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Editor-in-Chief: Prof. Dr. Mangesh Tiwaskar

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Telmisartan plus Metoprolol Succinate is contraindicated in severe bradycardia, second or third degree heart block, cardiogenic shock, decompensated cardiacfailure, and sick sinus syndrome (unless a permanent pacemaker is in place). **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. 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 patents 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 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. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, 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. Initiate Telmisartan at low doses and titrate slowly in these patients. Impaired Renal Function As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function 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 anticipate an effect similar to that seen withACE inhibitors. Dual Blockade of the Renin-Angiotensin-Aidosterone System (RAS) 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, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on Telmisartan and other agents that affect the RAS. Do not co-administer aliskiren with Telmisartan in patients with diabetes. Avoid concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR <60 mL/min/1.73 m²). Metoprolol ischemic Heart Disease Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Metoprolol succinate, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 to 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate Metoprolol succinate, and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing Metoprolol succinate in patients treated only for hypertension. Heart Failure Worsening cardiac failure may occur during up-titration of Metoprolol succinate. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of Metoprolol succinate. It may be necessary to lower the dose of Metoprolol succinate or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of Metoprolol succinate. Bronchospastic Disease PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta, cardio-selectivity, however, Metoprolol succinate may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because beta, -selectivity is not absolute, use the lowest possible dose of Metoprolol succinate. Bronchodilators, including beta,- agonists, should be readily available or administered concomitantly. Pheochromocytoma If Metoprolol succinate is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle. Major Surgery Avoid initiation of a high-dose regimen of extended-release Metoprolol in patients undergoing noncardiac surgery, since such use in patients with cardiovascular risk factors has been associated with bradycardia, hypotension, stroke and death. Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. Diabetes and Hypoglycemia Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Hepatic impairment Consider initiating Metoprolol succinate therapy at doses lower than those recommended for a given indication; gradually increase dosage to optimize therapy, while monitoring closely for adverse events. Thyrotoxicosis Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm. Anaphylactic Reaction While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction. Peripheral Vascular Disease Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Calcium Channel Blockers Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly. **Use in Pregnancy and lactation:** Pregnancy: Telmisartan can cause fetal harm when administered to a pregnant woman. 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. There are no adequate and well-controlled studies of Metoprolol in pregnant women. Therefore, when pregnancy is detected, discontinue the combination of Telmisartan plus Metoprolol as soon as possible. Lactation: There is no information regarding the presence of Telmisartan in human milk, the effects on the breastfed infant, or the effects on milk production. Telmisartan is present in the milk of lactating rats. Metoprolol is excreted in breast milk in very small quantities. Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with the combination of Telmisartan plus Metoprolol.

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Jyotirmoy Pal
President, Association of Physicians of India

MALARIA

Malaria, a mosquito-borne parasitic disease, is a major global health concern, with a significant burden in tropical and subtropical countries. According to the World Health Organization (WHO), approximately 247 million malaria cases and 6,19,000 deaths were reported globally in 2021, with a substantial proportion occurring in Africa and Southeast Asia. India remains a hotspot for malaria, being particularly vulnerable due to its dense population, large rural areas, and monsoon-driven climatic conditions that support mosquito breeding and proliferation.

Prior to independence, the burden of the disease was very high in our country. In 1947, when India became independent, 75 million malaria cases in a population of 330 million were estimated. Over the decades, with various policies and health programmes implemented by the government of India, starting from the National Malaria Control Programme in the 1950s to Intensified Malaria Control Project in 2005 and National Framework for Malaria Elimination 2016, the cases have declined to 2 million in 2023. Development of malaria vaccines is another milestone towards global elimination of malaria.

However, in spite of stringent control measures and strides in the health programs, there are several emerging issues that are complicating the scenario and acting as obstacles in our pathway towards malaria elimination. This includes: issues of insecticide resistance among the vector mosquitoes, emerging drug resistance leading to treatment failures, changing faces of the disease with atypical presentations, increasing number of complicated or severe vivax malaria cases which was once thought to cause benign malaria and also new species like *Plasmodium knowlesi*.

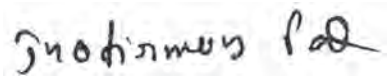
Malaria's treatment, control and eventual eradication remain pivotal to improve health outcomes and reducing economic losses in these regions. In this regard, more data on the present scenario is needed from all over the country. From the discovery of malaria transmission by Sir Ronald Ross in Presidency Hospital, now IPGMER & SSKM Hospital, Kolkata to the discovery of *Plasmodium knowlesi* at Calcutta School of Tropical Medicine, our country has always been a pioneer in scientific biomedical research.

The Association of Physicians of India is also committed in this regard to promote research and collaborate with our government to make the national programmes successful in all aspects.

Let us all stride towards Malaria elimination in India.

Jay Hind!

Jay API!



Dr Jyotirmoy Pal

EDITORIAL

The Unrelenting Epidemic of Diabetes in India: Do the Numbers Matter?

Viswanathan Mohan[1*], Mangesh Tiwaskar[2]

Globally, and in India, the prevalence of type 2 diabetes is rising rapidly. The estimated number of individuals with diabetes in India was 32 million in the year 2000, which rose to 63 million by 2012, 74 million in 2021,[1] and it is now 101 million, according to the ICMR–INDIAB Study.[2] The situation got even more alarming when a more recent report from the NCD Risk Factor Collaboration (NCD-RisC) survey reported the number of people with diabetes in India to be 212 million.[3] What is surprising is that the data from the ICMR–INDIAB study was mostly used to make these estimations by the NCD-RisC Collaboration. The difference in numbers is because, in the original ICMR–INDIAB study, we used the oral glucose tolerance test (OGTT) criteria to diagnose diabetes, while in the NCD-RisC survey, fasting glucose and/or HbA1c >6.5% was used as the criteria. We have shown earlier that use of HbA1c can lead to grossly elevated prevalence rates of diabetes.[4]

So that brings us to the question, do the numbers of people with diabetes in a country matter? Of course, they do, as governmental health policies are driven by the disability-adjusted life years (DALYs) and the morbidity and mortality due to a condition. However, in reality, it is not the number of people with diabetes that we are worried about but rather the number of people with complications of diabetes.

Having said that, there are three worrying trends as far as the epidemiology of diabetes in India is concerned.[5] Firstly, it is now affecting people at a younger age.[6] Secondly, earlier a disease of the affluent, diabetes has now started affecting the middle and even the lower socioeconomic strata. Thirdly, the disease, which was mostly confined to urban areas earlier, is now affecting the rural population as well. As the life expectancy of the nation is increasing, we can expect to have more cases of diabetes, as age is a nonmodifiable risk factor for diabetes. Hence, more than the prevalence of diabetes, one is more worried about the incidence of diabetes because this reflects the new-onset diabetes and gives us a better idea about the actual increase in diabetes in the community.[7]

Why is Diabetes Increasing So Rapidly in India?

While genetic factors are obviously important, the epidemic of diabetes is driven more by environmental factors. Excess carbohydrate consumption, particularly in the form of white rice or wheat, has been linked to type 2 diabetes (T2D).[8,9] Conversely, changing white rice to brown rice with legumes leads to lower glucose and insulin responses.[10]

While we can attempt to prevent diabetes in those with prediabetes by changing lifestyle habits, doing this at a national level is not easy. Hence, what we should put most effort into is preventing the complications of diabetes. This is a more realistic goal, and it can be achieved by attaining the ABC targets of therapy (i.e., A1c <7.0%, BP < 140/90 mm Hg, cholesterol, especially LDL cholesterol <100 mg/dL or lower). We have shown that it is possible for people with T2D to live for 40 or even 50 or more years if these targets are achieved.[11,12]

However, there are several challenges in achieving these targets.[13] The ICMR–INDIAB study showed that only 7% of people with T2D achieved all three targets.[14] Elevated glucose levels lead not only to microvascular complications but also to cardiovascular disease (CVD) and mortality.[15] Conversely, good control of diabetes can help to reduce markers of inflammation[16] and also prevent accelerated aging.[17]

So, the short answer to the question posed in the title of this editorial—do the numbers of people with diabetes matter—is: YES, the numbers of people with diabetes do matter, particularly in relation to complications of diabetes. Assuming that even 20% of people with diabetes develop complications, this would mean that there would be 20 million people who are at risk of blindness, kidney failure, amputations, and heart attacks. This implies a huge financial burden, not only for the individual and the family but also for society and the health system—something a country like India can ill afford. Hence, the only thing we can do is either prevent diabetes or, in those who already have diabetes, keep the ABC parameters under control. The good news is that if we focus on the ABC targets of therapy, not only the microvascular and macrovascular complications but also the newly emerging complications of diabetes, like metabolic dysfunction-associated steatotic liver disease (MASLD) or Alzheimer's, can be prevented or slowed down. The time to act is NOW!

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ORIGINAL ARTICLE

Zeroing in on Hepatic Steatosis Screening in Patients with Type 2 Diabetes Mellitus: A Retrospective Analysis of the Vicious Trifecta-Obesity, Nonalcoholic Fatty Liver Disease, and Diabetes

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Abstract

Nonalcoholic fatty liver disease (NAFLD) and diabetes mellitus commonly coexist and act synergistically to drive worse prognosis for each other. Insulin resistance, obesity, and metaflammation are some of the important underlying pathologies.

Despite the overwhelming prevalence of NAFLD in type 2 diabetic patients, there exists neither a proper screening protocol nor any specific management guideline for the same.

With our study, we focus on three major diseases: diabetes, obesity, and NAFLD. We established collinearity among hemoglobin A1C (HbA1c), body mass index (BMI), and liver stiffness [kilopascals (kPa)] using multivariate linear regression. We were able to express kPa as a weighted average of the other two variables. Moreover, using correlation plots, we calculated critical values for both HbA1c and BMI as 6.57 and 26, respectively, beyond which the risk of liver fibrosis is accentuated significantly. We used the same cutoff values in our data to veritably prove that patients had increasing severity and frequency of hepatic steatosis/fibrosis as they exceeded the critical limit. Patients with both BMI and HbA1c below the cutoff had predominantly no/mild steatosis, while patients with both values exceeding the cutoff had predominantly severe steatosis/fibrosis on ultrasonographic imaging. Patients who had either of the two variables above the said limit had steatosis severity somewhere in between the two groups, highlighting that even one uncontrolled variable would significantly worsen the prognosis.

