that levels of serum IL-6 and IL-10 were significantly higher in the critically ill patient group compared to the moderate and severe COVID-19 patient groups. Their findings were further supported by conducting univariate logistic regression analysis. The levels of IL-10 and IL-6 were identified as prognostic markers for severe disease progression and served as indicators for early detection in patient subjects at elevated risk of severe disease.²³ The meta-analysis by Zeng et al. observed that inflammatory markers, particularly IL-6, CRP, and ESR, were associated with the severity of COVID-19. The study further suggested that measuring inflammatory markers may assist physicians in monitoring and assessing the severity and prognosis of COVID-19.²⁴ Zhou et al. reported that levels of IL-6, D-dimer, and serum ferritin were elevated in patients who did not survive compared to

surviving patients, correlating with disease severity. Their findings further indicated that lymphopenia, leukocytosis, elevated ALT, high levels of creatine kinase, D-dimer, serum ferritin, IL-6, creatinine, procalcitonin, and patient age were associated with patient deaths.²⁵ Gupta et al. reported that higher levels of inflammatory markers, namely CRP, serum ferritin, and IL-6 at the time of admission, were associated with an increased requirement for IMV and higher clinical period deaths among COVID-19 ICU patient subjects.²⁶ Havaladar et al. reported that serum ferritin levels could be used to assess COVID-19 cases admitted to the ICU. The study further stated that the trend of biomarkers was not useful for predicting the outcome.²⁷

Limitations of the Study

The study sample size of the cohort is small, and the observations were limited to a tertiary care center; therefore, multicentric data was not compared. Disease severity was disproportionately divided amongst the groups. The computed tomography severity score was not included in this study. Treatment details were not specified due to dynamic changes in global treatment protocols. Progressive multivariate binary logistic regression analysis was not conducted to estimate indices linked with the severity and outcomes of COVID-19 patients. Therefore, for a more comprehensive understanding, multicentric prospective studies with larger sample sizes are warranted to validate the results observed in the aforementioned study.

CONCLUSION

The serum potassium, blood urea, SGOT, SGPT, CRP, D-dimer, serum ferritin, IL-6, and NEWS scores at admission were significantly elevated in the S group compared to the NS group. The mean duration of ventilator required, ICU stay, and hospital stay was significantly longer

in the S group compared to the NS group. The percentage of patients who required HFNC, NIV, and IMV was significantly higher in the S group compared to the NS group. The mortality rate was also significantly higher in the S group compared to the NS group. There was a significant association between infection-related biomarkers and inflammatory cytokines such as CRP, D-dimer, serum ferritin, and IL-6 at admission and the severity and outcome of COVID-19 infection.

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Spontaneous Intracranial Hypotension: Role of Computed Tomography-guided Cervical Epidural Blood Patch



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ABSTRACT

Background: Lumbar epidural blood patch (EBP) is not successful in all cases of cerebrospinal fluid (CSF) leak, particularly in the cervicothoracic region. The present study is a retrospective analysis of a cohort of patients who had undergone computed tomography (CT)-guided cervical EBP for spontaneous intracranial hypotension (SIH) due to CSF leak in the cervical region.

Methods: We retrospectively collected data from March 2009 to 2020. Our inclusion criteria were (1) clinical syndrome associated with CSF leak, (2) headache coming on shortly after assuming the erect position and relief achieved by lying down, (3) CT myelography evidence of CSF leak in the cervical region, and (4) patient not responding to conservative management for 7 days. Exclusion criteria were patients with bleeding diathesis and infection. There were six females and four males. Ages ranged from 32 to 57, with an average of 42 years. On presentation, all patients underwent contrast-enhanced magnetic resonance imaging (MRI) and CT myelography. Cervical EBP was done under CT scan guidance. Assessment of headache was done on a 10-point numerical rating scale (NRS) before and after the procedure. Results are categorized into complete relief, partial relief, and no relief categories.

Results: Nine out of 10 patients were completely recovered. One patient was partially recovered. The average NRS scale was 9.6 before treatment, which became 0.4 after EBP. No neurological or vascular complications were seen.

Conclusion: Computed tomography-guided cervical EBP is an optimum and effective way of treating SIH due to a leak in the cervical region. It has a higher success rate than lumbar EBP. However, prospective randomized controlled trials of cervical vs lumbar EBP will further validate our observation.

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INTRODUCTION

Headaches due to spontaneous intracranial hypotension (SIH) can be disabling with the potential to cause serious complications. These headaches are caused by cerebrospinal fluid (CSF) leak through a dural tear. The brain and spinal cord float in the CSF due to buoyancy effect. The seepage of CSF leads to downward displacement of the brain and spinal cord, causing traction on pain-sensitive dural sleeves of the cranial nerves and distortion of periventricular pain-sensitive regions. The brainstem, especially the pons, sags against the clivus, and mental status changes ranging from confusion to coma may be seen. These changes are reversible with restoration of CSF volume and flotation of the brain within the skull. Typically, these headaches get aggravated by upright posture, coughing, laughing, and the Valsalva maneuver. It is relieved by lying flat.^{1,2} It can get further complicated by subdural hematoma, seizure, and even fatal tonsillar herniation. The orthostatic nature of the headache may turn into a chronic, continuous, debilitating condition. The first line of treatment is conservative, which is effective in 85% of cases.² When conservative management fails, an epidural blood patch

(EBP) is recommended as definitive treatment. Lumbar EBP is commonly done for CSF leak headaches. However, it will not be successful in all cases, particularly when the leak is located in the cervicothoracic region. We retrospectively analyzed a cohort of patients who had undergone CT-guided cervical EBP for SIH. A review of the literature in this regard was carried out.

METHODS

We retrospectively collected data from March 2009 to March 2020. Inclusion criteria were (1) clinical syndrome associated with CSF leak, (2) headache coming on shortly after assuming the erect position and relief achieved by lying down, (3) computed tomography (CT) myelography evidence of CSF leak in the cervical region, and (4) patients not responding to conservative management for 7 days. Exclusion criteria were patients with bleeding diathesis and infection. There were six females and four males. Ages ranged from 32 to 57, averaging 42 years. Assessment of headache was done on a 10-point numerical rating scale (NRS) before and after the procedure. All patients had undergone contrast-enhanced magnetic resonance imaging (MRI) and

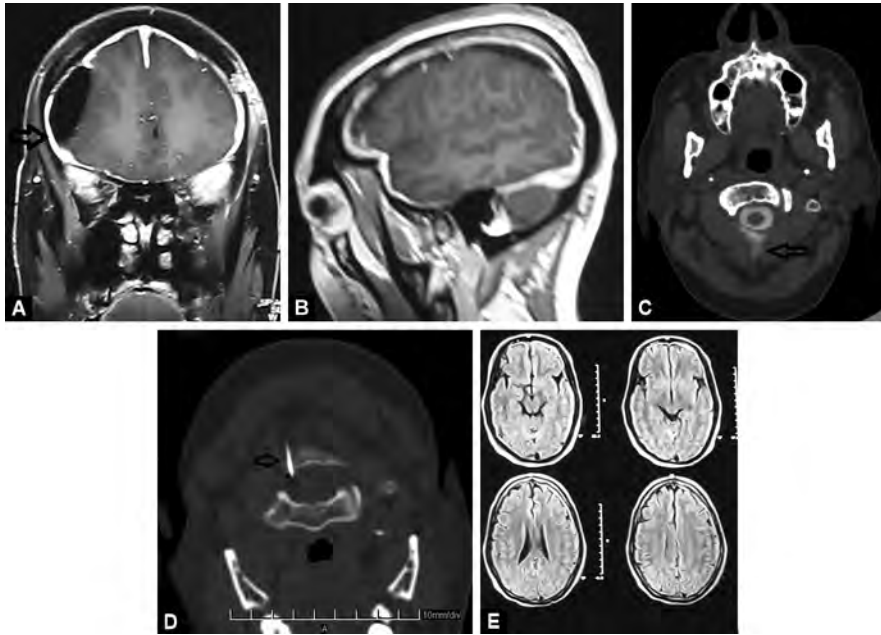
CT myelography. The site of the leak was determined by noting the maximum density and maximum anteroposterior thickness of the leaked contrast. The extent of the epidural leak in the craniocaudal direction was also assessed. Patients were posted for CT-guided cervical EBP after confirming the CSF leak on CT myelography. The result was categorized into complete relief, partial relief, and no relief categories.

Technique of Cervical Epidural Blood Patch Procedure

Procedures were done in the prone position on a multislice spiral CT scanner (Siemens, Munich, Germany). All patients underwent the procedure under local anesthesia, with a standby anesthetist present (Figs 1 and 2). The anesthetist marked the antecubital vein or any other prominent vein to be punctured later in the prone position. The back of the neck was prepared and draped aseptically. An epidural puncture needle (Vygon, Paris, France), 18G for the lower cervical and 22G for the upper cervical, was used. The location and needle track were marked on the CT scan with the help of a 23G hypodermal needle used for infiltrating the local anesthetic agent. We preferred a posterior midline or paramidline approach. Entry of the Tuohy needle was through the interlaminar space, directed toward the lateral recess. Care was taken to keep the needle tip posterior to the intervertebral foramen. The epidural needle attached to an air-filled syringe was inserted using the loss of resistance (LOR) technique. A few

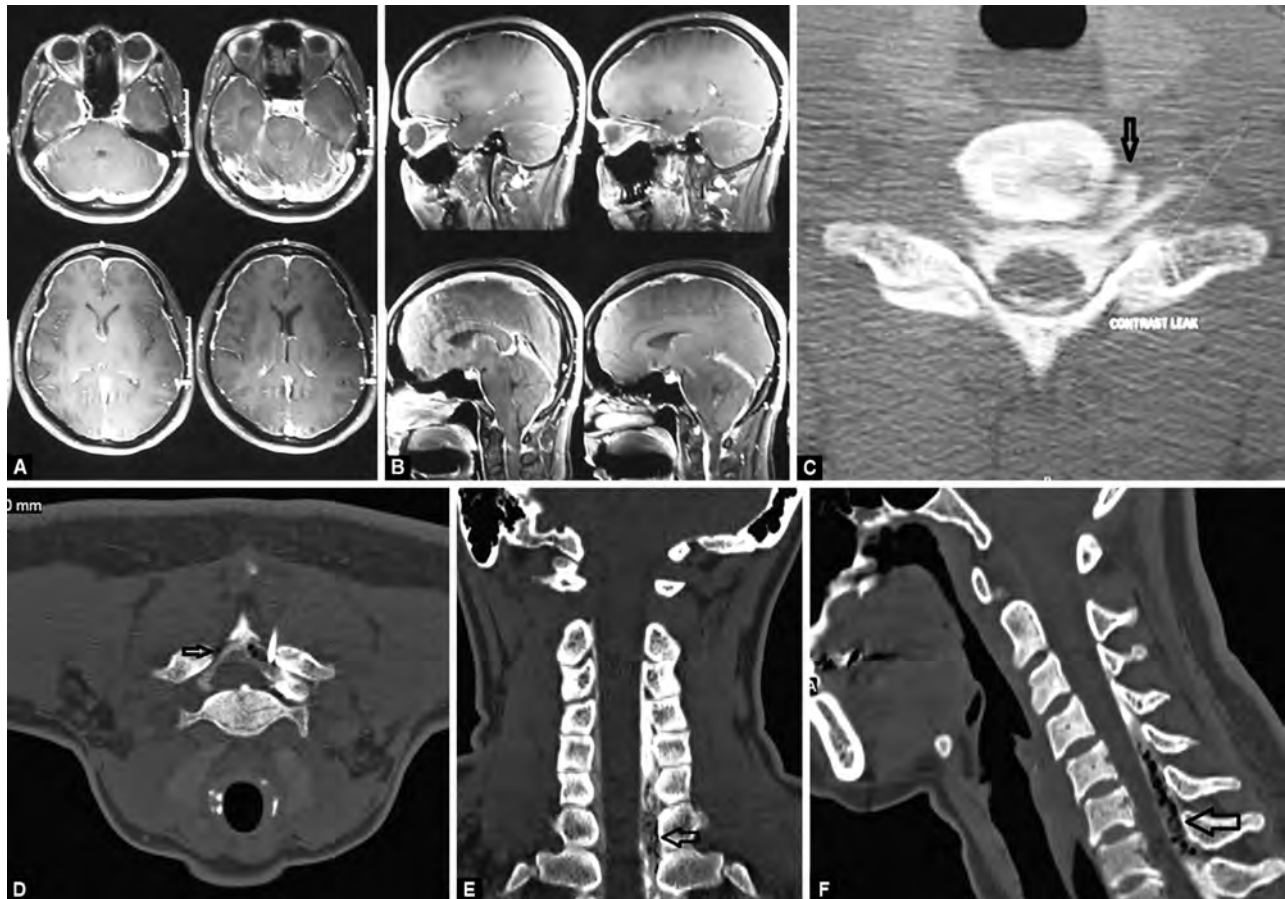
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Figs 1A to E: (Clockwise) Contrast-enhanced MRI coronal (A) and sagittal; (B) showing dural enhancement. Note the subdural hygroma with pneumocephalus underneath the enhancing dura (empty black arrow) in the coronal plane (A) this patient had blunt trauma due to a road traffic accident. Image (C) axial image of CT myelography showing Contrast leak at C1-2 level posteriorly (empty black arrow). Axial image of CT under guidance (D) showing placement of the needle in epidural space (empty black arrow). 3 months after EBP, a follow-up MRI (E) showing resolution of subdural hygroma

bubbles of air were injected, and a CT scan was repeated to confirm the position of the needle in the epidural space. Utmost care was taken to avoid puncturing the dura. We preferred not to use iodinated contrast media as it would hinder the density of injected blood. CT fluoroscopy was used whenever required for real-time guidance. At this point, the anesthetist drew 10 mL of blood from the vein marked earlier. Heparin was not used in the syringe. The autologous blood was slowly injected at a speed of 0.3–0.5 mL per second. The injection was stopped when 5–8 mL of blood was injected or the patient developed pain and heaviness in the neck, whichever came earlier. There was continuous monitoring of the patient's vital parameters throughout the procedure. All anesthesia equipment, like the oxygen cylinder and medications, were kept on standby. Postprocedure CT was performed to assess the extent and volume of the injected blood. After termination of the injection, the needle was removed, and a pressure dressing was applied. The patient was turned into the supine position and mobilized gradually after 2 hours. Patients



Figs 2A to F: (A) MRI axial; (B) Saggital show dural enhancement; (C) Axial image of CT myelography showed contrast leak at C6-7 level on lateral aspect along the exiting nerve sheath (empty black arrow); (D) Epidural placement of needle shown by empty black arrow. Post-EBP showed spread of epidural blood in (E) Coronal and (F) Saggital CT scan images. Note the extent of spread axially (D) along the circumference of thecal sac and longitudinally (E) up to 4 vertebral levels

Table 1: Summary of demographic and clinical details of patients

Age	Gender	Presentation	Etiology	Pre-NRS	Post-NRS	Leak	BV	Recovery
57	M	HA, vertigo	Spontaneous	10	0	C1-2	8	Complete
32	F	HA, vertigo	Spontaneous	10	0	C6-7	7	Complete
48	M	HA, tinnitus	Spontaneous	8	0	C6-7	7	Complete
38	F	HA, vertigo	Spontaneous	10	0	C6-7	7	Complete
42	F	HA	Spontaneous	10	0	C6-7	6	Complete
46	M	HA	Spontaneous	10	0	C6-7	6	Complete
44	F	HA, fainting	Spontaneous	10	0	C6-7	6	Complete
32	F	HA, tinnitus	Spontaneous	8	0	C1-2	5	Complete
40	M	HA	Spontaneous	10	0	C6-7	5	Complete
38	F	HA	Spontaneous	10	4	C6-T1	8	Partial

BV, Volume of blood injected; F, female; HA, headaches; Leak, level of dural leak; M, male; NRS, 10-point numerical rating scale for pain

were shifted to the intensive care unit (ICU) for observation. Clinical assessments were conducted at 15 minutes, 8 and 24 hours. Patients were discharged 24 hours after the procedure. Headache was measured on a 10-point NRS before and after the procedure. Demographic and clinical details are summarized in the manuscript [Table 1](#). On discharge, patients are advised to engage in light activities, maintain adequate hydration, and take analgesics as needed. They are asked to follow-up after 15 days, 1 and 6 months. They are advised to report any recurrence or worsening of symptoms at any time. Follow-up MRI with gadolinium-enhanced imaging is scheduled at 3 months postprocedure.

RESULTS

Nine out of 10 patients were completely recovered. One patient had partial recovery. The average NRS scale was 9.6, which decreased to 0.4 after EBP. Nine out of 10 patients had an NRS of zero after EBP. Relief started immediately in nine out of 10 patients and progressed to complete relief within 8 hours. These nine patients showed persistent relief at 1 and 6 months follow-up. One patient had only partial relief (NRS 4) in the first 24 hours and did not improve further. No neurological or vascular complications were observed. The most common level of leak was at C6-C7 in seven out of 10 patients, while two out of 10 patients had leaks at C1-C2. The leak was observed on the posterolateral or lateral aspect in nine out of 10 patients. The one patient who showed partial relief had an anterior tear with a leak in C6-T1. We suggested a second session of EBP, but the patient refused, as well as surgical intervention. He was lost to follow-up after 3 weeks and was considered in the partial relief category. No patient had a history of trauma; therefore, all were labeled as SIH. We did not find any associated connective tissue disorder.

DISCUSSION

Epidural blood patch has been a known procedure since 1955. CT-guided cervical EBP is a recent, technically refined, and target-oriented advancement of it.³ If EBP is performed away from the site of the actual dural tear, it may not be successful in all patients. Therefore, every effort should be made to determine the site of the leak and seal it for definitive cure. Technologically advanced imaging makes it possible to pinpoint the exact location of the tear in most cases. Conventional myelography, CT myelography, MR myelography, and radioisotope cisternography are imaging modalities with varying sensitivity and specificity. CT myelography is the most sensitive of all, demonstrating the exact location and extent of the leak. MR myelography is particularly sensitive for detecting slow or intermittent leaks. The use of intrathecal gadolinium contrast media, though "off-label," can enhance diagnostic yield.⁴ Contrast-enhanced MRI classically depicts the intracranial changes following CSF leak. The classical features include subdural hematoma or hygroma, prominent dural enhancement, enlargement of the pituitary fossa, sagging of the brain with crowding of the posterior fossa, descending transtentorial herniation, and engorgement of the epidural venous plexus. The most common site is the lower cervical and upper thoracic regions.^{3,4} The sensitivity of radioisotope cisternography is low, but it can detect active leaks. We prefer CT guidance because it is more precise in locating the point of leak and helps assess the quantity and distribution of blood in the epidural space. CT guidance, with better resolution and multiplanar capability, is less likely to be associated with complications compared to conventional fluoroscopy.^{5,6} The interlaminar route with a midline or paramidline approach is relatively safer than transforaminal and anterior cervical intradiscal approaches.

Most of the vital vascular structures are either in the intervertebral foramen or anterior to the spinal cord. It is easier to advance the needle through the interlaminar approach in the prone position.⁵⁻⁷ In cases where the leak is more anterior, the feasibility of the anterior cervical intradiscal approach in the supine position has been demonstrated in the literature. However, its safety and validity have yet to be proven.⁷ The choice of the needle has implications for the final outcome of the EBP procedure. We use an 18G needle for the lower cervical and a 22G needle for the upper cervical regions. Sharp needles are more likely to cause injury compared to blunt needles. The Tuohy epidural needle is a hollow hypodermic needle, slightly curved at the end to help prevent puncture of the dural membrane. It has centimetric graduations to ensure insertion to a predetermined depth. The transparent hub allows visualization of any reflux of blood or CSF. Extra-long needles are available for obese patients. The two most often used techniques for epidural space localization are LOR and hanging drop (HD).^{8,9} The LOR technique is most commonly reported in published trials and is our preferred choice. The needle is inserted with an air-filled syringe attached to it. As soon as the needle enters the epidural space, which has subatmospheric pressure, air is sucked in, confirming arrival in the epidural space.^{8,9} We did not use iodinated contrast media as it may hinder the density of injected blood, and there are concerns about its epileptogenic properties.

Cervical EBP can achieve the primary outcome in a single session compared to multiple sessions of lumbar EBP. It reduces radiation risk costs and spares patients the agony of multiple hospital visits. Selective cervical EBP directly plugs the hole in the dura along with tamponade and increases hydrostatic pressure. Therefore, relief seen in this study was uniform irrespective of the site

of the leak. In contrast, EBP performed away from the site of the leak relies only on the hydrostatic effect. Hence, lumbar EBP is less successful for cervical leaks.¹⁰ The cephalad spread of blood from lumbar EBP reaching the cervical space has been demonstrated, but in most cases, the upward spread is limited to 4–5 vertebral levels.¹¹ The amount of blood used in cervical EBP is less than in lumbar EBP. Typically, 5–8 mL of blood is sufficient in most cases of cervical EBP to achieve optimum results. Lower cervical regions may require a greater quantity compared to upper cervical regions.^{12,13}

Sensations of pain and pressure in the neck were noted during injection; however, no permanent complications were seen in this study. Potential complications include compressive radiculopathy or myelopathy.³ The complication rate is lower with the interlaminar approach compared to the transforaminal approach. Traumatic cervical spinal cord injury, embolic infarction of the spinal cord or brain, and dissection of the vertebral artery are theoretically possible but are more commonly associated with transforaminal access and injection of particulate solutions, such as in epidural steroid injections.^{3,5,6,14–16} Antithrombotic therapy should be withheld prior to EBP in consultation with a cardiologist. Coagulation profile abnormalities should be corrected before the procedure; an INR value >1.5 is advised. We prefer to schedule it as the first case of the day with fumigation of the CT scan gantry room the night before the procedure.

A prophylactic antibiotic dose is advisable. Refractory SIH cases not responding to EBP can be managed by fibrin glue sealant. Very rarely, surgical repair may be required.^{17,18}

CONCLUSION

Computed tomography-guided cervical EBP provides optimal results for patients with SIH due to cervical dural leak. It is feasible, safe, and durable, with a single session often sufficient. CT myelography effectively demonstrates the leak. The LOR technique of epidural needle insertion with an air-filled syringe achieves precise epidural access. However, prospective randomized controlled trials comparing cervical vs lumbar EBP will further validate our observations for better management of patients with SIH due to cervical epidural leaks.

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A Study of Association of Insulin Resistance with Pregnancy-induced Hypertension

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ABSTRACT

Background: Preeclampsia is one of the important causes of maternal and fetal mortality and morbidity. One of the important risk factors for the development of diabetes is insulin resistance (IR).

Aims: To evaluate the association of IR with pregnancy-induced hypertension (PIH) and its severity.

Materials and methods: Data from 70 pregnant females who had completed 20 weeks of gestation and developed PIH were analyzed and compared with 30 appropriate controls. All females underwent measurement of fasting glucose level, fasting insulin level, and blood pressure.

Results: The mean age of the women in the control group was 26.17 years, and in the study group, it was 27.09 years. All females had completed 20 weeks of gestation. Around 86.6% of women in the control group, 54.1% with a variable degree of preeclampsia, and 48.6% of women with eclampsia were at 33–38 weeks of gestation. At the time of sampling, 13.3% of women in the control group, 45.81% of women with preeclampsia, and 51.3% of women with eclampsia were at 26–32 weeks of gestation. The mean IR among the control group was 1.37, in preeclampsia, it was 2.11, and in eclampsia, it was 3.58 with a *p*-value of 0.000, which is very highly significant. In this study, the severity of the disease was found to be directly proportional to IR.

Conclusion: Pregnancy complicated with preeclampsia and eclampsia showed more IR in comparison to pregnant women with normal blood pressure, and this relationship is independent of the age of pregnant women.

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INTRODUCTION

Adaptation to a sedentary lifestyle and high-calorie, saturated fat, and high-sodium-containing food intake has resulted in a higher incidence of hypertension, obesity, and insulin resistance (IR) nowadays. IR is related to a high-risk of cardiovascular disease and various metabolic abnormalities even without obesity and type 2 diabetes.¹

A rapid, cost-effective, and easy method for diagnosing IR is homeostasis model assessment of insulin resistance (HOMA-IR).²

The etiology of pregnancy-induced hypertension (PIH) is multifactorial, and some hypotheses related to etiopathogenesis have been explored and are as follows³:

- Abnormal trophoblastic invasion and placental ischemia.
- Immune-mediated factors.
- Genomic imprinting.
- Nutritional factors.
- Inflammatory and vascular changes due to maternal maladaptation.

It is a dynamic process with central components like vasospasm, increased pressor response, uteroplacental insufficiency, and hematological changes adding to the pathogenesis of PIH. PIH leads to adverse fetal and maternal outcomes like low birth weight, increased risk of cardiovascular mortality, and eclampsia.⁴

AIMS AND OBJECTIVES OF THIS STUDY

- The primary aim of this study was to study the level of IR in patients with preeclampsia and eclampsia.
- The primary goal is to set a correlation between preeclampsia/eclampsia and IR and to evaluate any clinical application of such correlation.

MATERIALS AND METHODS

The study was conducted at LLRM Medical College, Meerut, Uttar Pradesh, India. Patients from the medicine/gynecological outpatient department (OPD) and inpatient department (IPD) were selected randomly into three groups as per the National High Blood Pressure Education Program (NHBPEP) Working Group guidelines.

Inclusion Criteria

Pregnant females aged over 18 years who had completed 20 weeks of gestation and were diagnosed with preeclampsia or eclampsia were included in the study.

Exclusion Criteria

All females with diabetes mellitus, chronic kidney disease (CKD), or autoimmune rheumatoid (AR) disease, undergoing treatment for diabetes mellitus, thyroid

disease, females with acute infections, and pregnant females with preexisting hypertension were excluded from the study.

Measurement of Hypertension

In this study, pregnant women were diagnosed with PIH if two blood pressure readings of 140/90 mm Hg or greater were noted at least 4 hours apart. Blood pressure was measured in the right arm at the level of the heart with an appropriately sized cuff. Before the blood pressure measurement, the patient was made to sit and given a chance to rest for at least 10 minutes.

Detailed histories of any medication for hypertension were taken. The average systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated as the average of three consecutive measurements. Hypertension was defined as per the American College of Obstetricians and Gynecologists (ACOG) guidelines, with SBP of 140 mm Hg and above or DBP of 90 mm Hg and above.

Measurement of Proteinuria

Almost 24-hour urine collection was conducted to diagnose proteinuria, with a value greater than 300 mg/24 hours considered significant.

Insulin Resistance

The HOMA-IR index (insulin $\mu\text{U/mL} \times \text{glycemia mmol/L} / 22.5$) was used to quantify IR. All participants in the study group were subjected to the measurement of body mass index (BMI), hemoglobin A1c (HbA1c), insulin levels, fasting blood sugar, complete hemogram, liver function test (LFT), kidney function test (KFT), fasting lipid profile (FLP), 24-hour urinary protein, and ultrasonography.

All the data was compiled and analyzed by applying appropriate statistical tests.

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OBSERVATIONS AND RESULTS

A total of 100 pregnant women were included in the study, out of which 24 were in the preeclampsia group, 46 in the eclampsia group, and 30 in the control group (normotensive) (Table 1).

The mean age of the women in the control group was 27.16 years, and in the study group, it was 28.05 years, which was comparable. In our study, the maximum number of women were in the age-group between 20 and 30 years in both the study and control groups. In the control group, 50% of women were primigravida and 50% were multipara, while in the study group, 71.4% were primigravida and 28.6% were multipara (Table 2).

Table 3 shows the period of gestation at the time of sampling. Around 86.6% of the women in the control group, 54.1% of women with a variable degree of preeclampsia, and 48.6% of women with eclampsia were in the late trimester at the time of sampling. Around 13.3% of women in the control group, 45.8% of women with preeclampsia, and 51.3% of women with eclampsia were in early gestation at the time of sampling (Table 3).

Table 4 shows that the mean fasting insulin levels among the control group were 5.943 ± 1.515 and 12.794 ± 4.150 $\mu\text{U/mL}$ among

the cases. Statistically significant results with a p -value of ≤ 0.000 were ascertained.

Table 5 shows that the mean fasting insulin levels in preeclampsia patients and eclampsia patients were 8.146 and 15.231 $\mu\text{U/mL}$, respectively, compared to 5.493 $\mu\text{U/mL}$ in the control group. Statistically significant results with a p -value of ≤ 0.001 were secured.

Table 6 shows that the mean fasting blood glucose among cases was 96.62 mg/dL and among controls was 95.85 mg/dL. However, the difference between the two was not statistically significant (p -value 0.7626). The mean IR among the control group was 1.37, in preeclampsia, it was 2.11, and in eclampsia, it was 3.58. When compared to controls, the IR values in both preeclampsia and eclampsia groups were higher and highly significant statistically with a p -value of ≤ 0.001 (Tables 7 and 8).

Table 4: Fasting Insulin levels among cases and controls

	N	Mean	SD
Controls	30	5.943	1.515
Cases	70	12.794	4.150

* p -value ≤ 0.001

Table 5: Fasting insulin levels among various groups

	N	Mean	SD
Controls	30	5.493	1.515
Preeclampsia	24	8.146	2.346
Eclampsia	46	15.231	2.620

* p -value = 0.001

Table 6: Fasting blood glucose (mg/dL) level among cases and controls

	N	Mean	SD
Controls	30	95.85	9.804
Cases	70	96.62	17.634

* p -value = 0.7626

Table 7: Insulin resistance among cases and controls (HOMA-IR)

	N	Mean	SD
Controls	30	1.37	0.917
Cases	70	3.08	0.404

* p -value ≤ 0.001

Table 8: Insulin resistance among various groups (HOMA-IR)

	N	Mean	SD
Control	30	1.37	0.917
Preeclampsia	24	2.11	0.211
Eclampsia	46	3.58	0.126

* p -value ≤ 0.001

DISCUSSION

Preeclampsia and eclampsia are conditions unique to pregnancy and are some of the main causes of mortality and morbidity in both the mother and fetus. Although the precise etiology of preeclampsia and eclampsia remains unclear, generalized vasospasm and endothelial dysfunction constitute the fundamental pathophysiology.^{5,6}

It has been suggested that hyperinsulinemia poses a risk for both coronary artery disease and peripheral vascular disease. This risk results from exposure to elevated insulin levels, which alter endothelial function.⁷

Insulin resistance appears to include both cytotoxic and oxidative stress mechanisms, which are very similar to those thought to induce endothelial dysfunction in preeclampsia, even if the precise mechanism causing endothelial dysfunction is still unknown. Preeclampsia/eclampsia and atherosclerosis, however, have remarkably similar pathophysiology. Thus, compared to pregnant normotensive women, it has been hypothesized that insulin levels are higher in preeclampsia/eclampsia patients.⁸

We have compared the fasting plasma insulin levels of normotensive and preeclampsia/eclampsia patients in this study. According to the current study, the mean level of IR was 1.37 in the normotensive group, 2.11 in the preeclampsia group, and 3.58 in the eclampsia group. We observed that both preeclampsia and eclampsia patients have a significant degree of IR, and that eclampsia patients have higher IR than preeclampsia patients. The results were comparable with those of studies by Sierra-Laguado et al.,⁹ Chen et al.,¹⁰ and Lakshmi Prabha et al.¹¹

The results of our investigation were similar to a study done by Lakshmi Prabha et al.¹¹ on 50 normotensive and 50 preeclamptic women, with IR scores of 5.69 and 12.46, respectively. Additionally, this study showed that in preeclampsia, IR is strongly correlated with SBP. In a study conducted by Chen et al.¹⁰ in 50 normotensive and 50 preeclamptic women showed IR levels of 1.63 vs 4.34, respectively. Statistically significant values of 0.014 were obtained during this study. In another study conducted by Sierra-Laguado et al.,⁹ with 78 normotensive and 39 preeclamptic women. The IR values, as determined by log HOMA-IR, were 0.25 in the study group and 0.15 in the control group; $p = 0.026$. Other research has found that preeclampsia patients have higher fasting insulin levels than normotensive pregnant women. Malek and Kaboudi¹² used 16 normotensive and 16 preeclamptic women in their investigation. Preeclamptic

Table 1: Number of women in the study

Group	Number
Preeclampsia	24
Eclampsia	46
Controls	30
Total	100

Table 2: Parity distribution

Parity		Group		Total
		Control	Study	
Primi	Count	15	50	65
	%	50%	71.4%	65%
Multi	Count	15	20	35
	%	50%	28.6%	35%
Total	Count	30	70	100
	%	100%	100%	100%

p -value = 0.030

Table 3: Period of gestation at the time of sampling

Group	26–32 weeks	33–38 weeks
Control	4 (13.3%)	26 (86.6%)
Preeclampsia	11 (45.8%)	13 (54.1%)
Eclampsia	24 (51.3%)	22 (48.6%)

* p -value ≤ 0.01

women had a higher fasting insulin value of $25.3 \pm 1.4 \mu\text{U/mL}$ compared to normotensive pregnant women ($16.2 \pm 13 \mu\text{U/mL}$; $p \leq 0.01$). A total of 60 normotensive pregnant women and 30 preeclamptic women participated in the study, according to Marandi et al.¹³ The fasting insulin values were 8.92 ± 4.4 vs $11.44 \pm 6.72 \mu\text{U/mL}$, respectively, with a p -value of 0.005. When comparing preeclampsia to normotensive pregnancy, prior research has shown greater fasting insulin levels and IR. The current study's supportive findings reinforce this observation. In our study, the mean fasting plasma insulin levels in preeclampsia, eclampsia, and control group patients were 8.146, 15.213, and 5.493 $\mu\text{U/mL}$, respectively and the p -value of ≤ 0.001 was found to be highly significant. Mean value of IR in preeclampsia, eclampsia, and control group patients was 2.11, 3.5, and 1.37, respectively. This pattern showed IR to be directly proportional to the severity of the disease as the highest IR was found in the eclampsia group. Higher IR in women with eclampsia is indicative of a direct correlation between the severity of the disease and IR.