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Introduction

Nonalcoholic fatty liver disease (NAFLD), defined as hepatic steatosis on imaging or histology in the absence of secondary causes of hepatic fat accumulation, accounts for the most common cause of chronic liver disease worldwide.[1] NAFLD encompasses a spectrum that includes hepatic steatosis (NAFL), nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. NAFLD is associated with multiple comorbidities, viz., type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome, and hypertension. Of these, T2DM not only is the most important risk factor for developing NAFLD, but also is the most important clinical predictor of adverse clinical outcomes.[2]

The prevalence of NAFLD varies widely depending on the population studied and the methodology applied. While the prevalence of NAFLD in the world population is estimated to be 25%, NAFLD may be present in up to 55–60% of patients with diabetes. The prevalence of biopsy-proven NASH and advanced fibrosis in asymptomatic type 2 diabetics is 20 and 5–7%, respectively.[3–5] In obese adults with T2DM, the prevalence has been estimated to be >70%.[5]

With the increasing burden of diabetes, it is, in turn, expected to raise the burden of NAFLD. Despite the staggering prevalence, there is no protocol yet to screen patients with diabetes for NAFLD. Furthermore, even if established, the management guidelines for such a patient are vague.[4]

Apropos of prospective studies suggesting a link between obesity, T2DM, and liver fibrosis in NAFLD, we targeted these three diseases.[6] We hypothesized that with just hemoglobin A1C (HbA1c) and body mass index (BMI) values, among the diabetes sample, we can identify the susceptible strata prone to developing liver fibrosis. This outpatient department (OPD)-based categorization of DM patients could justify NAFLD testing in select patients without burdening the economy, healthcare personnel, or the patients. The key objectives are: (1) to ascertain if the three variables [HbA1c, BMI, kilopascals (kPa)] share a linear relationship, (2) to evaluate if kPa shows its biological relevance with BMI and HbA1c, and (3) to calculate the critical values of HbA1c and BMI, which could then be used as two-variable checkpoint to predict patients with high propensity to develop liver fibrosis.

Materials and Methods

Study Population and Data Collection

This is a retrospective cross-sectional study performed on the 2020–2022 patient data obtained from the emergency and medicine wards of Government Medical College and associated group of hospitals, Kota. Individuals aged between 30 and 80 years were selected. The study population included cases of T2DM. Following an explanation of the nature and purpose of the study, those subjects willing to participate were included after Ethical Committee clearance and obtaining informed consent.

Any patient with previously or newly diagnosed T2DM was included, irrespective of pharmacotherapy. Men consuming >20 gm of alcohol per day, women consuming >10 gm of alcohol per day, known cases of liver diseases such as those secondary to positive hepatitis B surface antigen or anti-hepatitis C virus antibody, and the presence of past clinical and radiological evidence of

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other chronic liver diseases were excluded. After the inclusion and exclusion criteria were met, we had a total of 100 patients.

Study Definitions

Criteria for diagnosing diabetes mellitus as per World Health Organization-3/American Diabetes Association-4 (WHO3/ADA4) criteria: symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L or 200 mg/dL, or fasting plasma glucose ≥7.0 mmol/L or 126 mg/dL, or HbA1c ≥6.5%, or 2-hour plasma glucose ≥11.1 mmol/L or 200 mg/dL after 75 gm oral glucose tolerance test.[7] HbA1c level was measured by high-performance liquid chromatography (HPLC) technique.

Anthropometric measurements [height (m), weight (kg), BMI, and waist–hip ratio (WHR)] were also done. BMI was calculated as weight in kg divided by the square of height in m, expressed as kg/m^2. A trained technician measured the waist circumference to the nearest 0.1 cm in the horizontal plane, at the level of the high point of the iliac crest at minimal respiration. Although the BMI cutoff to classify underweight is universal (i.e., <18.5 kg/m^2), WHO uses two sets of cutoffs to classify obesity. For the Asian population, a BMI of 23–27.4 and ≥27.5 kg/m^2 denotes overweight and obesity, respectively, while for the western population, the range is 25–29.9 and ≥30 kg/m^2. We used the former definition for our study population.[8] Thrombocytopenia and hypoalbuminemia were defined as a platelet count of <1.5 L/mm^3 and serum albumin <3.5 mg/dL, respectively.[9] An elevation of both alanine and aspartate transaminase was considered at levels >40 IU/dL.[9]

Fibroscan

Liver stiffness was assessed for all patients using FibroScan-402® by an experienced examiner. Patients were in the dorsal decubitus position, with the right arm in maximal abduction, above the head. After gel application, the probe was positioned perpendicular to the skin surface over one of the intercostal spaces adjacent to the right lobe of the liver (typically the 9th–11th intercostal space on the right, mid-axillary line). A portion of the parenchyma free of large vessels, >6 cm thick, was chosen; liver stiffness was measured at a depth of 25–65 mm, in a 1 cm × 4 cm area. At least 10 valid measurements were obtained, with a success rate defined as the number of valid acquisitions divided by the attempts, >60%, and a ratio of the interquartile range to the median of 10 measurements ≤0.3. The results are expressed in kPa with a range from 1.5 to 75 kPa. The normal value for an adult human is between 5 and 6.5 kPa, and values above 6.5 and 7 kPa suggest fibrosis.[9] For convenience, to address the research question in our study, we assume the threshold minima of 6.5 kPa.

Statistical Analysis

To establish liver stiffness as an outcome of the linear combination of HbA1c and BMI, a multivariate regression model was performed. The degree of linearity of their pairwise relationship (HbA1c vs liver stiffness; BMI vs HbA1c; and BMI vs liver stiffness) was tested using the Pearson correlation coefficient. An initial kPa cutoff value of 6.5 was used to derive values for BMI, HbA1c, and again kPa.[9] To establish each of HbA1c, kPa, and BMI as a dependent variable, and the other two variables as its covariates, a linear line of fit was employed to the correlation plots, and the cutoff values were obtained through linear extrapolation.

A subsequent analysis was performed on the same data of 100 people. We applied the BMI and HbA1c cutoffs to determine the risk strata for NAFLD and divided the patients into three groups. We corroborated the reliability of the results using serology (transaminase, thrombocyte, and albumin levels) and imaging (ultrasonography-guided liver imaging).

Results

The multivariate regression model performed for 100 observations yielded significance for the intercept, x_1, and x_2. The R^2 value was 0.636, and the adjusted R^2 value was 0.629. The F statistic compared against the constant model was 83.1 and was statistically significant ($p < 0.0005$) (Fig. 1 and Table 1).

Further, the Pearson's correlation tests for the linear relationship between the variables HbA1c, BMI, and kPa were significant for all three cases (kPa vs HbA1c, HbA1c vs BMI, and BMI vs kPa).

Regressing the liver stiffness (kPa) cutoff value of 6.5 on HbA1c in the kPa vs HbA1c correlation plot yielded an HbA1c of 6.57. Subsequently, regressing the obtained HbA1c cutoff value of 6.57 on BMI in the BMI vs HbA1c correlation plot yielded a BMI of 26 (Figs 2A to C and Table 2).

The difference between the original kPa cutoff (6.5) and the BMI-derived kPa cutoff (6.58) was 0.08. It can be observed from the deduced kPa difference of 0.08 that the covariance condition assumes a minimal value.

The purpose of this test was to express kPa as a weighted average of BMI and HbA1c. The statistically negligible difference between the initial kPa and the derived kPa authenticates the two derived critical values for BMI and HbA1c, that is, 26 and 6.57, respectively.

Any patient above the threshold for both variables can be strongly suspected to have liver fibrosis and can be a good candidate for further evaluation, aggressive lifestyle modifications, and pharmacotherapy for NAFLD. Any patient who has either one variable above the threshold can be

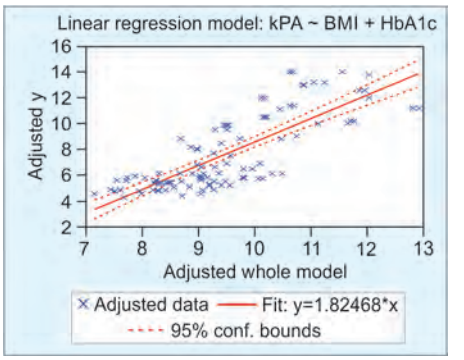


Fig. 1: Multivariate linear regression model: kPa ~ BMI + HbA1c: prediction for kPa across the full range of observed values for BMI and HbA1c. The solid red line denotes the fitted data while the 95% confidence interval is designated by the two dotted red lines

Table 1: Multivariate regression done on two variables: HbA1C and BMI

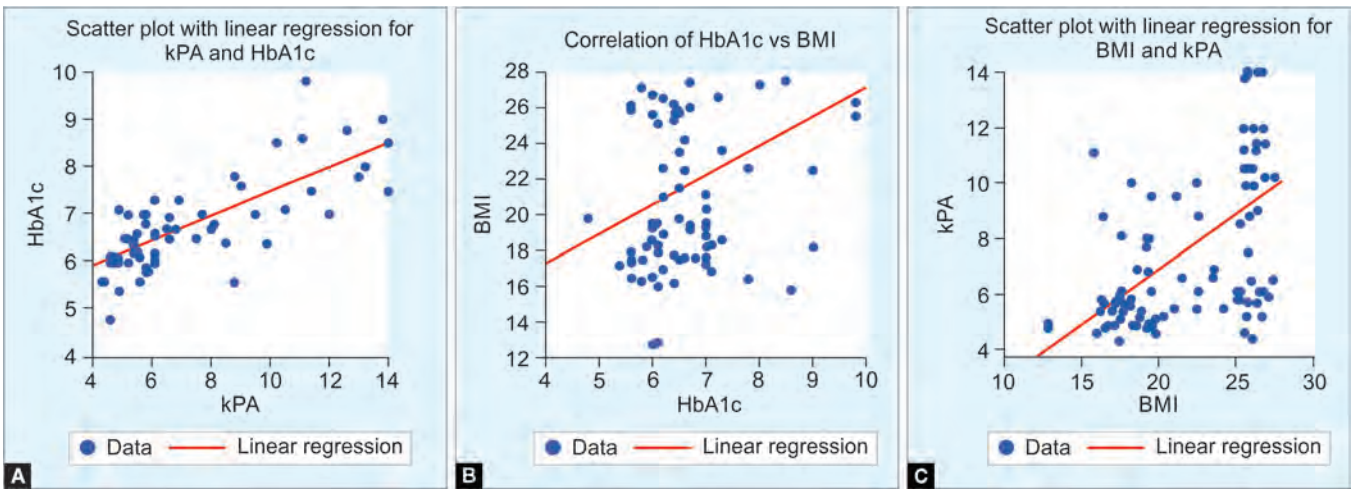
	Estimate	*SE*	*t-stat*	*p-value*
Intercept	–9.6705	1.3583	–7.1196	2.0523e-10
x_1	0.22059	0.048031	4.5927	1.3417e-05
x_2	1.8113	0.19689	9.1994	8.501e15

The number of observations were 100; the statistics for estimated coefficients showed significance for intercept and x_1 and x_2; R^2: 0.636; p-value = 1.35e-21

Table 2: Correlation results between the three variables—kPa vs HbA1C, HbA1c vs BMI, and BMI vs kPa

Correlation features	*Correlation coefficient*	*p-value*
kPa and HbA1c	0.7495	0.00039
HbA1c and BMI	0.4387	0.00069
BMI and kPa	0.5882	0.00023

All the three correlation plots showed significant results with $p < 0.05$



Figs 2A to C: Pearson's correlation tests (scatter plot with linear regression) for variables HbA1c, BMI, and kPa: (A) kPa vs Hba1c, (B) Hba1c vs BMI, and (C) BMI vs kPa. As evident by the positive slopes, all the graphs show a positive correlation between the tested variables and all three were statistically significant (explained in Table 2)

Table 3: Assessing patients after applying derived critical cutoff values

		Group A: A1c <6.57 and BMI <26	*Group B: A1c ≥6.57 or BMI ≥26*	*Group C: A1c ≥6.57 and BMI ≥26*
Total patients		36	42	22
USG-hepatic steatosis grading	Grade ≤I	24 (66.6%)	13 (30%)	0
	Grade II	12 (33.3%)	25 (59%)	4 (19%)
	Grade III	0	4 (9%)	18 (81%)
Thrombocytopenia		0	0	1
Hypoalbuminemia		0	0	1
Elevated transaminases		3	4	16

made aware of the increased propensity of developing NAFLD.