AGE AND GESTATION

Insulin resistance, patient age, and gestational age did not significantly correlate in this investigation.

The study group's mean age was 27.16 years and the control group's age was 28.05 years, with the difference being

statistically insignificant. However, the control group and study group had statistically significant mean gestational ages of 35.06 and 32.5 weeks, respectively. While no research has been conducted on the relationship between IR values and the severity of the disease, several studies have found a strong positive correlation between the two. Patients with PIH had higher fasting insulin levels than normotensive pregnant women, with statistically significant p -values.

CONCLUSION

According to the current study, pregnant women with preeclampsia and eclampsia typically exhibit higher levels of IR than normotensive pregnant women. The study also highlighted the age-independent nature of the association between PIH and IR. The current investigation demonstrated a direct relationship between IR and PIH severity.

Recommendations

- Future studies with a large sample size are needed in patients with PIH to further study IR in such patients.
- Regular screening of preeclamptic women for diabetes and vascular disorders is highly recommended.

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Metformin Hydrochloride 500/850/1000 mg SR + Glimepiride 0.5/1/2/3/4 mg

Metformin Hydrochloride 500 mg SR + Glimepiride 1 mg

Metformin Hydrochloride 850 mg SR + Glimepiride 3 mg

Metformin Hydrochloride 850 mg SR + Glimepiride 2 mg

Metformin Hydrochloride 1000 mg SR + Glimepiride 4 mg

Metformin Hydrochloride 1000 mg SR + Glimepiride 3 mg

Methanolic Hydrochloride 500 mg CB - Glucoside 0.5 mg

Metformin Hydrochloride 1000 mg SR + Glimepiride 0.5 mg

Metformin Hydrochloride 1000 mg SB + Glimepiride 1 mg

Metformin Hydrochloride 1000 mg SR + Glimepiride 2 mg

Additional information is available on request.
Last updated: March 13, 2023

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Indication: As an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 Diabetes Mellitus (T2DM).

Recommended Dosage: As directed by the Physician

Method of Administration: Oral

Warnings and Precautions: Dapagliflozin, Metformin and Glimepiride should not be used in patients with type 1 diabetes and must not be used for the treatment of diabetic ketoacidosis. **Lactic acidosis** - Lactic acidosis, a rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. **Hypotension** - Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating dapagliflozin particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients, or patients on loop diuretics. Before initiating dapagliflozin in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy. **Genital Mycotic Infections** - Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately. **Hypoglycemia** - Patients receiving insulin and insulin secretagogues (e.g., sulfonylurea) may be at risk for hypoglycemia. Therefore, a reduction in the dose of the sulphonylurea or insulin may be necessary

Precautions for use

Pregnancy: Limited data on Dapagliflozin, Glimepiride & Metformin Tablets use during pregnancy. Advise patients to inform their healthcare provider if pregnant or planning pregnancy before initiating treatment.

Nursing Mothers: Udaapa Gold is not recommended in breastfeeding. Hence, if you are breastfeeding, inform your doctor if you are breastfeeding or planning to breastfeed.

Pediatric Use: The safety and effectiveness of Udaapa Gold in pediatric patients under 18 years of age have not been established.

Renal Impairment: Dapagliflozin - Use of dapagliflozin is not recommended when eGFR is less than 45 mL/min/1.73 m²

Glimepiride: To minimize the risk of hypoglycemia, the recommended starting dose of glimepiride is 1 mg daily for all patients with type 2 diabetes and renal impairment.

Contraindications: Udaapa Gold is contraindicated in patients with: Severe renal impairment (eGFR below 30 mL/min/1.73 m²), end stage renal disease or patients on dialysis; History of a serious hypersensitivity reaction to any of the excipients of this Tablet, dapagliflozin, such as anaphylactic reactions or angioedema, or hypersensitivity to metformin HCl, Sulfonamide derivatives, such as glimepiride, other sulfonylureas, other sulfonamides; Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin; Hepatic insufficiency; Acute alcohol intoxication, alcoholism; Lactation.

For Additional Information/full prescribing information, please write to us: USV Private Limited, Arvind Vitthal Gandhi Chowk, B.S.D Marg, Govandi, Mumbai - 400088
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10/500 XR | 10/1000 XR | 5/500 XR

CVD: Cardiovascular Disease; HF: Heart Failure; CKD: Chronic Kidney Disease; FDC: Fixed dose combination; n: Number of patients.
¹ L. Ravikumar et al. Cardiol Cardiovasc Med 2023; 7:141-144. # PubMed and Google Scholar on 21st March 2024.
² Singh M et al. Endocr Pract. 2022 Jul;28(7):1009-1016.

Abridged Prescribing Information

UDAPA-S

Dapagliflozin and Sitagliptin Tablets

Composition: Each Film Coated Tablet Contains: Dapagliflozin Propanediol Monohydrate eq. to Dapagliflozin (10 mg) Sitagliptin Phosphate Monohydrate IP eq. to Sitagliptin (100 mg). **Indications:** For the treatment of type 2 diabetes mellitus inadequately controlled on Metformin monotherapy. **Recommended Dosage:** As directed by the physician. **Method of Administration:** Oral. **Adverse Reactions:** Female genital mycotic infections, nasopharyngitis, and urinary tract infections are most common adverse reactions associated with dapagliflozin. While, upper respiratory tract infection, nasopharyngitis, and headache are most common adverse reactions associated with sitagliptin. **Warnings and Precautions:** **Risk of Volume Depletion in Elderly:** Before initiating Dapagliflozin and Sitagliptin, assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. **Ketoacidosis in Patients with Diabetes Mellitus:** Assess patients who present with signs and symptoms of metabolic acidosis for ketoadicosis regardless of blood glucose level. If suspected, discontinue UDAPA-S, evaluate and treat promptly. Before initiating UDAPA-S, consider risk factors for ketoacidosis. Patients on UDAPA-S may require monitoring and temporary discontinuation of therapy in SGLT2 inhibitors known to predispose to ketoacidosis. **Thrombosis and Pyelonephritis:** Evaluate for signs and symptoms of urinary tract infections and treat promptly. If indicated. **Hypoglycemia:** Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with Dapagliflozin and Sitagliptin. **Neck Stiffness and Facial Swelling:** Assess patients who present with pain or tenderness, erythema, or swelling in the genital or perineal area, a sore with fever or malaise. If suspected, initiate prompt treatment. **Genital Mycotic Infections:** Monitor and treat if indicated. **Contraindications:** Patients with a history of hypersensitivity reaction to the active substance or to any of the excipients. In patients with varying degrees of renal impairment, adjusting the dosage is advised based on the severity of the condition. Prohibited medications include strong CYP2C8 inhibitors, drugs increasing/decreasing hypoglycemic action, drugs known to cause QT prolongation, or other oral hypoglycemic agents other than study medications.

Updated on 20th March 2024

Phadke U et al. Chron Diabetes Res Pract. 2024;3:37-52.

Abridged Prescribing Information

UDAPA-M

Composition: Each Film Coated Tablet Contains: Dapagliflozin (5/10 mg) + Metformin Hydrochloride IP (500/1000 mg) (As Extended Release). **Indications:** For the treatment of type 2 diabetes mellitus. **Recommended Dosage:** As directed by the physician. **Method of Administration:** Oral. **Adverse Reactions:** Female genital mycotic infections, nasopharyngitis, urinary tract infections, diarrhea, and headache. Other adverse reactions that occurred at a <2% higher incidence are influenza, nausea, back pain, dizziness, cough, and urination discomfort. **Warnings and Precautions:** **Lactic Acidosis:** In UDAPA-M treated patients with a diagnosis of strong risk factors of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin. **Hypoglycemia:** Dapagliflozin causes intracellular glucose correction. Symptomatic hypoglycemia can occur after initiating dapagliflozin, particularly in patients with impaired renal function, elderly patients, or patients on loop diuretics. **Ketoacidosis:** Patients treated with UDAPA-M who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoadicosis regardless of blood glucose levels as ketoadicosis associated with UDAPA-M may be present even if blood glucose levels are less than 250 mg/dL. **Acute Kidney Injury:** Renal function should be evaluated prior to initiation of UDAPA-M and monitored periodically thereafter. Use of UDAPA-M is not recommended when the eGFR is less than 45 mL/min/1.73 m². UDAPA-M is contraindicated in patients with an eGFR below 30 mL/min/1.73 m². **Unusual and Pyelonephritis:** Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. **Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. UDAPA-M may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. **Neck Stiffness and Facial Swelling:** Assess patients who present with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, initiate prompt treatment. **Genital Mycotic Infections:** Monitor and treat if indicated. **Contraindications:** Patients with severe renal impairment or with eGFR <45 mL/min/1.73 m². History of serious hypersensitivity reaction to metformin or dapagliflozin, acute/chronic metabolic acidosis.

USV Private Limited, Arvind Vitthal Gandhi Chowk, B.S.D Marg, Govandi, Mumbai - 400088 Updated on 20th March 2024



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Haplotype-based Analysis of 6q24-25 for Association with Rheumatoid Arthritis

Liyakat Ali Gauri^{1*}, Ummed Singh², Subhita Choudhary³, Ravidutt⁴, Nadeem Liyakat⁵, Ambreen Liyakat⁶

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a multisystem inflammatory disorder. Family history of RA is an important risk factor as it is strongly linked with the inherited HLA-DR4 (most specifically DR0401 and 0404). The aim of this study is to conduct the haplotype-based analysis of 6q24-25 and evaluate its association with RA.

Materials and methods: Case-control study which included all patients attending outpatient department (OPD) at Sardar Patel Medical College, Bikaner, Rajasthan and volunteers (only for blood samples). Blood samples of patients were collected. As per inclusion and exclusion criteria, a total of 103 subjects lacking history of disease were included under control group, while 48 cases were recruited as study group. Any significant departure of genotype distribution is evaluated using Hardy-Weinberg equilibrium by Chi-squared test.

Results: Case-control association was done using data from 151 genomic deoxyribonucleic acid (DNA) samples, which were allele typed. RA is significantly associated with >305bp (the longer allele of D6S1053 corresponding to 11 tetramer (GATA) repeats. Differences in individual allele frequency within the control population and RA cases were observed which shows the bimodal distribution of the 10 alleles of D6S1053 short tandem repeat (STR) marker observed in the cohort tested by us. No significant association with the risk for RA is shown by the allele for D6S1053 and the mutant allele 118G. Similarly, OPRM1 gene's haplotype frequency for rs1799972 for D6S1053 allele has not shown any added risk with the wild allele 17C compared to controls. The polymorphism showed that 17T depicted a higher odds ratio of 1.3 with an associated risk of 1.15 in the presence of longer allele of D6S1053. Significance observed between short allele and RA was lost when haplotype analysis for the two genes were taken together. There was no difference observed between the short or long allele and 17T/C while there was a significant difference observed when haplotype frequencies were compared with alleles of A118G and the long and short allele of D6S1053.

Conclusion: We concluded that the short allele of μ -opioid receptor (MOR) gene offered a clear protection from a risk of getting RA.

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INTRODUCTION

Rheumatoid arthritis (RA) is a multisystem inflammatory disorder leading to articular cartilage destruction and subsequent joint ankylosis.¹ Although the exact etiology of RA is unknown, autoimmunity is key to its chronic course and progression.²

The incidence of RA is 3 in 10,000/year while prevalence rate of RA is 1%. Onset is unusual before 15 years of age. Incidence of RA rises as the age progresses until age of 80 years. Women are three to five times more commonly affected than men³ and smokers are affected four times more than nonsmokers. Prevalence rate is 2–3% among first-degree relatives and has genetic concordance of approximately 15–20% among monozygotic twins.⁴

Family history is a key risk factor as RA is strongly associated with HLA-DR4 (DR0401 and 0404).⁵ RA may very rarely have a spontaneous remission; the natural course of the disease consists of progressive damage

to joint structures, leading to deformities and disability.⁶

Currently, many immunopathogenetic study models for genes like MIF, CTLA4, PADI4, and SLC22A4 are under further research. Rapidly advancing pharmacogenetics promises individualized therapies as per patient's genetic profile.⁷

Genetic variation in μ -opioid receptors (MORs) can alter behavior by modulating the expression of the endogenous opioid system. A common single nucleotide polymorphism (SNP) in the MOR gene OPRM1 A118G can result in an amino acid exchange at a glycosylation site of the MOR.⁸

Many studies on substance abuse genetics have focused on the μ opiate receptors. Two polymorphisms have received the most attention involving exon 1: C17T, resulting in a valine substitution in place of alanine, and A118G, resulting in an aspartic acid substitution in place of asparagine.^{9–11} The frequency of variability in the minor T allele at position 17 in different groups of

population ranges from about 1% in white¹² and Eastern Asian cohorts¹³ to 15–20% in cohorts of African-Americans¹⁴ or Indians of northern area.¹⁵ Kapur et al. in a cohort study on North Indian men observed the presence of TT genotype in 12 cases of opiate dependence with no control being involved.¹⁵ The aim of current study is to identify haplotype oriented analysis of 6q24-25 and association of RA with it.

MATERIALS AND METHODS

A case-control study was conducted, including all patients attending the outpatient department (OPD) at Sardar Patel Medical College, Bikaner, Rajasthan. Volunteers for blood samples were age and gender matched. Blood samples from both case and control group volunteers were collected after obtaining informed consent (either from the patients or their guardians) following a proper explanation of the study's objectives. The study included 103 subjects without any disease history as controls and 48 subjects with the disease as cases, considering the predecided inclusion and exclusion criteria as mentioned.

Inclusion Criteria

All patients suffering from RA with age of 16 years following latest diagnostic criterion.

Exclusion Criteria

- All cases of RA who are seriously ill with other associated illnesses like hepatic and renal failure, malignancies, etc.

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- Rheumatoid arthritis patients with associated another connective tissue disease (CTD) like scleroderma, mixed connective tissue disease (MCTD), etc.

Procedure: A detailed clinical history and family history of the patients was gathered as per decided proforma.

Diagnostic Criteria

The 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR)¹⁶ following were the criteria of classification of RA:

Classification criteria for RA		Score
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (metacarpophalangeal, proximal interphalangeal, thumb interphalangeal, metatarsophalangeal, wrists)	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative rheumatoid factor (RF) and negative anti-cyclic citrullinated peptide antibodies (ACPA)	0
	Low-positive RF or low-positive ACPA (<3 times ULN)	2
	High-positive RF or high-positive ACPA (>3 times ULN)	3
Acute-phase reactants	Normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR)	0
	Abnormal CRP or abnormal ESR	1
Symptom duration	<6 weeks	0
	>6 weeks	1

Blood Sampling Procedure

Venous blood samples were collected from patients and the control group using disposable sterile syringes in prelabeled vials and sent to the lab. After receiving the samples in the lab, serum was separated from the blood using centrifugation in a plain vial and stored at -20°C until it was sent to the genetic study lab.

Deoxyribonucleic Acid Isolation

Deoxyribonucleic acid (DNA) is isolated as per standard isolation protocol of DNA (Kapur

et al., 2007)¹⁵ and quantification is done as per ultraviolet spectroscopy. DNA is qualified on (0.8%) agarose.

Polymerase Chain Reaction for D6S1053

Blood samples from RA subjects and controls were processed in the genomics lab at Birla Institute of Technology and Science (BITS) Pilani. Polymerase chain reaction (PCR) for the D6S1053 short tandem repeat (STR) marker was carried out at BITS Pilani, and the results are presented in the results section. A total of 151 samples were studied during the course of this study. A PCR reaction (10 μL) was set using specific primers for amplifying D6S1053 markers and DNA.

D6S1053 FW	5'-TATTCAAAGGCAGCAAAGC-3'
D6S1053 RW	5'-GCTTGCAGACAGCCTATTGT-3'

Reagent	Volume
DNA	3 μL
Master mix	2.5 μL
Taq	0.10 μL
Water	4.4 μL
Total	10 μL

Polymerase chain reaction was run using Veriti cyclor and the PCR conditions used are listed below:

PCR conditions	Temperature and time
Denaturation	95°C —5'
Denaturation	95°C —45"
Annealing	58°C — $\Delta 0.1^{\circ}\text{C}$ —30"
Extension	72°C —30"
Cycles	40 cycles
Final extension	72°C —6'

Gel electrophoresis for analyzing the PCR product and allele-typing: 10% polyacrylamide gel electrophoresis gel was cast to separate the amplified PCR products and identify the allele based on the size of the fragment obtained.

Reagent	Volume
30% bisacrylamide	3.3 mL
5X TBE	2 mL
10% APS	100 μL
TEMED	10 μL
Water	4.59 mL
Total reaction volume	10 mL

TBE, tri-borate EDTA; APS, ammonium persulfate; TEMED, tetramethyl ethylene diamine

Horizontal electrophoresis was carried out at approximately 75V for 1.5 hours. DNA fragments were detected using ethidium bromide stain and visualized on a ultraviolet

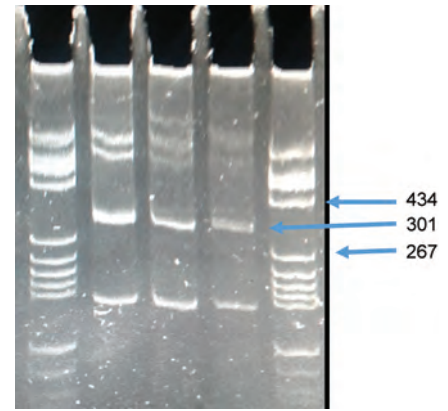


Fig. 1: 10% polyacrylamide gel electrophoresis gel for separating D6S1053 gene product

transilluminator and the resultant gel picture of separating D6S1053 gene products was obtained and captured as shown in Figure 1.

Statistical Analysis

Significant departure of genotype distribution from Hardy–Weinberg equilibrium was examined using the Chi-squared test. For the genotype of both cases and control groups, risk for short (<305 bp), GATA₁₃ repeats, and long allele (>305 bp) of the D6S1053 STR marker was studied. Genotype frequency comparison was done using the chi-square test, while allelic frequency comparison was done using Fisher's exact test.

RESULTS

Case–control association was done using data from 151 genomic DNA samples which were allele typed. Table 1 provides the allele distribution of D6S1053 in both case and control subjects. RA is significantly associated with >305bp (the longer allele of D6S1053 corresponding to 11 tetramer (GATA) repeats. Differences in individual allele frequency within the control population and RA cases were observed (Tables 1 and 2) which shows the bimodal distribution of the 10 alleles of D6S1053 STR marker observed in the cohort tested by us.

Cases and controls were compared for haplotype distribution frequency. The short allele present with 118A allele showed a 1.5 times greater risk with a risk ratio of 1.2. The mutant allele 118G along with the allele for D6S1053 showed no significant risk association with R. Similarly, compared to the control group, no added risk was observed with the wild allele 17C of haplotype frequency for rs1799972 of the OPRM1 gene with alleles for D6S1053. The polymorphism showed that 17T depicted a higher odds

ratio of 1.3 with an associated risk of 1.15 in the presence of the longer allele of D6S1053 (Tables 3 and 4). The significance observed between the short allele and RA was lost when haplotype analysis for the two genes were taken together (Table 5). There was no difference observed between the 17T/C alleles and the short or long allele. However, a significant difference was observed when haplotype frequencies were compared with alleles of A118G and the long and short allele of D6S1053 (Table 6).

DISCUSSION

Genetic variation in MORs can alter behavior by modulating the expression of the endogenous opioid system. A common SNP in the MOR gene OPRM1 A118G can result in an amino acid exchange at a glycosylation site of the MOR.⁸

In our study, case-control association was done using data from 151 genomic DNA samples which were allele typed. Differences in individual allele frequency within the control population and RA cases were observed (Table 1) which shows the bimodal distribution of the 10 alleles of D6S1053 STR marker observed in the cohort tested by us.

In a study conducted by Jawaheer et al.,¹⁷ evidence for linkage at 1p13 (D1S1631), 6p21.3, and 18q21 (D18S858) (with $p < 0.05$) was observed, and this evidence is replicated in the current study. Combined analysis of both datasets, including 512 families, observed evidence of linkage at the level of $p < 0.005$ at 1p13 (D1S1631), 1q43 (D1S235), 6q21 (D6S2410), 10q21 (D10S1221), 12q12 (D12S398), 17p13 (D17S1298), and 18q21 (D18S858). Additionally, linkage at HLA was confirmed with $p < 5 \times 10^{-12}$.

Another study conducted by Scherer et al.¹⁸ showed that in ACPA-positive patients polymorphisms at rs675520 and rs9376293 were linked with radiographic severity grading of joint damage.

In our present study, cases and controls were compared for haplotype distribution frequency. The short allele present with 118A allele showed a 1.5 times greater risk with a risk ratio of 1.2. The mutant allele 118G along with the allele for D6S1053 showed no significant risk association. Similarly, compared to the control group, no added risk was observed with the wild allele 17C of haplotype frequency for rs1799972 of the OPRM1 gene with alleles for D6S1053. The polymorphism showed that 17T depicted a higher odds ratio of 1.3 with an associated risk of 1.15 in the presence of the longer allele of D6S1053.

In our study, haplotype analysis for MOR and D6S1053 genes in control and

Table 1: Allele frequency of the D6S1053 polymorphism

Amplicon size	(GATA)n repeats	Allele	Allele frequency n (%)	
			RA cases N = 48	Control N = 103
289	7	1	3 (0.01)	13 (0.06)
293	8	2	0 (0)	12 (0.05)
297	9	3	12 (0.04)	20 (0.09)
301	10	4	15 (0.05)	30 (0.12)
305	11	5	8 (0.03)	38 (0.17)
309	12	6	6 (0.02)	24 (0.09)
313	13	7	4 (0.01)	14 (0.06)
317	14	8	24 (0.08)	18 (0.08)
321	15	9	14 (0.05)	21 (0.12)
325	16	10	10 (0.02)	16 (0.06)

Table 2: Bimodal distribution: allele frequency n (%)

Amplicon size	(GATA)n repeats	Allele	Allele frequency n (%)	
			RA cases N = 48	Control N = 103
<305	<11/<11	Shorter	17 (35)	49 (48)
>305	>11/>11	Longer	31 (65)	54 (52)

Table 3: Genotype frequency of the short and long allele of D6S1053

	N	<11/<11	<11/>11	>11/>11
Control	103	49	13	41
Cases	48	17	4	27

Table 4: Allele frequency of short and long allele of DS61053

	N	2N	<11	>11
Control	103	206	111 (0.538)	95 (0.462)
Cases	48	96	38 (0.395)	58 (0.605)

Chi-square = 3.62; $p = 0.02$; odds ratio = 0.5; CI 95% = 0.3–0.9; risk ratio = 0.76; CI 95% = 0.5–0.9; $p = 0.02$

Table 5: Haplotype analysis for MOR and D6S1053 genes in control and test patients

	<11/17C	>11/17C
Cases	83	75
Control	44	40
	<11/17T	>11/17T
Cases	17	25
Control	56	60

For <11/17C and >11/17C, Chi-square = 3.62; $p = 0.92$; odds ratio = 0.994; CI 95% = 0.585–1.69; risk ratio = 0.996; CI 95% = 0.755–1.32; Pfisher = 1.0; for <11/17T and >11/17T, $p = 0.49$; odds ratio = 1.3; CI 95% = 0.671–2.81; risk ratio = 1.15; CI 95% = 0.84–1.56; Pfisher = 0.47

Table 6: Haplotype analysis for MOR and D6S1053 genes in control and test patients

	<11/118A	>11/118A
Cases	43	64
Control	82	80
	<11/118G	>11/118G
Cases	57	36
Control	18	20

For <11/118A and >11/118A, Chi-square = 3.62; $p = 0.12$; odds ratio = 1.5; CI 95% = 0.93–2.5; risk ratio = 1.2; CI 95% = 0.97–1.50; Pfisher = 0.06; for <11/118G and >11/118G, $p = 0.2$; odds ratio = 0.57; CI 95% = 0.26–1.2; risk ratio = 0.74; CI 95% = 0.49–1.09; Pfisher = 0.17

cases for <11/17C and >11/17C showed Chi-square = 0.01, $p = 0.92$, odds ratio = 0.994, CI 95% = 0.585–1.69, risk ratio = 0.996, CI 95% = 0.755–1.32; Pfisher = 1.0. And also for <11/17T and >11/17T, the following observations were made, Chi-square = 0.47 with odds ratio of 1 and p -value of 0.49, CI 95% = 0.671–2.81, risk ratio = 1.15, CI 95% = 0.84–1.56; Pfisher = 0.47.

Also it was noted in our present study that, haplotype analysis for MOR and D6S1053 genes in control and cases for <11/118A and >11/118A showed Chi-square = 2.41, $p = 0.12$, odds ratio = 1.5, CI 95% = 0.93–2.5, risk ratio = 1.2, CI 95% = 0.97–1.50; Pfisher = 0.06, and those for <11/118G and >11/118G showed Chi-square = 1.16, $p = 0.2$, odds ratio of 0.57 and CI 95% = 0.26–1.2, risk ratio = 0.74, CI 95% = 0.49–1.09; Pfisher = 0.17.

Lack of associations in a particular population of specific ancestries can be illustrated by a very low allele frequency or by the monomorphism of the allele locus. In general, many of the susceptibility loci associated with RA are shared across diverse populations.^{19,20}

In our present study, no difference was observed between the short or long allele and 17T/C. However, a significant difference was observed when haplotype frequencies were compared with alleles of A118G and the long and short allele of D6S1053.

CONCLUSION

We concluded that the short allele of the MOR gene, irrespective of being wild type or mutant variant, offered protection from

the risk of developing RA. However, analysis of the long allele along with A118G showed a marginally increased risk of RA. To further confirm these findings, a large cohort study is needed. It was also observed that the long and short alleles differed in the folding of the ribonucleic acid (RNA) synthesized, with the short allele having lower free energy for folding, making it more stable. This stability could be imparting the protective role of this allele, as observed in the cohort of patients studied.

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Medical Negligence by Postgraduate Students and Residents: The Liability Trail

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ABSTRACT

Postgraduate students or physicians in training are bound to make mistakes. In medical negligence litigation involving the postgraduate students, the supervising faculty members as well as the hospital where the alleged act has occurred could also be found liable. In this review article, the applicable legal principles and a brief summary of the case laws are presented.

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All medical professionals, whether they are postgraduate students, nurses, full-fledged specialists, or medical college faculty, are professionally liable for their respective performances. However, when it comes to medical negligence by the postgraduate students or physicians in training, a few pertinent questions arise—are postgraduate students considered mere students or specialists? Is it fair to hold the physicians in training liable as they are bound to make mistakes? Can anyone else be liable for the medical negligence of the postgraduate students? This review article will address these pertinent legal issues and focus on the applicable legal principles, along with an overview of various case laws pertaining to medical negligence by postgraduate students, mainly from Western jurisprudence. The authors are hopeful that this write-up will enlighten postgraduate students and their teachers regarding their duty toward patients and the legal implications of their negligent acts.

MEDICAL NEGLIGENCE/ PROFESSIONAL NEGLIGENCE/ MEDICAL MALPRACTICE

The exact definition of medical negligence is not available in any of the enacted Indian laws, and the legal framework for medical negligence in India is primarily based on tort law. It is described as the lack of a reasonable degree of care and skill or negligence on the part of a medical practitioner during his professional practice, which would result in bodily harm, financial loss, physical or mental ill health, or death of the patient. In the Laxman Balakrishna Joshi case, the honorable Supreme Court of India laid down the basic features of medical negligence in India, as given below.¹

In order to make the doctors liable for negligence, the following legal elements

need to be proved by the patients or the plaintiffs in the court of law:

- The doctor should owe the duty of care to the patient; in other words, there has to be an established legal doctor–patient relationship.
- Having established the duty of care, there needs to be a breach of such duty of care by the medical professional.
- Further, this breach of duty of care should result in injury.
- If the patient (plaintiff) succeeds in proving all these, only then does the medical professional become liable for medical negligence and have to pay the damages. Thus, the onus of proving negligence or the burden of proof clearly lies with the patient (plaintiff) in most cases.

The duty of care further includes:

- Duty of care in deciding whether to undertake the case or not.
- Duty of care in deciding what treatment to give.
- Duty of care in the actual administration of that treatment.

TYPES OF MEDICAL NEGLIGENCE IN MEDICAL PRACTICE

The lack of reasonable care and skill or willful negligence on the part of a doctor in respect of acceptance of a patient, history taking, examination, diagnosis, investigation, treatment—medical, surgical, anesthesia, and childbirth, or any other branch of medicine, or even the follow-up of the patients resulting in any injury or damage to the patient, would amount to medical negligence. Subjecting the patient to medical or surgical treatment without valid consent would also fall under the ambit of medical negligence.

REASONABLE STANDARD OF CARE OR STANDARD OF CARE

This is the yardstick, measure, or benchmark by which the court evaluates the conduct of the medical professional in an alleged case of medical negligence and is called the “standard of care.” Thus, the court compares the current doctor’s conduct with that of the “standard of care” and decides the case.^{1,2} The standard of care as prescribed by the Honorable Supreme Court of India in Dr Laxman Joshi’s case¹ is as follows.

“The practitioner must bring to his task a reasonable degree of skill and knowledge and must exercise a reasonable degree of care. Neither the very highest nor a very low degree of care (i.e., of an average medical professional) and competency judged in light of the particular circumstances of each case is what the law requires.”

If the alleged act of the medical professional falls below the reasonable standard of care, then he is liable for negligence. Thus, the plaintiff (patient in case of medical negligence) must first prove the standard of care applicable in the case and then show that it was breached by the physician to succeed in a professional liability lawsuit.

STANDARD OF CARE APPLICABLE FOR THE POSTGRADUATE STUDENTS

As discussed above, the complainants need to prove that the postgraduate doctor did not act as per the standard of care. An extensive search in legal and medical literature did not yield any case laws pertaining to medical negligence by postgraduate students or residents in India and also the standard of

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care applicable to them. Hence, the authors are forced to cite case laws from Western jurisprudence. Unfortunately, the standard of care for postgraduate students is not preset even in the Western world and is evolving over the years, differing from case to case³ as depicted in the case laws presented here.

EXAMPLES OF CASES REPRESENTING DIFFERENT STANDARDS OF CARE APPLIED TO THE POSTGRADUATE STUDENTS

Standard of Care is Same as That of Another Resident of Similar Skill and Training Level

Rush v Akron General Hospital, 171 NE2d 378, 381 (Ohio Ct App 1957)⁴

In this case, a junior resident treated a patient with glass door-related injuries, and a few pieces of glass were left behind in the wound. The patient sued him for failing to remove all the glass pieces embedded in the wound. The court dismissed the case with the opinion that the standard of care for a junior resident cannot be that of a fully qualified surgeon or any emergency care physician. It is sufficient if the junior resident possesses the same standard as that of a resident with the same level of training.

Standard of Care of a General Practitioner Working in the Emergency Department

Jenkins v Clark, 454 NE2d 541; Ohio Ct App (1982)⁵

In this case, the resident failed to identify myocardial infarction in the electrocardiogram done, resulting in the death of the patient. The court held that residents in the emergency department (ED) should have the standard of care of a general practitioner working in the ED and held the resident liable for negligence in Ohio, United States of America.

Standard of Care of a Specialist When the Resident is Practicing within That Specialty

Pratt v Stein, 444 A.2d 674 (Pa. Super. 1982)⁶

Over here, a 2nd-year resident was held liable for negligence when he prescribed a toxic dose of neomycin resulting in deafness in the patient. The court applied the standard of care to a specialist.

Centman v Cobb, 581 N.E.2d 1286 (Ind. Ct. App. 1991)⁷

In this case, a 2nd-year resident was alleged to have caused lithium

poisoning by prescribing a very high dose. The court held him liable with the contention that when the resident delivers patient care, their conduct should be held to the same standard as that of a specialist physician.

Gonzalez v St John Hospital & Medical Center, 739 NW2d 392 (Mich Ct App 2007)⁸

In this case, the court held a 3rd-year surgery resident liable for negligence when he failed to diagnose intraabdominal hemorrhage, which led to the death of the patient. The court reasoned that the standard of a specialist should be applied to all those who limit their training to a particular branch of medicine. However, the court did not differentiate between the years of training.

Standard of Care of a General Practitioner

Bahr v Harper-Grace Hospitals, 497 NW2d 526 (Mich Ct App 1993)⁹

In this case, a Michigan court, while reviewing an appeal in which a resident who had managed a patient with pneumonia and suffered a brain injury following a cardiac arrest, held that the resident was not liable for negligence. The court reasoned that the resident falls under the standard of care offered by a general physician and not that of a specialist.