To verify, we used the cutoff values from our study data as an *ad hoc* analysis. The dataset was divided into three groups: group A, B, and C, that is, patients with both values below the cutoff, either of the values above the cutoff, and both values above the cutoff, respectively. Then we compared the severity of hepatic steatosis as well as selected markers of hepatic dysfunction (transaminitis, thrombocytopenia, hypoalbuminemia). The results were as follows:

Evidently, group C had moderate to severe steatosis (81% severe and 19% moderate steatosis). Two-thirds of group A had no/mild steatosis, while group B had 30, 59, and 9% of no/mild, moderate, and severe steatosis, respectively. The table clearly shows the pattern of increasing severity of NAFLD from groups A to C (Table 3).

Only one patient (out of the 100) had both thrombocytopenia and hypoalbuminemia. The patient was in group C, further corroborating that the cutoffs can be used to screen patients with high risk for liver steatosis/fibrosis. About 16 out of 22 patients in group C had elevated liver enzymes, while only three and four patients in groups A and B, respectively, had raised transaminases.

Discussion

Nonalcoholic Fatty Liver Disease in Diabetes—Need for Action

The coexistence of diabetes and NAFLD has been well established, as has the prevalence of obesity in both subsets.[10] NAFLD increases the risk of developing diabetes, and regular HbA1c check-ups are warranted for people with established fatty liver, but no protocol exists for NAFLD screening in patients with diabetes. The extent to which type 2 diabetes increases an individual's risk of developing NAFLD is less defined and difficult to study. NAFLD may be seen in up to 70% of patients with diabetes, but the majority of them are asymptomatic.[4] The existence of unrecognized liver pathology in diabetic patients—and the probability of its accessible and feasible screening—is what we wanted to address in our study.[4,11]

Though clinically nonspecific or silent, NAFL/hepatic steatosis can still progress to steatohepatitis and further to end-stage liver disease. Even in cases where no inflammation or fibrosis is noted, NAFL is not benign—it greatly influences the severity of hepatic insulin resistance.[12] NAFLD and T2DM act synergistically to drive adverse outcomes of each other.

Obesity, Nonalcoholic Fatty Liver Disease, and Type 2 Diabetes Mellitus—Mechanism of Interaction

Overweight and obesity are abnormal or excessive fat accumulations presenting a health hazard. A crude population measure of obesity is the BMI, with a BMI of 27.5 or more considered obese and a BMI ≥23.5 considered overweight for the Asian population.[6] Obesity, diabetes, and fatty liver are three very intricately associated entities with proven overlapping pathophysiology for all three.[13] Obesity is crucial in determining the severity of insulin resistance in T2DM, as well as the onset and severity of fatty liver. Obesity and dyslipidemia are risk factors for the development of diabetes and are clearly implicated in the prevalence and severity of developing NAFLD.[4]

Obesity triggers insulin resistance through the accumulation of excess lipid within the liver and skeletal muscle, as well as in the heart, liver, and pancreas. The disparity

between calorie intake and expenditure, deposition of excess calories in the liver, and lipolysis of visceral adipose tissue results in hepatic triglyceride excess. This sets off a chain of events involving M1 macrophages, reactive oxygen species, cytokines like interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), adipokines like adiponectin and leptin, and enzymes like acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). The trigger for this metaflammation is yet unclear, but the outcome is similar, leading to insulin resistance, hepatic inflammation, necrosis, and fibrosis. It is important to note that obesity is not only a risk factor for hepatic fibrosis through the progression of NAFLD but also has a synergistic effect on superimposed or secondary hepatic injury (Figs 3 and 4).[6]

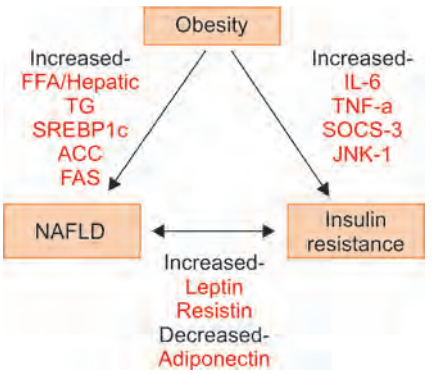


Fig. 3: Proposed mechanisms of interaction among obesity, insulin resistance, and NAFLD. The mediators are color-coded based on the source of origin (red, liver; brown, adipose tissue). ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; FFA, free fatty acid; IL-6, interleukin-6; JNK, c-Jun NH2-terminal kinase; SREBP1c, sterol regulatory element-binding protein 1c; TG, triglyceride; TNF-α, tumor necrosis factor-α.[6] Image adapted from Chiang DJ et al. 2011.[6]

Obesity, Nonalcoholic Fatty Liver Disease, and Type 2 Diabetes Mellitus—Collinear Variables?

To adjudicate the same, we conducted a multivariate regression with kPa as the dependent variable and BMI and HbA1c as the predictor variables. A statistically significant relationship between the *y*-intercept with x_1 and x_2 (y = kPa, x_1 = BMI, x_2 = HbA1c) corroborates our hypothesis that they indeed share a linear relationship. The possible rationale has already been discussed. Some animal models have proven a causal relation between increased fat accumulation, insulin resistance, and progression to fibrosis,[6,14] but no such causality could be ascertained in our study.

Critical Cutoff Values

Once the correlation was done between the variables and was found to be statistically significant, critical values were extrapolated. For a kPa of 6.5, HbA1c was 6.57; the BMI cutoff at an HbA1c of 6.57 was 26. To establish the covariance of multicollinearity, at a BMI of 26, the kPa cutoff was found to be 6.58.

The derived cutoffs are very close to the critical values used for WHO/ADA diagnosis guidelines, whether it be HbA1c or BMI. This reinforces the need to routinely check weight, height, waist, along with blood pressure, at every visit. Since we established liver stiffness' linear dependence on both obesity and T2DM, we can positively infer that both diseases need to be kept in good check for a reduced risk of NAFLD progression. Studies proving diabetes as an independent risk factor for progression to liver fibrosis and reversal of NAFLD in patients postbariatric surgery substantiate our result.[5,15–17]

The Two-variable Check for Nonalcoholic Fatty Liver Disease Prediction in Diabetes

The final purpose of this two-variable check (BMI, HbA1c) was to avoid blanket testing of all diabetes patients, yet ensure timely diagnosis of hepatic steatosis in them. The subanalysis done on our 100 patients' dataset, using the two critical values, formed three groups: A, B, and C.

The progressive severity and increased frequency of hepatic steatosis among the three groups easily validate this simple yet effective screening tool. It clearly accentuates the increased risk in patients with even one critical value. Despite multiple studies proving a strong association between obesity, diabetes, and NAFLD, this is the first study to devise objective values proving the

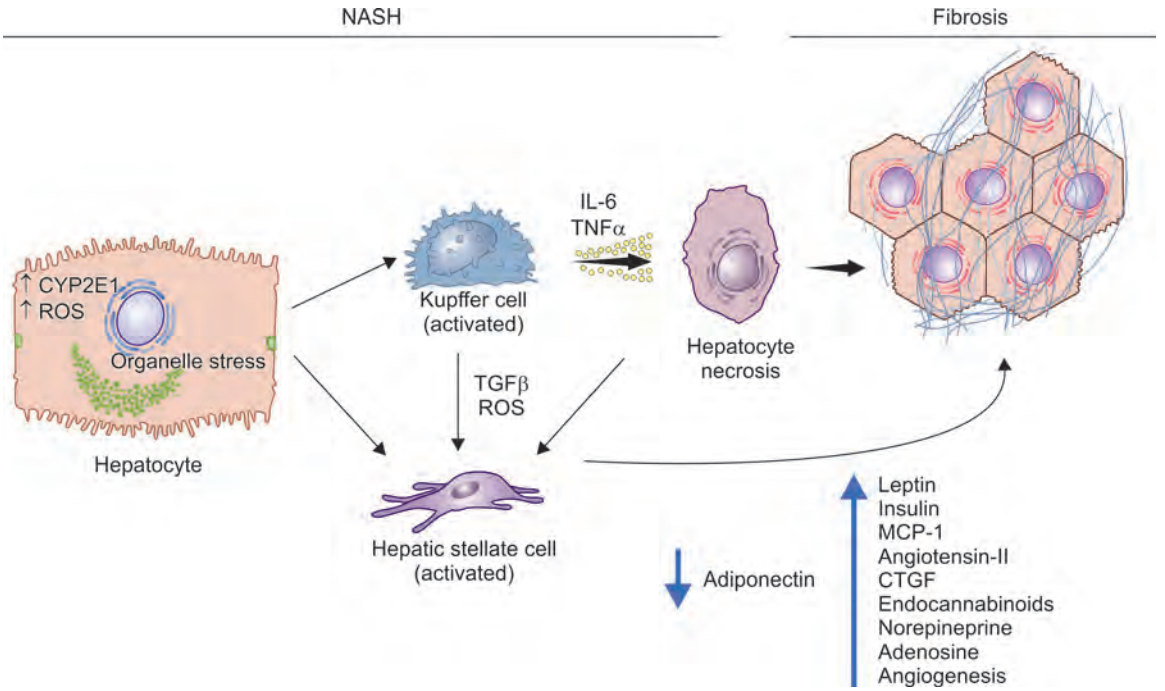


Fig. 4: Potential pharmaceutical targets of interest in the progression of NASH to fibrosis in the setting of obesity and insulin resistance. CTGF, connective tissue growth factor; MCP-1, monocyte chemoattractant protein-1; ROS, reactive oxygen species; TGF-α, transforming growth factor-α.[6] Image adapted from Chiang DJ et al. 2011.[6]

same. The timely diagnosis and management of NAFLD in T2DM would not only reduce the probability of diabetes-associated complications but would independently lower the cardiovascular risk of the patient.[18]

While we have multiple scores like the Fibrosis-4 (FIB-4) index, NAFLD fibrosis score, and APRI score, they may be unable to detect asymptomatic early hepatic steatosis cases with normal serology. As evident from our study, only one patient had thrombocytopenia and hypoalbuminemia. Transaminases are unable to diagnose or predict the prognosis of NAFLD with acceptable sensitivity. This has been proven in multiple studies and corroborated by the results of our study: with one-third of patients in group A having moderate and about 70% of group B having moderate to severe steatosis, only three and four patients showed an increase in liver enzymes, respectively. Conversely, with 16 patients out of 22 having elevated liver enzymes in group C, it may be indicative of it being a consequence of advanced liver injury rather than a mere marker of its existence.[11,19]

The application of this screening tool on a larger dataset, a comparison with existing scoring models, as well as calculating the sensitivity, specificity, and predictive value, is the next step of our project. Whether the proven collinearity persists when extrapolated to the community at large is yet to be determined through large randomized trials.

Conclusion

The increasing prevalence of diabetes mellitus and the unmet need for screening NAFLD in this predisposed population must be recognized. As it may not be economical and practical to test all patients with hyperglycemia for fatty liver, we devised an easily applicable method to highlight a target group. Our study was able to prove liver stiffness as a weighted average of BMI and HbA1c. Additionally, it showcases how obesity and hyperglycemia are independently and synergistically associated with increased risk of hepatic steatosis. Using these two variables, it is possible to anticipate NAFLD in the DM population who would benefit from further evaluation and management, irrespective of symptoms. The efficacy of this screening tool and the collinearity between the BMI, kPa, and HbA1c need to be proven on a larger, multicentric dataset in a randomized trial for better evidence-based management.

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ORIGINAL ARTICLE

Ventilator-associated Pneumonia: A Prospective Observational Study

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Abstract

Background: The danger of ventilator-associated pneumonia (VAP) is maximum in the early course of a hospital stay. The published Indian data on VAP are limited.

Objectives: The primary objectives were to find the occurrence and clinical outcome of VAP in the intensive care unit (ICU), whereas the secondary objectives were to find risk factors and microbiological profile of VAP.

Materials and methods: About 138 patients admitted to ICU who were intubated for >48 hours were enrolled in this prospective observational study. Risk factors such as age, chronic lung disease, length of mechanical ventilation (MV), clinical outcome, presence of nasogastric tube, previous antibiotic exposure, reintubation or intubation ≥7 days, change in the ventilator circuit, and use of sedatives/paralytic agents were noted. The endotracheal aspirate was sent to the laboratory for species identification and sensitivity testing. Discrete and continuous variables were compared by Fisher's exact test and Mann–Whitney *U* test, respectively. Multiple logistic regression analysis was done to explore the significant risk factors linked with VAP.

Results: The occurrence of VAP was 34.7/1,000 MV days, whereas 21.7% of MV patients developed VAP. Mortality was 50% in VAP patients. Age >55 years, prolonged ventilation, and chronic lung disease were significantly associated with VAP. The most common isolate was *Acinetobacter baumannii*, followed by *Klebsiella pneumoniae*. Multidrug resistance (MDR) and extensive drug resistance were observed in 13.3 and 66.7% of isolates, respectively.

Conclusion: There was a high incidence and mortality of VAP in ICU patients. Strict implementation of VAP bundles and adherence to infection control protocols are needed.

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Introduction

The hospital-acquired pneumonia manifesting 48 hours or more after the commencement of mechanical ventilation (MV) is labelled as ventilator-associated pneumonia (VAP).[1] In the early course of a hospital stay, danger of VAP is maximum. It is projected to be 3, 2, and 1%/day during the first 5 days, >5–10 days, and >10 days of MV, respectively.[2] The overall occurrence of VAP is estimated to be 13.6 infections/1,000 MV days,[3] whereas it is 3.5–46/1,000 infection/MV days in Asian countries[4] according to the International Nosocomial Infection Control Consortium data. There is a lack of published Indian data on VAP. The present research aimed to find the incidence, risk factors, microbiological profile, and clinical outcome of VAP in the intensive care unit (ICU) of a tertiary care hospital.

Materials and Methods

Patients >18 years of age admitted to the ICU of a tertiary care hospital, Pune, between June 2015 and November 2016 who were on MV for >48 hours were enrolled in this prospective observational research. An approval of the Institutional Ethics Committee was obtained before the commencement of the research. Patients who had preexisting pneumonia before intubation, patients who developed pneumonia within <48 hours of intubation, and patients who were discharged or died within 48 hours of intubation in the ICU were excluded from the study. We obtained written informed consent from each patient's next of kin after explaining the research protocol in detail.

The information such as date of birth, sex, the diagnosis on admission, date of intubation and extubation, date of discharge or death from the ICU, etc. were noted. All the patients were followed up daily and assessed for the signs and symptoms of VAP. Duration of ICU stay and MV was noted.

The risk factors for the occurrence of VAP such as age, gender, chronic lung disease (like chronic obstructive pulmonary disease, asthma, interstitial lung disease, cystic fibrosis), prior history of chest surgery, the presence of a nasogastric tube, use of agents that increase gastric pH [e.g., proton pump inhibitors (PPIs) and H2 blockers], antibiotic exposure in the past 3 months, reintubation or prolonged intubation (defined as ≥7 days),[5] change in the ventilator circuit, and use of sedatives or paralytic agents were noted.

Ventilator-associated pneumonia was defined as the presence of a new or progressive radiographic infiltrate plus at least two of three clinical features, namely, high temperature (>38°C), leukocytosis or leukopenia, and purulent secretions.[6] Multidrug resistance (MDR) was defined as nonsusceptibility to at least one agent in three or more antimicrobial groups.[7] Extensively drug-resistant (XDR) was defined as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories). XDR gram-negative bacilli were defined by resistance to all commonly used systemic antibiotics except colistin, tigecycline, and aminoglycosides.[7] Pan drug-resistance (PDR) was defined as nonsusceptibility to all agents in all antimicrobial classes (i.e., no agents tested as susceptible for that organism).[7] Pan-resistance refers to gram-negative bacilli with diminished susceptibility to all of the antibiotics recommended for the empiric treatment of hospital-acquired pneumonia and VAP, including cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam, ciprofloxacin, and levofloxacin.[8] Extended-spectrum beta-lactamase (ESBL) was defined as resistance to third generation cephalosporins and monobactams.[9] A VAP prevention bundle was followed to manage all the patients, as it is a routine protocol in our tertiary care hospital.

Endotracheal aspirate specimens were used for microbiological evaluation, including Gram stain and quantitative cultures. Briefly, 0.01 mL samples were plated on sheep blood agar, chocolate agar (CA), and MacConkey agar using a 4 mm Nichrome wire loop (Hi-Media, Mumbai, India). All plates were incubated overnight at 37°C, and CA plates

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were incubated at 37°C in a candle jar. All plates were checked for growth after 24 hours and again after 48 hours of incubation. The cutoff of $>10^5$ colony-forming units (CFU)/mL for identifying a bacterial cause of VAP was used.[10] Species identification and sensitivity testing were done by an automated VITEK (bioMérieux, Inc., USA) method using appropriate cards.[11]

Fagon et al.[12] observed the occurrence of VAP in 49/567 (8.6%) patients. A sample size of 121 patients was calculated by a formula: $N = (Z_\alpha)^2\ p(1 - p)/d^2$, where Z_α, a standard normal variate at 5% type 1 error = 1.96, p is the expected proportion in the population based on a previous study (8.6%), and d = absolute error of 5%.[13] We included 138 patients in the present study. The primary outcome measures were to find the incidence and death or recovery of VAP patients admitted to a tertiary-level medical ICU. The secondary outcome measures were to find risk factors, microbial species identification, and sensitivity to antimicrobial agents.

Statistical Analysis

The proportion of VAP was determined by calculating the number of patients with VAP out of the total mechanically ventilated patients. Total ventilator days were calculated, and the incidence of VAP was determined as the number of cases per 1,000 ventilator days. The comparison of the distribution of discrete and quantitative variables was done using Fisher's exact test and the Mann–Whitney U test, respectively. Multiple logistic regression analysis was done to explore the significant risk factors associated with VAP. A p-value of <0.05 was considered significant.

Results

In the current research, 145 patients were screened, and seven were excluded (two died, five withdrew consent). About 138 patients were included in the final analysis. The median age of the study participants was 52 years (interquartile range 18–87 years), and 57.2% were males. Metabolic encephalopathy, intracranial bleeding, and trauma were the most common admission diagnoses. The median duration of MV was significantly higher ($p = 0.001$) in patients who developed VAP compared to patients who did not develop VAP (8 vs 5 days). The median length of ICU stay was significantly longer ($p = 0.002$) among patients who developed VAP (13 days) compared to patients who did not develop VAP (9 days).

Out of 138 cases included in the study, the incidence of VAP was 34.7/1,000 MV days, while 30/138 (21.7%) of MV patients developed VAP. As evident from Table 1, out of 30 patients who developed VAP, 15 (50%) died, whereas out of 108 patients who did not develop VAP, 20 (18.5%) died (p-value = 0.002).

On univariate analysis, age above 55 years, chronic lung disease, reintubation, prolonged MV, and change in the ventilator circuit were the significant risk factors associated with VAP. There was no statistically significant link between VAP and sedation/use of paralytic agents, prior antibiotic, PPIs, nasogastric tube, and prior history of chest surgery. Multivariate analysis showed that age >55 years [hazard ratio (HR) 13.7, (95% CI, 1.6–114.1, $p = 0.015$)], prolonged ventilation [HR 15.8, (95% CI, 5.1–49.6, $p = 0.001$)], and chronic lung disease [HR 7.6, (95% CI, 1.4–41.8, $p = 0.020$)] were statistically associated with VAP (Table 2).

Of 30 patients who had VAP, the isolates were predominantly gram-negative, and only one (3.33%) was gram-positive, that is, *Staphylococcus aureus*. The most common isolate was *Acinetobacter baumannii*, followed by *Klebsiella pneumoniae*. As depicted in Table 3, all the isolates (100%) were ESBL, four isolates (13.3%) were MDR, and 20 (66.7%) were XDR.