Clark v University Hospital, 914 A.2d 838 (N J Super 2006)¹⁰

In this case, a resident had failed to reinsert a nasogastric tube, resulting in the patient's aspiration. The Superior Court of New Jersey held the resident not liable for negligence, with the opinion that the standard of care to be applied to the resident was that of a general practitioner.

Standard of Care is Higher than That of General Practitioner and Lesser than That of a Specialist

Jistarri v Nappi, 549 A2d 210 (Pa Super Ct. 1988)¹¹

In this case, an orthopedic resident was held liable for negligence when a tight wrist cast caused injury to a patient. The court held that the standard of care offered by the resident should be higher than that of a general practitioner and somewhat less than that of a qualified orthopedic specialist. However, the ruling was considered nonspecific and lacked precedential value for future litigations.

Thus, the medical negligence liability of postgraduate students/residents in training remains unsettled, especially regarding the applicable standard of care.

LIABILITY OF THE SUPERVISING PHYSICIANS/TEACHING FACULTY

When medical students make mistakes in hospitals, they may be held liable for damages if patients are harmed by their negligence. Along with them, their supervising physicians/teaching faculty and the hospitals where they work may also be held liable for the medical negligence that has occurred. The legal principles by which the supervising physicians/teaching faculty and the hospitals are held liable for the negligent acts of their students are highlighted here. However, there are no codified laws in place to make them liable, except for well-accepted legal principles or doctrines. The liability of the supervising specialists or teaching faculty members arises from the following legal principles and obligations.

- Vicarious liability.
- Direct liability arises from the breach of duty of care in the form of failure to supervise.

Vicarious Liability

Every person is legally responsible or liable for their own acts of commission or omission. However, there could be situations where a third party bears the liability for another person's acts of commission or omission.^{12,13} This liability is based on the type of relationship between the two parties. For example, an employer is legally held responsible for the negligent acts of their employees while acting within the scope of their employment. However, the actual perpetrator cannot escape liability just because their employer is vicariously liable. Vicarious liability is a type of indirect legal responsibility for injury caused.^{14,15}

Vicarious liability is based on two doctrines:^{12,13}

- Qui facit per alium facit per se.
- Respondeat superior (respondent superior).

Qui facit per alium facit per se means he who does an act through another is deemed to have done it himself, and respondeat superior (Latin) translates to "let the master answer," "look to the man higher up," or "let the superior respond."

In the healthcare context, vicarious liability of hospitals and physicians implies that they may be responsible for the negligent acts of their subordinates. The doctrine of respondeat superior may be applied to the physician-hospital and/or physician-assistant sub-contexts. The overall application of the doctrine of respondeat superior implies

that superiors are responsible for the acts of those who are answerable to them.¹² Thus, in medical negligence litigations, primarily the postgraduate students and then the attending physicians or specialists are vicariously held liable for wrongdoing toward the patients.¹⁴

Proving Vicarious Liability and Negligence

The plaintiff/patient has to prove that the postgraduate student was acting as per the instructions of the attending physician/specialist on call and that the student was under his control. The plaintiff also needs to prove that the attending physician owed a duty of care to him and that there was a breach of that duty, which resulted in damages as a direct consequence of the breach. However, if the postgraduate acts beyond the course and scope of his training, then the doctrine may not be applicable.¹²

Direct Liability or Failure to Supervise

In addition to vicarious liability or indirect liability, attending physicians could also have direct liability arising from the breach of duty of care in the form of failure to supervise the postgraduate students/residents.¹⁴ However, this liability is not automatically assigned to the supervising physician when their student makes mistakes. The patient/plaintiff needs to prove that the attending physician was careless or negligent in monitoring, supervising, or controlling the resident's conduct.⁹

Liability of the Hospitals or Medical Training Institutions

The hospitals or medical training institutions become vicariously liable for the negligence done by all their employees, whether they are postgraduate students, specialists, or any other person involved in patient care, irrespective of their status as permanent, temporary, visiting, or in any other capacity.¹⁶ This liability arises from the grounds of respondent superior for its employees. The postgraduate students bring financial benefits to the hospitals through their involvement in patient care. The hospitals also have control over all their employees in the form of appointment, control of their performances, and ownership of property, machinery, and medical equipment used in patient care.¹² Hospitals draw patients to their facilities through their reputation, advertisements, etc., and these factors also contribute to their vicarious liability for the acts of their employees.

Liability of the Medical Superintendents, Deans, Principals

Medical colleges become liable because they are responsible for the training of postgraduate students, having accepted them into the institution and posted them to work in affiliated hospitals. Secondly, medical institutions are the employers of the teaching faculty and other staff. As sponsors of medical training, medical colleges need to share vicarious liability along with the faculty who are in charge of the postgraduates.¹⁴

CASE LAWS PERTAINING TO VICARIOUS LIABILITY OF SUPERVISING PHYSICIANS, HOSPITALS, TEACHING INSTITUTIONS

Mozingo v Pitt County Memorial Hospital, 415 SE2d 341 (NC 1992)¹⁷

An obstetrician on call was held liable for negligent supervision regarding the birth injuries of a baby delivered by the postgraduate resident, even though she arrived after the delivery.

Maxwell v Cole, 482 NYS2d 1000 (NY Sup Ct 1984)¹⁸

In this case, the patient died of septic shock due to bladder perforation during elective tubal ligation. The court held not only the supervising faculty liable but also the head of the Department of Obstetrics, even though he had no direct connection with the management of the patient. The court reasoned that he owed a supervisory duty over all his subordinates.

Felice v Valleylab, Inc., 520 So2d 920 (La Ct App 1988)¹⁹

In this case, where a resident performed circumcision surgery without the presence of a specialist and injured the patient, both the supervising surgeon was held liable for failure to supervise and the medical school was held liable for allowing the operation in violation of its own policy.

INDIAN CASE LAWS ON VICARIOUS LIABILITY OF THE HOSPITALS

Kerala High Court

In *Joseph Pappachan v. Dr George Moonjerly* [1994 (1) KLJ 782 (Ker. HC)],²⁰ in support of the doctrine of vicarious liability, the court stated that

"Persons who run hospitals are, in law, under the same duty as the humblest doctor: whenever they accept a patient for treatment, they must use reasonable care and skill to ease him of his ailment.

The hospital authorities cannot, of course, do it by themselves; they have no ears to listen to the stethoscope and no hands to hold the surgeon's scalpel. They must do it through the staff which they employ, and if their staff is negligent in giving treatment, they are just as liable for that negligence as anyone else who employs others to do his duties for him."

Madras High Court

In *Aparna Dutta v. Apollo Hospitals Enterprises Ltd.* [2002 ACJ 954 (Mad. HC)],²¹ it was held that the hospital, as the provider of medical services, is expected to ensure the provision of such services. In cases where there is a deficiency of service or where an operation has been performed negligently without bestowing normal care and caution, the hospital must also be held liable. The hospital cannot escape liability by stating that there is no master-servant relationship between the hospital and the surgeon who performed the operation. The hospital is liable in cases of established negligence, and it is not a defense to claim that the surgeon is not an employee or servant of the hospital.

National Consumer Dispute Redressal Commission

In *Rekha Gupta v. Bombay Hospital Trust & Anr.* [2003 (2) CPJ 160 (NCDRC)],²² the National Consumer Disputes Redressal Commission (NCDRC) held that the hospital authorities are responsible not only for their nursing and other staff but also for anesthetists and surgeons who practice independently but admit or operate on a case. It does not matter whether these practitioners are permanent or temporary, resident or visiting consultants, or work full-time or part-time.

EXCEPTIONS WHICH ABSOLVE RESIDENT LIABILITY AND FACULTY LIABILITY

Resident Liability

In situations where a postgraduate student has acted beyond their capabilities because the supervising physician is unavailable due to managing another medical emergency, this could be considered a legal excuse.²³

If the resident is compelled or forced by their supervising specialist to act, then they may not be held liable for the negligent act.

Supervising Faculty Liability

The postgraduate student is acting beyond the scope of his training.

DISCUSSION

Thus, in the liability trail concerning medical negligence caused by postgraduate students, the responsibility begins with them and ends with the Dean of a medical college or hospital head in the case of a nonteaching institution. However, despite existing legal principles and doctrines, court judgments have been unpredictable and confusing. There is no codified law that permits a concession in the quality of medical care to promote the education and training of postgraduate students. Postgraduate students, teaching faculty, and the institution should collectively ensure safe and appropriate patient care. PG students should seek guidance and supervision from their respective teaching faculty, and the faculty, in turn, are legally obliged to provide such supervision to avoid vicarious and direct liability for negligent supervision. However, what constitutes adequate supervision remains a debatable issue in the legal scenario.¹⁴

Having professional liability coverage not only for specialists but also for postgraduate students, along with nursing and non-medical personnel, is of great help in times of adversity.²⁴ Though nothing can prevent a patient from suing medical professionals, adhering to legal principles and norms can at least alleviate the stress and anxiety associated with medical negligence litigations. It also puts one in a good position to defend against claims, especially

as the law on resident/postgraduate student liability continues to evolve, particularly regarding the applicable standard of care.¹³

It is unfair to hold a resident to the standard of a fully trained physician, whether a generalist or specialist. Their work hours should be more devoted to learning rather than defending malpractice lawsuits. It is imperative to establish a legal framework in the form of legislation to protect residents/postgraduate students and allow them to focus on their training programs without the fear of litigation. Teaching institutes should implement training policies aimed at minimizing patient injury. Residents must be aware of their limitations while treating patients, and teaching faculty should be proactive rather than passive supervisors, actively working to reduce patient risks.²³

Limitations of the Article

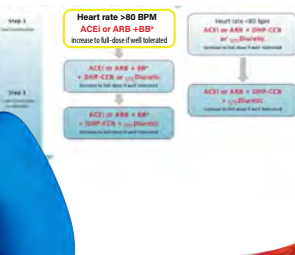
It appears challenging to find Indian case laws specifically addressing various aspects of medical negligence by postgraduate students.

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Life and Times of Yellapragada SubbaRow

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ABSTRACT

Dr Yellapragada SubbaRow was an Indian-born American biochemist who made numerous discoveries in various fields of science. Born in 1895 into a poor family, he went on to have medical training at the Madras Medical College, Chennai, Tamil Nadu, India. After many hardships, he arrived in the United States of America and earned a diploma in tropical medicine and a PhD in biochemistry from Harvard. His illustrious career began with the isolation of phosphorus in body fluids along with Fiske. They discovered phosphocreatine and adenosine triphosphate (ATP) as well. He later became the director of Lederle Laboratories, where he discovered the tetracycline antibiotic group, which saved many lives. He synthesized many vitamins, including folic acid, niacin, and biotin. In 1948, he discovered methotrexate (MTX) for childhood cancer, which paved the way for many chemotherapeutics and is also used in the management of several autoimmune conditions. Despite numerous medical advancements made by SubbaRow, awareness in the scientific world regarding his life and many contributions remains underrecognized. This article discusses SubbaRow's life, academics, and achievements in a nutshell.

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EARLY DAYS

SubbaRow was born into a poor Niogi Brahmin family in a small village in Bhimavaram of the erstwhile Madras Presidency (now West Godavari district, Andhra Pradesh) on 12th January 1895 (Fig. 1). He had a difficult childhood. He was the third of seven children. Due to illness, his father, Jagannatham, had to retire from his job in the government revenue services.¹ His mother, Venkamma, was a strong woman who was always willing to give up everything to ensure that their children grew up well despite their poverty. He passed matriculation on his third attempt. His father died of beriberi 2 months before his exam.² Later, he went to Madras Presidency College, Chennai, Tamil Nadu, India to study intermediate. His mother had to sell her jewellery to fund his studies, and his roommate, Narayana Moorthy, used to support him financially in college.^{2,3}

SubbaRow was undecided about his objectives and couldn't decide which one to pursue money vs power or science vs religion. Finally, he realized that true happiness comes from serving others, so he joined the Ramakrishna Mission to become a saint. He put his studies on hold for 2 years. He practiced yoga every day, becoming increasingly interested in Advaita and religion, which his mother did not like. He couldn't become a saint because the Ramakrishna Mission required his mother's written consent, which Venkamma refused to provide. The saints at the Ramakrishna Mission pushed him to pursue a medical career instead to serve the community.¹ SubbaRow enrolled at

Madras Medical College, Chennai, Tamil Nadu, India, with financial assistance from Kasturi Suryaprakasha Row in 1915. After completing his medical degree, he married Suryaprakasha Row's daughter, Seshagiri, on 10th May 1919.^{2,3} Around 2 months before his wedding, he had severe diarrhea resembling tropical sprue, which no then available modern medicine could cure. However, Dr Achanta Lakshmipathi's Ayurvedic drugs cured him. This Ayurvedic medicine incidentally was made from *Eclipta alba*, a plant that was later discovered to be a good source of folic acid.⁴

SubbaRow began wearing khadi surgical gowns while in medical school in response to Gandhi's call to boycott British goods, which irritated his surgical professor, M C Bradfield. As a result, despite performing well in exams, in 1921 he received a lesser Licentiate of Medicine and Surgery (LMS) certificate instead of a full MBBS degree.¹⁻³ He learned about the research opportunities at the Harvard School of Tropical Medicine from a visiting Rockefeller investigator, Dr Strong, who, impressed by the zeal of SubbaRow, agreed to admit him to the Boston School of Tropical Medicine.¹⁻³ Unfortunately, his elder brother Purushotham, who was arranging a travel scholarship for SubbaRow through his business contacts, died of a sprue-like illness. His second brother, Krishnamoorthy, also died 1 week later due to sprue.^{3,5} The deaths of his brothers fueled his desire to research and develop therapies for these diseases. He tried to obtain admission to Madras Medical Services but could not get it due to his lower LMS qualification.

He subsequently became a professor of Anatomy and Physiology at Dr Lakshmipathi's Ayurvedic College in Madras (Fig. 2).³ SubbaRow was fascinated by the curative powers of Ayurvedic medicine and compiled a compendium on Ayurvedic treatments. He believed in Ayurveda's tri-dosha theory—health and disease are simply the harmonious or discordant workings of the protoplasm (kapha), which provides the fluid matrix for the play of life. Internal thermomechanism (pitta) regulates metabolism. The "vata" principle is believed to control all neuromuscular activity, including sensations, thoughts, and emotional impulses. The salary offered at the Ayurvedic college was inadequate, and there were no resources to conduct research. So SubbaRow tried again to find opportunities in the United States of America.²



Fig. 1: SubbaRow Portrait (1948) by Philip Rane

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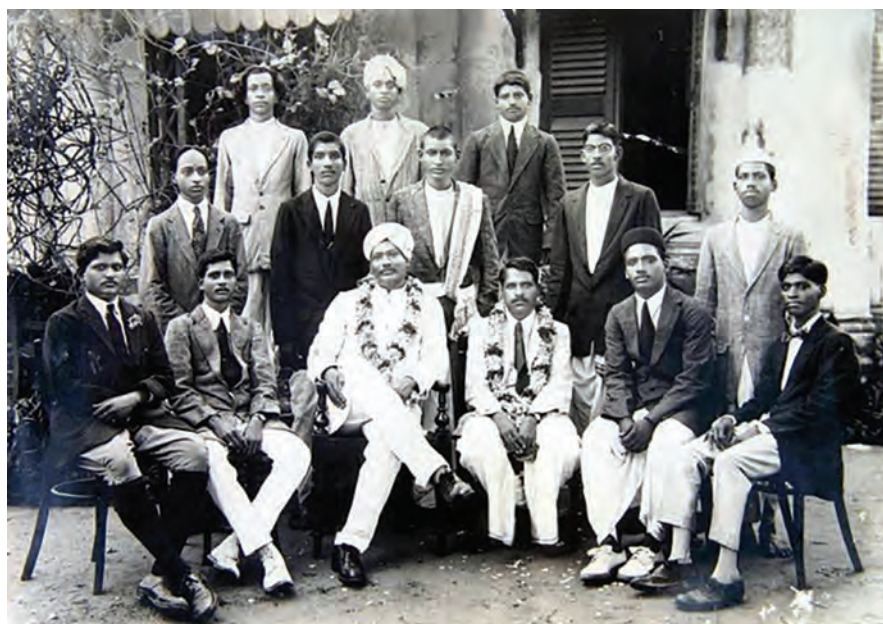


Fig. 2: SubbaRow (fourth from left, sitting) with Achanta LakshmiPathi (third from left, sitting) at his farewell from Madras Ayurvedic Medical College in 1920

IN THE UNITED STATES OF AMERICA

Malladi Satyalingam from the MSN Charities and his father-in-law financially supported him in studying tropical medicine, and he finally arrived in Boston on 26th October 1923. He was \$50 short of his registration fee, and Dr Strong helped him to get registered in the School of Tropical Medicine. Nevertheless, to sustain himself throughout his year at the school, he had to do night work at Peter Bent Brigham Hospital to clean patients' bedpans.^{2,4} He had a special interest in parasitology. His first work was on *Entamoeba in vitro* cultivation, which was unsuccessful, but it did help him learn lab techniques and research procedures.¹

In 1924, SubbaRow graduated from the School of Tropical Medicine. He then enrolled in Harvard Medical School for a PhD in Biochemistry and joined as a junior faculty. His child was born at the same time, but 9 months later died due to erysipelas.^{2,3} Professor Otto, the head of Tropical Medicine, assigned SubbaRow to work under Cyrus Fiske. Along with Fiske, SubbaRow developed a calorimetric method for estimating phosphorus in body fluids and tissues, termed the Fiske-SubbaRow method. This research was published in the *Journal of Biology and Chemistry*³ in 1925 and was the most frequently cited article (>20,000 citations) globally.⁶ The same work made his entry into biochemistry textbooks.

GAINING A FOOTHOLD IN RESEARCH

In those days, scientists were trying to find answers to the question of the origin of muscle contraction. In 1907, two Cambridge scientists proposed that it is caused by lactic acid. Later, Otto Meyerhof proposed that lactic acid is a breakdown product of glycogen. Arnibold of London discovered that heat is released during glycogen's breakdown into lactic acid, earning him later a Nobel Prize.³ According to Zee Embden, blood sugar and phosphorus combine to form hexose phosphate, which is then converted to lactic acid.⁷ SubbaRow and Fiske broadened their research in this area. SubbaRow conducted calorimetric experiments on cat muscles for which he used to hunt domestic cats.³ SubbaRow and Fiske discovered phosphocreatine in 1927, which forms due to a chemical reaction between phosphoric acid and creatine. They also found that the muscle contains two-thirds phosphocreatine at rest, which gradually decreases as the muscle contracts and returns to normal once the muscle reaches a state of relaxation. They identified that ATP is the energy released during this process and is the source of life.⁸ It was a groundbreaking discovery and was published in the April 1927 issue of "*Science*."⁹ Lohman also independently discovered ATP around the same time and published his work earlier than Fiske, so he got credit for the discovery of ATP. Nonetheless, Meyerhof and Hill were awarded the Nobel Prize in Physics in 1922 for their work.⁷ SubbaRow and Fiske were never

brisk displays of their work, which may have contributed to their underappreciation. Furthermore, SubbaRow was a firm believer in teamwork and never took credit for his efforts. He used to say, "Victories in science are rare to achieve single-handedly; no man should get the (entire) credit." He used to write down his recent developments in research and discoveries in his letters to his wife, and he made a point of not disclosing these findings to others. He received his PhD from Harvard the same year and continued as a teaching fellow at Harvard until 1940.¹

PERNICIOUS ANEMIA AND TROPICAL SPRUE

Dr George H Minton and Dr William P Murphy of Boston discovered that whole liver meal cured pernicious anemia. SubbaRow secured a liver concentrate in 1935 and showed that in 15 mg injectable doses, it was as effective as an entire liver meal using charcoal adsorption and ethanol elution procedure. The research, however, slowed down due to Fiske's withdrawal and a lack of funds and human resources. During his experiments on liver extracts, he discovered niacin, biotin, and pantothenic acid vitamins.^{1,10} However, credit for their discovery has gone to other scientists. After being denied a permanent academic job at Harvard, in 1940, SubbaRow joined Lederle Laboratories, a part of American Cyanamid (now a division of Wyeth, owned by Pfizer), as an associate director of research. He was promoted to director of research in 1942.¹⁻³ He desired to work in an environment that provided modern scientific facilities and did not require him to worry about money. SubbaRow asked William Berenberg, the head of Lederle if he would accept only half of his annual salary if the company could build a new research building at Pearl River.¹¹

His search for a cure for tropical sprue, which had threatened his own life and killed his two brothers, continued for 18 years, along with other experiments. Lucy Wills observed that folate can cure anemia during pregnancy, and Bob Stokstad identified its chemical structure.¹² The team of folic acid boys (Fig. 3) led by SubbaRow isolated a chick growth factor and prepared a microbial fermentation broth from the liver.^{3,12} Folic acid was discovered in crystalline form in both liver extract and broth in 1941. It cured patients suffering from sprue. After some time, there were reports that patients treated with folic acid improved their blood levels; however, a few developed neurological problems.¹³ SubbaRow thought there was another factor responsible for those symptoms and conducted additional research. He isolated



Fig. 3: Folic acid boys (left to right): J H Mowat, R B Angier, Y SubbaRow, and J Semb, four of the 16 organic chemists who discovered folic acid

a pink solution from the liver but failed to recognize it. Merck Lab announced the isolation of concentrated crystalline pink vitamin B₁₂ in due course.^{1,3}

PROLIFIC RESEARCH OUTPUT AT THE LEDERLE

At Lederle, he prepared patent forms for penicillin, riboflavin, and other vitamins from 1940 to 1943. Later, he concentrated his research on the discovery of antibiotics. Under the supervision of SubbaRow, Benjamin Duggar discovered the world's first tetracycline antibiotic, aureomycin, in 1945.¹⁴ For this research, soldiers from the United States who fought in World War II were asked to collect soil samples from the battlefield and bring them back to Lederle.^{1,3} Duggar successfully grew a mold actinomycete (*Streptomyces aureofaciens*, strain A377) from these soil samples. Chlortetracycline, the first tetracycline, was discovered from this mold and was named aureomycin because of the golden yellow color of the substance. This was the first-ever broad-spectrum antibiotic discovered, acting against both gram-positive and gram-negative bacteria.¹⁵ This discovery was presented at a symposium on 21st July 1948, just 2 weeks before SubbaRow's death. Polymyxin, which is still commonly used in cattle feed today, was also discovered during this process.⁴ When India was dealing with a plague epidemic in 1994, doxycycline, a tetracycline derivative, helped to limit and control the spread of the disease. Thus, SubbaRow repaid his debt to his motherland.³

SubbaRow synthesized a purified form of Gramicidin, which was already discovered by Dubos in 1940. SubbaRow initiated a new project in 1941 to protect American soldiers in the Pacific wars who were prone to parasitic diseases during the war and brought those infections back home.^{1,3} He developed an orally administrable nonmetallic drug, diethylcarbamazine, a piperazine compound, while working with cotton rats infected with *Litomosoides carinii* in 1947.¹⁶ Diethylcarbamazine has been the World Health Organization (WHO) approved drug used in filariasis since then.

ANTICANCER RESEARCH

SubbaRow's journey from the discovery of antibiotics to developing anticancer drugs was fascinating and unexpected. Richard Lewisohn of the Mount Sinai Hospital discovered that folic acid suppressed breast cancer growth in mice.³ How does a substance act as both a growth promoter and a suppressor? SubbaRow's team observed that folic acid extracted from the liver increased cancer cell growth while folic acid extracted from fermentation broth stopped cell growth. Teropterin, the chemical compound in the broth, had three glutamate residues compared to folic acid in the liver.¹⁷ It had been tested in children with leukemia with promising results. Teropterin caused complete regression of breast tumors in 40% of the mice, and intralesional injection of this compound brought about a remarkable prolongation of life and considerable easing of pain in Babe Ruth, the baseball legend suffering from a tumor in the neck. These observations gave

a ray of hope for cancer cure.^{3,4} SubbaRow later discovered analogous compounds of pteropterin, methyl pteric acid, and pteroyl aspartate and brought them to Boston to collaborate with Sidney Farber, who was also working on antifolates at the time.^{18,19} Between November 1947 and April 1948, Farber tried these antifolates on 16 children with acute undifferentiated leukemia. In 10 children, there was a temporary remission. In 1948, Farber et al. published the most favorable results of five children in the *New England Journal of Medicine*.²⁰ Despite being criticized by scientists for the toxicities of antifolates, this study remains one of the most cited and significant works in the treatment of leukemia.

At the same time, a chemist working under SubbaRow discovered aminopterin, which was 100 times more potent than these compounds and was very effective in leukemic children. However, the safety margin was narrow. SubbaRow focused his efforts on developing a better molecule, which led to the discovery of MTX. For this discovery, Dr SubbaRow was hailed as the "Father of Targeted Cancer Chemotherapy," laying the groundwork for cancer chemotherapy.³

HOW MTX BECAME A THERAPY FOR RHEUMATOID ARTHRITIS

Aminopterin was shown to have antiproliferative effects on connective tissue while being studied for its effects on leukemic children. Gubner, along with Oleson, an associate of SubbaRow, showed that aminopterin suppressed inflammation in rats with formalin arthritis.²¹ Based on this observation, in 1951, Gubner administered aminopterin to seven patients with rheumatoid arthritis (RA). Six out of seven patients showed clinical improvement, although flare-ups started soon after discontinuation of the medicine. Among these six patients, one also had psoriasis along with RA and experienced improvement in both the skin lesions and arthritis.²¹ Ever since dermatologists started using MTX for psoriasis, rheumatologists were initially hesitant to use MTX, an anticancer drug, for diseases such as RA. At the same time, Flinch was awarded the Nobel Prize for their use of corticosteroids in RA, which increased interest in using steroids for RA. Over the next decade, Hoffmeister and a few community-based rheumatologists in the United States demonstrated that MTX was effective in RA in open-label trials.²² Weinblatt et al. conducted the first randomized placebo-controlled trial of low-dose MTX in RA on 28 patients in 1983, and the results were promising.²³ This study, which paved the way for other landmark

trials on MTX in RA and led to MTX Food and Drug Administration (FDA) approval, was funded by Lederle Laboratories, where MTX was manufactured by SubbaRow. However, there was concern about MTX toxicity, which prompted further research. SubbaRow's folic acid has been shown to reduce the adverse effects of MTX in studies by Morgan et al.²⁴ Despite the development of other conventional disease-modifying agents and biologics, MTX remains an anchor drug not only in RA but also in a variety of autoimmune rheumatic diseases and vasculitis.

CONCLUSION

SubbaRow authored over 100 papers and left behind a substantial number of unpublished works. Nobel Prize winner George Hitchings once commented that Fiske did not allow SubbaRow to come into the limelight, leading to others rediscovering some of the nucleotides isolated by SubbaRow years later. SubbaRow was known for his humility, belief in teamwork, and never seeking credit for his discoveries; perhaps this is why he never achieved prominence.²⁵

At the age of 53, on 9th August 1948, SubbaRow died peacefully in his sleep due to a massive heart attack. His obituaries were published in numerous newspapers and journals worldwide, including Science, the New York Times, the New York Herald-Tribune, and others. He was referred to as "one of the most eminent medical minds of the century" by The Herald-Tribune. Doron K Antrim wrote in "Argosy," an American magazine in the 1950s, "You have probably never heard of Dr Yellapragada SubbaRow. Yet because he lived, you may be alive and well today; because he lived, you may live longer."¹¹ His commemorative memorial plaques were placed at Lederle Laboratories (Fig. 4) and Emmanuel Baptist Church, Ridgewood, New Jersey (Fig. 5).^{3,4}

American Cyanamid honored him with a plaque at Pearl River and also built a memorial library in his name (Fig. 6).³ His bust was erected at Rangaraya Medical College, Kakinada, Andhra Pradesh, the National Institute of Nutrition, and Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India (Fig. 7).³ Clifford Hesseltine discovered a new fungus in 1953 and named it "*Subbaromyces splendens*" in his honor (Fig. 8).²⁶ Manohara Chary and Ponnuri Ramarao found another species of the same fungus at Osmania University of Hyderabad and named it "*Subbaromyces aquatica*." The Indian Centennial Committee issued a postal stamp in 1995, his centennial year (Fig. 9).^{3,4} The timeline of important events in SubbaRow's life is summarized in Table 1.

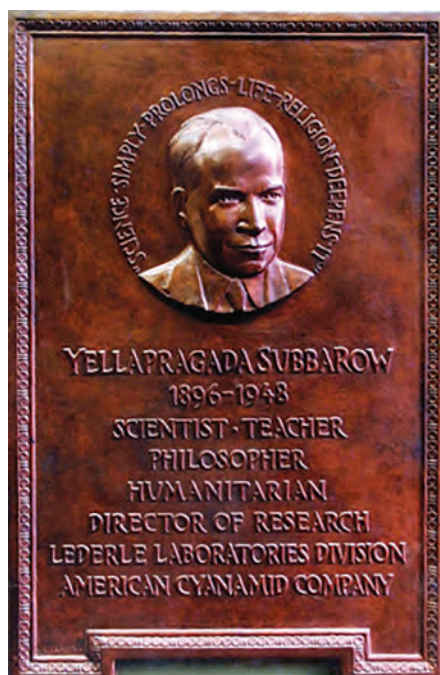


Fig. 4: Subbarow memorial plaque at Lederle Laboratories



Fig. 6: SubbaRow Memorial Library, Pearl River, New York, United States of America



Fig. 7: SubbaRow's bust at the Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India



Fig. 5: The commemorative plaque of SubbaRow at the Emmanuel Baptist Church, Ridgewood, New Jersey (1948)

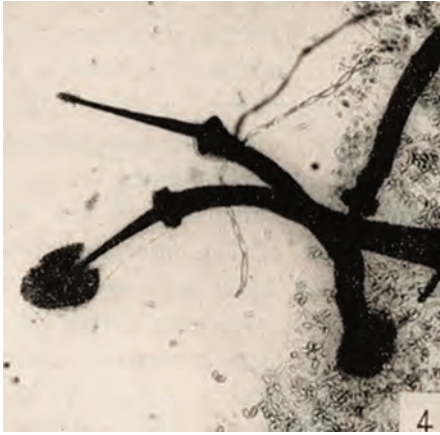


Fig. 8: *Subbaromyces splendens*, a fungus discovered by Clifford Hesselte in 1953, was named after SubbaRow



Fig. 9: Postal stamp commemorating SubbaRow (1995)

Table 1: Dr SubbaRow: timelines

Year	Milestones/awards/achievements
12 th January 1895	Born in Bhimavaram, West Godavari, Andhra Pradesh, India
1912	Passed Matriculation from Hindu High School, Chennai, Tamil Nadu, India
1913	Studied Intermediate at the Presidency College, Chennai, Tamil Nadu, India
1915	Joined Madras Medical College, Chennai, Tamil Nadu, India
1921	Received LMS Degree from Madras Medical College, Chennai, Tamil Nadu, India
1921	Professor at Ayurvedic Medical College, Chennai, Tamil Nadu, India
26 th October 1922	Arrived in Boston, Harvard School of Medicine, City of Boston, Massachusetts
1924	Diploma in Tropical Medicine
1925	Estimation of phosphorous in body fluids along with Cyrus Fiske, known as the Fiske–SubbaRow method
1927	Discovered phosphocreatine along with Fiske
1929	Discovered ATP along with Fiske
1930	PhD in biochemistry from Harvard University, City of Boston, Massachusetts
1940	Associate Director at Lederle Laboratories
1940	Synthesized purified form of Gramicidin
1942	Became Director of Lederle
1945	Synthesized folic acid in a crystalline form
1945	Discovered niacin, pantothenic acid, and biotin
1945	Aureomycin was discovered by Benjamin Duggar under the guidance of SubbaRow
1947	Discovered diethylcarbamazine citrate
1948	Synthesized polymyxin
1948	Discovered methotrexate
8 th August 1948	Died due to a massive heart attack in the United States of America
1953	A new fungus was named <i>Subbaromyces splendens</i> in his honor
1995	Indian government honored him with a postal stamp on his centenary year
1995	His bust was erected at the National Institute of Nutrition, Hyderabad, Telangana, India

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Evolution of a Pandemic and Changing Concepts in the Case Definition

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ABSTRACT

Pandemics result in a huge burden of cases, which paralyze the healthcare system. Proper planning and awareness of case definition at different stages of the pandemic are important for the effective utilization of resources. In this short article, we are describing the stages of a pandemic, how it ends, and the case definition at each stage of the pandemic with special reference to the recent COVID-19 pandemic.

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INTRODUCTION

Any pandemic starts with infection in a local area, which rapidly spreads subsequently to almost all areas of the world. Well-established international travel facilities accelerate this spread. The recent COVID-19 pandemic, due to severe acute respiratory syndrome coronavirus 2 infection, initially started in Wuhan, China, and subsequently spread all over the world.¹ An infection that can be transmitted through the air has a high propensity to spread rapidly. Various measures like quarantine, physical distancing, personal hygiene, and the use of face masks and other protective measures help to control the spread.