Discussion

We documented a high incidence of VAP in our research at a tertiary-level care center in Western India, which is comparable to the study conducted by Ranjan et al.[14] It was reported that the incidence of VAP was three times higher in limited-resource countries,[3,15] while some reported rates were more than eightfold higher than those in industrialized countries.[16] Reasons for the high rate of VAP may include the lack of uniform implementation of VAP bundles,[17] lack of experience in infection control and surveillance, insufficient human and health supply resources accessibility, and a lack of comprehensive lawful framework backing infection control programs, including mandatory surveillance and hospital accreditation policies.[18]

Table 1: Outcome of ventilated patients

Outcome	*VAP*		*Total n (%)*	*p-value*
	Present n (%)	*Absent n (%)*		
Discharged	15 (50.0)	86 (79.6)	101 (73.2)	0.002
DAMA	0 (0.0)	2 (1.9)	2 (1.4)	
Death	15 (50.0)	20 (18.5)	35 (25.4)	
Total	30 (100.0)	108 (100.0)	138 (100.0)	

Fisher's exact test was used; VAP, ventilation-associated pneumonia; DAMA, discharged against medical advice

Table 2: Multivariate analysis of the statistically significant risk factors

Variable	*Hazards ratio*	*95% confidence interval of hazards ratio*	*p-value*
Age >55 years	13.72	1.65–114.17	0.015
Prolonged ventilation	15.83	5.05–49.63	0.001
Chronic lung disease	7.57	1.37–41.80	0.020
Reintubation	0.85	0.08–9.23	0.897
Circuit change	5.1	0.36–72.0	0.231

Table 3: Bacterial isolates from tracheal aspirate and mortality observed

Organism	*ESBL*	*MDR*	*XDR*	*PDR*	*Mortality*
A. baumannii	11	2	9	0	6
K. pneumoniae	9	2	7	0	5
Pseudomonas aeruginosa	5	0	4	0	3
Stenotrophomonas maltophilia	2	0	0	0	0
S. aureus	1	0	0	0	0
Escherichia coli	1	0	0	0	0
Sphingomonas paucimobilis	1	0	0	0	1
Total	30 (100.0%)	4 (13.3%)	20 (66.7%)	0 (0.0%)	15 (50.0%)

ESBL, extended-spectrum beta-lactamase; MDR, multidrug resistance; PDR, pan drug-resistance; XDR, extensively drug-resistant

In the present study, age above 55 years, history of chronic lung disease, and protracted intubation were significantly linked with the incidence of VAP. Celis et al. documented an association between VAP and older age.[19] Chronic lung disease is a documented risk factor for VAP, as observed in a study conducted by Celis et al.[19] The compromised immunity can be due to the presence of structural lung disease, the need for repeated hospitalization, and the use of antibiotics and corticosteroids.[20] Ranjan et al. documented an increased duration of MV associated with VAP.[14] This may be because of the impaired reflexes resulting from prolonged intubation, thereby increasing the risk of aspiration.[21] This underlines the importance of proper weaning protocols.

In our study, reintubation and frequent change in the ventilator circuit were associated with VAP, albeit only in univariate analysis. Reintubation is a documented risk factor for VAP.[22] The likely reason is increased vulnerability to aspiration in the interval between extubation and reintubation.[22] The Centers for Disease Control and Prevention, Atlanta, advises that ventilator circuits be replaced no more often than every 48 hours.[23] Hess et al. recommend the use of the same devices for up to 7 days.[24] Sedation, use of paralytic agents, and prior antibiotic use were linked with VAP.[14,25] In the present research, there was no statistically significant link between VAP and sedation/use of paralytic agents or prior antibiotic use.

Although the literature suggests a relation between the use of PPIs, the use of a nasogastric tube, and a prior history of chest surgery with VAP, we did not find any such association. This was perhaps due to the appropriate use of these interventions only when indicated or the sample size being inadequate for measuring the association of many risk factors.

Acinetobacter baumannii, followed by *K. pneumoniae*, were the most common bacteria isolated among patients with VAP in our study. This is in accordance with many studies.[26,27] *A. baumannii* is linked with higher death rates,[14] which can explain the high deaths associated with VAP in our study, since a high number of patients were XDR isolates. There are studies documenting the rising prevalence of ESBL in hospital as well as community settings, which can be due to the rampant use of antibiotics and the lack of antibiotic policies.[18,28,29] The mortality rate in the present research is comparable with other studies.[21,30] The death rates in cases with VAP infections ranged from 20% to as much as 76%, with higher rates reported among cases with MDR infections.[12]

The strength of the present research is that the data were collected prospectively, based on a standardized VAP definition, and the method of sample collection followed the latest and current guidelines on VAP. A few limitations of our study include the fact that the progression of a pulmonary infiltrate was not used or included to define VAP. The risk factors such as emergency intubation, intrahospital transport, subglottic suction, semi-recumbent position, and maintaining cuff pressure were not assessed. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was not observed. Patients in the ICU can die due to a variety of reasons, such as other organ dysfunction, and we did not assess VAP-attributable and risk-adjusted mortality. As this was a single-center study, the findings cannot be generalized to other populations. Multicentric prospective studies with a large sample size should be undertaken to corroborate the results described in the present manuscript.

Conclusion

The incidence of VAP was 34.7/1,000 MV days, while 21.7% of MV patients developed VAP. Mortality was 50% in VAP patients. Age >55 years, prolonged ventilation, and chronic lung disease were significantly associated with VAP. The most common isolate was *A. baumannii*, followed by *K. pneumoniae*. MDR and XDR were observed in 13.3 and 66.7% of isolates, respectively. The study highlights the high incidence and mortality of VAP. This calls for strict implementation of VAP bundles and adherence to infection control protocols.

Conflict of Interest

The manuscript has been read and approved by all the authors, that the requirements for authorship, as stated earlier in this document, have been met, and that each author believes the manuscript represents honest work.

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Book Review

HIV-AIDS in India & Developing Countries

By Yanamadala Murali Krishna. 122 pp. Hyderabad, India, Anupama Printers, 2024. Rs. 155. US $7.99 (outside India). ISBN: 978-81-969150-7-0

The author Yanamadala Murali Krishna is a full-time AIDS medical specialist with vast experience of treating HIV/AIDS in Andhra Pradesh for more than two decades. This book covers a multitude of issues from discovery of AIDS-like illness in year 1981, to promise of AIDS vaccine and the challenge of global HIV treatment equity with regard to generic medicine availability in developing countries. The author's expertise shines through his nuanced analysis of the complex factors driving the epidemic, including social, economic, cultural, and political elements.

This book provides a comprehensive overview of the HIV-AIDS epidemic development in India and other developing nations and its impact on communities, responses from governments, NGOs and individuals. There is in-depth analysis of the epidemic's drivers, including poverty, gender inequality, and migration. The author has put a great effort in covering all aspects of the virus, infection, disease and their impact on human health and social life. The author has effectively illustrated the architecture and epidemiology of HIV infection. Immense knowledge has been imparted to the readers about relevant sources and ways of transmission of the infection. The information is easy to read and in simple understandable language for healthcare workers as well as general public who care for people living with HIV (PLHIV). Appropriate indications of testing and management have also been taken care in appropriate sections. The Indian perspectives of the disease, stages and its treatment have been narrated very well.

The associations with other communicable infectious diseases like TB and other special circumstances such as pregnancy have also been covered very well. He has very well elaborated the elements of HIV prevention. The author YM Krishna has beautifully added a human touch by sharing the personal stories and experiences of those affected with this uncurable disease. The author has broken the rigid myths associated with the infection acquisition, transmission and development of the disease. The book re-emphasizes important role of universal precaution practice by all healthcare professionals for prevention of blood-borne infections like HIV and hepatitis viruses. The author emphasizes the importance of cultural sensitivity and community engagement in effective HIV/AIDS management. The book outlines the positive rather than a miserable outlook to people living with the disease.

Dr YM Krishna's expertise and passion for the subject makes this book on HIV-AIDS a must-read for anyone committed to understanding and addressing this global health challenge faced due to HIV-AIDS especially in resource-limited countries of South-East Asia and Africa.

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ORIGINAL ARTICLE

High-sensitivity Troponin in Predicting Coronary Artery Disease for Primary Prevention in Indian Population

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Abstract

Objectives: Cardiovascular diseases (CVDs) have become a major cause of mortality in India and abroad. Various risk scores have been formulated to estimate CVD risk. The preferred biomarker for the detection of myocardial cell necrosis is cardiac troponin. Highly sensitive troponin assays are now available. Computed tomography coronary angiogram (CT-CAG) is the standard noninvasive modality to identify as well as exclude coronary artery disease (CAD). Our study aims to correlate high-sensitivity troponin I (hs-cTnI) and the QRESEARCH cardiovascular (CV) risk algorithm (QRISK3) score against CT-CAG and determine whether, by using these data, we can detect or rule out CAD accurately by noninvasive means alone.

Materials and methods: We evaluated 100 subjects who presented with chest pain (primary prevention population) to the cardiology outpatient department. A detailed history was obtained, and blood investigations, including hs-cTnI, were conducted. The QRISK3 score was calculated, and CT-CAG was performed for all. Hs-cTnI >6 was considered significant. Those who had >50% diameter stenotic lesion(s) were deemed to have significant CAD.

Results: In our study with 100 subjects, 80 had hs-cTnI <6, and 20 subjects had hs-cTnI >6. The QRISK3 score did not show any statistical correlation with hs-cTnI. The hs-cTnI levels were compared with CT-CAG results and found that 80% of subjects with elevated hs-cTnI had CAD.

Conclusion: A strong correlation between elevated hs-cTnI levels and CAD by CT-CAG was established by our study. The early detection of CAD will prompt early management and delay further progression of the disease.

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Introduction

Coronary artery disease (CAD) has become a major cause of cardiovascular (CV) morbidity and mortality in this century, irrespective of economic status. The transition from communicable to noncommunicable diseases in India has been rather brief. Cardiovascular disease (CVD) affects Indians at least a decade earlier, progresses faster, and has a high fatality rate, often impacting the most productive years of life. The threat of CVD in an individual's lifetime is substantial, and the condition is frequently silent or may strike without warning, emphasizing the importance of prevention. Premature CVD, over 75%, is preventable, as estimated by the World Health Organization (WHO). Risk factor modification can reduce the CVD burden on individuals as well as on the healthcare sector.[1]

The CVD risk factors illustrated by the INTERHEART study included hypertension, diabetes, dyslipidemia, smoking, and abdominal obesity. The risk factors were consistent across the population and socioeconomic statuses. This established uniform approaches for the primary prevention of CVD worldwide. For the prevention and early initiation of treatment of CAD, there is a need for early detection, control of risk factors, and their management.[2]

Coronary artery disease is a pathological process wherein there is deposition of obstructive or nonobstructive atherosclerotic plaque in the epicardial coronary arteries. CAD is a double-edged sword. It can be stable for long periods but can suddenly become unstable secondary to a plaque rupture or erosion. CAD is chronic, mostly progressive, and dangerous, even during asymptomatic times.

A careful history can often generate a high degree of certainty in diagnosing CAD. Myocardial ischemia presents with chest discomfort (angina) located in front of the chest, most commonly near the sternum. Accompanying symptoms include shortness of breath, fatigue, nausea, burning sensation, anxiety, or a sense of impending doom. The discomfort usually lasts ≤10 minutes in most individuals. Aggravation of symptoms after a heavy meal, postexercise, or early in the morning are classic features of angina. Sublingual nitrates rapidly relieve this angina.[3]

Assessment of anemia, high blood pressure, valvular heart disorders, cardiomyopathy, and arrhythmias is an essential part of the physical examination. Calculating body mass index (BMI), examining all peripheral pulses, checking for carotid and femoral bruits, and measuring the ankle–brachial index (ABI) complete the CV examination. Signs of other associated conditions, including thyroid and renal disease, should always be looked for.[4]

A 12-lead electrocardiogram (ECG) should be done in patients with chest pain without an alternative noncardiac cause. The dynamic ST-segment changes recorded on ECG during ongoing anginal pain play a major role in diagnosing myocardial ischemia. The European Society of Cardiology (ESC) 2019 guidelines recommend a transthoracic echocardiogram to exclude alternate causes of angina, identify regional wall motion abnormalities (RWMA), measure the left ventricular ejection fraction (LVEF) for risk stratification, and evaluate diastolic function. A chest radiogram should be performed for those in heart failure, those with atypical presentations, and those with a suspicion of lung disease.[5]

Several biomarkers, including total creatine kinase (CK), creatine kinase-myocardial band (CK-MB), lactate dehydrogenase, and aspartate aminotransferase,[6] were earlier used to assess CV risk. A lack of sensitivity and specificity to myocyte necrosis led to the need for newer, more specific molecules.

Cardiac troponins (cTn) are structural proteins in the contractile apparatus of cardiac myocytes. After myocyte cell death, they are released into circulation. They are biomarkers of choice for detecting myocyte injury, diagnosing myocardial infarction (MI), and risk stratifying patients in whom there is a suspicion of acute coronary syndrome (ACS).[7] Troponin assays have evolved over the years, and cTn can be detected in about 20–50% of healthy individuals, whereas

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hs-cTn can be detected in about 50–90% of healthy individuals.[8]

Hs-cTn is highly cardiac-specific and can predict CV events, morbidity, and mortality.[9] It improves risk prediction by established risk scores, including ESC and the Framingham risk score (FRS), and is also cost-effective in the long run.[10]

The ARCHITECT high-sensitivity troponin I (hs-cTnI) assay was one of the first hs-cTnI assays to be commercially available. It has the ability to detect hs-cTnI values in 96% of apparently healthy subjects (limit of detection: 1.2 ng/L). The upper reference limit (URL, 99th percentile) was 26 ng/L. The reference limit for men was 34 ng/L and for women was 16 ng/L. Among various studies comparing different ethnic groups, the URLs are consistent, similar to this assay.[11] A coefficient of variation of <10% at 6 ng/L in pooled serum was achieved when assay precision was assessed locally.[12]

A number of CV risk scoring systems incorporating various risk factors have been formulated to estimate atherosclerotic cardiovascular disease (ASCVD) risk and guide primary prevention strategies. FRS, the World Health Organization/International Society of Hypertension (WHO/ISH), the American College of Cardiology and American Heart Association (ACC/AHA), and the QRISK3 score are a few of them. Many of these risk scores do not take into account factors such as type 2 diabetes mellitus, South Asian ancestry, or a history of premature CAD in the family.

The QRISK3 score predicts the risk of developing CV disease over the next 10 years in individuals aged 25–84 years. Chronic kidney disease (stage 3, 4, or 5), migraine, corticosteroid use, systemic lupus erythematosus (SLE), atypical antipsychotic use, psychiatric illness, erectile dysfunction, and blood pressure variability were also included in the score along with traditional risk factors. The updated risk algorithms provided appropriate measures of absolute risk in the general population, which were also validated in a separate cohort.[13]

The early diagnosis and severity assessment of CAD are essential for appropriate management. The evaluation of the coronary vasculature by indirect means of stress testing has its own limitations.[14] Conventional CAG remains the gold standard investigation for diagnosing obstructive CAD in high-risk individuals.[15]

Individuals with an intermediate risk of CAD may benefit from computed tomography coronary angiogram (CT-CAG).[16] The ability to diagnose and characterize the distribution and morphology of coronary atherosclerotic plaque can be used to improve short- and long-term CV risk stratification.[17] Coronary artery calcium (CAC) detected by CT identifies subclinical CAD and adds prognostic value independent of traditional risk scores.[18]

Sixty-four-slice CT-CAG has a negative predictive value of 95–97%, thus avoiding the need for further testing, as it can reliably rule out the presence of CAD. This reduces the need for conventional CAG in low- to intermediate-risk patients.[19,20]

In low-risk group patients, CT-CAG has higher accuracy values.[21] In symptomatic patients where CAD cannot be excluded by clinical assessment alone, the ESC 2019 guidelines recommend (class 1, level B evidence) CT-CAG or noninvasive functional imaging as a primary investigation to diagnose CAD. The CT-CAG assessment of CAD is a single-observer assessment. To reduce the margin of subjective error, adding fractional flow reserve (FFR) to CT-CAG has been recommended in a few studies.[5]

Our study aimed to add diagnostic value by incorporating hs-cTnI into the QRISK3 score in existing practice to exclude CAD. The objective was to study the sensitivity, specificity, and positive and negative predictive values of hs-cTnI in comparison with the gold standard CT-CAG, as well as the application of the QRISK3 score and its sensitivity relative to hs-cTnI.

Materials and Methods

Our study was conducted in the department of cardiology at Apollo Main Hospital, Chennai, from 1st February 2020 to 31st December 2021. It included 100 subjects aged 18 years and above who presented with atypical or noncardiac chest pain and subjects with risk factors who wanted to know their cardiac status. Patients with documented CAD, heart failure with left ventricular ejection fraction <40%, and chronic kidney disease (CKD) with glomerular filtration rate <30 mL/minute/1.73 m^2 were excluded.

All participants were surveyed with a detailed history and examination. Biochemical investigations, including hemoglobin, fasting lipid profile, fasting blood sugar, serum creatinine, and hs-cTnI levels (ARCHITECT hs-cTnI assay), were conducted. A 320-slice CT-CAG was performed using the Canon-Toshiba ONE PRISM edition CT scanner. Plain CT chest imaging was followed by ECG-gated 0.5 mm axial volumetric helical CTA in the coronary arterial phase.

Study subjects were risk stratified based on the QRISK3 score and measurement of hs-cTnI into low-, intermediate-, and high-risk groups. Subjects who had >50% stenosis in one or more of the major epicardial coronaries or their major branches on CT-CAG were deemed to have significant CAD.

Statistical Methods

All continuous variables are represented by mean ± standard deviation if they are normally distributed. Nonnormally distributed continuous variables are expressed as median (interquartile range). Categorical variables are expressed as percentages.

The comparison of categorical variables was done using either the Chi-squared test or Fisher's exact test, and the comparison of continuous variables was performed using the independent sample *t*-test. Data analysis was carried out using IBM Statistical Package for the Social Sciences (SPSS) Statistics, Windows version 25. All *p*-values <0.05 were considered statistically significant.

Results

In this study, the majority, that is, 58 (58.0%) of the study subjects, belonged to the age-group of 41–60 years. The average age was 55 years. Out of 100 study subjects, 77 (77.0%) were male, and 23 (23.0%) were female. The study included 49 (49%) diabetics and 51 (51%) nondiabetics. Additionally, 68 (68%) subjects were hypertensive, while 32 (32%) were nonhypertensive (Table 1).

Among the 100 subjects, 80 (80%) had hs-cTnI values <6, whereas the remaining 20 (20%) had hs-cTnI values >6. All subjects underwent 320-slice CT-CAG. Among them, 44 (44%) had no CAD, 31 (31%) had insignificant CAD (<50% stenosis in one or more of the major epicardial coronaries or their major branches), and 25 (25%) had significant CAD (>50% stenosis in one or more of the major epicardial coronaries or their major branches).

Among the 100 subjects, 66 (66%) had no vessel involvement, 11 (11%) had single-vessel disease (SVD), 10 (10%) had double-vessel disease (DVD), and 13 (13%) had triple-vessel disease (TVD) (Table 2).

Study subjects were stratified based on the QRISK3 score and hs-cTnI measurement into low (<10), intermediate (10–20), and high-risk groups (>20). The QRISK3 score classified 37 subjects as low risk, 34 as intermediate risk, and 29 as high risk. Among the 20 subjects with hs-cTnI >6, 16 were in the low-to-intermediate risk group, and 4 were in the high-risk group. In the group with hs-cTnI <6, 25 subjects were high risk, 25 were intermediate risk, and 30 were low risk. The Chi-squared test showed no statistical significance correlating the QRISK3 score and hs-cTnI level (Table 3).

The comparison of hs-cTnI levels with CT-CAG showed that out of the 80 subjects

who had hs-cTnI <6, 40 (50%) had no CAD, while 40 (50%) had CAD. Among the 20 subjects with hs-cTnI >6, 4 had no CAD, while 16 had CAD, accounting for 80% of the subjects (Table 4).

Table 1: Baseline characteristics of study subjects

Parameters	*Frequency*	*Percent*
Men	77	77.0
Women	23	23.0
Type 2 diabetes mellitus (DM)	49	49.0
Hypertension (HTN)	68	68.0
Smoking	18	18.0
Alcohol	3	3.0
Stroke/carotid disease	2	2.0
Family history of CAD	11	11.0
Receiving lipid lowering medications	72	72.0
Receiving antiplatelet drugs	48	48.0
Dyslipidemia	39	39.0

The Chi-squared test showed statistical significance with a *p*-value of 0.016, indicating that subjects with hs-cTnI values >6 have a higher risk of having CAD.

Discussion

In our study with 100 subjects, 80 subjects had an hs-cTnI <6, and 20 subjects had hs-cTnI >6. The mean QRISK3 score for hs-cTnI <6 was 15.5925 ($p = 0.848$), and hs-cTnI >6 was 16.1950 ($p = 0.855$). Though numerically these values were higher in the subjects with hs-cTnI >6, it was not found to be statistically significant.

Study subjects were stratified based on QRISK3 score and measurement of hs-cTnI into low (<10), intermediate (10–20), and high-risk groups (>20). QRISK3 score classified 25 subjects with hs-cTnI <6 and 4 subjects with hs-cTnI >6 into the high-risk category. There was no statistical significance, *p*-value being 0.446.