STAGES OF PANDEMIC AND CASE DEFINITION

Outbreak, endemic, epidemic, and pandemic are common terminologies used to describe disease prevalence in epidemiology. They do not indicate the severity of the illness under consideration. Endemic denotes the consistent presence of a disease in a particular geographical area or population, with stable prevalence and predictable spread. An unexpected increase in the disease affecting a large number of people in a particular area or population is represented by an epidemic. A pandemic refers to an epidemic with exponential disease growth that crosses geographical boundaries or continents. The World Health Organization (WHO) divides the evolution of a pandemic into six phases, which are important from an epidemic standpoint.² Identifying the cases and halting the spread of the disease are the two important aspects of controlling a pandemic.

The clinical case definition is an important concept during a pandemic to

identify probable cases and to prioritize investigations, treatment, and control measures. Those satisfying clinical case definitions will be subjected to diagnostic laboratory tests, such as throat swab reverse transcription polymerase chain reaction tests done in those with suspected COVID-19. Clinical case definitions may change according to the stages of the pandemic spread (Table 1).

Even though the WHO has already described 6 phases of a pandemic, which are important from an epidemiological point of view, they do not clearly represent the stages to which a clinician is exposed. Clinically relevant stages and case definitions according to these stages will be useful for practicing doctors worldwide. So, the development of a pandemic is divided into four distinct clinical stages. Every pandemic starts with an outbreak in a particular area and the spread of the disease to that geographical area. If a person carrying the organism travels to a distant place and comes in contact with the people there, it results in the spread of infection at that distant place. In the early stages, case definitions differ between the area where the outbreak was first noticed and areas where cases are imported. In stage I, also known as the outbreak stage, those who had exposure to infectious sources (e.g., from animal contact) develop the disease. In stage I, or the stage of imported cases, individuals who came from the area where cases are reported develop the disease, leading to its spread to distant places. In the second stage or the stage of local transmission, infection is seen in those who had contact with people carrying the infectious agents. In the second stage or the stage of local transmission, infection is observed in those who had contact with people carrying the infectious agents. In stage III, or the stage of community

transmission, people become infected even without contact with individuals carrying the infectious agent. This progresses to the final and full-blown stage—stage IV, or the stage of the epidemic, which, when it spreads across multiple countries or continents, is termed a pandemic (Fig. 1). Clinical case definitions need to be modified according to the stage of the pandemic to identify cases and plan preventive and therapeutic strategies. In stage I, individuals who develop clinical symptoms suggestive of the disease under consideration and have a history of contact with the infectious source or an imported case fall under the case definition. In stage II, anyone presenting with clinical features and a history of contact with infected individuals falls under the case definition. In stage III, individuals with clinical symptoms who reside in the affected geographical area, regardless of a history of contact, are included in the case definition. During stage IV, individuals with clinical symptoms are considered cases regardless of their geographical location. In other words, anyone can be classified as a case during stage IV of the pandemic.

All these clinical case definitions fail to account for asymptomatic cases, which can be significant, as in the case of COVID-19, where asymptomatic carriers contribute to a significant proportion of infective cases.³ Contact tracing and extensive testing will help to identify asymptomatic cases.

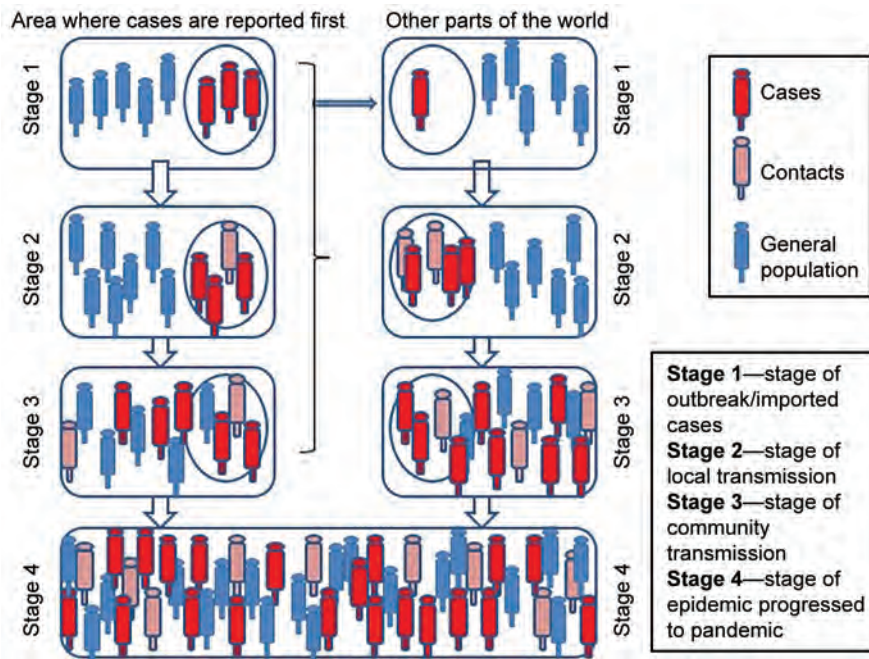
During a pandemic, if control measures are not adopted, it will lead to a very large number of cases occurring in a short span of time, paralyzing the healthcare system. Measures such as quarantine, physical distancing, lockdowns, use of face masks, and hand hygiene are implemented to flatten the disease curve. As a result of

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Table 1: Changing clinical case definition according to stages of the pandemic

Changing clinical case definition according to stages of the pandemic			
In the geographical area where cases are reported first		At a different geographical area where cases are imported	
Stages of pandemic	Case definition	Stages of pandemic	Case definition
Stage I or stage of the outbreak	All those with symptoms suggestive of acute infection (caused by the agent responsible for the pandemic) with a history of contact with infectious sources in the locality where the outbreak was reported	Stage I or stage of imported cases	All those with symptoms suggestive of acute infection (caused by the agent responsible for the pandemic) in people who recently traveled to the locality where the outbreak was reported
Stage II or stage of local transmission	All those with symptoms suggestive of acute infection (caused by the agent responsible for the pandemic) in people who had direct contact with the confirmed or suspected case-carrying infectious agent	Stage II or stage of local transmission	All those with symptoms suggestive of acute infection (caused by the agent responsible for the pandemic) in people who recently traveled to the locality where cases are reported or had contact with those who traveled to the locality recently
Stage III or stage of community transmission	All those with symptoms suggestive of acute infection (caused by the agent responsible for the pandemic) in people who live in the locality where the infection is reported, irrespective of history of contact with suspected or confirmed cases		
Stage IV or the stage of the epidemic, progressed to pandemic	All those with symptoms suggestive of acute infection (caused by the agent responsible for the pandemic) in people who live in a different locality (than the area where the infection is reported), irrespective of history of contact with suspected or confirmed cases		


Fig. 1: Stages of the pandemic

these restrictions and the awareness of the increased morbidity and mortality of the disease, people experience panic in the initial stages of a pandemic. If the pandemic persists for an extended period, the level of stress related to the disease may be overshadowed by other financial and social stressors, prompting authorities to relax strict disease control measures like lockdowns and quarantine before the pandemic officially ends.

END OF PANDEMIC OR EPIDEMIC

It is interesting to see how a pandemic or epidemic ends. The end of an epidemic is defined as "the reduction of disease incidence, prevalence, morbidity, and mortality to a locally acceptable level."⁴ The end of a pandemic never signifies the eradication of the disease. Theoretically, we consider the end of a pandemic or epidemic when the disease decreases to an endemic level.

Some diseases persist as cyclical epidemics or endemic diseases. Pandemics conclude at varying times across different geographical areas and also at different times within the same geographical area for different groups. In practice, the end of a pandemic signifies the lifting of public health restrictions, which are also influenced by political, social, and economic factors, allowing for a return to normal life.

Experts describe two types of the end of the pandemic—the social end and the medical end.⁵ The social end denotes the relaxation of various control measures like lockdowns and quarantine. This often happens before the actual end of the pandemic, driven by financial and social stresses that overshadow concerns about the disease. These factors force authorities to ease various control measures. The medical end of the pandemic denotes the real end of the pandemic. The end of the epidemic is perceived differently across various academic disciplines, such as epidemiologists, anthropologists, policymakers, and historians, as they use different parameters to determine when the epidemic has concluded.

Farr's Law, formulated by Dr William Farr, states that epidemic events rise and fall in a roughly symmetrical pattern, resulting in a bell-shaped curve.⁶ But it is not applicable to all pandemics, as we witnessed in the recent COVID-19 pandemic, where there is a rapid rise and slow fall, resulting in an asymmetrical pattern.

How Does a Pandemic End?

There is no single answer to this question. The factors contributing to the control of a pandemic are multiple, and the major factors are the following:

- Vaccination and the development of immunity will help prevent further spread of the infection.
- A large number of people get infected and develop herd immunity, which will help prevent further spread of the infection.
- Various control measures directed toward society include lockdowns and quarantine.
- Various personal control measures include the use of face masks and hand hygiene.

- Improved nutrition and immunity.
- Improvement in sanitation.
- A biological shift in the host, vector, or agent.
- Genetic variation in the causative organism may result in a less severe case.
- The pandemic becomes seasonal, and the virus becomes endemic.
- Viruses morph from pandemic pathogens into endemic sources of infection.

CONCLUSION

To conclude, clinical case definitions are important for proper resource allocation during a pandemic, and they may change according to the stages of the pandemic.

Understanding the various stages of the pandemic is crucial for effective management.

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Gabapentin-induced Multifocal Myoclonus

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ABSTRACT

Background: Gabapentin is the most commonly preferred agent for neuropathic pain in general practice as it is usually well tolerated, but occasionally, its toxicity may occur at standard doses, especially in elderly individuals, even without any prior comorbidities.

Case: We present an elderly male with normal renal parameters, who was started on gabapentin for neuropathic pain. He developed multifocal myoclonus all over the body within few days after starting gabapentin and subsided completely after withdrawal of the drug.

Conclusion: Acute hyperkinetic movement disorders such as multifocal or segmental myoclonus in elderly patients warrant a prompt review of recent drug history, especially gabapentin, even in the background of normal renal function.

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INTRODUCTION

Gabapentin is one of the first-line drugs used for neuropathic pain due to its tolerability in the majority. However, it can rarely cause a hyperkinetic movement disorder that occasionally simulates seizure-like activity, causing panic for the patient and presenting a complex puzzle for the physician. Various cases have been reported on myoclonus induced by gabapentin in patients with coexistent renal insufficiency, static encephalopathy, and prior epilepsy.^{1,2} We report on one of our elderly patients with normal renal parameters who was started on gabapentin for neuropathic pain and developed myoclonus, which resolved promptly after cessation of the medication. We present this case to highlight considerations regarding pharmacokinetic properties in the geriatric population.

CASE DESCRIPTION

A 66-year-old male with a prior history of transient ischemic attack and well-controlled bronchial asthma presented with neuropathic pain involving the left lower limb. He had no focal neurological deficits except for sluggish bilateral ankle jerks. Routine blood parameters were within normal limits. Magnetic resonance imaging (MRI) of the lumbosacral spine showed intervertebral disc protrusion at the L4-L5 level causing neural foraminal narrowing on the left without significant cord compression. He was started on gabapentin 600 mg/day for its analgesic properties, with mild symptomatic benefit. However, after 4 days of initiating medication, he presented with sudden onset continuous, shock-like, brief jerky movements involving

the face, both upper limbs and lower limbs. These movements were aggravated in the sitting position and partially relieved in the supine position, ceasing completely during sleep. There was neither fever nor alteration in the sensorium nor derangement of blood parameters, including serum ammonia, renal, and liver function tests. Electroencephalogram (EEG) showed normal awake and sleep records with no electrical correlate of the jerks (Fig. 1). MRI of the brain showed no significant abnormality. The possibility of drug-induced subcortical multifocal myoclonus was considered, and gabapentin was withdrawn. Following withdrawal, there was significant resolution of myoclonus by the 7th day and complete cessation by the 3rd week. He was started on duloxetine 30 mg for neuropathic pain and tolerated it well.

DISCUSSION

Drug-induced movement disorders (DIMD) represent a treatable subgroup with a mean age of presentation around 35.8 ± 17 years in a recent study of 97 patients in the Indian population. A previous study of 125 patients in Western populations showed an average age of 60 years, which is almost similar to that of our patient.^{1,2} Of all the described DIMD, myoclonus forms a small proportion, while parkinsonism, dystonia, and dyskinesias constitute the majority.¹ The incidence of myoclonus with gabapentin is estimated to be about 12.5% in one study, with a mean age of onset at 29.2 years. All patients in the study had underlying refractory epilepsy and were on gabapentin dosages ranging from 800 to 3200 mg/day, taken for an average duration of 8 weeks.³

Myoclonus is defined as sudden, brief, and shock-like movements characterized by either abrupt muscle contraction (positive myoclonus) or sudden cessation of muscle contraction (negative myoclonus).⁴ Myoclonus can be further classified based on its origin (cortical, subcortical, brainstem, spinal, and peripheral), distribution (focal, segmental, multifocal, and generalized), and etiology (physiological essential, epileptic, symptomatic, and psychogenic). Among the symptomatic subclass, the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria have included eight categories of DIMD.⁵ The most common drugs implicated are dopamine receptor-blocking agents like neuroleptics, antiemetics, and gastrointestinal prokinetic agents, followed by selective serotonin reuptake inhibitors (SSRIs), phenytoin, opioids, and anesthetic medications such as propofol, fentanyl, sevoflurane, and morphine, in addition to gabapentin.^{1,6}

Gabapentin taken orally is absorbed through a combination of diffusion and facilitated transport using a saturable L-amino acid transport mechanism. Due to this mechanism, its bioavailability varies inversely with dose, reaching peak plasma levels approximately 3–3.2 hours after ingestion.^{7,8} Cerebrospinal fluid and brain tissue concentrations attained are 20 and 80%, respectively. Gabapentin acts by increasing the extracellular gamma-aminobutyric acid (GABA) concentration and inhibiting ectopic discharges from damaged nerves, in addition to its central antiallodynic effect.⁹ Gabapentin is not metabolized in humans and is eliminated by first-order kinetics in urine. It does not typically have significant clinically relevant drug interactions, except for reduced absorption by about 20% when given concomitantly with antacids.¹⁰

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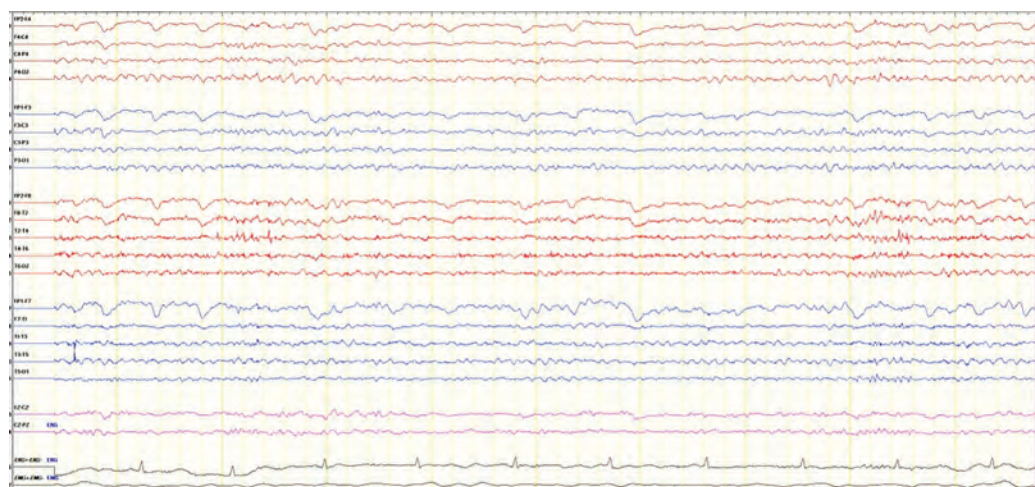


Fig. 1: Electroencephalogram showed no electrical correlate with the jerks

There are various case reports of hyperkinetic movement disorders caused by gabapentin in patients with preexisting renal failure, epilepsy, and static encephalopathy. However, our patient had no such prior comorbidities but developed myoclonus at a lower dose with marginal benefit. This suggests that in elderly individuals, gabapentin should be started at the lowest dosage and up-titrated as slowly as possible. Patients should also be warned about these rare side effects, which may simulate seizure-like phenomena.

Gabapentin is well tolerated in young adults, while elderly individuals seem to be more susceptible to rare side effects despite seemingly normal renal parameters. This susceptibility may be explained by reduced creatinine clearance or altered pharmacokinetics associated with aging.

CONCLUSION

Gabapentin is Food and Drug Administration-approved for treating postherpetic neuralgia and neuropathic pain due to its efficacy and tolerability, with minimal drug interactions and adverse effects. However, it may rarely

cause acute onset myoclonus, which should be communicated to the patient and diligently observed by the clinician.

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1. Research project: (A) Concept; (B) Organization; (C) Execution.
2. Data analysis: (A) Design; (B) Execution; (C) Review and critique.
3. Manuscript preparation: (A) Writing of the first draft; (B) Review and critique.
LP: 1A, 1B, 1C, 2A, 3A.
VAA: 1C, 2B, 3A.
MJ: 1A, 1B, 2C, 3B.
PA: 1B, 2C, 3B.
PR: 2C, 3B.
DN: 2C, 3B.

ETHICAL COMPLIANCE STATEMENT

Informed written consent was obtained and documented from the patients. We confirm that we have read the journal's position on

ethical publication issues and affirm that this work is consistent with those guidelines.

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Navigating Cardiovascular Risk and Lipid Management in Indian Patients: Key Messages from the Lipid Association of India 2024 Consensus Statement IV



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ABSTRACT

Effective lipid management is crucial for preventing atherosclerotic cardiovascular disease (ASCVD). The Western lipid guidelines may not apply to Indian subjects because of the vast differences in cardiovascular (CV) disease epidemiology. To overcome this challenge, the Lipid Association of India (LAI) in 2016 proposed an ASCVD risk stratification algorithm. The appropriate low-density lipoprotein cholesterol (LDL-C) goals for various risk groups were proposed, with an LDL-C target of <50 mg/dL recommended for the first time globally for patients in the very high-risk group. Subsequently, in 2020, an extreme risk group was added because of observations that patients with more severe or extensive ASCVD, along with multiple risk factors and comorbidities, had increased rates of adverse CV events and could benefit from more intensive LDL-C lowering. The extreme risk group was subdivided into categories A and B, with LDL-C targets as low as 30 mg/dL or lower. The availability of further evidence regarding the significance of novel risk factors and the availability of new LDL-C lowering therapies necessitated refining the ASCVD risk assessment algorithm, defining LDL-C targets for subjects with these risk factors, and incorporating recommendations for attaining very low LDL-C levels in a defined, select group of patients. Accordingly, the LAI expert group recently published the Consensus Statement IV, which is a comprehensive document addressing several key issues about risk stratification and dyslipidemia management in Indian subjects. LDL-C and nonhigh-density lipoprotein cholesterol (non-HDL-C) are not only primary and co-primary targets for lipid-lowering therapy but also risk factors for ASCVD risk stratification. Apolipoprotein B is a secondary target. The risk assessment algorithm has been updated to incorporate several nonconventional yet relevant CV risk factors. Additionally, the role of subclinical atherosclerosis has been highlighted. The CV risk due to subclinical atherosclerosis has been considered equivalent to that of established ASCVD, and hence, similar LDL-C targets have been recommended. Furthermore, a new risk category—extreme risk group category C has been added for the small subgroup of patients who continue to experience ASCVD sequelae despite achieving LDL-C levels of 30 mg/dL or lower. An ultralow LDL-C target (10–15 mg/dL) has been recommended along with optimal control of risk factors and guideline-directed management of comorbidities. Dyslipidemia management should be effective with sustained LDL-C lowering. In high-risk situations (e.g., acute coronary syndrome), the LDL-C target should be achieved as early as possible, preferably within the first 2 weeks. The present document summarizes the key messages from the LAI Consensus Statement IV.

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The Lipid Association of India (LAI) in 2016 proposed an atherosclerotic cardiovascular disease (ASCVD) risk assessment algorithm and defined low-density lipoprotein cholesterol (LDL-C) goals based on risk stratification.¹ An LDL-C goal of <50 mg/dL was proposed for the first time globally for patients in the very high-risk group, which included those with established ASCVD, diabetes with two or more major ASCVD risk factors or target organ damage, and homozygous familial hypercholesterolemia (HoFH).¹ These goals were more stringent than the LDL-C targets recommended by other major societies at that time. Even in 2019, the European Society of Cardiology guidelines recommended an LDL-C goal of <55 mg/dL for ASCVD patients.²

The American College of Cardiology expert consensus statement in 2022 recommended an LDL-C level of <55 mg/dL for individuals with multiple ASCVD events or one major ASCVD event associated with one or more high-risk conditions.³ Subsequently, the LAI recommendations were revised in 2020, and an extreme risk group was added to the risk stratification algorithm.^{4,5} This was done to suitably address the lipid-associated risk of individuals who were at markedly increased risk of experiencing future cardiovascular (CV) events due to severe or extensive ASCVD along with multiple CV risk factors or comorbidities. It was also important to incorporate new evidence generated with proprotein convertase subtilisin/

kexin type 9 (PCSK9) inhibitor monoclonal antibodies, showing that achieving even lower LDL-C levels beyond those achieved with statin therapy was associated with further reduction of CV risk.^{6,7} In fact, ultralow LDL-C levels achieved with treatment were associated with incremental benefits without any safety concerns.⁸ Several subgroup analyses from PCSK9 inhibitor trials showed that patients at the highest risk achieved the greatest benefit. In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study, high-risk subgroups such as those with diabetes mellitus, recent myocardial infarction, multivessel coronary artery disease

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(CAD), or peripheral arterial disease had increased event rates and accordingly obtained more reduction in adverse CV events with even lower LDL-C levels achieved by the PCSK9 inhibitor monoclonal antibody evolocumab in addition to statins, thus supporting the highest risk, highest benefit strategy.^{9–11}

The extreme risk group defined by LAI was further subdivided into category A and category B. In category A, an LDL-C goal of <50 mg/dL was recommended, with an optional LDL-C goal of 30 mg/dL or lower, while in category B, an LDL-C goal of 30 mg/dL or lower was recommended. A comprehensive risk-benefit conversation between the physician and the patient was recommended before embarking on such intensive lipid-lowering therapy.^{4,5}

The LAI guidelines categorically state that the first priority for lipid management is the achievement of the LDL-C goal, followed by nonhigh-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apo-B) goals.^{1,4,5,12,13} Lifestyle management and control of all modifiable risk factors, comorbidities, and secondary causes of dyslipidemia, if any, are recommended for all subjects, along with suitable lipid-lowering therapy as needed. To achieve recommended LDL-C goals, statins remain the drug of choice, followed by ezetimibe and bempedoic acid.^{4,5,14} PCSK9 inhibitors may be required only in a minority of patients who do not attain recommended LDL-C goals with the above therapies.⁵ If the LDL-C goal is achieved but non-HDL-C remains above the goal, omega-3 fatty acids, preferably icosapent ethyl, are recommended, and fenofibrate can also be considered in addition to maximally tolerated LDL-C lowering therapy.^{12,15} To maximally lower the lipid-associated CV risk, it is important to target apo-B as well after reaching LDL-C and non-HDL-C goals. This can be achieved by further intensifying the lipid-lowering therapy.

The major strength of the LAI guidelines, since their inception, has been their recognition of the epidemiological characteristics of ASCVD and prevailing socioeconomic circumstances in India, and their adaptation to these realities. The following are the key concepts underlying the LAI recommendations:

- Several studies have shown that Indians have LDL-C values about 10 mg/dL lower than their Western counterparts. At the same time, Indian subjects also tend to have a higher incidence, prevalence, and severity of ASCVD, associated with higher case fatality rates. Hence, the LDL-C goals proposed by the European and American

guidelines cannot be directly applied to Indians, who may require more intensive LDL-C lowering. LAI has consistently proposed more stringent LDL-C goals for Indian subjects.

- Indian subjects tend to have higher non-HDL-C and apo-B levels, with high discordance between LDL-C and non-HDL-C levels.¹⁶ Therefore, more intensive lipid-lowering is needed to achieve the non-HDL-C and apo-B targets, providing yet another rationale for lowering LDL-C targets.
- ASCVD manifests in Indian subjects at a younger age than in Western populations. Hence, any risk stratification tool based on age is not applicable to Indians. To overcome this challenge, LAI developed a unique CV risk assessment algorithm that relies less on age.
- The presence of atherosclerosis in any form (including nonobstructive plaques) identifies individuals who are at increased risk of developing clinically manifest atherosclerotic disease and deserve intensive risk factor modification to halt the progression of the atherosclerotic process. Denying them the advantage of early, aggressive LDL-C lowering due to otherwise perceived low risk (e.g., because of young age) misses the opportunity to curb atherosclerosis in its nascent phase. Recognizing this, the LAI has clearly emphasized the role of subclinical atherosclerosis in triggering intensive LDL-C lowering, regardless of other ASCVD risk factors. Such an approach seems ideal for a population with a high burden of premature ASCVD.

The latest "LAI 2023 Update on CV Risk Assessment and Lipid Management in Indian Patients: Consensus statement IV," incorporates these fundamental principles along with the latest evidence regarding ASCVD prevention and, more specifically, lipid management.¹⁷ The salient points of the consensus statement are summarized below.

- As discussed above, these recommendations are based on the following key considerations—(1) ASCVD occurs at a younger age in Indian subjects despite lower baseline LDL-C, in contrast to other populations, and is associated with higher mortality; (2) early and sustained LDL-C lowering leads to more benefits; and (3) the higher the baseline risk, the greater the benefit from intensive LDL-C lowering.
- In view of the early onset of ASCVD, early detection and initiation of dyslipidemia treatment at a younger age in high-risk

patients is very important. Even a minor decrease in LDL-C achieved earlier results in several-fold greater CV event reduction than starting treatment at a later age.

- Low-density lipoprotein cholesterol and non-HDL-C levels are not only treatment targets but also risk factors, as higher baseline levels result in progressively increasing CV risk.
- Low-density lipoprotein cholesterol is the primary target, non-HDL-C is the co-primary target, and apo-B is the secondary target.
- The lipoprotein(a) screening should be done at age 18 or earlier to assess the risk of premature ASCVD.
- Family history replicates numerous genetic, epigenetic, and environmental risk factors. Hence, a family history of premature CAD is considered a high-risk feature, independently warranting an LDL-C target of <70 mg/dL.
- Nonalcoholic fatty liver disease with fibrosis grades II and III, metabolic syndrome, chronic kidney disease stage 3B/4, apo-B greater than 130 mg/dL, lipoprotein(a) 50 mg/dL or higher, coronary artery calcium (CAC) score 1–99 but <75th percentile for age, gender, and ethnic group, and extreme elevation of a single risk factor are other high-risk features that place the individual in the high-risk group with an LDL-C target of <70 mg/dL.
- Elevated triglyceride levels (fasting >150 mg/dL or nonfasting >175 mg/dL), lipoprotein(a) level 20–49 mg/dL, increased waist circumference (>90 cm in men and >80 cm in women), impaired fasting glucose (fasting blood glucose 100–125 mg/dL), high sensitivity C-reactive protein >2 mg/L, air pollution, inflammatory joint diseases, premature menopause, preeclampsia, gestational diabetes, or polycystic ovary syndrome, high polygenic risk score, and human immunodeficiency virus infection are considered risk modifiers. Their presence in patients with low/moderate risk may place them in a higher risk group, thereby necessitating lower LDL-C targets.
- All patients with diabetes mellitus should be initiated on dyslipidemia treatment on day 1 of diagnosis. The recommended LDL-C goal is <70 mg/dL, with a lower target of <50 mg/dL if there is target organ damage or two or more major ASCVD risk factors. In those with diabetes and ASCVD (extreme risk group A), more intensive LDL-C lowering to an optional target of 30 mg/dL or lower may be preferable, whereas in patients with ASCVD and diabetes with target organ damage or

two or more major ASCVD risk factors, the LDL-C target is 30 mg/dL or lower. The above LDL-C targets need to be attained by week 12.

- All ASCVD patients must achieve LDL-C <50 mg/dL. If there is a history of recurrent acute coronary syndrome or polyvascular disease (extreme risk group B), a target of 30 mg/dL or lower is recommended.
- In acute coronary syndrome, the lipid profile should be done at emergency triage and repeated within 2 weeks of initiating lipid-lowering therapy. All patients should be started on combination therapy with high-intensity statin plus ezetimibe at presentation to the emergency department. The treatment is intensified every 2 weeks until LDL-C goals are achieved, preferably by week 4.¹⁸
- Any form of subclinical atherosclerosis (including nonobstructive carotid, femoral, or coronary plaques or ankle-brachial index <0.9) is considered equivalent to ASCVD, with similar LDL-C targets as for clinically manifest ASCVD.
- Patients with CAC scores of 1–99 but <75th percentile for age, gender, and ethnic group are defined as a high-risk group with an LDL-C target of <70 mg/dL. Coronary calcium score values greater than the 75th percentile for age, gender, and ethnicity, or values between 100 and 299, are classified as a very high-risk group with an LDL-C target of <50 mg/dL. If the CAC score exceeds 300, then the individual falls into extreme risk group A with an optional LDL-C target of 30 mg/dL or lower.
- Heterozygous familial hypercholesterolemia (HeFH) without ASCVD is included in the very high-risk group with an LDL-C goal of <50 mg/dL, whereas HeFH with ASCVD is included in the extreme risk group A with an optional LDL-C target of 30 mg/dL or lower. HoFH is incorporated in the extreme risk group A with an LDL-C target of <50 mg/dL and an optional target of 30 mg/dL or lower, while HoFH with ASCVD is listed in the extreme risk

group B with a mandatory LDL-C target of 30 mg/dL or lower.

- A new extreme risk group category C has been created for very few patients who continue to have recurrent ASCVD events despite holistic ASCVD risk reduction through optimal lifestyle intervention, aggressive lipid-lowering therapy, use of therapies targeting nonlipid risk (e.g., anti-inflammatory agents such as colchicine), and guideline-directed management of underlying conditions like diabetes and hypertension. In these patients, it is recommended to lower LDL-C to 10–15 mg/dL.

The LAI expert group envisages that these latest recommendations will facilitate more appropriate dyslipidemia management among Indian subjects, leading to a reduction in CV risk. At the same time, the LAI guidelines also emphasize comprehensive ASCVD risk reduction and management, beyond just lipid-lowering therapy.

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Cervicofacial Actinomycetoma Presenting with Black Grain: A Rare Clinical Scenario

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ABSTRACT

Mycetoma is a chronic skin and subcutaneous tissue infection characterized by a triad of localized swelling, draining sinuses, and grains or granules (composed of aggregations of the causative organism) within the sinus tracts. It is caused by filamentous higher bacteria (known as actinomycetoma) or fungus (known as eumycetoma). Usually actinomycetoma presents with white-yellow grains and majority of eumycetoma causes black grains. However, actinomycetoma caused by *Streptomyces* sp. produces large brown-black grain, which is often misdiagnosed as eumycetoma, therefore confirmation by culture is necessary. Here, we present a case of 28-year-old female presenting with typical features of mycetoma at cervicofacial region. On direct microscopy (40x) with potassium hydroxide (KOH) mount of discharge released from sinuses showed large and black grains, initially raising a suspicion of eumycetoma, but later, it was confirmed by culture as actinomycetoma caused by *Streptomyces* sp. Patient is now symptomatically better on treatment. Production of black grain by actinomycetoma is a rare clinical scenario.

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INTRODUCTION

Mycetoma is a relatively uncommon, granulomatous infection of skin and subcutaneous tissue which can also extend deeper into the underlying bone. Based on the causative organism, it has two distinct entities, one is eumycetoma caused by fungus and other is actinomycetoma caused by bacteria of the order Actinomycetales.^{1,2} It most commonly involves lower extremity specially foot. It also involves (in the decreasing order of frequency) the hand, upper extremities, and other areas of the body that may be exposed by carrying thorny brush or firewood, including the upper back, neck, and head, but face is rarely involved.² Though both actinomycetoma and eumycetoma have similar clinical presentation in the form of painless indurated swelling with discharging sinuses, treatment of two entities vary completely, so it is essential to distinguish them. Histopathological examination of the deep-seated biopsy material and Gram

stain and potassium hydroxide (KOH) mount microscopy can be used to differentiate between the grains of eumycetoma and actinomycetoma, but for confirmation, culture is necessary.³ Usually black grains are seen in eumycetoma while yellow-white grains are seen in case of actinomycetoma, but a variation in grain color is seen depending on etiological agent (Table 1).² Here, we present a case of cervicofacial actinomycetoma caused by *Streptomyces* sp., which was initially thought to be a case of eumycetoma due to black grain, but a final diagnosis of actinomycetoma by *Streptomyces* sp. was reached based on culture findings.