The hs-cTnI levels were compared with the gold standard CT-CAG, which showed that out of the 80 subjects who had hs-cTnI <6, 40 (50%) of them had no CAD, and 40 (50%) had any CAD. Out of the 20 subjects with hs-cTnI >6, 4 subjects had no CAD, and 16 of them had any CAD, which accounts for 80% of the subjects. The Chi-squared tests showed statistical significance with a *p*-value of 0.016, showing that the subjects with hs-cTnI values >6 have a greater risk of having CAD.

In the study conducted by Findlay et al.,[22] 3rd Joint British Societies' (RiskJBS) risk score identified high CV risk (65%) in a large proportion of UK-based South Asian patients. In contrast, ACC/AHA and WHO risk scores, using the same population, identified high risk only in 28.7% and 21.3%, respectively. In a study by Bansal et al.,[23] RiskJBS recognized a higher proportion of "high cardiovascular risk" in South Asian patients when compared to WHO and ACC/AHA risk scores. This study reclassified a significant proportion of the same patients into the low-risk category.

In a study by Jain et al.,[24] taken from the MASALA and MESA cohorts (The Mediators of Atherosclerosis in South Asians Living in America—MASALA; The Multi-Ethnic Study of Atherosclerosis—MESA), South Asian adults without ASCVD at baseline, with optimal CV health metrics and lower ASCVD risk scores, had lower coronary artery calcium scores

Table 2: Distribution of CAD on CT-CAG

		Frequency	*Percent*	*Valid percent*	*Cumulative percent*
Valid	Non-CAD	44	44.0	44.0	44.0
	Insignificant CAD	31	31.0	31.0	75.0
	Significant CAD	25	25.0	25.0	100.0
	Total	100	100.0	100.0	

Table 3: Distribution of QRISK3 category and hs-cTnI

			hs-cTnI		*Total*
			hs-cTnI <6	*hs-cTnI ≥6*	
QRISK 3 category	<10	Count	30	7	37
		% within QRISK category	81.1%	18.9%	100.0%
		% within hs-cTnI <6	37.5%	35.0%	37.0%
	10–20	Count	25	9	34
		% within QRISK category	73.5%	26.5%	100.0%
		% within hs-cTnI <6	31.3%	45.0%	34.0%
	>20	Count	25	4	29
		% within QRISK category	86.2%	13.8%	100.0%
		% within hs-cTnI <6	31.3%	20.0%	29.0%

Table 4: Distribution of hs-cTnI between no CAD and CAD

			hs-cTnI		*Total*
			hs-cTnI <6	*hs-cTnI ≥6*	
CTCAG	No CAD	Count	40	4	44
		% within CTCAG	90.9%	9.1%	100.0%
		% within hs-cTnI <6	50.0%	20.0%	44.0%
	CAD	Count	40	16	56
		% within CTCAG	71.4%	28.6%	100.0%
		% within hs-cTnI <6	50.0%	80.0%	56.0%

and hence lower risk of CAD. The South Asian population with borderline or intermediate ASCVD risk scores would benefit from further screening using coronary artery calcium (CAC) scores or CT-CAG for early detection and management of CAD.

Due to such discrepancies between the individual risk scores, there can be potential inaccuracies in CV risk estimation if different risk scores are utilized, with relative under- or overestimation of risk prediction. This could lead to major inconsistencies in healthcare advice and influence treatment decisions in a population already recognized as having a high prevalence of premature-onset CVD. Our study included the QRISK3 score, which has South Asian ancestry as a component. Though numerically the score correlated with higher hs-cTnI levels, we found no statistical significance.

Our study showed that subjects with hs-cTnI values >6 have a higher risk of having CAD with a significant *p*-value of 0.016. This study supports other studies that showed a correlation between high hs-cTnI levels and CAD and its severity.

Limitations

The study included only 100 subjects, of which only 20 subjects had an hs-cTnI value >6. If the study had more subjects with an hs-cTnI value >6, then the QRISK3 score would have shown a better correlation with the hs-cTnI values. However, since our study was a prospective randomized study, the subjects were randomly included, and the distribution could not be controlled.

Conclusion

This study suggests that there is a strong correlation between elevated hs-cTnI levels and the presence of CAD by CT-CAG. QRISK3 score was found to be elevated in patients with elevated hs-cTnI levels, although it was not statistically significant. In the Indian population, where CVD is premature and often silent, assessment of risk scores (preferably QRISK3 in the Indian population), hs-cTnI levels, and CT-CAG will help rule out CAD in low- to intermediate-risk group subjects.

CT-CAG provides insight into coronary anatomy and rules out CAD due to its high negative predictive value, eliminating the need for further evaluation in certain patients. In cases of significant CAD, the patient will require further evaluation with a conventional CAG.

The early detection of CAD in the primary prevention population will prompt early management in the form of lifestyle modifications or pharmacotherapy, which can retard disease progression. CT-CAG is the preferred noninvasive modality of choice in the low-risk population, expediting evaluation and avoiding unnecessary interventions.

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ORIGINAL ARTICLE

A Comparative Study of Risk Factors across Young and Old Acute Ischemic Strokes: A Hospital-based Study in North India

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Abstract

Background: Stroke is an important cause of death and disability. Prevalence of stroke differs with age. The risk factors in young differ in comparison to the old age-group. In this study, risk factors of stroke in young are compared to the old age-group.

Aim: To compare the established risk factors in young and old acute ischemic strokes.

Materials and methods: The study was conducted at the neurosciences department of Santokba Durlabhji Memorial Hospital, Jaipur, a tertiary referral center in North India, from June 2015 to December 2016. It was a hospital-based analytical type of observational, cross-sectional study. One hundred fifty stroke patients above 18 years of age were included in young (<50 years) or old age (>50 years) groups. The risk factors of stroke were defined in terms of hypertension, diabetes mellitus, dyslipidemia, ischemic heart diseases, valvular heart disease, history of transient ischemic attack or stroke, smoking, oral contraceptive pill, raised serum homocysteine, and low serum vitamin B_{12} levels.

Results: Of 150 patients, 75 patients were in the young stroke group and 75 patients in the old stroke group. Out of these 150 patients, 66.67% were males and 33.33% were female patients. The mean age (in years) of young patients was 41.64, while in old stroke patients it was 65.8. Thirty-eight percent in the young group and 72% in the old group had hypertension. Diabetes was found in 16% and 32% in the young and old group, respectively. High serum homocysteine was seen in 64% young and 73% old. Low serum vitamin B_{12} was found in 25% young and 32% old. Venereal disease research laboratory (VDRL) was reactive in 1.3% in young and 4% in old. Antinuclear antibody (ANA) was positive in 6.6% in young and 2.6% in old. From those tested, antiphospholipid antibody (APLA) was positive in 3.64% in young and 4.16% in old.

Conclusion: Cardioembolic stroke was found equally in old as in young. The number of patients with rheumatic heart disease showed comparatively higher numbers in the young group, while atrial fibrillation was higher in the old age-group, signifying the importance of detailed cardiac workup and Holter monitoring in the old age-group when indicated. Serum vitamin B_{12} and homocysteine levels should be done routinely in the evaluation of ischemic stroke irrespective of the age of onset of stroke(s), as their levels were impaired equally in both young and old age-groups in our study. Dyslipidemia, traditionally regarded as a risk factor in old, also showed deranged values in the form of raised serum cholesterol and triglycerides in both age-groups. Positive VDRL, ANA, and APLA showed an increased trend in the old age-group in our study compared to the young age-group. Hypertension, diabetes mellitus, and inadequate physical activity were significant risk factors associated with the old group.

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Introduction

Stroke is the most common life-threatening neurological disease globally. It is the third leading cause of death and disability worldwide, with an incidence of 400–800 per 1,00,000 individuals each year.[1] Although stroke is predominantly a disease of middle age and the elderly, recent studies suggest that rates of stroke in the younger population (<50 years of age) have been increasing.[2] It has emerged as an important cause of morbidity and mortality in young adults, especially in developing countries.[3] Stroke in the young is particularly tragic because of its potential to create a long-term burden on the victims, their families, and the community.[4] Traditional risk factors for stroke, such as hypertension and diabetes, are more frequent in older adults, whereas some other permanent or transient risk factors—such as smoking, use of oral contraceptives, migraine, trauma, use of illicit drugs, and pregnancy or puerperium—have a more important role in the young age-group.[5] It is anticipated that by 2050, 80% of stroke patients will be from the developing regions of the world.[6] Additionally, there is growing evidence for an increasing trend in the incidence of stroke in young adults.[7] Accurate classification of ischemic stroke is critical for guiding treatment decisions and determining the prognosis of individual patients. The purpose of this study is to compare risk factors in young (≤50 years of age) and old (>50 years of age) acute ischemic stroke patients and to assess whether different stroke subtypes (TOAST classification) are associated with specific risk factors.

Materials and Methods

The study was conducted at the neurosciences department of Santokba Durlabhji Memorial Hospital cum Medical Research Institute, Jaipur, a tertiary referral center in North India, from June 2015 to December 2016. It was a hospital-based analytical type of observational, cross-sectional study. For this study, 150 patients of age greater than 18 years, of either gender, who presented with acute ischemic stroke and gave consent, were included. Those having hemorrhagic stroke, transient ischemic attack (TIA), or brain malignancy were excluded. All eligible patients fulfilling the inclusion criteria were divided into two groups: old (i.e., >50 years of age) and young (i.e., <50 years of age). Risk factors in each group were identified, including diabetes mellitus, hypertension, rheumatic heart disease, ischemic heart disease, peripheral vascular disease, migraine, transient ischemic attack, smoking habit, alcohol intake, physical activity, food habit, and family history. All relevant investigations were conducted in the designated hospital laboratory and radiology department, including magnetic resonance imaging/computed tomography (MRI/CT) along with vascular imaging—CT/MR angio, carotid Doppler, or digital subtraction angiography (DSA)—and other reports procured. Along with routine blood tests, serum homocysteine, vitamin B_{12}, and folic acid levels were done in all the patients. Venereal disease research laboratory (VDRL), antinuclear antibody (ANA), antiphospholipid antibody (APLA), and lumbar puncture

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for cerebrospinal fluid (CSF) analysis were done only in those patients where clinically indicated.

Results

Demographics of the study are shown in Table 1. In this study, a total of 150 patients were enrolled, and the young and old patient groups had 75 members each. Out of these 150 patients, male patients were predominant in both groups. The mean age in the young group was 42 years and in the old group was 66 years.