CASE DESCRIPTION

A 28-year-old female presented with a diffuse swelling with discharging sinuses over the right side of the neck extending up to lower jaw. It appeared 5 years ago as a painless papule which then gradually increased in size over next few years and

showed transient response to short courses of antibiotic therapy. During the early illness, the swelling was associated with mild dull aching pain, blackish discharge, and low-grade intermittent fever. These associated symptoms relieved later with only persistence of discharge. The patient also complained of difficulty in neck movements, but there was no history of dysphagia, dyspnea, trismus, and difficulty in chewing or mouth opening. There was no history of dental procedure and trauma at that site. On examination, the swelling was 15 × 10 cm in size, nontender, firm in consistency, and had multiple discharging sinuses with blackish discharge and skin discoloration (Fig. 1). Complete blood count, liver function test, and renal function test did not reveal any abnormality. Hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV), and HIV (human immunodeficiency virus) counselling and testing Centre known as integrated counselling and testing centres (ICTC) were nonreactive. Imaging of the involved area



Fig. 1: Patient on presentation with swelling of neck and multiple discharging sinuses

Table 1: Mycetoma grain color and etiological agent²

Grain color	Etiological agent
Actinomycetoma	
Yellow/white	<i>Nocardia</i> sp., <i>A. maduræ</i>
Brown/black	<i>Streptomyces</i> sp.
Red	<i>A. pelletieri</i>
Eumycetoma	
Black	<i>Madurella</i> sp., <i>Falciformispora</i> sp., <i>Trematosphaeria</i> sp., <i>Exophiala</i> sp., <i>Curvularia</i> sp., <i>Pheoacremonium</i> sp., <i>Phialophora verrucosa</i> , <i>Emarellia</i> sp., etc.
Yellow/white	<i>S. apiospermum</i> complex, <i>Aspergillus</i> sp., <i>Fusarium</i> sp., <i>Acremonium</i> sp., <i>Diaporthe phaseolorum</i> , etc.

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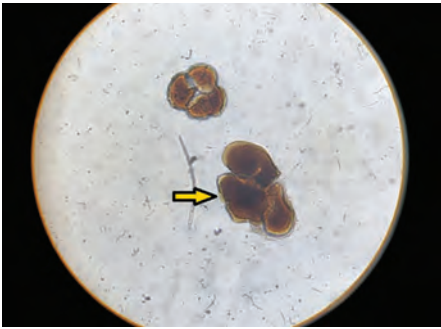


Fig. 2: Black grains of actinomycetoma under KOH mount microscopy

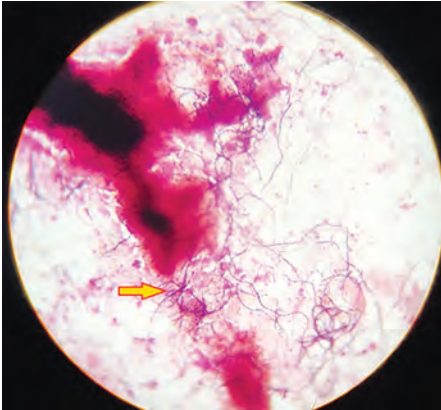


Fig. 3: Gram-positive, branching, and filamentous bacteria under microscope

showed no underlying bone involvement. Pus from lesion was collected using sterile precautions and sent for microbiological examination. Gram staining showed some gram-positive coccobacilli and KOH revealed large, black, hard, and multifaceted granules with fungus-like elements (Fig. 2). It was broken down into fragments after impacted with cover slip. Crushed granules were inoculated for culture on Sabouraud dextrose agar (SDA) and Löwenstein–Jensen (LJ) media. After 10 days of incubation on LJ media, chalky and white colonies were found, which on Gram stain demonstrated gram-positive, branching, and filamentous nonacid fast bacteria (Fig. 3).

Diagnosis of mycetoma is established by combination of clinical features, histopathology examination, and culture. For this typical presentation, we considered mycetoma to be the likely diagnosis. Initial microbiological examination showing black grains with fungus-like elements raised a suspicion of eumycetoma. However, no antifungal treatment was started as final diagnosis was awaited for culture reports, which revealed bacterial etiology. Based on the combined findings of black, hard, large grain, and culture showing gram-positive branching filamentous nonacid fast bacteria, it was diagnosed a case of actinomycetoma caused by *Streptomyces* sp. The patient was

started on oral amoxicillin (500 mg per capsule thrice daily), cotrimoxazole (two double strength tablets twice daily), and clindamycin (600 mg thrice daily). After the initial 2 weeks of the treatment, clinical response in terms of reduction in size of swelling and discharge was noted. On follow-up with same treatment, swelling decreased in size further. However, patient developed drug-induced liver injury while on treatment for 3 weeks and, as a result, amoxicillin and cotrimoxazole were stopped and only clindamycin was continued. Patient is currently under follow-up.

DISCUSSION

Mycetoma was first recognized in Madurai district of South India from where it was commonly known as Madura foot, but now, it is known to be prevalent in other countries.^{2,4} It usually follows thorn prick injury or any trauma that leads to ulceration.^{5,6} After traumatic inoculation, they enter into the skin and cause localized infection that is locally aggressive but does not commonly disseminate. Early diagnosis and treatment can dramatically reduce morbidity associated with this condition. So, it is important for clinicians to be aware of its clinical presentation, available diagnostic methods and the treatment options. Patient with mycetoma presents with papular or nodular lesions and drainage of purulent material via sinus tract formation. It spreads slowly in a sporotrichoid fashion. Ultimately, there is fibrosis and destruction of underlying soft tissue and bone.⁷ Eumycetoma is most commonly caused by *Madurella mycetomatis*, *Trematosphaeria grisea*, and *Scedosporium apiospermum* complex whereas actinomycetoma is caused by members of the order Actinomycetales, most commonly *Nocardia brasiliensis*, *Actinomadura madurae*, *Actinomadura pelletieri*, and *Streptomyces somaliensis*.² Though worldwide, *M. mycetomatis* is the most common cause but *Nocardia* sp. and *T. grisea* are the most common causes of mycetoma in India.² Both worldwide as well as in India, most mycetoma cases were actinomycetoma.^{1,2,6}

Mycetoma is more common in males than females, with an overall sex ratio of 5:1, possibly relating to differences in occupational and other outdoor activities rather than gender differences in susceptibility.^{1,2} The condition is commonly seen in 20–40-year-old age-group.²

Black grains are mainly produced by eumycetoma. The most common fungi that produce black grain are *M. mycetomatis*, *T. grisea* and *Falciformispora senegalensis*. Among actinomycetoma, *S. somaliensis* usually produce brown-black grain.²

Human actinomycetoma caused by *Streptomyces*, though rare, has been reported in some cases.^{8,9} *Streptomyces* is an aerobic, gram-positive, and filamentous bacteria with extensive well-developed substrate mycelium that does not fragment and produces aerial hyphae with chains of spores.¹⁰ On culture, it produces dry, powdery, or chalky white colonies that emit pungent, earthy, or musty odor.^{9,10} *Streptomyces* is differentiated from *Actinomyces* by being aerobic and from *Nocardia* by being nonacid fast organism that does not fragment into bacillary form.⁹ These characteristic features, along with culture, differentiate *Streptomyces* from other actinomycetes, particularly *Nocardia* sp.⁹ However, identification and speciation of *Streptomyces* is a difficult task because these organisms show marked genetic instability and variability.⁹ Culture is still the gold standard for final etiological diagnosis.⁹ So, for identification of this organism from clinical specimen, high index of suspicion is necessary.⁹ Samples must be investigated both cytologically and microbiologically.⁹ In our case, after cytological examination, an initial diagnosis of eumycetoma was considered, but final diagnosis of actinomycetoma caused by *Streptomyces* was established by culture. Very few data are available on effective treatment of *Streptomyces* infection. The most commonly reported combination regimens for actinomycetoma include parenteral aminoglycosides and oral sulfonamides or dapsone.² Other aminoglycoside and sulfonamide combination regimens include streptomycin or gentamicin in combination with either cotrimoxazole or dapsone. Other regimens include streptomycin with either sulfadoxine pyrimethamine or rifampicin; a combination of penicillin, cotrimoxazole, and gentamicin followed by amoxicillin and cotrimoxazole. Also, regimens that include amoxicillin clavulanate, tetracycline, imipenem–cilastatin, rifampicin, linezolid, clindamycin, or fusidic acid are used.² Ramam et al. described a modified two-step treatment for actinomycetoma. In first step in intensive phase, they used intravenous gentamicin, 80 mg twice daily, and oral cotrimoxazole, 1600/320 mg twice daily, for 4 weeks. It was followed by a maintenance phase with same dose of cotrimoxazole and 100 mg twice daily dose of doxycycline till 5–6 months after complete healing of all sinuses.¹¹ Almost all the patients had significant clinical response. Welsh et al. described a regimen which resulted in 63% cure after one to four cycles. The combination regimen included 3 weeks of intramuscular or intravenous amikacin (15 mg/kg/day) in two divided doses along with 5 weeks of oral cotrimoxazole (40/8 mg/kg/day)

(one cycle of treatment).^{12,13} Mycetoma caused by *Streptomyces* is often treated by penicillin, amikacin, sulfonamides, linezolid, or tetracycline but the cure rate may be low with sulfonamides.¹⁴ Prolonged antibiotic therapy and poor antibiotics penetration within mycetoma tissue are major hindrance factors for treatment-refractoriness in these cases.

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Moyamoya Disease: A Rare Presentation and Literature Review



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ABSTRACT

Moyamoya disease is a rare vasculopathy involving the vessels of the central nervous system, predominantly the internal carotid arteries. A 21-year-old female patient from the Murshidabad district of West Bengal presented to us with an altered sensorium. She was referred to us from another hospital in Kolkata, where she was diagnosed and being treated as a case of ischemic stroke 2 weeks prior to the presentation. There was a significant past history of excruciating headaches, which would be more at night, and did not have any other obvious aggravating or relieving factors. On examination, the plantar was bilaterally extensor, and the patient was afebrile with no signs of meningeal irritation. Neuroimaging with noncontrast computed tomography (CT) head revealed a large right-sided middle cerebral artery (MCA) territory infarct along with acute hemorrhage in the left basal ganglia region. Upon a thorough perusal of the course of treatment at the previous hospital, it was ascertained that there was no usage of antiplatelet or anticoagulant agents there. A magnetic resonance (MR) angiogram of the intracranial blood vessels was therefore ordered, which was suggestive of moyamoya disease. Therefore, it was concluded that the spontaneous and near-simultaneous occurrence of infarct and hemorrhage was due to the vascular anomalies induced by moyamoya disease, making this case an uncommon presentation of a very rare disease.

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INTRODUCTION

Moyamoya disease is a rare occlusive vasculopathy usually involving the branches of the internal carotid artery, although any portion of the anterior circulation may be involved. It was first discovered by Japanese surgeons Takeuchi and Shimizu in 1957,¹ soon after the technique of percutaneous carotid angiography was developed by Shimizu.² The hallmark feature of this disease is hypoplasia of the supraclinoid fragments of bilateral internal carotid arteries, which in turn leads to the development of collaterals, causing an abnormal vascular network at the base of the brain.³ In fact, the word "moyamoya" is a Japanese word for something hazy, like a "puff of cigarette smoke."³ Moyamoya disease is often accompanied by the presence of certain hallmark risk factors; in which case, it is known as moyamoya syndrome. In their absence, it is called moyamoya disease.⁴ The risk factors associated with moyamoya syndrome include race (10 times more common in East Asians, particularly Koreans and Japanese),⁵ and certain diseases and genetic syndromes, as enumerated in the Table 1.⁵

Pathologically, this disease is characterized by the fibrocellular thickening of the intima, wavy undulation of the internal elastic lamina, attenuation of the tunica media, and a decrease in the outer diameter of the affected vessels.⁶

Clinically, moyamoya disease can be divided into ischemic, hemorrhagic, epileptic, or other manifestations.⁷ Ischemic manifestations predominate in children,⁸ while hemorrhagic (which can be both intraparenchymal as well as subarachnoid hemorrhage) is the usual manifestation in adults.⁹ Very rarely, as in our case, both might coexist. Among other manifestations, headache is the most common symptom, arising out of chronic cerebrovascular insufficiency, which also provides the stimulus for collateral formation, which is what is seen as a "puff of smoke" on angiography.

CASE

A 21-year-old married female, student by occupation, resident of Murshidabad district of West Bengal, India, was referred to our hospital in a comatose state. The previous hospital's discharge summary, where she was admitted 2 weeks back with complaints of left-sided hemiparesis and altered mental status, stated that she had been diagnosed as a case of ischemic stroke on the basis of clinical and computed tomography (CT) brain findings, and she was being managed conservatively. The discharge summary even stated that aspirin was not given throughout the course of the disease as the infarct was large and there was substantial risk of hemorrhagic transformation. However, there was a sudden drop in sensorium on day 14 of stay at the previous hospital, when

the relatives of the patient decided to bring her to us.

The patient's husband and parents were inquired about the past medical history. There was a past history of excruciating headaches since the last year, at a frequency of 2–3 attacks per month, which would start acutely, mostly at night, without any aggravating factors. The headaches would persist for variable durations ranging from 5 to 45 minutes and would end spontaneously with time, with no relief from over-the-counter medications. The headache would not be associated with nausea, vomiting, or nasal congestion/tearing, and movement would not aggravate it. In fact, the patient would often be seen running from one corner of the room to the other, trying to bang her head against the walls in search of relief. There was no history of any episode similar to the presentation in the past, neither of any family member suffering from a similar disease. There was no history suggestive of fever, trauma to the head, cardiac disease, malignancy, thyrotoxic

Table 1: Associations with moyamoya syndrome

Common conditions associated with moyamoya syndrome:

- Sickle cell anemia
- Neurofibromatosis type 1
- Graves' disease
- Down syndrome
- Cranial irradiation

Relatively rarer conditions

- Systemic lupus erythematosus
- Turner syndrome
- Noonan syndrome
- Alagille syndrome
- Sneddon's syndrome

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features, seizure disorder, migrainous features, oral contraception, radiation to the head, addiction to drugs, tuberculosis, rheumatic fever, or exposure to sexually transmitted diseases. She was being treated in the line of migraine by her primary care physician but was not compliant with medications.

Upon clinical examination, the Glasgow Coma Scale of the patient was E1V2M5. The patient was afebrile, and there were no signs of meningeal irritation. Plantar response was bilaterally extensor. Pupils were sluggishly reactive. Deep tendon reflexes were exaggerated on the left side and diminished on the right. The patient was immediately admitted, and an urgent noncontrast CT brain (Fig.1) was done, closely followed by a MR imaging (MRI) brain (Fig.2), which revealed a large acute hematoma in the left basal ganglia region, along with a subacute infarct in the right MCA territory, as displayed in the following images.

Prompt measures were taken to reduce the intracranial pressure in the intensive care unit. In the meantime, a thorough evaluation was started to rule out other causes of stroke in young individuals (Table 2).

When all other systemic causes of stroke were ruled out, an MR angiogram of the intracranial vessels was done, which surprisingly revealed marked occlusive disease of the complete anterior circulation (Fig.3) and the fabled "puff of smoke" appearance (Fig.4), which is classical of moyamoya disease. Accordingly, a diagnosis of moyamoya disease was made, and the fact that the patient had developed infarct and hemorrhage within a span of 2 weeks made the presentation extremely unique.

Unfortunately, even with the best of efforts, the patient could not be salvaged,

and she expired on day 4 of admission at our institution.

DISCUSSION

The pathogenesis of stroke in moyamoya disease is multifactorial. While the progressive occlusion of the larger caliber vessels causes the development of collaterals, if the natural history of the disease is of a shorter duration, as in this case, there is an increased propensity to develop ischemic stroke. At the same time, microaneurysm formation is accentuated at the bifurcation points of medium-to-large caliber vessels, and the rupture of those can cause intracranial hemorrhage, much like hypertensive cerebrovascular disease does. In adults, the progressively increasing occlusive process is usually halted, compared to children, in whom there is constant progression. As a result, hemorrhages are more common in adults while infarcts occur more frequently in children. Since this patient was 21 years old, she was probably at the interface of two such processes, causing her to develop both hemorrhage and infarct in such a short span of time.

The severity of moyamoya disease is graded based on the degree of occlusion as well as the degree of collateral formation. The original staging system created by Suzuki (Table 3) was based on catheter angiography; however, newer MR angiography-based techniques are now being increasingly used.

Since catheter angiography was not done in our case, the Suzuki grade of the patient cannot be commented upon.

Currently, there is no known medical treatment that can modify the disease process in moyamoya disease or moyamoya syndrome. The only two classes of medicines that can slow the disease process to some extent are antiplatelets/anticoagulants and vasodilators,¹⁰ with calcium channel blockers providing only symptomatic relief from intractable migraine/headaches/refractory transient ischemic attacks, which are common in these patients. Children with moyamoya usually require lifelong therapy with aspirin, with a dose of 81 mg for children <6 years of age, and variable doses for adults. Anticoagulants like warfarin are rarely used; however, low molecular weight heparin is being increasingly used nowadays at 0.5 mg/kg, particularly for children undergoing surgery, which precludes the use of aspirin. In these cases, aspirin is held for 10 days prior to surgery, during which time heparin is used as a "bridge" to provide anticoagulation, and aspirin is restarted after the procedure.

Table 2: List of baseline investigations

Parameter	Value
Complete blood count (hemoglobin/white blood cell/platelet)	11.5 gm%/10800/mm ³ /2.5 lacs/mm ³
Kidney function tests (urea/creatinine)	38/1.2 mg/dL
Liver function tests: Serum glutamate pyruvate transaminase/serum glutamic oxaloacetic transaminase/alkaline phosphatase/total bilirubin	38/42/26/0.6
Free thyroxine	0.42 (within normal range)
Thyroid stimulating hormone	3.4 (within normal range)
Two-dimensional echocardiogram with saline bubble study	Normal study
High-performance liquid chromatography	Normal study: no abnormal hemoglobin (hemoglobin S) was detected
Antinuclear antibody by human epithelial type 2 method	Negative
Autoantibody panel	Negative
Prothrombin time/international normalized ratio	12.4 seconds/1.1
Sickling test	Negative

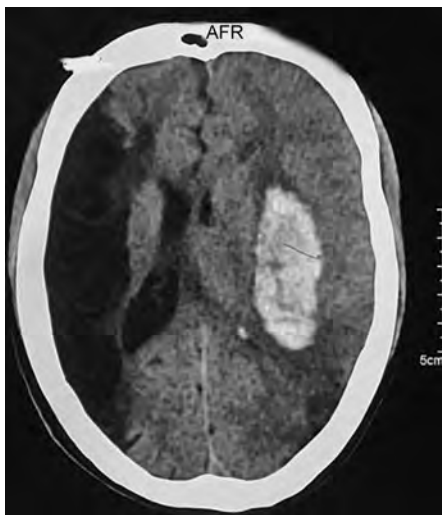


Fig. 1: An urgent noncontrast CT scan of the brain was performed at the time of presentation at our institution

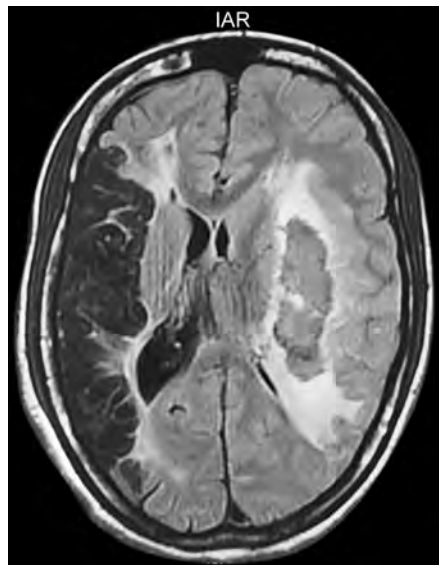


Fig. 2: Axial T2-FLAIR sequence MRI of the brain showed a subacute infarct in the right MCA territory and an acute hematoma in the left basal ganglia region with perilesional edema and ventricular compression



Fig. 3: Magnetic resonance angiogram showed streaking of the supraclinoid internal carotid arteries along with the anterior cerebral and middle cerebral arteries

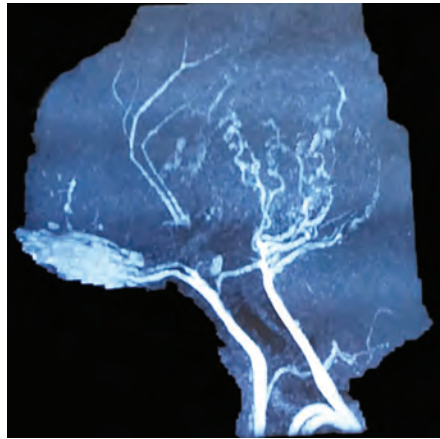


Fig. 4: Magnetic resonance angiogram (sagittal view) showed the classical "puff of smoke" appearance

Table 3: Suzuki grading of moyamoya disease

Grade	Definition
I	Narrowing the apex of the ICA*
II	Incipient moyamoya vessels
III	Progressive stenosis of the ICA and intensification of moyamoya vessels
IV	Development of collaterals from the ECA**
V	Intensification of ECA collaterals and reduction of moyamoya vessels
VI	ICA occlusion and disappearance of moyamoya vessels

**ECA, external carotid artery; *ICA, internal carotid artery

Surgical management options have increased by leaps and bounds in recent years. Surgical procedures that may be done include direct as well as indirect revascularization procedures. Direct procedures include bypass procedures like superficial temporal artery-middle cerebral artery (MCA) bypass, first performed by Yasargil and Donaghy.¹¹ It is the most common direct revascularization procedure, with an added benefit of supporting the anterior cerebral artery territory by means of leptomeningeal anastomoses. Other direct revascularization procedures include

superficial temporal artery-anterior cerebral artery, superficial temporal artery-posterior cerebral artery, and occipital artery-posterior cerebral artery anastomoses. Grafts used in these anastomoses may be high-flow bypass (saphenous vein graft) or intermediate-flow graft (radial artery graft). The chief problems associated with direct revascularization procedures are the unavailability of good grafts and the complications of the surgery. Outcomes are poorer in children; hence, direct revascularization procedures are preferred in adults.

Indirect revascularization procedures are mainly performed on children, with the principle being the usage of pedicle-based grafts to cause neovascularization of the cortical surface. The main advantage over direct revascularization procedures is the considerable ease of the surgery, with the compromise being that neo-vessels take months to develop. Procedures used are:

- Vascularization procedures: Encephalomyosynangiosis (EMS). Encephaloarteriosynangiosis (EAS). Encephalomyoarteriosynangiosis (EMAS). Encephaloduroarteriomyosynangiosis (EDAMS). Encephalodurogaleosynangiosis.
- Multiple burr holes: Mainly used as a rescue neovascularization procedure.

- Omental transplantation: Showed 98% improvement in cerebral neovascularization. The main indication of this procedure is in children with anterior cerebral artery and posterior cerebral artery involvement.¹²

CONCLUSION

Moyamoya disease is a diagnosis of exclusion. Far more common is the moyamoya syndrome, which occurs secondary to the presence of other risk factors as mentioned in Table 3. It is also imperative that in the presence of any of these risk factors, the treating physician addresses them. In conditions like sickle cell anemia, which is one of the commonest culprits behind the syndrome, regular blood transfusion markedly reduces the risk of life-threatening stroke. The elusive moyamoya disease, however, is extremely rare, with a high mortality rate and more research is needed to elucidate its etiopathogenesis. Although treatment options, predominantly neurosurgical, are currently developing at a rapid pace, with the passing of time, one can only expect the outcomes to improve.

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A Very Rare Side Effect of a Very Commonly Used Drug: Pantoprazole-induced Seizure

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ABSTRACT

Pantoprazole is an extensively used proton pump inhibitor (PPI) for acid peptic disease. PPI rarely cause hypomagnesemia. Hypomagnesemia is commonly associated with hypokalemia and hypocalcemia. Severe hypomagnesemia and hypocalcemia can cause seizures. Here, we report a patient on long-term pantoprazole who presented with generalized tonic-clonic seizures and had severe hypomagnesemia, hypocalcemia, hypokalemia, and secondary hyperparathyroidism. When patients on long-term PPI present with seizures, hypomagnesemia/hypocalcemia has to be excluded.

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CASE DESCRIPTION

A 69-year-old woman with coronary artery disease on clopidogrel, aspirin, atorvastatin, telmisartan, metoprolol, and pantoprazole since the last 3 years presented with one episode of generalized tonic-clonic seizures followed by prolonged postictal confusion. There was no history of fever, headache, vomiting, diarrhea, or weight loss. There was no history of recent diuretic use. On examination, she had blood pressure of 150/90 mm Hg. There was a lateral tongue bite, and she was confused. Computed tomography (CT) of the head and magnetic resonance imaging (MRI) of the brain were normal. Electrocardiogram (ECG) showed T-wave inversion in inferolateral leads with QTc 457 ms. Biochemical evaluation showed severe hypomagnesemia, hypokalemia, and hypocalcemia (Table 1). Her corrected calcium and ionized calcium were low. Fractional excretion of magnesium was 1.21, suggesting a nonrenal mechanism of hypomagnesemia. Urine potassium:creatinine ratio was 26 mEq/gm, suggestive of renal potassium loss. Arterial blood gas analysis showed mild respiratory alkalosis. Electroencephalogram taken the next day was normal. Her vitamin D level (39.01 ng/mL) and serum alkaline phosphatase were normal. Serum intact

parathyroid hormone (PTH) level was elevated to 114 pg/mL (normal 15–65 pg/mL). She was treated with intravenous magnesium sulfate and intravenous calcium gluconate followed by oral calcium carbonate (1000 mg) and calcitriol (0.5 µg) daily. She became asymptomatic by the next day. Her ECG changes reverted to normal after correction of hypomagnesemia and hypokalemia. Repeat QTc was 415 ms. Meanwhile, her pantoprazole was changed to ranitidine. Her serum magnesium and potassium levels became normal by the next day, and calcium levels improved to normal level by the fifth day.

The association between PPI therapy and hypomagnesemia has been recognized since 2006.^{1,2} PPIs are proposed to decrease the activity of transient receptor potential melastatin 6 (TRPM6), which causes reduced magnesium absorption from the intestine. PPI-induced hypomagnesemia (PIH) occurs in <1% of patients on PPI. PIH is more common in the elderly and is commonly associated with diuretic use. PIH is a class effect and is reported with all PPIs. This risk is more in patients with PPI use of over 1 year.³

Hypomagnesemia is usually associated with hypokalemia. Magnesium binds to the inner surface of the renal outer medullary potassium (ROMK) channel in the cortical collecting duct, limiting potassium efflux. With hypomagnesemia, this inhibition is lost, causing increased potassium loss through the kidneys as was in our case.

Magnesium is a cofactor necessary for PTH production in parathyroid glands. Hypomagnesemia can be associated with either low (hypoparathyroidism) or high PTH levels (PTH resistance).^{4,5} Hypomagnesemia blocks the release of PTH and decreases the sensitivity of target organs to PTH and causes a biochemical picture simulating hypoparathyroidism. Our patient presented

with seizures and had hypomagnesemia, hypokalemia, and hypocalcemia with elevated PTH levels. When elderly patients on PPI present with seizures and hypomagnesemia, hypomagnesemic hypoparathyroidism should be ruled out. Deprescribing PPIs or prescribing ranitidine may be considered in such cases. The hypomagnesemia can be partially corrected by high dose oral magnesium supplementation and resolves on withdrawal of PPIs.^{6,7}

In conclusion, PPI use can inhibit active magnesium transport in the intestine and can eventually deplete total body magnesium stores and present with severe complications of hypomagnesemia.

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Table 1: Blood biochemistry

Blood parameters	Result	Normal range
Fasting blood glucose	97 mg%	70–110 mg%
Creatinine	1.02 mg%	0.7–1.4 mg%
Sodium (Na)	141.2 mEq/L	136–145 mEq/L
Potassium (K)	3 mEq/L	3.8–5.5 mEq/L
Calcium (Ca)	5.5 mg%	8.8–10.5 mg%
Phosphorus (P)	2.97 mg%	2.5–3.5 mg%
Magnesium (Mg)	1 mg%	1.9–2.6 mg%

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Symptomatic Palatal Tremors in a Rare Treatable Neurometabolic Disorder: A Case Report

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ABSTRACT

Background: Palatal tremor (PT) is an involuntary, rhythmic and oscillatory movement of the soft palate. Two types of PTs—essential palatal tremor (EPT) and symptomatic palatal tremor (SPT) are described. SPT is caused by a lesion in the triangle of Guillain and Mollaret which is formed by the ipsilateral red nucleus, ipsilateral inferior olivary nucleus and contralateral dentate nuclei. EPT reveals no underlying structural pathology.

We describe two consecutive patients with PT—a rare clinical sign in a rare distinct clinical entity cerebrotendinous xanthomatosis (CTX) which is an autosomal recessive neurometabolic disorder characterized by a myriad of neurological signs of progressive ataxia, parkinsonian features pyramidal signs, epilepsy; peripheral neuropathy, and nonneurological features of early cataract, xanthomas and infantile-onset diarrhea. These cases emphasize the expanding phenotype of CTX featuring PTs and suggest that this clinical sign is underdiagnosed in CTX.

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INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive neurological disorder characterized by hallmark nonneurological features of early cataracts, xanthomas, and infantile-onset diarrhea on the background of a myriad of neurological features of progressive ataxia, parkinsonian features pyramidal signs, epilepsy; peripheral neuropathy and it is caused by defective sterol 27 hydroxylase, encoded by CYP27A1 gene, which is responsible for conversion of cholesterol into bile acids. Defect in this enzyme results in abnormal accumulation of cholestanol and cholesterol, mainly in the central nervous system, eyes, tendons, and vessels.¹

CASE 1

A 27-year-old female born out of a consanguineous marriage, with delayed motor and language milestones, with intellectual disability, operated for cataracts

at the age of 10, developed painless progressive swellings over both ankles at 18 years. She had a progressive neurological disability in the form of dysarthria, hypersalivation, feeding difficulties, ataxia, postural abnormalities with recurrent falls, and behavioral abnormalities in the 3rd decade.

Examination revealed seborrhea, hypersalivation, mask-like face, wide opened mouth with crowded incisors with a vacuous smile, bilateral posterior corneal opacities, with bilateral symmetrical, fusiform, nontender, soft, and nonfluctuating swelling over the Achilles tendon (Fig. 1). Patient had continuous, (Video 1) involuntary, rhythmic, and palatal myoclonus not associated with any audible click. The patient also had poor attention, apathy, hypotonia in distal upper limbs, spasticity in lower limbs, bipyramidal signs, release reflexes, bilateral cerebellar signs, bradykinesia, and postural instability. Her blood investigations and lipid profile were normal. X-ray showed soft tissue

radiodense opacity noted on the region of the Achilles tendon depicted in solid arrows (Fig. 1).

Magnetic resonance imaging (MRI) brain (Fig. 2) showed hyperintensity in bilateral basal ganglia on T1 weighted sagittal image. The dentate nucleus appeared hypointense on T1 and hyperintense on T2 weighted image with bilateral, symmetrical diffuse cerebellar, and cortical atrophy suggestive of cerebral xanthomatosis.

The patient was treated with oral ursodeoxycholic acid (UDCA) and hydroxymethylglutaryl-CoA (HMG-CoA) inhibitors. The patient subsequently showed subtle improvements in cognitive functions. Falls and hypersalivation subsided, feeding difficulties improved, palatal myoclonus marginally improved, and the patient is in regular follow-up.

CASE 2

A 35-year-old male who is having intellectual disability, with no formal education, developed cataracts at the age of 13 years got operated, and developed soft, lobulated nonfluctuating swellings over both ankles from the age of 20 years, which gradually progressed in size. The patient presented with unsteadiness while walking, clumsiness of activities, tremulousness of hands, complex partial seizures, and pathological laughter in the 4th decade.

On examination, the patient has dolichocephaly, premature graying of scalp hair and beard, seborrhoea over the midline of the face, hyperpigmentation over the face, multiple sebaceous cysts over the body, and multiple xanthomas over the Achilles tendon. On slit lamp examination, showing posterior corneal opacities were noted. Neurological examination revealed



Fig. 1: Bilateral fusiform tendon xanthomas with soft tissue radiodense opacity noted on the region of the Achilles tendon depicted in solid arrows

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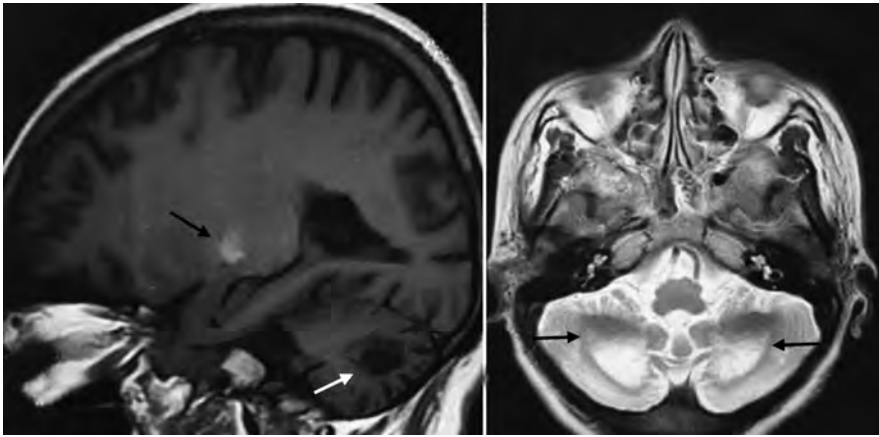


Fig. 2: T1 weighted sagittal image showing hyperintensity in basal ganglia and hypointensity in the dentate nucleus and T2 weighted axial image shows hyperintensities in bilateral dentate nuclei

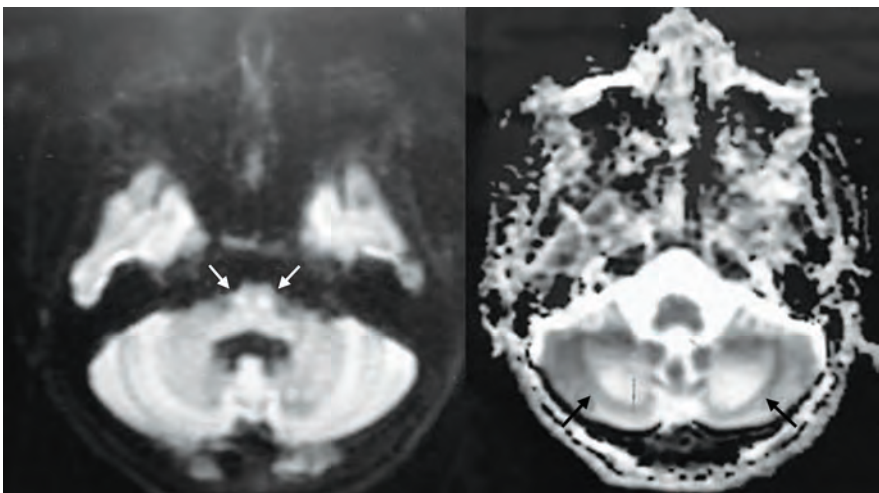


Fig. 3: Diffusion-weighted axial image shows bilateral inferior olive hyperintensities with enlargement (white arrows) isointense dentate nuclei and ADC sequence showing hyperintense signal in the same

impaired attention, executive dysfunction, and pathological laughter. The patient had bilateral pyramidal signs with pancerebellar features with continuous, involuntary rhythmic, and palatal myoclonus not associated with any audible click.

His blood investigations were normal, and serum cholestanol levels were elevated. MRI brain (Fig. 3) diffusion sequence shows bilateral inferior olive hyperintensities with enlargement and isointense dentate nuclei with apparent diffusion coefficient (ADC) sequence showing hyperintense signal in the same.

The patient was treated with oral UDCA and HMG-CoA inhibitors but did not show any clinical improvement.

DISCUSSION

In our patients, the PT was associated with the entire myriad of neurological (progressive ataxia, parkinsonian features progressive neuropsychiatric manifestations, and

bipyramidal features) and nonneurological clinical signs such as tendon xanthomas and juvenile cataracts which are considered diagnostic hallmarks of CTX.¹ Common causes of symptomatic palatal tremor (SPT) are cerebrovascular disease, encephalitis, multiple sclerosis, trauma, and neurodegenerative disease. Among these, all have an acute to subacute onset of illness, except those secondary to neurodegenerative disease, as in our patient.

Palatal tremor (PT) has been observed in a variety of neurodegenerative diseases like olivopontocerebellar atrophy, Alexander's disease, progressive supranuclear palsy, spinocerebellar ataxia type 20,² spastic paraplegia type 7,³ and neuroferritinopathy.⁴

Movement disorders occur rarely in CTX and are usually a late, less prominent feature with an incidence of 23%.⁵ Parkinsonism was the most frequently reported movement disorder seen in 9% of all patients,⁶ followed by dystonia, myoclonus, and postural tremor.

The reported incidence of "extrapyramidal signs" in CTX is 21–33%.⁷ CTX is a treatable cause of movement disorders and is hence to be considered in the evaluation of the same. In CTX, other neurologic features dominate and movement disorders tend to be overlooked.⁸

The mean age at diagnosis was 35 ± 11 years and that of Parkinsonian symptoms was 40 ± 12 years, and 38 ± 15 years in the case of the other movement disorders.⁸ In both our cases, cognitive impairment was the initial manifestation followed by pyramidal, cerebellar, and atypical Parkinson's features.⁹ PTs were found incidentally on clinical examination and lacked any pertaining symptoms.

The second most reported movement disorder in CTX is dystonia, mostly multifocal in nature. The occurrence of dystonia in CTX is probably due to dysfunction of sensorimotor integration and abnormal cerebellar output.⁹ Our patients did not have dystonia. In a cohort of 62 cases of CTX, only 11 patients had myoclonus of whom only five had PTs/myoclonus and the rest had myoclonus involving the limbs.⁹ Dysfunction in the dentato-rubro-olivary pathway contributes to hypertrophic olivary degeneration, which could in turn play a role in the occurrence of palatal myoclonus.¹⁰ Postural tremors are seen in a minority of patients and are likely part of a Parkinsonian, dystonic, or cerebellar syndrome.

Exogenous administration of chenodeoxycholic acid (CDCA) has a negative feedback effect that reduces the synthesis of bile acid, thus preventing the accumulation of cholestanol. CDCA is known to halt the progression of the disease. The drug, CDCA, is not available in India and is very expensive, hence, UDCA was tried on our patients. It has been observed that the combination of CDCA and HMG-CoA inhibitors is more effective. Treatment with CDCA normally arrests and prevents the development of new neurological symptoms with limited effect on movement disorders. After significant pathology has occurred, the effect of treatment is limited and deterioration may continue. The effect of L-dopa is controversial, with a mild or temporary effect in most patients but our patients did not show much response. The transsynaptic degeneration of the dentato-rubro-olivary pathway produces hypertrophy of the inferior olivary nucleus which is a neural substrate for PTs.¹⁰ Diffusion-weighted images of our patients showed hyperintensities of the olivary nucleus.

As our patient had the hallmark features of CTX, we did not subject the patient to genetic analysis. Genetic testing in presymptomatic family members of affected patients should be

done and UDCA therapy instituted to prevent the development of disabling neurological disease manifestations.

CONCLUSION

Movement disorders represent a rare clinical feature in CTX and among them, SPTs are very rarely reported in the literature. CTX must be included in the preexisting list of neurodegenerative causes of PT. CTX should be considered in the differential diagnosis of movement disorders, particularly in early-onset cases, especially when associated with other neurological features (especially cognitive impairment, pyramidal and cerebellar signs) and/or with systemic features (such as diarrhea, cataracts, and tendon xanthomas). Hyperintense signals of the olivary nucleus are a characteristic

radiological sign of CTX and the substrate for PT. Genetic testing in presymptomatic family members of affected patients should be done and therapy instituted to prevent the development of disabling neurological disease manifestations.

SUPPLEMENTARY MATERIAL

Video 1: Palatal tremor.

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Sialadenitis in Antineutrophil Cytoplasmic Antibodies Vasculitis

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is a pauci-immune vasculitis typically involving upper and lower respiratory tract involvement and crescentic glomerulonephritis. Salivary gland involvement in GPA is rare. When it occurs in GPA, it is commonly seen with sinonasal and lung involvement and rarely with renal involvement. Easy accessibility of salivary glands allows early biopsy and timely treatment. In our case with GPA, salivary gland involvement was unresponsive to cyclophosphamide but remitted with rituximab.

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INTRODUCTION

Granulomatosis with polyangiitis (GPA), is a pauci-immune vasculitis characterized by necrotizing granulomas. The symptoms of GPA vary depending on the organs affected. It typically exists as a triad of upper and lower respiratory tract involvement and crescentic glomerulonephritis. Other common symptoms include fever, ocular involvement like scleritis, joint involvement, skin lesions,

myocarditis, and central or peripheral nerve involvement. Involvement of salivary glands is very rare. Here, we report a rare case of bilateral parotid and submandibular gland involvement secondary to GPA.

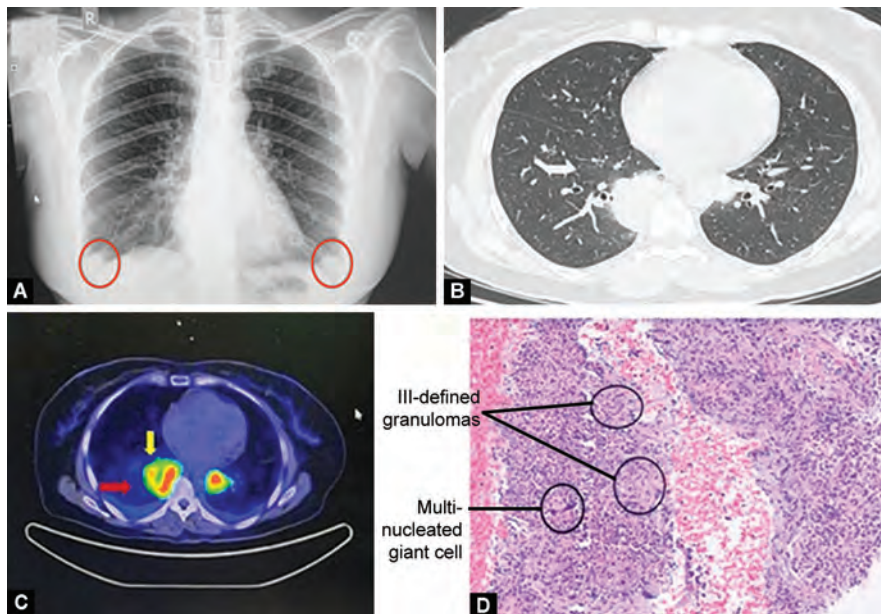
CASE

A 54-year-old female was symptomatic for 2 weeks with a dry cough, pleuritic chest pain, intermittent fever, and streaky

hemoptysis. There was a weight loss of 6 kg in 1 month. There was no past history of tuberculosis (TB) or contact with TB patients. She was a nonsmoker and lacked any allergic tendencies. There were no other articular, extra-articular, or systemic features.

On examination, there was tachycardia (100/minute). The rest of the vital signs were normal. There was no lymphadenopathy, nasal polyps, or tonsillar hypertrophy. Apart from the bilateral basal crepitations, the rest of the systemic examination was unremarkable.

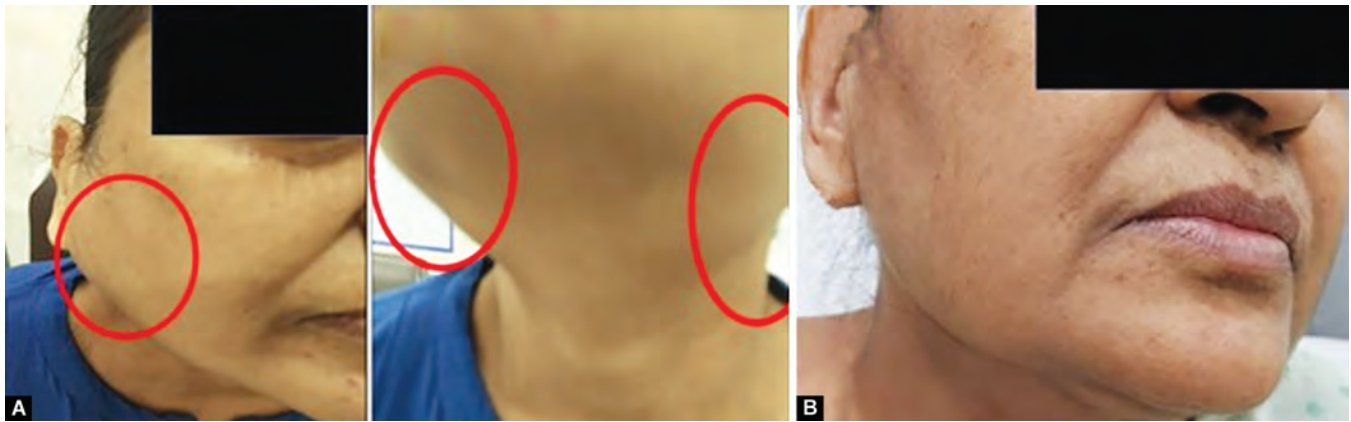
Investigatory reports were—hemoglobin: 8.9 gm/dL ($n = 13$ gm/dL); total white blood cells (WBC): 14340/mm³ ($N: 90\%$); platelets: 6.8 L/mm³ ($n = 4.5$ L/mm³); erythrocyte sedimentation rate (ESR): 85 mm/hour ($n = 20$); and a C-reactive protein (CRP): 81 gm/dL ($n = 6$ gm/dL). Liver function and kidney function tests were normal. A routine urine routine examination was normal. X-ray chest showed pleural-based soft tissue densities in the bilateral lower lobe (Fig. 1A). High-resolution computed tomography (HRCT) of the chest revealed heterogeneously enhancing necrotic lesions in bilateral lower lobes and pleural-based nodules along with peribronchial ground glass opacities, peribronchial wall thickening, and subcentimetric lymphadenopathy (Fig. 1B). The workup for infections including blood culture, sputum culture, and sputum for mycobacteria growth indicator tube (MGIT)/Gene Xpert was negative. The whole-body positron emission tomography (WB-PET) scan was normal except for showing metabolic activity in the nodules



Figs 1A to D: (A) X-ray chest PA view showing pleural-based soft tissue densities (marked in red) in bilateral lower lobes; (B) HRCT of the chest showing heterogeneously enhancing necrotic lesions in bilateral lower lobes along with pleural-based nodules, peribronchial ground glass opacities, peribronchial wall thickening, and subcentimetric lymphadenopathy; (C) Whole body PET scan showing metabolically active multiple necrotic pleural-based nodules/masses predominantly along the mediastinal and parietal pleura in the lower lobes (marked in red) of both lungs along with metabolically active peribronchial wall thickening involving bilateral main bronchi and lower lobe bronchi (marked in yellow) leading onto consequential consolidation in lower lobes of both lungs; (D) Histopathology of CT-guided lung biopsy showing multiple epithelioid granulomas, few multinucleated giant cells with dense inflammation of PMNs, lymphocytes, plasma cells, and eosinophils along with fibrinoid necrosis and leukocytic angiitis

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Figs 2A and B: (A) A bilateral parotid enlargement marked in red; (B) The resolution of parotid enlargement after four doses of injection rituximab



Fig. 3: Histopathology of submandibular gland biopsy showing granulomatous sialadenitis with vasculitis with moderate lymphocytic, plasmacytic, polymorphonuclear, epithelioid granulomas with giant cells, and leukocytoclastic vasculitis

and peribronchial wall thickening found on the HRCT chest (Fig. 1C). CT-guided biopsy from the right lower lobe lung lesion showed multiple epithelioid granulomas with a few multinucleated giant cells and dense inflammation of neutrophils, lymphocytes, plasma cells, and eosinophils along with fibrinoid necrosis and leukocytic angiitis (Fig. 1D). Serology for C-antineutrophil cytoplasmic antibodies (ANCA) (1:100 2+) and PR3 (>200) was strongly positive. A diagnosis of GPA was made and she was treated with pulse methylprednisolone 500 mg for 3 days followed by oral prednisolone 0.5 mg/kg/day and an injection of cyclophosphamide 500 mg as per the European Vasculitis Society (EUVAS) protocol.

However, in 2 weeks, she developed bilateral firm swelling in the parotid region causing pain while chewing and needing nonsteroidal anti-inflammatory agents, analgesics, and gabapentin (Fig. 2A). The CRP had risen to 142 gm/dL. Ultrasonography of the parotid region showed acute inflammation in parotids, submandibular, accessory parotids, and sublingual glands. The prednisolone dose was increased to 1 mg/kg/day and cyclophosphamide injections were continued

Table 1: The trend of investigations with respect to rituximab

	Before rituximab	After two doses of rituximab	After three doses of rituximab	After four doses of rituximab	1 month after rituximab doses were over
Hemoglobin(g/dL)	10	11.3	11.1	11.4	11.3
TLC (mm ³)	8030	10600	10100	12400	11000
Platelet (mm ³)	3.48 L	3.19 L	3.76 L	3.43 L	3.75 L
CRP (gm/dL)	61	21	17	56	1.6
Creatinine (gm/dL)	0.4	0.8	0.9	0.8	0.8

at a higher dose of 800 mg. In spite of three doses of cyclophosphamide and steroid doses of 1 mg/kg/day for a month, the parotid swelling remained persistent. The pain was so severe that she needed an opioid patch. However, previous symptoms of dry cough, fever, and streaky hemoptysis had responded very well to immunosuppression.

Refractoriness of the parotid swelling despite high-dose immunosuppression prompted us to rule out other causes. CT neck showed bulky bilateral parotid glands with diffuse fatty infiltration, few nodular areas, and a soft tissue thickening in the nasopharynx. Polymerase chain reaction (PCR) for Epstein-Barr virus and cytomegalovirus was negative. Human immunodeficiency virus enzyme-linked immunosorbent assay and mumps immunoglobulin M/immunoglobulin G (IgM/IgG) were negative. Serum angiotensin convertase enzyme (ACE) was normal at 18 gm/dL; IgG4 levels was 1.2 gm/L (n —up to 1.4 gm/L). A submandibular gland biopsy was done and showed granulomatous sialadenitis with vasculitis with moderate lymphocytic, plasmacytic, polymorphonuclear infiltrates, epithelioid granulomas with giant cells, and leukocytoclastic vasculitis without evidence of IgG4 disease (Fig. 3). This confirmed that the glandular enlargement was a part of the GPA.

Four doses of injection cyclophosphamide 800 mg were completed. However, the parotitis worsened. A repeat CT scan of the chest also

showed the progression of nodules in the chest. So, she was treated with four doses of injection rituximab 500 mg once every week and a slow taper of steroids by 5 mg every week. Serial CRP values improved (Table 1).

On tapering steroids to 10 mg/day, she developed Bell's palsy which responded to a dose hike of prednisolone. Seven weeks after the last dose of rituximab, the parotid swelling and pain have decreased significantly (Fig. 2B). She no longer needs any pain relievers, and steroids have been successfully tapered to 10 mg/day.

Discussion

Salivary gland involvement in GPA is a rare feature seen in 1–3% of the GPA cases in the literature.¹ It was first described by Fahey et al. in 1954.² There are approximately 60 cases reported in the literature so far. In the case series on GPA from north India of 105 patients by Sharma et al.,³ 60 patients from south India by Shobha et al.,⁴ and 42 patients from western India by Singh et al.,⁵ salivary gland involvement was not found in any patient.

In the systematic literature review by Chandwar et al.¹ of 58 patients of GPA with salivary gland involvement, the average age of patients was 50 with a slight male predominance. Our patient was a 54-year-old female. The parotid gland was the most commonly involved in 88% of patients.

About 52% had bilateral parotid involvement. Submandibular gland involvement was seen in 22% of cases. In the systematic literature review by Akiyama et al.⁶ of 53 patients, almost 50% of patients had a fever, 47% had pain, and 19% had weight loss. Both parotid and submandibular glands were involved in 14%. Our patient had both parotids as well as submandibular gland involvement and a significant weight loss of 6 kg. The parotid involvement in GPA could be sterile parotitis, sterile parotid abscess, cutaneous fistula, or facial nerve involvement.¹

Salivary gland involvement in GPA is commonly seen along with ear, nose, throat (ENT) (74%) and lung involvement (67%).^{1,6} Less commonly there is renal (29%), CNS (16%), ocular, and mucocutaneous (12%) involvement along with salivary gland involvement. Salivary gland involvement is associated with less serious manifestations of GPA and it may be a good prognostic factor. Patients with salivary gland involvement had lower mortality and morbidity.⁷ Lower mortality was also reported by Specks et al.⁸ possibly due to the easy accessibility of salivary glands for an early biopsy and subsequent treatment. In the last decade, there has been a reduction in the trend of renal involvement in cases of GPA with salivary gland involvement.⁷ It could be due to increasing awareness of this manifestation and hence an early referral and treatment. Our patient did not have renal involvement. She had GPA limited to the lungs. Central nervous system (CNS) involvement in cases of GPA with salivary gland involvement predominantly involves hearing loss (44%) and facial nerve palsy (17%).⁷ Facial nerve palsy is commonly seen on the side of parotid involvement possibly due to close proximity due to direct injury by the inflamed parotid. Facial nerve involvement in GPA could also be seen due to inflammation in the nervorum. Our patient also had subtle facial nerve palsy which resolved on higher doses of steroids.

The most common causes of bilateral parotitis are infections like mumps, Epstein–Barr virus, cytomegalovirus, human immunodeficiency virus, bacteria, and TB. *Staphylococcus aureus*, a well-established infective cause of GPA, can also cause parotitis.⁷ Bilateral parotid enlargement in GPA could also be a coexistence of Sjogren's syndrome, sarcoidosis, or IGG4. Chronic parotitis can also be seen with lymphomas and malignancies. All these differential diagnoses need to be ruled out diligently. Pakalniskis et al.⁹ reported low signal intensity on T2 weighted image on magnetic resonance imaging (MRI) to be suggestive of necrotic foci and a characteristic marker of GPA involvement of salivary glands. These findings were seen in our case as well. However, the gold standard is a tissue diagnosis. In our patient, we ruled out all other differential diagnoses with appropriate tests and confirmed that it was indeed GPA parotitis by the classical histopathology findings on submandibular biopsy.

In the literature, salivary gland involvement in GPA has been known to respond well to high-dose steroids and cyclophosphamide.¹⁰ However, in that study, 21% had a relapse of the GPA per se while only two patients had a relapse of salivary gland involvement.⁶ Both these patients responded to the treatment with an injection of rituximab. Rituximab has been used successfully in refractory GPA with 61.3% of patients achieving complete remission.¹⁰

CONCLUSION

Our patient with biopsy-proven GPA developed bilateral recalcitrant sialadenitis. Care was taken by the means of blood tests and histopathology to rule out other differential diagnoses and confirm GPA of the salivary gland. The sialadenitis did not respond to steroids and needed rituximab.

Salivary gland involvement in GPA though rare is known and needs appropriate investigations and aggressive treatment.

WRITTEN AND INFORMED CONSENT FOR DATA AS WELL AS PUBLICATION

Written (signed) and informed consent was obtained from the patient for accessing the data records as well as for publication of the case in this reputed journal.

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Atrial Fibrillation Secondary to Levothyroxine Overdose with Underlying Secondary Infection

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ABSTRACT

This case report presents the clinical course and management of a 62-year-old female patient with atrial fibrillation (AF) secondary to levothyroxine overdose along with an underlying secondary infection. The patient was admitted with sudden onset dyspnea, altered sensorium, and neurological deficits. Upon examination, she exhibited tachycardia, irregular heart sounds, and extensive crepitations in the respiratory system. Her electrocardiogram (ECG) showed an absent P wave with a varying RR interval. Laboratory investigations revealed abnormal thyroid function tests (TFTs) and raised polymorphonuclear cells, in addition to hyperglycemia. The patient was managed in the intensive care unit (ICU) with bilevel positive airway pressure (BiPAP) and supplemental oxygen, treated for AF with intravenous (IV) amiodarone, and her blood sugar was controlled with insulin infusion. Discontinuation of levothyroxine therapy was advised. Subsequently, her AF was terminated, and sinus rhythm was restored. Her neurological examination showed right-sided hemiplegia with aphasia. After 1 week of treatment, her TFTs normalized, and she was discharged on appropriate medication.

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INTRODUCTION

Atrial fibrillation (AF) stands as the most prevalent arrhythmia observed in clinical practice, and it is linked with significant outcomes such as symptoms, hemodynamic instability, escalated cardiovascular mortality, and stroke. The initiation of AF due to medications is more prone to occur in patients with risk factors and concurrent ailments that accompany AF, including hypertension, thyroid irregularities, sleep apnea, and heart conditions. Additional contributing factors encompass advanced age, alcohol consumption, familial predisposition, among others.¹ Al-Makhamreh et al. carried out a retrospective study which determined that the prevalence of thyroid disorders in patients with AF was 10.5%. The findings indicated that 90% of these cases were attributed to hypothyroidism, while hyperthyroidism accounted for only 6.1%.² Studies have indicated a link between genetically higher FT3:FT4 ratios and hyperthyroidism and an elevated occurrence of AF.³ Levothyroxine overdose is a potential trigger for AF, and underlying infections can exacerbate this condition. We present a case of AF secondary to levothyroxine overdose along with an underlying secondary infection, leading to significant clinical manifestations and neurological deficits. There are reports on hypothyroidism and AF, but no such

evidence was found for overdosing and hyperthyroidism in India.

CASE DESCRIPTION

A 62-year-old female presented to us with complaints of sudden onset dyspnea and altered sensorium for the past 7–8 hours. The patient had a history of a right-sided stroke 3 years ago and was on levothyroxine 150 µg daily for hypothyroidism diagnosed 6 months ago at a different hospital. On admission, the patient was unresponsive to deep stimuli, had pallor on examination, and the rest of the general physical examination was unremarkable. The respiratory rate was 40 breaths per minute, the heart rate ranged between 170 and 180 beats per minute, the temperature was 37.0°C, and a varying pulse. Respiratory system examination revealed bilateral extensive crepitations. Cardiac examination indicated tachycardia with irregular heart sounds. The patient's saturation of peripheral oxygen (SpO₂) was 48% and blood pressure was 210/100 mm Hg. The CHA2DS2-VASc score was five. Neurological examination could not be performed initially due to the patient's altered sensorium.

Investigations

Routine investigations revealed hemoglobin—10.9 gm/dL, leukocytosis (22,100/µL), neutrophilia (82%), indirect hyperbilirubinemia (1.87 mg/dL), mild transaminitis (aspartate

transaminase—73.3 U/L, alanine aminotransferase—48.8 U/L). Serum creatinine was 1.2 mg/dL, blood sugar levels of 321 mg/dL; urine examination showed sugar + and ketones +, and epithelial cells <2. Urine microscopy was normal, and the erythrocyte sedimentation rate (ESR) was 45 mm at 1 hour (Table 1). The thyroid function test (TFT) revealed elevated free T3 and T4 levels and low thyroid stimulating hormone (TSH) levels (Table 2). Electrocardiogram (ECG) showed an absent "P" wave with varying "RR" intervals (Fig. 1). Blood culture was sent for culture and sensitivity. We were unable to perform a chest X-ray due to the hospital's lack of a portable X-ray machine, which was complicated by the patient's bedridden state. The patient was diagnosed with probable AF secondary to a levothyroxine overdose with an underlying secondary infection.

The patient was taken to the intensive care unit (ICU) and started on bilevel positive airway pressure (BiPAP) with supplemental oxygen of 10 L. Intravenous (IV) furosemide 40 mg and IV amiodarone 150 mg were administered slowly, which resulted in the termination of AF and restoration of sinus rhythm (Fig. 2). Hyperglycemia was treated with a rapid-acting insulin infusion. For the underlying infection, the patient was started on Inj. cefoperazone/sulbactam 1.5 g TID empirically, and levothyroxine therapy was discontinued. After treatment, the patient's SpO₂ improved to 93%, and her respiratory rate normalized to 16–24 breaths per minute. Neurological examination revealed right-sided hemiplegia with aphasia. Subsequently, the patient's consciousness improved, and urine output became normal. Blood culture report suggested *Staphylococcus aureus* with

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sensitivity to multiple antibiotics, including cefoperazone. The patient was discharged after seven days of hospitalization; she was afebrile, and there was complete normalization of blood parameters. The patient was discharged on medications including oral amoxicillin for 1 week, clopidogrel, and atorvastatin. On follow-up, the patient's TFT had returned to normal levels (Table 2).

DISCUSSION

Atrial fibrillation constitutes a notable arrhythmia linked to various risk factors, including thyroid dysfunction. The frequency of AF rises with age, exemplified by its prevalence ranging from 6.4% among individuals aged 64–69 years to 28.5% among those aged over 85 years.⁴ The pathophysiology of AF is defined by changes in both the electrical and structural components within the atrial myocardium. The most significant connection with AF is observed in cases of overt hyperthyroidism (characterized by low TSH levels and elevated T4 levels). This condition can lead to a threefold increase in the likelihood of developing AF; however, it remains relatively uncommon. More recently, instances of subclinical hyperthyroidism (low TSH levels with normal T3/T4 levels), typically seen as harmless, have been linked to a heightened risk of AF as well (with a hazard ratio ranging around 1.5). The exact mechanisms underlying the development of AF in thyroid disorders are not yet fully comprehended, but experimental research suggests that both elevated and diminished TSH levels might instigate slowing of atrial electrical conduction and fibrotic changes, thereby promoting the substrate for AF.⁵ Etiology-related elements that elevate the likelihood of AF include aging, myocardial infarction, hypertension, chronic obstructive pulmonary disease, obesity, hypo/hyperthyroidism, and medications. Indications observed in AF include palpitations, fatigue, dyspnea, chest discomfort, dizziness, fainting, or the individual might display no symptoms at all.⁶ In the scenario under consideration, the individual exhibited a rapid onset of breathlessness and changes in cognitive function. These manifestations might arise from an underlying infection and a history of stroke. Gong et al. conducted a nested case-control study in a population-based setting, revealing that among 189,672 elderly individuals undergoing levothyroxine treatment, the use of levothyroxine at dosages exceeding 0.075 mg/day is linked to a heightened risk of AF when compared to lower levels of exposure.⁷ In our case, we believe that an excessive amount of

Table 1: Lab parameters

Lab values	Pretreatment (17/5/23)	Posttreatment (23/5/23)
Blood		
Hemoglobin (gm/dL)	10.9	9.4
Red blood cell count hematocrit test	3.74	3.25
Mean corpuscular volume	29.1	25.7
Hemoglobin (gm/dL)	77.8	79.1
Leukocytes		
Total count	22,100	10,800
Neutrophils	82	60
Lymphocytes	14	16
Eosinophils	01	01
Monocytes	00	00
Platelets	4.96	2.62
ESR	45	50
General random blood sugar	327	151
Serum creatinine	1.2	1.2
Liver function test		
Serum glutamic oxaloacetic transaminase	73.3	31.5
Serum glutamate pyruvate transaminase	48.8	26.4
Bilirubin		
Total	2.68	1.39
Direct	0.81	0.75
Indirect	1.87	0.64
Electrolytes		
Sodium	142.4	144.8
Potassium	2.79	3.05
Chloride	109	113.5

Table 2: Thyroid function test

Lab values	Pretreatment (17/05/23)	At discharge (23/05/23)	Reference range
TFT			
Free T4 (pmol/L)	75.4	29.2	12–30
Free T3 (pmol/L)	30.8	6.1	3.5–6.5
TSH (mU/L)	0.01	0.5	0.45–4.5

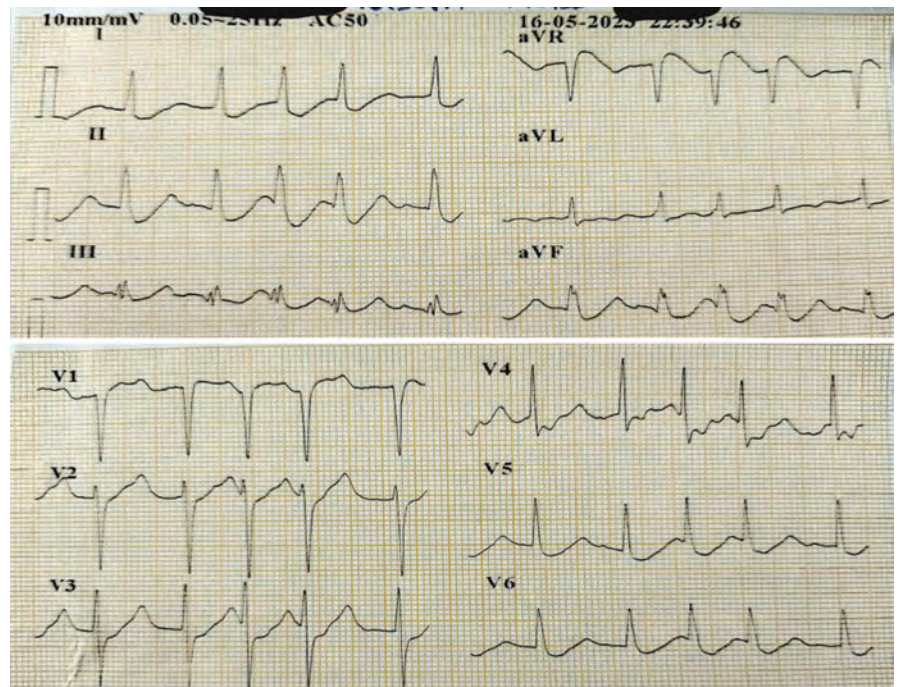


Fig. 1: Electrocardiogram 1—at admission

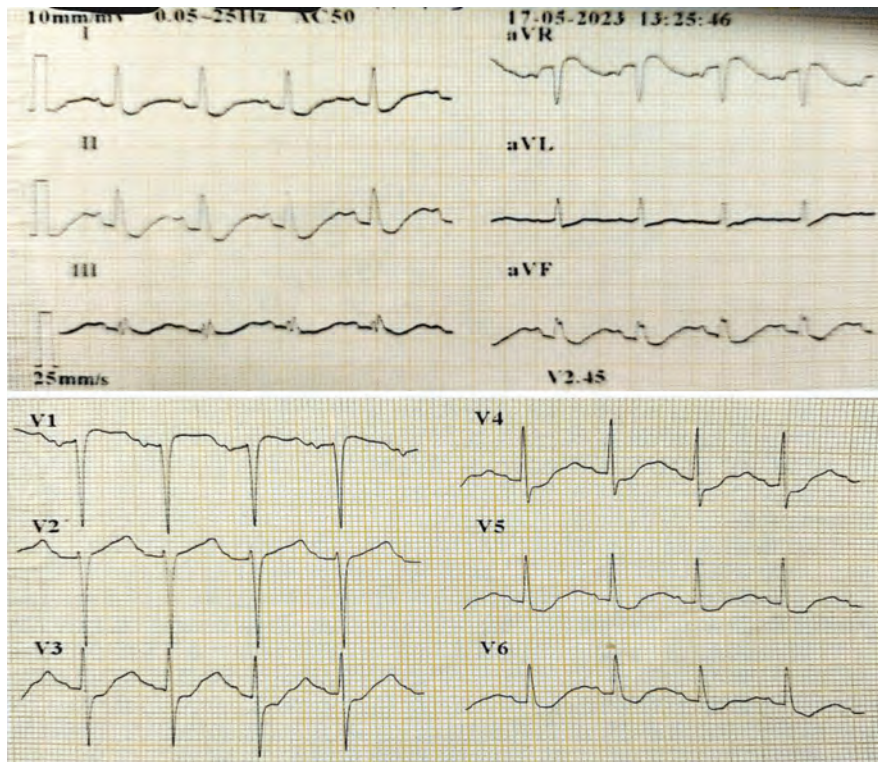


Fig. 2: Electrocardiogram 2—after treatment

levothyroxine could be the contributing cause of AF. Moreover, preexisting infections added to the complexity of the clinical scenario. In this particular instance, symptoms such as breathing difficulties, high blood pressure, elevated temperature, unusual ECG findings, and the positive response to

amiodarone, antibiotics, and the cessation of levothyroxine support the conclusion of AF due to an overdose of levothyroxine, compounded by an underlying secondary infection. Prompt recognition and appropriate management are crucial in stabilizing patients with AF.

CONCLUSION

This case highlights the importance of recognizing AF secondary to levothyroxine overdose with an underlying secondary infection. Timely management with appropriate interventions, including amiodarone, insulin infusion, and discontinuation of levothyroxine therapy, can lead to successful resolution of AF and normalization of thyroid function. Careful monitoring of patients receiving levothyroxine therapy is necessary to prevent potential adverse events.

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Hypoglycemia and Multivitamins

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ABSTRACT

Insulin autoimmune syndrome (IAS) is a rare condition triggered by exposure to various drugs containing sulfhydryl compounds, proton pump inhibitors, supplements, plasma proteins, viral infections like measles, influenza, hepatitis C, and autoimmune conditions like Graves' disease and systemic lupus erythematosus.^{1–3} We report two patients with recurrent episodes of hypoglycemia who were then diagnosed with IAS due to the consumption of α-lipoic acid (ALA) present in a multivitamin supplement. Eating small, frequent meals containing complex carbohydrates and steroids helps normalize blood glucose levels and reduce the insulin autoantibodies (IAA) to undetectable levels.⁴

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INTRODUCTION

Insulin autoimmune syndrome (IAS), also known as Hirata's disease, is characterized by spontaneous episodes of hypoglycemia associated with high serum levels of insulin and insulin autoantibodies (IAA) without any prior exposure to exogenous insulin or pathological abnormalities of pancreatic islets. It affects both sexes equally and is predominantly seen in the 4th decade in females and the 6th decade in males. IAS occurs after exposure to specific environmental stimuli in genetically predisposed individuals, leading to the formation of IAA.^{5,3}

CASE DESCRIPTION

Case 1

A 61-year-old lady presented with episodes of early morning hypoglycemia for 15 days, associated with hunger pangs, sweating, and tremors. Her breakfast is usually delayed, but recently, she prefers it at 4:30 am. Glucose monitoring at the time of symptoms showed HGT of 45–60 mg/dL, and she felt better after eating food. Her postprandial sugars were normal or high. She has recently gained about 2 kg in the last 3 weeks. She is a recently detected diabetic (glycated hemoglobin 6.4) on lifestyle modification with no access to insulin or oral hypoglycemic agents. She consumes pantoprazole for gastritis occasionally. She is a known hypertensive on losartan and was diagnosed with coarctation of the aorta in 1981. No history of hypothyroidism, adrenal insufficiency, renal or liver diseases, or recent infection. Her body mass index was 26.6 kg/m², heart rate was 76/minute, and blood pressure was 130/80 mm Hg. No goiter was observed on examination, but acanthosis nigricans were present. Systemic examination was

unremarkable. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), liver function tests (LFT), and renal function tests (RFT) were normal. Thyroid stimulating hormone (TSH) was 2.5; serum cortisol was 15 mcg/dL (normal). A triphasic computed tomography (CT) scan of the abdomen showed no focal enhancing lesion in the pancreatic parenchyma. No other solid mass lesion was identified. Serum insulin (fasting) was >300 mU/L (2.6–37.6), serum C-peptide was above 30 ng/mL, insulin antibody was positive (>100) (negative <10), Antinuclear antibody (ANA) blot showed nucleosome, Mi-2—borderline positive, and antithyroid peroxidase antibody (anti-TPO) was positive. On detailed history taking, she mentioned the consumption of multivitamin B-fit CD containing α-lipoic acid (ALA) (sulfhydryl group). Human leukocyte antigen (HLA) typing report was sent in view of clinical suspicion of IAS, which came positive for the HLA-DRB1 allele. Thus, the diagnosis of IAS due to ALA was made. She improved with complex carbohydrate meals and steroid—prednisolone 50 mg/day, which were gradually tapered and stopped after 4 months. IAA started decreasing in 4 months and was undetectable after 8 months.

Case 2

A 68-year-old lady presented to the emergency department with altered sensorium, restlessness, and sweating. She had tachycardia of 110 beats/minute, and HGT was 32 mg/dL. She was started on intravenous 25% dextrose, after which her sensorium improved. She had a history of recurrent episodes of increased perspiration, giddiness, palpitations, headaches, and hunger pangs on and off for 1.5 years, relieved after consuming meals and aggravated postmorning walk and midnight postmeals. The frequency of

such episodes had increased to twice a day in the past 6 months. She has been known to be hypertensive for the past 7 years and underwent a right thyroidectomy 1 year ago for papillary carcinoma of the thyroid. Her appetite was fair, and she had a 12-hour gap between dinner and breakfast. She received the COVID-19 vaccine in 2021. On admission, CBC, LFT, RFT, and ESR were normal. Fasting blood sugar (FBS) was 72, postprandial blood sugar (PPBS) was 88, TSH was 2.4 (normal), and serum cortisol was 12 mcg/dL (normal). Her fasting insulin levels were >300 (high), postprandial insulin was >300 (high), and C-peptide levels were 25 ng/mL. Anti-TPO and ANA were negative. Serotonin, plasma metanephrine, nonmetanephrine, and urine 5-hydroxyindoleacetic acid were normal. Our differential diagnosis for endogenous hyperinsulinemic hypoglycemia included insulinoma and insulin autoimmune hypoglycemia. A triphasic CT scan of the abdomen was normal. Being nondiabetic, she had no history of consumption of oral hypoglycemic agents. The insulin antibody was positive at 61.5 (high). On further inquiry, she mentioned consuming multivitamin B29 for 2 years (post-COVID-19), which contains ALA (sulfhydryl group), a known trigger for IAS. HLA-typing was not performed as the relatives were unwilling to do so. Thus, the diagnosis of IAS due to ALA was made. She was started on small, frequent meals with complex carbohydrates, and her condition improved. Her sugars began to improve after 2 weeks and normalized within a few months.

DISCUSSION

Insulin autoimmune syndrome occurs due to IAA against a circulating antigen and was previously considered a type III hypersensitivity reaction.⁶ IAA have properties such as high binding capacity but low affinity for insulin molecules. They form large antigen-antibody complexes

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with insulin, which have a high spontaneous dissociation rate, leading to an inappropriately high concentration of unbound insulin and recurrent hypoglycemic episodes.⁷

The hallmark feature of IAS is hypoglycemia, presenting with symptoms suggesting autonomic and neurological involvement. Autonomic features include hunger pangs, anxiety, tremors, and sweating. Neuroglycopenic features include irritability, confusion, syncopal episodes, and seizures.⁸ Our patient had recurrent hypoglycemic episodes associated with sweating, hunger pangs, one episode of loss of consciousness, and altered sensorium requiring hospitalization. IAS shows correlation with HLA class II, specifically HLA-DR4 and DRB1*0406.^{9–11} The higher incidence of IAS in Japan compared to the Western population can be attributed to the higher prevalence of HLA-DRB1*0406 in Asians.¹²

It is proposed that drugs containing sulfhydryl compounds may induce autoantibody formation by interacting with the disulfide bonds present in the insulin molecule.¹³ ALA contains two

sulfur atoms, which are reduced to two sulfhydryl compounds, promoting the development of IAA.¹⁴ Detailed history taking, including drug history, and maintaining a high clinical suspicion in a hypoglycemic patient with elevated insulin and C-peptide levels are essential for the early diagnosis of IAS. Considering the widespread use of multivitamin tablets, clinicians should be mindful of the potential toxicities and the possibility of rare conditions such as IAS due to nutritional supplements containing ALA.

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Cytomegalovirus Pneumonia in Patients with Severe COVID-19

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ABSTRACT

Severe pneumonia accounts for 15% of the total severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, and the affected patients require hospitalization and oxygen support. In addition, 5% of patients with severe coronavirus disease 2019 (COVID-19) experience acute respiratory distress syndrome and sepsis, which contributes to the high mortality rate. Moreover, the risk of severe COVID-19 increases with age and is the highest among elderly people over 70 years of age. Notably, these pneumonia cases can be attributed to the reactivation of latent cytomegalovirus (CMV). We hereby report two cases of patients with COVID-19 who required prolonged mechanical ventilation and were later diagnosed with secondary CMV pneumonia. These cases support the theory that in some patients with severe COVID-19, there is a possibility of CMV reactivation, contributing to the disease's severity and pathogenesis. These cases also highlight the risk involved in using steroids for a long time and the requirement of routine evaluation for CMV infection in patients with COVID-19 who require prolonged mechanical ventilation or have difficulty weaning off from the ventilator support.

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ESTABLISHED FACTS AND NOVEL INSIGHTS

Established Facts

Severe pneumonia accounts for 15% of the total severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.

Novel Insights

- The reactivation of latent cytomegalovirus (CMV) in severe coronavirus disease 2019 (COVID-19) pneumonia contributes to disease worsening.
- The timely introduction of antiviral (ganciclovir) can improve the chances of survival.
- The use of tofacitinib along with corticosteroids in COVID-19 patients may lead to the reactivation of CMV.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2. It has rapidly spread worldwide; as of June 2021, there were over 178 million confirmed cases globally and 3,860,481 deaths.¹ Importantly, >85% of patients with COVID-19 are either asymptomatic or have mild to moderate disease. Approximately, 15% of patients with severe COVID-19 are men, and they usually have underlying health conditions, such as diabetes, hypertension, obesity, chronic respiratory diseases, and cardiac diseases. In addition, COVID-19 is severe in elderly individuals, especially those in the 7th decade,

but the reason for variations in the severity of COVID-19 in different individuals remains unclear.² The latent human CMV reactivation in COVID-19-infected people is attributed to immunosuppression or inflammation. The reactivation of CMV has also been linked with the dysregulation of immune function, which results in immunological aging, also known as immunosenescence.³

We observed patients with severe COVID-19 pneumonia and concomitant CMV pneumonia who required significant oxygen support and prolonged mechanical ventilator support. Therefore, we hereby present two cases of COVID-19 with secondary CMV pneumonia.

CASE DESCRIPTION

Case 1

A 74-year-old woman with no known comorbidities presented at our hospital with a 10-day history of fever, cough, and breathlessness. On examination, she had a pulse rate of 120 beats/minute, oxygen saturation of 85% at room air, a temperature of 99.8°F, and BP of 120/78 mm Hg. She was tachypneic, and systemic examination revealed bilateral crackles in the chest on auscultation. Her nasal swab for SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) was positive. Her inflammatory marker levels were elevated (Fig. 1); therefore, she was admitted and was started on supplemental oxygen therapy, antibiotics, methylprednisolone (40 mg

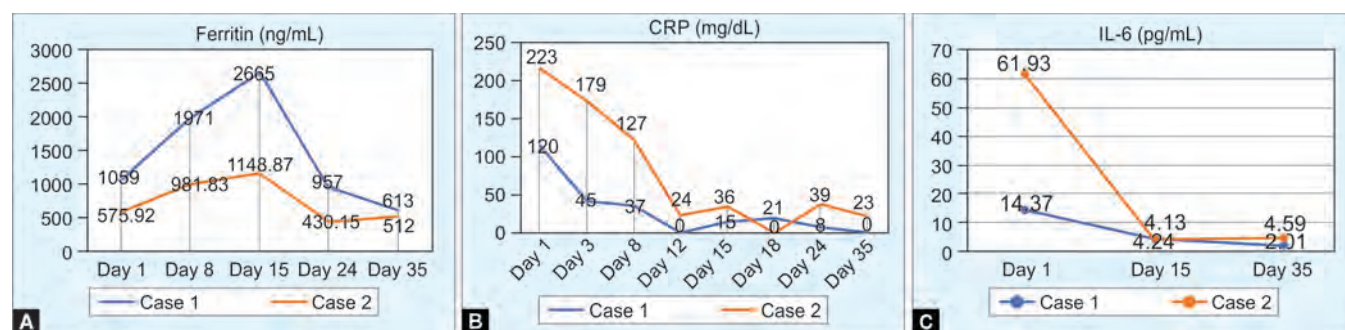
twice daily), remdesivir, tofacitinib (on a compassionate use basis), and prophylaxis for venous thromboembolism. Gradually, her oxygen saturation levels improved. On day 16 of hospitalization, her oxygen saturation dropped to 87%, and she developed severe acute respiratory distress syndrome that was managed with a nonbreathing mask, vasoactive drugs, methylprednisolone, and prone positioning. Nevertheless, she remained hypoxemic and was maintained on nonbreathing mask support. Chest radiography revealed bilateral chest infiltrations. Interestingly, laboratory investigations and cultures did not reveal any evidence of a coinfection. However, her breathlessness and oxygen saturation progressively worsened over time. Repeat screening tests for other coexisting bacterial, viral, and fungal infections were performed. Given the bilateral lung infiltrates and persistent lymphopenia, CMV was detected in serum using PCR (2,070 copies) on day 20 of hospitalization. On day 27 of hospitalization, her computed tomography scan of the thorax showed ground glass opacity with septal thickening in bilateral lungs, predominantly in bilateral upper lobes, suggestive of acute alveolitis (COVID-19/CMV-related). This result confirmed CMV pneumonia coinfection, resulting in bilateral chest infiltrations (Fig. 2) and respiratory failure. The patient was initiated on intravenous ganciclovir, and the dose was determined using body weight. The patient started improving, her fever subsided, her oxygen requirement was reduced, and laboratory evidence of inflammation abated (shown in the line diagram).

Case 2

A 73-year-old man presented to our hospital with a 5-day history of fever, chills, and shortness of breath. His SARS-CoV-2

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Figs 1A to C: Increased levels of inflammatory markers in cases 1 and 2; (A) Ferritin; (B) C-reactive protein; (C) IL-6

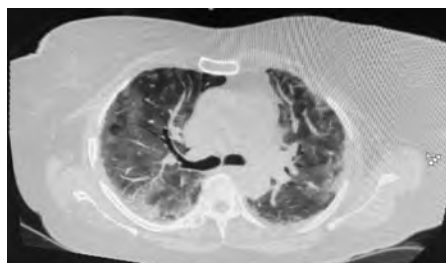


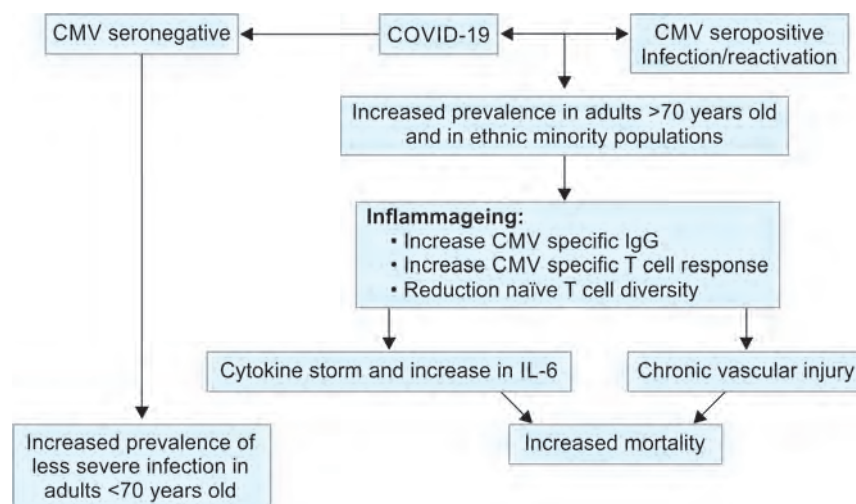
Fig. 2: A computed tomography scan of the thorax showed ground-glass opacity with septal thickening in bilateral lungs, predominantly in bilateral upper lobes, suggestive of acute alveolitis (CMV-related); areas of early interstitial fibrosis with septal thickening with bronchiolar prominence in bilateral lungs, predominantly in the lower lobes suggestive of sequelae of COVID-19

RT-PCR test result was positive. He was admitted, and on examination, he was febrile, tachypnoeic, and hypoxemic. On investigation, his inflammatory markers were elevated (Fig. 1). He was started on supplemental oxygen therapy (15 L/minute), antimicrobial agents, remdesivir, tofacitinib, and dexamethasone (6 mg daily). He continued to receive steroids, but he did not show much recovery and remained dyspneic with high oxygen requirements. His chest radiograph showed further worsening. The patient was tested for CMV infection, and his serum PCR for CMV was positive (305,100 copies) on day 27 of hospitalization. Subsequently, ganciclovir was administered intravenously. The patient started improving gradually—the fever subsided, saturation was maintained at 3 L/minute at the time of discharge (on 42 days of hospitalization), and inflammatory markers decreased. He was doing well and maintained saturation at room air during a follow-up 15 days after discharge.

DISCUSSION/CONCLUSION

These reports describe elderly sick patients who were coinfecting with COVID-19 and CMV and required prolonged oxygen supplementation. There is a paucity of

Flowchart 1: The correlation between COVID-19 infection and CMV seropositivity, culminating in higher rates of COVID-19-related mortality in the elderly population



available data regarding the concomitant disease of CMV with SARS-CoV-2, and the available reports have primarily emphasized the gastrointestinal manifestation of CMV infection.

Cytomegalovirus (CMV) prevalence increases with age, and CMV infection causes immune dysregulation in the elderly by targeting the peripheral T-cells and potentiating the release of inflammatory cytokines such as interleukin 6 (IL-6).² The thymus is essential for the production of progenitor cells, which are responsible for the development of T-lymphocytes, a function that reduces with increasing age. Hence, there is a significant correlation between advanced age and the risk of mortality from SARS-CoV-2 infection. According to Poloni et al., CMV-specific T-cell responses in elderly individuals are explained by the process of CMV-induced T-cell memory escalation observed in preclinical models.⁴ In elderly individuals, the reduction in CD8+ T-cells makes it difficult to produce an immune response to fight novel viruses such as SARS-CoV-2.⁵ Infection by CMV during the acute phase causes immunosuppression by blocking antigen presentation and

natural killer, B-cell, and T-cell responses (Flowchart 1).

Both COVID-19 and CMV infections trigger an immune pathway characterized by lymphopenia, a cytokine storm with increased levels of IL-1 β , IL-2, IL-2R, IL-6, IL-8, IL-10, IL-17, granulocyte colony-stimulating factor, tumor necrosis factor α , and chemokines, such as monocyte chemoattractant protein 1, macrophage inflammatory protein 1 α , and interferon-inducing protein. Thus, both viruses contribute to the cytokine storm in COVID-19. The cytokine storm, together with weak interferon feedback, contributes to the severe manifestations of COVID-19.³

Cytomegalovirus (CMV) reactivation in patients with COVID-19 is detrimental and is associated with prolonged intensive care unit (ICU) stay and higher mortality rates. In a study of 38 patients on mechanical ventilation in the ICU, 50% of the patients showed evidence of CMV reactivation.⁶ An elderly patient coinfecting with SARS-CoV-2 and CMV died after 5 days in the ICU. A total of 15 out of 59 COVID-19-positive patients who were on systemic corticosteroids had CMV infections during their ICU stays.⁷

Most of the patients in these studies were on systemic corticosteroids, which may lead to reactivation of CMV, but in our report, patients received remdesivir and tofacitinib along with corticosteroids. In their report, Cugley et al. provided evidence of CMV reactivation in patients receiving tofacitinib for rheumatoid arthritis.⁸ In our report, both patients had severe COVID-19 disease with respiratory failure, received tofacitinib with systemic corticosteroids, and developed CMV reactivation, which further led to prolonged hospital stay and oxygen requirement. Although Janus kinase inhibitors are included in the management of severe COVID-19 diseases along with corticosteroids, physicians need to be vigilant as they have the potential to cause CMV reactivation.

It is challenging to discriminate the incidence of worsening COVID-19 pneumonia from other lower respiratory tract infections, which depend solely on either clinical or radiological findings. In particular, the number of patients requiring prolonged oxygen supplementation may be likely underestimated. Therefore, clinicians must consider CMV pneumonia in the differential

diagnosis when they encounter unexplained worsening or relapse of respiratory failure in critically ill patients with COVID-19, especially in those with unexplained lingering lymphopenia who require oxygen supplementation.

STATEMENTS

Statement of Ethics

Subjects have given their written informed consent to publish their case (including publication of images). Information revealing the subject's identity has been avoided.

Consent to Publish Statement

Consent to publish was obtained from the participants.

Author Contributions

Pooja Khosla contributed to the study design and data collection, analysis, and interpretation. Kamal Jain and Vinus Taneja drafted and revised the manuscript for intellectual content. All authors approved the final version of the manuscript.

Data Availability Statement

Data is available and can be found in the hospital information system.

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Successful Thrombolysis of an Obstructive Prosthetic Mitral Valve Thrombosis Using Alteplase



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SUMMARY

A 48-year-old man with a history of mitral valve replacement (MVR) in March 2019 for rheumatic heart disease (RHD) and ischemic stroke in August 2019 presented with a history of sudden onset angina of 6 hours duration. He admits to defaulting oral anticoagulant (OAC) intake for the last 50 days. On arrival, he had atrial fibrillation with hemodynamic instability [blood pressure (BP) 70/40 mm Hg, saturation of peripheral oxygen (SpO₂) 80% at room air and heart rate approx 140/minute], which was managed with intravenous diltiazem and hemodynamic stability achieved (BP 116/72 mm Hg, heart rate 86/minute). Urgent transthoracic echocardiogram (TTE) and fluoroscopy confirmed obstructive prosthetic mitral valve thrombosis. Though available recommendations suggest surgical intervention for the left-sided valve involvement in a stable patient, in view of the nonavailability of a surgical facility, the patient was thrombolized with Alteplase, a recombinant tissue plasminogen activator (rtPA). Since the patient was stable, a "long fibrinolytic protocol" of Alteplase 10 mg bolus, 50 mg during the 1st hour, and 20 mg each during the 2nd and 3rd hour (total of 100 mg) was given. Subsequent TTE revealed a mean gradient of 5 mm Hg, and cine fluoroscopy showed improved mitral valve motion, thereby indicating successful thrombolysis. The patient felt symptomatically relieved within 6 hours and is presently on OAC therapy with strict drug compliance.

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BACKGROUND

Prosthetic valve thrombosis (PVT) is a rare but life-endangering complication of mechanical prostheses, with high mortality ranging from 25 to 41%.¹ Though surgical treatment is preferred over thrombolytic therapy in critically ill left-sided obstructive PVT, the availability of surgical facilities is a major limiting factor. While there are limited case reports on PVT, especially originating from countries not having robust health infrastructure, here we describe a case of left-sided obstructive PVT, its management with thrombolytic therapy due to lack of surgical facility and its outcome.

CASE PRESENTATION

A 48-year-old Indian male underwent mitral valve replacement (MVR) in March 2019 for rheumatic heart disease (RHD). Postprocedure, he had an ischemic stroke of the left middle cerebral artery territory in August 2019. He presented with a history of sudden onset anginal type of chest pain of 6 hours duration (New York Heart Association Class IV). He admits to defaulting oral anticoagulant (OAC) intake for the last 50 days. On arrival, he was hemodynamically unstable with blood pressure (BP) of 70/40 mm Hg, saturation of peripheral oxygen (SpO₂) of 80% at room air and heart rate of approx 140/minute, which was irregularly irregular in rhythm. On

auscultation, he had variable S1 with muffled heart sounds, and the mitral click was not audible. An electrocardiogram (ECG) confirmed atrial fibrillation with fast ventricular rate (FVR). However, his liver enzymes were normal, and troponin T was negative. He was managed with intravenous diltiazem and controlled ventricular rate (CVR) with hemodynamic stability achieved (BP 116/72 mm Hg, heart rate 86/minute). Urgent transthoracic echocardiogram (TTE) showed impaired mitral leaflets movement with a mean gradient of 35 mm Hg and no perivalvular leak. A thrombus of size 0.5 cm² was visualized (Fig. 1). Fluoroscopy showed impaired motion of the mitral valve leaflet (Fig. 2A). Based on the clinical picture, TTE findings and fluoroscopy imaging, a diagnosis of obstructive PVT was made.²⁻⁴

TREATMENT

In view of the nonavailability of the surgical facility, the patient was thrombolized with Alteplase, a recombinant tissue plasminogen activator (rtPA) 10 mg bolus, 50 mg during the 1st hour, 20 mg each during the 2nd and 3rd hour (total of 100 mg).

OUTCOME AND FOLLOW-UP

The patient had symptomatic improvement with easing of anginal chest pain within 6 hours of thrombolytic therapy. Subsequent TTE revealed a mean gradient of 5 mm Hg,

and fluoroscopy showed improved mitral valve motion, thereby indicating successful thrombolysis (Fig. 2B). He was shifted to a definitive cardiothoracic center had the need for surgery arise in future. However, the patient continued to be stable in New York Heart Association (NYHA) class II for the next 3 months of follow-up. He was advised and counseled for strict OAC therapy compliance.

DISCUSSION

Valvular heart disease, which carries significant morbidity and mortality, affects around 100 million people across the globe.⁵ There are various guidelines regarding the management of PVT, the most significant being the 2020 American College of Cardiology/American Heart Association (ACC/AHA) guideline for the management of patients with valvular heart disease and the 2017 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines for the management of valvular heart disease.^{6,7} In an ideal setup, the factors favoring systemic fibrinolysis versus surgery for PVT are given in Table 1 (adapted from 2020 ACC/AHA guideline for the management of patients with valvular heart disease). However, in developing countries that do not have robust health infrastructure, the availability of surgical facilities is a major limiting factor.

For left-sided PVT, the ACC/AHA guideline has a class IB recommendation for emergency surgery in patients with NYHA class II to IV symptoms, class IIaB recommendation for fibrinolytic therapy in patients with NYHA

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class I to II symptoms and a small thrombus ($<0.8 \text{ cm}^2$).⁶ The 2017 ESC/EACTS guidelines have spelt out a detailed management protocol for left-sided obstructive PVT, giving emphasis on adequate anticoagulation post-valve replacement (Fig. 3). In both of these guidelines, fibrinolysis is the treatment of choice for critically ill patients where the surgical facility is not available.

Roudaut et al., in the Heart journal in 2007, proposed “long and short” fibrinolytic protocols based on the hemodynamic status of the patient.² Rescue fibrinolysis using a “short protocol” is recommended for hemodynamically unstable patients or in whom surgery is contra-indicated with either rtPA 10 mg bolus followed by 90 mg in 90 minutes or Streptokinase 1.5 million IU in 60 minutes. “long protocol” is recommended for hemodynamically stable patients with

rtPA 10 mg bolus, 50 mg during the 1st hour, 20 mg each during 2nd and 3rd hours (or) urokinase 4500 U/kg/hour over 12 hours (or) Streptokinase 0.5 million IU in 20 minutes followed by 1.5 million IU over 10 hours. Available literature claims the advantage of the use of Tenecteplase as a fibrinolytic agent over Alteplase in regards to increased success and decreased complication; however, there is not enough evidence or randomized trials to prove the same.⁸

In our patient, we followed the “long protocol” since we achieved stable hemodynamic status postintravenous diltiazem for atrial fibrillation. Our case highlights the need to adopt fibrinolytic treatment protocols in PVT, especially in resource-limited settings. Also, our case adds to the available literature in determining the optimal fibrinolytic agent of choice.

LEARNING POINTS/TAKE HOME MESSAGE

- A high index of suspicion for obstructive PVT should arise in patients presenting with overt heart failure and with a history of poor compliance to OAC therapy.
- Meticulous clinical examination and careful TTE with measurement of mean pressure gradients help in clinching the diagnosis of PVT.
- Though there are clear guidelines for the management of obstructive PVT, the

Table 1: Systemic fibrinolysis versus surgery for PVT (adapted from 2020 ACC/AHA guideline for management of patients with valvular heart disease)⁶

Favor surgery	Favor fibrinolysis
Readily available surgical expertise	No surgical expertise is available
Low surgical risk	High surgical risk
Contraindication to fibrinolysis	No contraindication to fibrinolysis
Recurrent valve thrombosis	First-time episode of valve thrombosis
NYHA class IV	NYHA classes I, II, or III
Large clot ($>0.8 \text{ cm}^2$)	Small clot ($\leq 0.8 \text{ cm}^2$)
Left atrial (LA) thrombus	No LA thrombus
Concomitant coronary artery disease (CAD) in need of revascularization	No or mild CAD
Other valve disease	No other valve disease
Possible pannus	Thrombus visualized
Patient choice	Patient choice

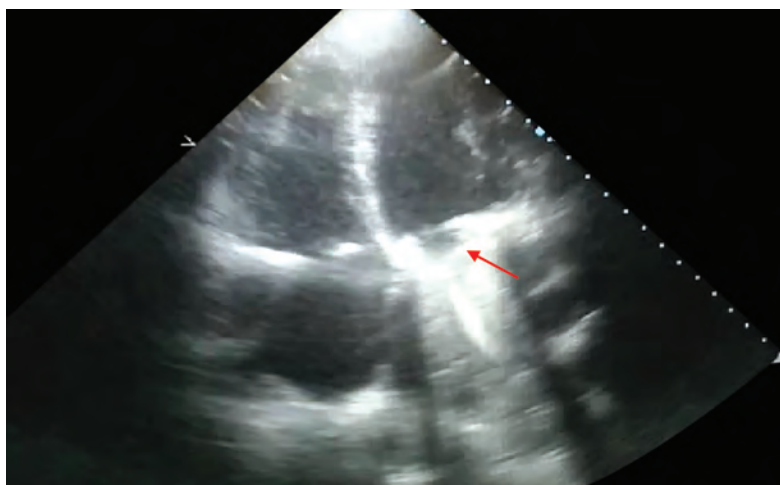


Fig. 1: Transthoracic echocardiogram (TTE) showing impaired mitral valve

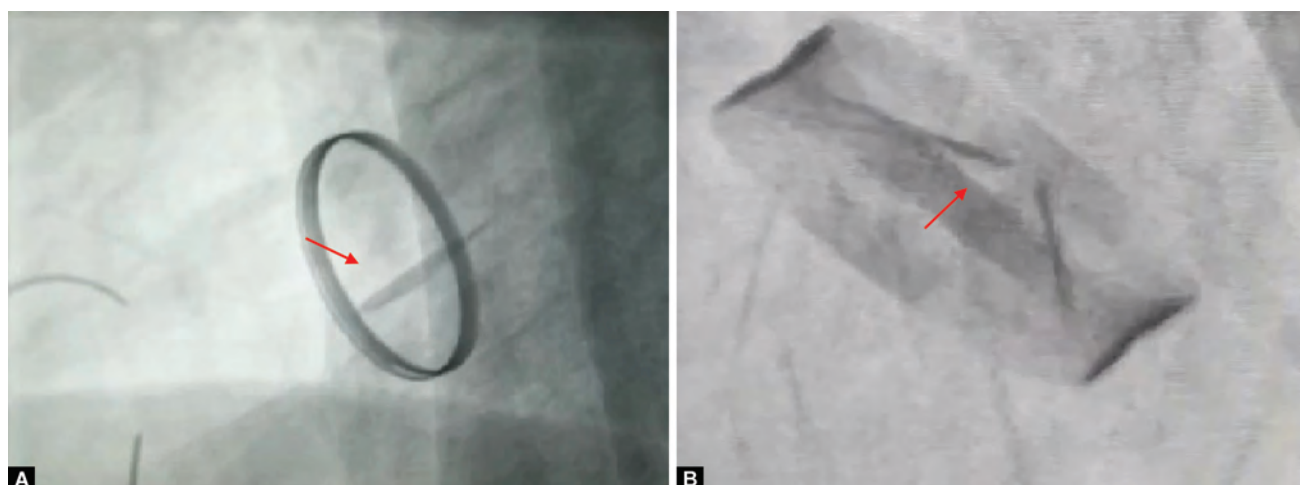


Fig. 2: Cine fluoroscopy showing impaired mitral valve motion in A and improved mitral valve motion in B

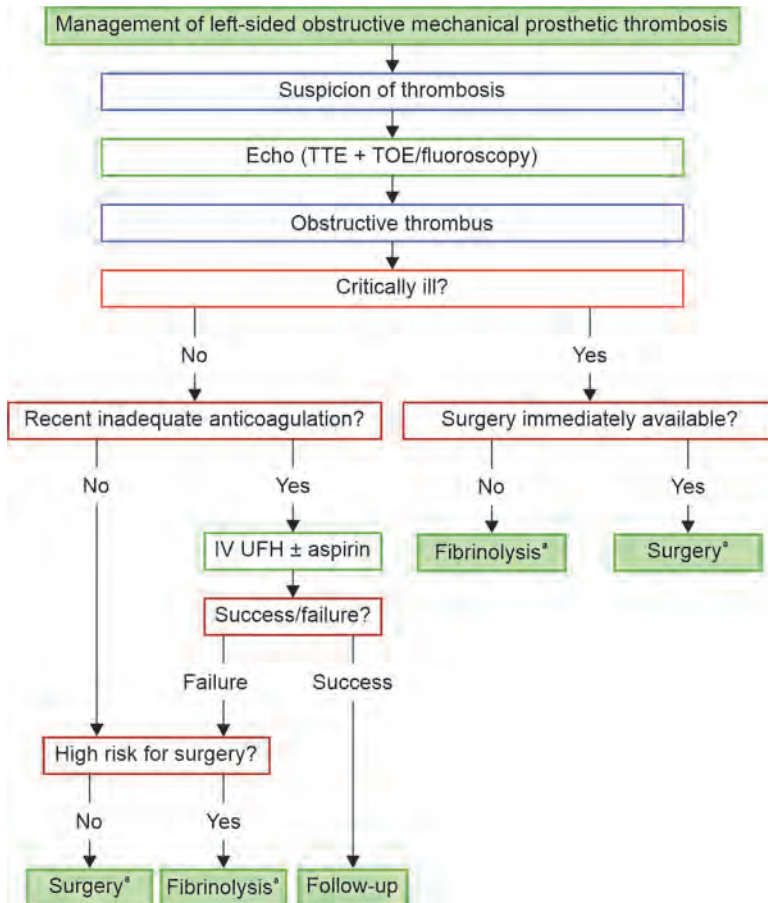


Fig. 3: Management of obstructive left-sided PVT. Adapted from 2017 ESC/EACTS guidelines for the management of valvular heart disease⁷

availability of surgical facilities is a major limitation. Institutions should adopt and put in place “treatment protocols” suiting their available facilities for effective management of PVT without any treatment dilemmas.

- Thrombolytic therapy is the treatment of choice for critically ill patients where surgical facility is not available.

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Disseminated Histoplasmosis Presenting as Pyrexia of Unknown Origin in a Rheumatoid Arthritis Patient

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ABSTRACT

We present a case of a 56-year-old female with rheumatoid arthritis (RA) who has been on methotrexate for 9 years and has been complaining of high-grade fever for the past 1 month with no localizing signs and symptoms. She was thoroughly evaluated before being labeled as pyrexia of unknown origin. Histoplasmosis was suspected after bone marrow aspiration smear examination. The presence of histoplasma antigen in the urine confirmed our diagnosis. Fever responded after 2 weeks of liposomal amphotericin B and patient discharged in stable condition on tablet itraconazole.

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INTRODUCTION

Histoplasmosis is one of the most common endemic mycosis in the United States, although it is an underrecognized disease in India.¹ There have only been a few large-scale studies of its prevalence in India. It is endemic to India's north-eastern states—Delhi, Haryana, Uttar Pradesh, West Bengal, and the Gangetic plains.²

Histoplasma capsulatum is an intracellular dimorphic fungus that exists as mold and yeast. Infection occurs through inhalation of histoplasma macroconidia into the lungs, where they transform into yeast.

Macrophages play an important role in lymphatic spread, lymph node involvement, and dissemination causing hematogenous spread to the reticuloendothelial system. T cell immunity helps in recovery from histoplasmosis; hence, immunocompetent individuals usually clear the infection. It is most common in immunocompromised individuals, such as those with human immunodeficiency virus (HIV), diabetes, or on tumor necrosis factor alpha (TNF- α) inhibitor medication, who are at risk for more severe disease.³ A study conducted in Chennai showed that around 62.5% of people with histoplasmosis had an underlying immunocompromised condition.¹ We present a case of disseminated histoplasmosis in a 56-year-old female from Madhya Pradesh who was receiving low-dose methotrexate therapy.

CASE DESCRIPTION

A 56-year-old female presented with a 1-month history of high-grade fever, chills, and rigors with no history of rashes, diarrhea, abdominal discomfort, cough, burning micturition, chest pain or palpitations, or

headache. She was having rheumatoid arthritis (RA) and has been on tablet methotrexate 7.5 mg weekly for 9 years. She did not have joint pain or other indicators of a disease flare when she presented. There has been no recent travel or contact with birds, animals, or their feces. On clinical examination, there was no lymphadenopathy, organomegaly, or auscultatory abnormalities.

She was thoroughly worked up in another hospital before coming to us. The only positive finding among the investigations was pancytopenia; the remainder of the tests, including blood culture, chest X-ray, and ultrasound abdomen, were all normal. She was tested negative for HIV infection. She had received various antibiotics, including doxycycline, carbapenems, still fever had not subsided. When the patient arrived at our hospital, she had persistent high-grade fever with no other localizing symptoms or signs. Meropenem injection was continued for the patient. Her complete blood count showed pancytopenia. The blood culture and urine culture were both sterile. During hospital stay, patient developed hypoxia and was having saturation of around 86% on room air. Contrast-enhanced computed tomography (CECT) of the abdomen and thorax (Fig. 1) revealed mild hepatosplenomegaly, subcentimeter abdominal lymph nodes, fissural collapse, and fibrotic bands in bilateral lungs, significant paraaortic lymphadenopathy, and subcentimeter subcarinal and other mediastinal lymph nodes. Bone marrow aspiration and bone marrow biopsy were done for fever workup, revealing many small uniform oval yeasts with eccentric nuclei clustered in histiocytes (Figs 2 and 3). Urinary histoplasma antigen was positive. Treatment with liposomal amphotericin B was started and continued

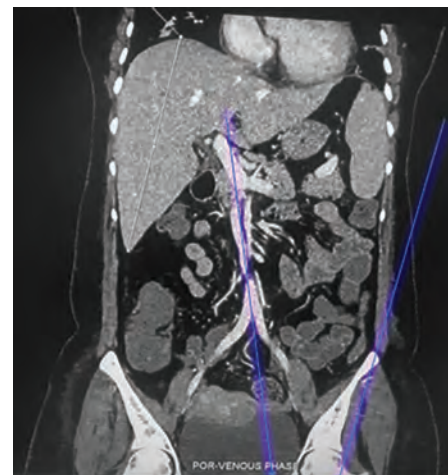


Fig.1: Contrast-enhanced computed tomography abdomen showing hepatosplenomegaly

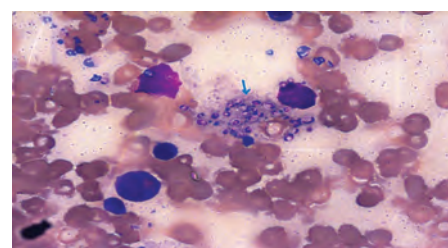


Fig.2: Bone marrow aspirate showing many small uniform oval yeasts with eccentric nuclei (arrow) clustered in a histiocyte (oil immersion $\times 1000$)

for 14 days. Her fever subsided after 5 days of amphotericin injection. She was discharged in stable condition on oral itraconazole.

DISCUSSION

Histoplasmosis is rare in India. We present a case of a 56-year-old female on low-dose

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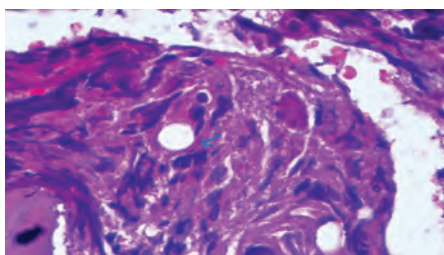


Fig. 3: Bone marrow biopsy showing many oval narrow based yeasts (arrow) within histiocytes (periodic acid–Schiff stain x400)

methotrexate who was diagnosed with disseminated histoplasmosis. She lived in a nonendemic area of histoplasmosis and had no history of travel to endemic areas or exposure to bird excrement or soil. She presented with pyrexia of unknown origin (PUO) and no other severe clinical indications of histoplasmosis. Histoplasmosis is a mycosis caused by soil-based fungus *histoplasma capsulatum*.⁴ It is the most prevalent endemic mycosis in United States.⁵ In India, it is endemic along Gangetic plains, especially in West Bengal and Uttar Pradesh. A retrospective assessment of all RA patients diagnosed between 1st January 1998 and 30th January 2009 at Rochester, Minnesota's Mayo Clinic was carried out by Olson et al. They identified 26 patients who satisfied the criteria for inclusion for histoplasmosis and had a confirmed diagnosis of RA.⁶ Panuganti et al. described a case of progressive disseminated histoplasmosis, which they believe was caused by immunosuppression caused by continuous methotrexate therapy and

oral steroids.⁷ Similar to our case, Roy et al. described widespread histoplasmosis after extended low-dose methotrexate therapy, with bone marrow biopsy confirming the diagnosis.⁸ Dussouil et al. described a patient with RA who received methotrexate and corticosteroid therapy and developed disseminated histoplasmosis that resembled dermatomyositis.⁹

The disease spectrum varies from acute to chronic, with asymptomatic and symptomatic periods. It might range from a limited disease to a widespread disease (Fig. 3). Histoplasmosis is more common in immunocompromised people, such as those with HIV, diabetes, on immunosuppressive medication, and posttransplant patients. It can present as pulmonary involvement alone or as lymphadenopathy, hepatosplenomegaly, oropharyngeal lesions, skin lesions, and sometimes adrenal involvement. Central nervous system (CNS) involvement can occur in the form of chronic meningitis, encephalitis, cerebral vasculitis, and focal lesions in brain/spinal cord. However, in our case, the patient presented with PUO and no clinically significant lymphadenopathy or organomegaly.

Treatment of disseminated histoplasmosis includes liposomal preparations of amphotericin B and azole group of drugs. Treatment usually lasts for 1 year.

CONCLUSION

Prolonged methotrexate treatment has been linked to disseminated histoplasmosis. When infection occurs, it is advisable to

discontinue methotrexate. Resumption of immunomodulatory medications in patients who developed histoplasmosis while on therapy must be done with caution, as there is a risk of significant relapse of the infection despite suppressive antifungal therapy. As there are no established testing strategies for identifying patients at risk of infection, healthcare providers must be vigilant for the development of active histoplasmosis.

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An Unusual Presentation of Extrapulmonary Tuberculosis in a Fibrocalculous Pancreatic Diabetes Patient

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ABSTRACT

Fibrocalculous pancreatic diabetes (FCPD) mellitus is a distinct type of diabetes that arises from chronic calcification of the pancreas in young, nonalcoholic individuals, predominantly in tropical regions. The characteristic triad of FCPD includes diabetes, abdominal pain, and steatorrhea. Additional notable features of the disease are its early age of onset, the presence of large intraductal stones, rapid disease progression, and a heightened risk of developing pancreatic cancer. Tuberculosis (TB) is a health concern worldwide and is responsible for a major health burden in developing countries like India. TB involving any organ other than the lungs is diagnosed as extrapulmonary tuberculosis (EPTB). EPTB with musculoskeletal involvement is often a difficult and delayed diagnosis because of unusual clinical presentations.

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INTRODUCTION

Fibrocalculous pancreatic diabetes mellitus (FCPD) is a distinct type of diabetes that arises from tropical calcific pancreatitis (TCP). It predominantly affects individuals from lower socioeconomic backgrounds who are often lean and visibly malnourished.¹ Key features of FCPD include abdominal pain during childhood, the presence of pancreatic stones, pancreatic duct dilation, and gland fibrosis during adolescence.² Diabetes typically manifests in early adulthood, is severe, and usually necessitates insulin therapy, although ketosis is uncommon. Despite significant advancements in diagnosing pulmonary tuberculosis (TB), confirming a diagnosis of extrapulmonary TB (EPTB) remains challenging in clinical practice due to the wide range of clinical symptoms and imaging findings.³ Cold abscesses are particularly rare and misleading among EPTB cases.^{4,5}

We report a case of a 21-year-old female who was newly diagnosed with FCPD and presented with multiple subcutaneous tuberculous abscesses and extensive bony destruction.

CASE DESCRIPTION

A 21-year-old woman was admitted to our hospital emergency department in an agitated state, with family members reporting uncontrolled blood glucose levels measured at a primary care facility. She reported experiencing generalized weakness and intermittent abdominal pain over the past 2 years, which was mild and diffuse. Additionally, she described

symptoms of frequent urination, excessive thirst, increased appetite, and significant weight loss over the last year. Her caregivers noted she had been experiencing a low-grade fever for the past 2 months. There was no family history of diabetes, and she had no history of alcohol or tobacco use. She came from a low socioeconomic background.

On examination, she was conscious, alert, and responsive to commands but febrile. There was mild pallor noted. Lymphadenopathy was absent. Her body mass index was notably low at 17.5 kg/m². There were no signs of insulin resistance, such as acanthosis or skin tags. The systemic examination appeared normal.

At the time of presentation, the random capillary blood glucose level was exceedingly high (>600 mg/dL). The patient's initial arterial blood gas (ABG) report is depicted in Table 1. Urine dipstick for ketone bodies was negative. Serum β -hydroxybutyrate was within normal limits (0.2 mmol/L). Her relevant investigations are summarized in Table 2. Electrocardiography (ECG), chest X-ray, and fundus examinations were normal. The X-ray of her abdomen in an erect posture revealed calcification along the distribution of

the pancreas (Fig. 1). Ultrasonography (USG) of the abdomen showed the presence of multiple large pancreatic calculi. Computed tomography (CT) of the abdomen revealed pancreatic atrophy, multiple abscesses (over the right anterior chest wall, left gluteus minimus muscle, and left obturator internus muscle), multiple retroperitoneal lymph nodes, and bony destruction over the anterior ribs and left side of the sacrum (Fig. 2). On magnetic resonance imaging (MRI) of the pelvis, there are abscesses noted in the left gluteus minimus muscle and left obturator internus muscle, with erosion observed on the left side of the sacrum (Fig. 3). Cartridge based nucleic acid amplification test (CBNAAT) of aspirated material from abscess (Fig. 4) detected mycobacterium TB with low sensitivity to rifampicin.

The patient achieved effective glycemic control using a basal-bolus insulin regimen and was started on antitubercular medications based on sensitivity results from a line probe assay. Pancreatic enzyme supplements were also administered. She received thorough counseling regarding the symptoms of both hypoglycemia and hyperglycemia. She was educated on dietary management and instructed on self-blood glucose monitoring. Additionally, she was informed about potential long-term complications, including pancreatic adenocarcinoma, and was advised to attend regular follow-up appointments. She was discharged in a stable condition.

DISCUSSION

Fibrocalculous pancreatic diabetes is an uncommon type of diabetes resulting from pancreatic calcification in nonalcoholics, predominantly affecting individuals

Table 1: Arterial blood gas analysis

Parameters	Patient's value	Normal range
pH	7.480	7.350–7.450
Partial pressure of carbon dioxide (pCO ₂)	35.2 mm Hg	35–45 mm Hg
Bicarbonate (HCO ₃)	25.6 mmol/L	22–26 mmol/L

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between the ages of 10 and 40. Although there is a significant male predominance,¹ the patient in this case is a 21-year-old female. Several factors are thought to play a role in the development of FCPD, such as genetic predisposition, malnutrition, cyanide toxicity from frequent cassava consumption, familial clustering, and increased oxidative stress resulting from deficiencies in vitamin C, vitamin A, and trace elements. However, the hypothesis linking cassava consumption to FCPD has been dismissed because case-control studies have not supported it as a risk factor.⁶ Genetic factors are considered the most significant contributors to the etiology of FCPD. Current evidence has established a connection between the serine protease inhibitor Kazal type 1 (SPINK1) gene and TCP.⁷

DIAGNOSTIC CRITERIA FOR FIBROCALCULOUS PANCREATIC DIABETES

Occurrence in a tropical country.⁸

Diabetes according to World Health Organization (WHO) study group criteria.¹

Evidence of chronic pancreatitis, indicated by pancreatic calculi on X-ray, or at least three of the following:

- Abnormal pancreatic morphology detected by ultrasound abdomen.
- Chronic abdominal pain starting in childhood.
- Steatorrhea.
- Abnormal pancreatic function test.

Exclusion of other causes of chronic pancreatitis, such as alcoholism, hepatobiliary disease, or primary hyperparathyroidism.

In our patient, the diagnosis of FCPD was supported by recurrent episodes of abdominal pain, diabetes without ketosis, and the presence of pancreatic calculi observed on abdominal USG and abdominal CT scan. In these patients, microvascular complications like nephropathy,⁹ neuropathy,¹⁰ and retinopathy¹¹ can occur, whereas

macrovascular complications are less frequent compared to type 2 diabetes mellitus. This reduced incidence of macrovascular complications may be attributed to their younger age, lean body mass, and lower cholesterol levels.¹²

Tuberculosis presents a considerable health hazard, especially for those with diabetes. The emergence of EPTB as a rising concern among diabetic individuals is notable. Diabetes, known for its

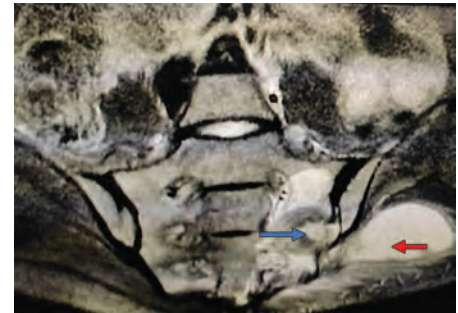


Fig. 3: T2-weighted MRI showing abscess in left obturator internus with the erosion of left side of the sacrum. The blue arrow depicts sacral erosion, and the red arrow depicts an abscess in the left obturator internus

Table 2: Summary of relevant investigations

Blood parameters		Patient's value	Normal range
Hemoglobin		7.5	12–16 gm/dL
Total leukocyte count		12,400	4,500–11,000/ μL
GAD65 antibody		3.2	<5 IU/mL
IA2-antibody		4.6	<7.5 IU/mL
Stimulated C-peptide		0.6	1.1–3.6 ng/mL
HbA1c		11.4%	<5.7%
Lipid profile	Triglyceride	82	<150 mg/dL
	Total cholesterol	108	Desirable <170 mg/dL
	LDL-cholesterol	76	Optimal <100 mg/dL
	HDL-cholesterol	48	>50 mg/dL (in female)
Serum amylase		240	40–140 IU/L
Serum lipase		168	40–140 IU/L
Serum calcium		9.5	8.5–10.5 mg/dL
Serum magnesium		1.62	1.6–2.6 mg/dL
Serum uric acid		2	3.5–6 mg/dL
Serum creatine		1.26	0.7–1.3 mg/dL
Liver function test		Normal	–

GAD, Glutamic acid decarboxylase; HbA1c, glycosylated hemoglobin; HDL, high density lipoprotein; IA, islet antigen; LDL, low density lipoprotein

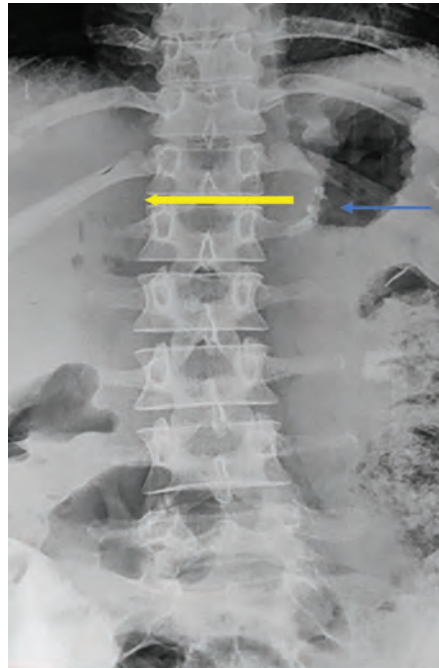


Fig. 1: Straight X-ray abdomen showing calcification beside transverse process of L1 vertebra in erect posture depicted by blue arrow



Fig. 4: Pus was ultrasonographically aspirated from the right anterior chest wall and sent for culture sensitivity and CBNAAT

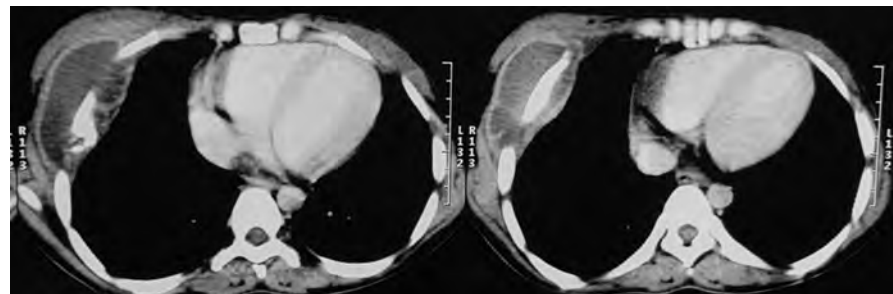


Fig. 2: Computed tomography scan of the abdomen showing abscess over right anterior chest wall depicted by the yellow arrow and rib destruction depicted by the red arrow

immunosuppressive effects, is increasingly acknowledged as an independent risk factor for TB. These conditions often coincide and exert mutual influence. Hence, it is crucial to maintain a low diagnostic threshold for identifying EPTB in diabetic patients. Effective management of EPTB can be achieved through short-course antitubercular chemotherapy, contingent upon maintaining adequate control of blood sugar levels throughout the treatment duration.

In FCPD, diabetes typically manifests as severe, often requiring insulin therapy to manage blood sugar levels. Ketoacidosis is rare among FCPD patients, likely attributed to various factors such as remaining pancreatic beta cell function, decreased glucagon reserves, limited availability of nonesterified fatty acids (NEFA) essential for ketone body synthesis, adipose tissue resistance to catecholamine-induced lipolysis, and deficiencies in carnitine affecting NEFA transport across mitochondrial membranes.^{13,14}

CONCLUSION

Fibrocalculous pancreatic diabetes, although rare, should be considered in young individuals with diabetes and abdominal pain, especially if they are malnourished. Maintaining strict glycemic control through proper diet and regular blood glucose

monitoring is crucial for preventing complications. Awareness of this condition is vital, as early detection can mitigate the risk of pancreatic cancer and diabetes-related complications. Given their compromised immune status, prompt diagnosis of infections, particularly TB, is essential with a low threshold for detection. An intriguing area of research involves investigating insulin resistance in FCPD individuals, which seems to be independent of intra-abdominal adipose tissue.¹⁶ To improve the quality of life for those with FCPD, research should delve into genetic and environmental factors to unveil novel therapeutic approaches.

DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent.

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Max Delbrück: Founder of Molecular Genetics

J V Pai-Dhungat



Alfred Hershey: Nobel Prize in Medicine or Physiology 1969, Guyana, 1995



Max Delbrück: Nobel Prize in Medicine or Physiology 1969, Grenada, 1995



Niels Bohr: Guinea-Bissau, 19**



DNA structure. Republic of China

Max Delbrück (1906–1981) attended the University of Göttingen, where he studied astrophysics initially, switching later to theoretical physics. He earned his PhD in physics from Göttingen in 1930. Delbrück then moved to England and Denmark. It was during this time that he met Niels Bohr and his argument that quantum mechanics might have a wider application to biology-inspired Delbrück to pursue biology.

Delbrück returned to Berlin to work under Meitner and Hahn (1932). During this time, Delbrück wrote about gamma rays (1933). However, Delbrück was also now interested in biology and began to study that field of science. He left Nazi Germany after receiving a fellowship from the Rockefeller Foundation in 1937 at the California Institute of Technology (Caltech), where he began to study biology and genetics and the reproduction of bacteriophages.

In 1938, he met biologist Emory Ellis and became interested in the bacteriophage research that Ellis was conducting to understand the role of viruses in cancer. In 1939, they published their paper, "The Growth of Bacteriophage," which detailed how viruses reproduce in one step, unlike cellular organisms, and described a technique to quantify and monitor the growth of phage in a specific host.

His role with the Rockefeller Foundation ended in 1939, but wanting to remain in America, Delbrück joined Vanderbilt University in Tennessee and taught physics from 1940

to 1947. He also continued his bacteriophage research at the Cold Spring Harbor Laboratory on Long Island in New York.

Delbrück met Italian microbiologist Salvador Luria from Indiana University in 1941, who was conducting bacteriophage research. Together, in 1943, they published "Mutations of Bacteria from Virus Sensitivity to Virus Resistance." Their groundbreaking research confirmed that phage-resistant bacterial strains form through a process of natural selection. Their work also detailed the experimental technique and the calculations for measuring mutation rates. Together with Alfred Hershey and Salvador Luria, he formed the Phage Group, a team of scientists involved in studying bacteriophages, in 1943. The Phage Group made discoveries toward explaining vital aspects of cell physiology. He became a United States citizen in 1945.

Delbrück discovered "genetic recombination" in 1946, where the genetic material of different bacteriophage strains invades a bacterial cell and then combines to create new types of viruses. In 1947, he returned to Caltech as a professor of biology and remained there for the rest of his career. During the late 1940s and 1950s, he became interested in sensory perception and studied the fungus *Phycomyces* to establish how it uses light and how light affects its growth. He continued his sensory perception research until he retired.

Delbrück founded the Institute of Genetics in Cologne, Germany, in 1959 to encourage research in molecular biology in his birth country.

Delbrück shared the 1969 Nobel Prize in Physiology or Medicine with Alfred Hershey and Salvador Luria "for their discoveries concerning the replication mechanism and the genetic structure of viruses."

Max Delbrück was unusual in 20th-century science for practicing both physics and biology and for the fact that, although substantial as a discoverer, his place is largely that of an inspirer in the creation of molecular biology, particularly for physicists. He died in Pasadena, California, in 1981, aged 74.

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Anticoagulant-induced Spinal Epidural Hematoma with Spontaneous Recovery

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Sir,

Spinal epidural hematoma is a rare entity, with an annual incidence of 1 per one million population worldwide. This condition, being a surgical emergency, has very high morbidity if left untreated. We report a case of anticoagulant-induced epidural hematoma, which spontaneously improved without surgery.

A 71-year-old male, a known case of rheumatic heart disease on acenocoumarin, was admitted with complaints of sudden onset of tight band-like sensation around the region of the upper back and trunk, numbness in his soles, weakness in both lower limbs, and acute painful retention of urine following strenuous exercise. On examination, he had normal cognition and cranial nerve function. Spinomotor system examination of the upper limbs was normal, with normal bulk in the lower limbs but reduced tone bilaterally. Power was 0/5 on the left side and 2/5 on the right lower limb, both proximal and distal. Reflexes were absent in bilateral knees and ankles, with bilateral plantar responses mute. All sensory modalities were diminished in the bilateral lower limbs up to the L1 level without any graded pattern. All blood investigation reports were normal except for international normalized ratio (INR), which was >9.21, for which injection vitamin K 10 mg was given as a stat dose. The repeat INR value was 4.3. Magnetic resonance imaging (MRI) of the thoracolumbar spine, plain and contrast, revealed an epidural hematoma at the D3–D8 level, with no spinal cord edema (Fig. 1). The patient was advised to undergo emergency surgery, but the procedure was deferred as the patient denied consent. Consequently, he was treated conservatively with steroids to reduce the inflammation. The patient improved symptomatically and was discharged in a stable condition with power 5/5. His repeat MRI revealed a significant reduction in the size of the hematoma, without any evidence of cord compression (Fig. 2).

Spinal epidural hematoma is a rare condition, accounting for <1% of spinal epidural space-occupying lesions. It can occur at any level but is most commonly found at the thoracic and cervical spinal cord levels. The source of bleed is not universally agreed upon, but venous bleeding

from the spinal epidural veins is considered the probable source. These veins lack valves, so changes in abdominal and thoracic pressure can affect the venous system. In many cases, including ours, a straining event is described prior to the occurrence of the hematoma.

Most common cause of nontraumatic spinal epidural hematoma is clotting disorders, which include both drugs induced and congenital, accounting for almost 33% of the cases as in our case.¹ Other causes of spinal epidural hematoma include vascular malformations, tumors, and in rare cases, uncontrolled hypertension. In our patient's case, who was on acenocoumarin, a warfarin derivative, with an initial INR value of 9.21, the bleed is considered to be caused by anticoagulation therapy. The high INR may have been exacerbated by ranitidine and acetaminophen, which he was taking over the counter intermittently.

Similar to our case, most patients present with severe pain, sometimes radiating,

corresponding to the segment of the spinal cord affected by the hematoma. This is typically followed by symptoms of spinal cord compression, which can develop over a period of hours to days.

Magnetic resonance imaging is the preferred investigation. The location and extent of the hematoma, degree of compression of the spinal cord, and changes in spinal cord signals can be identified on MRI of the spine. For patients unable to undergo MRI, such as those with mechanical heart valves or those taking warfarin leading to hematoma, computed tomography (CT) myelography is preferred over contrast-enhanced CT, as the latter often results in misdiagnosis.

Once the diagnosis is confirmed, emergency surgery should be performed as soon as possible. The preferred surgical procedure is hemilaminectomy, as most hematomas are located in the lateral or dorsolateral spinal canal. Nonsurgical treatment should only be attempted in patients with mild or nonprogressive neurological deficits. The rate of improvement post-surgery depends on the time interval from the onset of symptoms and the severity of the initial injury. According to a large international study comprising multiple case series of spinal epidural hematoma, there is an 18% chance of complete recovery and a 44% chance of partial improvement in spinal cord function.² In our case, patient improved completely with nonsurgical management. Similar cases of complete recovery without surgical management were reported by Brawn et al.³ and SreeHarsha et al.⁴

Spinal epidural hematoma should be considered by clinicians in the differential diagnosis of compressive lesions of the spinal cord, as early surgical decompression yields better outcomes. However, in cases where there is early recovery within the first few hours or ongoing improvement, and in situations where patients are unwilling to undergo surgery or surgery is contraindicated due to other compelling reasons, spontaneous recovery remains a possibility.⁴



Fig. 1: Magnetic resonance imaging spine—T2-weighted imaging—sagittal section—showing well-defined T2 hyperintense epidural lesion of size 16 × 0.8 × 0.9 cm extending from D3 to D9 vertebral levels, causing indentation and compression over the spinal cord, without change in spinal cord signal intensity



Fig. 2: Magnetic resonance imaging spine—T2-weighted imaging—sagittal section—showing lesion extending from D3 to D9 vertebral levels—14.2 × 0.2 cm in length, without any spinal cord compression—showing a reduction in size of the bleed

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Lobetron ABPI

Composition: Each Uncoated Tablet Contains: Lobeglitazone Sulfate 0.5 mg. **Indications:** Treatment of adult type 2 diabetes mellitus patients: as monotherapy or as dual oral therapy in combination with metformin or sulphonyl urea. **Common Adverse Reactions:** Headache, URTI, edema, hematuria, hyperglycemia, elevated liver enzymes. **Precautions:** Should be administered with caution in HF patients, patients who are on other oral hypoglycemic drugs, premenopausal women, patients with edema, elderly patients, risk of fractures, weight gain. **Contraindications:** known hypersensitivity to Lobeglitazone or its ingredients, HF, hepatic disorder, severe renal impairment, diabetic ketoacidosis, diabetic coma and pre-coma, type 1 DM patient, before and after surgery patients with severe infections/ severe trauma. **Dosage & Administration:** one tablet once daily.

BisotrakTM-T ABPI

Composition: each film-coated tablet contains: Bisoprolol Fumarate 2.5 mg/5 mg & Telmisartan 40 mg Tablets. **Indications:** for the treatment of mild to moderate hypertension. **Common Adverse Reactions:** dizziness, headache, bradycardia, worsening of pre-existing HF, feeling of coldness or numbness in the extremities, hypotension especially in patient with HF, GI complaints such as nausea, vomiting, diarrhea, constipation, asthenia, fatigue. **Precautions:** should be administered with caution in patients with bronchospasm, strict fasting, ongoing desensitization therapy, first-degree AV block, Prinzmetal's angina, peripheral arterial occlusive disease, general anesthesia, psoriasis or with a history of psoriasis, thyrotoxicosis, renovascular hypertension, kidney transplantation, intravascular hypovolemia, primary aldosteronism, aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy, diabetic patients treated with insulin or antidiabetics, hyperkalemia. **Contraindications:** known hypersensitivity to the Bisoprolol, Telmisartan, or to any of the excipients, acute HF or during episodes of HF decompensation requiring I.V. inotropic therapy, cardiogenic shock, second or third degree AV block (without a pacemaker), sick sinus syndrome, sinoatrial block, symptomatic bradycardia, symptomatic hypotension, severe bronchial asthma or severe COPD, severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome, untreated pheochromocytoma, metabolic acidosis, pregnancy, biliary obstructive disorders, renal insufficiency, severe hepatic impairment, concomitant use with Aldiskren-containing products in patients with diabetes mellitus or renal impairment. **Dosage & Administration:** one tablet once daily.



Zuventus

Zuventus House, Plot Y2, CTS No: 358/A2, Near Nahur Railway Station, Nahur (West), Mumbai - 400 078.

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

IF UNDELIVERED PLEASE RETURN TO

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