The risk factors, as seen in Table 2, included the following: 38.67% in the young and 72% in the old had hypertension, which was higher in the old age-group with statistical significance. Similarly, inadequate physical activity was 58.6% in the old age-group compared to 2.67% in the young and was statistically significant. Other risk factors like diabetes were found in 16 and 32% in the young and old groups, respectively. Ischemic heart disease (IHD) was present in 6.67 and 16% of patients in the young and old groups, respectively. About 13.33% in the young group and 2.67% in the old group had rheumatic heart disease (RHD). Smoking was found in 36% of the young group and 46.67% in the old group. Oral tobacco use was 9.33% in the young group and 6.67% in the old group. Alcohol consumption was 24% in the young group and 30.67% in the old group. Drug abuse was seen in 2.67% of patients in each group. There was one (0.67%) patient in the study population who was using oral contraceptives as a family planning measure; however, no statistical significance was seen.

Table 3 shows blood investigations. Twelve percent in the young group and 32% in the old group had raised fasting blood sugar levels. Raised total cholesterol was seen in 5.33% in the young and 8% in the old group, respectively. Raised low-density lipoprotein (LDL) cholesterol was seen in 29.33% in the young group and 22.67% in the old group. Serum homocysteine was raised in 64% of the

Table 1: Gender distribution in young and old groups

Gender	*Young group (N = 75)*		*Old group (N = 75)*		*Total (N = 150)*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Male	51	68.00	49	65.33	100	66.67
Female	24	32.00	26	34.67	50	33.33
Total	75	100.00	75	100.00	150	100.00

Table 2: Risk factor profile of patients in young and old groups

Risk factor	*Young group (N = 75)*		*Old group (N = 75)*		*Total (N = 150)*		*p-value**
	No.	*%*	*No.*	*%*	*No.*	*%*	
HTN	29	38.67	54	72.00	83	55.33	<0.001
DM	12	16.00	24	32.00	36	24.00	0.035
IHD	5	6.67	12	16.00	17	11.33	0.122
Migraine	4	5.33	3	4.00	7	4.67	1.000
RHD	10	13.33	2	2.67	12	8.00	0.035
Smoking	27	36.00	35	46.67	62	41.33	0.246
Oral tobacco use	7	9.33	5	6.67	12	8.00	0.763
Alcohol	18	24.00	23	30.67	41	27.33	0.464
Drug abuse	2	2.67	2	2.67	4	2.67	0.612
Oral contraceptive use	1	1.33	0	0.00	1	0.67	1.000
Inadequate physical activity	2	2.67	44	58.67	46	30.67	<0.001
Family history of stroke	2	2.67	3	4.00	5	3.33	1.000

*Among risk factors HTN and inadequate physical activity are found to be statistically significant

Table 3: Distribution of blood investigations of patients in young and old groups

Investigations	*Young group (N = 75)*		*Old group (N = 75)*		*Total (N = 150)*		*p-value**
	No.	*%*	*No.*	*%*	*No.*	*%*	
Raised fasting blood sugar	9	12.00	24	32.00	33	22.00	0.006
Raised total cholesterol	4	5.33	6	8.00	10	6.67	0.743
Low HDL cholesterol	27	36.00	42	56.00	69	46.00	0.022
Raised LDL cholesterol	22	29.33	17	22.67	39	26.00	0.457
Raised VLDL	28	37.33	41	54.67	69	46.00	0.049
Raised triglycerides	17	22.67	29	38.67	46	30.67	0.051
Raised S. homocysteine	48	64.00	55	73.33	103	68.67	0.291
Low S. vit B_{12}	19	25.33	24	32.00	43	28.67	0.470
Low S. folate	1	1.33	7	9.33	8	5.33	0.069
Reactive VDRL	1	1.33	3	4.00	4	2.67	0.612
Positive ANA	5	6.67	2	2.67	7	4.67	0.439
Positive APLA	2/55	3.64	1/24	4.16	3/79	3.80	<0.001

*In blood investigations APLA was found to be statistically significant

young group and 73.33% of patients in the old group. Low serum vitamin B_{12} was found in 25.33% in the young group and 32% in the old group. VDRL was positive in one (1.33%) patient in the young group and three (4%) in the old group. ANA was positive in 6.67% in the young group and 2.67% in the old group. Of those tested, APLA was positive in 3.64% in the young group and one (4.16%) patient in the old group and was statistically significant. The same has been represented in Figure 1.

As seen in Table 4, 18.67% in the young group and 29.33% in the old group had large artery atherosclerosis. Cardioembolism was found in 21.33% and 17% of patients in the young and old groups, respectively. Small vessel occlusion/lacune was found in 18.67% and 28% of patients in the young and old stroke groups, respectively. There were 12% in the young and 5.33% in the old group who had stroke of other determined cause. The same has been represented in Figure 2.

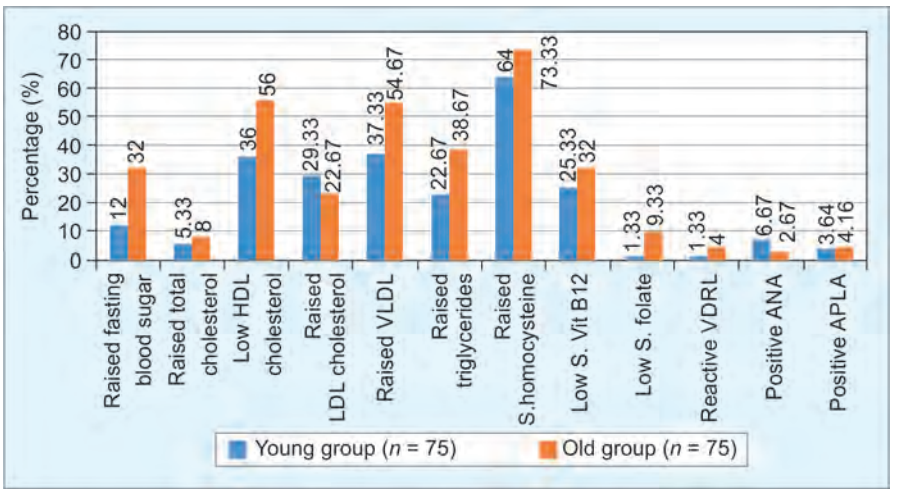

Fig. 1: Distribution of blood investigations of patients in young and old groups

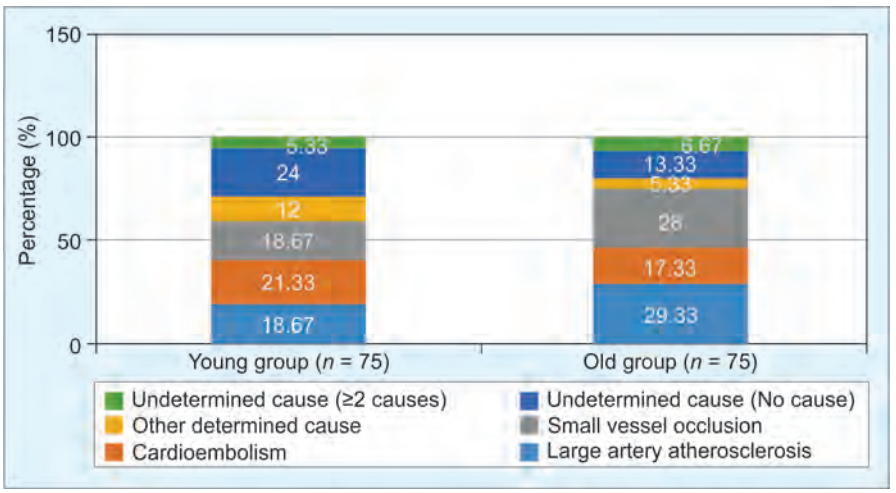

Fig. 2: Proportion of stroke subtypes as per TOAST classification in young and old group

Table 5 shows there were 2.67% in the young group and 1.33% in the old group who had large (nonlacunar) infarcts in the anterior circulation/ACA territory. There were 54.67% and 52% of patients in the young and old groups, respectively, who had MCA territory infarcts. Lacunar infarcts in the middle circulation were found in 12% in the young and 16% of patients in the old group. Large infarcts in the posterior circulation involving large arteries were found in 17.33% and 9.33% of patients in the young and old groups, respectively. Lacunar infarcts in the posterior circulation were found in 8% in the young group and 9.33% in the old stroke group.

Table 6 shows there were 21.33% of patients in the young group and 17.33% in the old group who had cardioembolic stroke. Different etiologies of cardioembolic stroke in patients in the young and old stroke groups, respectively, were as follows: atrial fibrillation 10 (62.50%) and 13 (100%), valvular heart disease 15 (93.75%) and 8 (61.53%), IHD 9 (56.25%) and 9 (69.23%), PFO 2 (12.50%) and 1 (7.70%), and infective endocarditis 2 (12.50%) and 1 (7.70%).

Table 7 shows nonvegetarians were 16% in the young group and 25.33% in the old group. Vegetarians were 84% in the young group and 74.67% in the old group.

Discussion

Stroke remains a significant cause of morbidity and mortality globally, with differing risk profiles between young and old patients.[8] The present study aimed to assess these differences in acute ischemic stroke patients in a North Indian cohort, particularly focusing on traditional and nontraditional risk factors. The most important general strategy for reducing the impact of stroke involves actions to achieve different levels of prevention. In this study, we compared these risk factors in young and old acute ischemic stroke patients and subtyped the ischemic stroke. In most previous studies in which hemorrhagic strokes are included, it becomes the most common type of stroke and hypertension the most common risk factor.

Table 4: Proportion of stroke subtypes as per TOAST classification in young and old groups

Stroke subtypes	*Young group (N = 75)*		*Old group (N = 75)*		*Total (N = 150)*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Large artery atherosclerosis	14	18.67	22	29.33	36	24.00
Cardioembolism	16	21.33	13	17.33	29	19.33
Small vessel occlusion	14	18.67	21	28.00	35	23.33
Other determined cause	9	12.00	4	5.33	13	8.67
Undetermined cause-A (no cause identified)	18	24.00	10	13.33	28	18.67
Undetermined cause-B (≥2 causes found)	4	5.33	5	6.67	9	6.00
Total	75	100.00	75	100.00	150	100.00

Table 5: Findings of MRI brain in patients in young and old groups

MRI brain	*Young group (N = 75)*		*Old group (N = 75)*		*Total (N = 150)*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Anterior circulation infarct (large artery)	2	2.67	1	1.33	3	2.00
Middle circulation infarct (large artery)	41	54.67	39	52.00	80	53.33
Middle circulation infarct (lacunar)	9	12.00	12	16.00	21	14.00
Posterior circulation infarct (large artery)	13	17.33	7	9.33	20	13.33
Posterior circulation infarct (lacunar)	6	8.00	7	9.33	13	8.67
More than one circulation infarcts (large artery)	4	5.33	8	10.67	12	8.00
More than one circulation infarcts (lacunar)	0	0.00	1	1.33	1	0.67
Total	75	100.00	75	100.00	150	100.00

Table 6: Distribution of different etiologies of cardioembolic stroke subtype in young and old stroke groups

Etiology	*Cardioembolic young group 16 (21.33%)*	*Cardioembolic old group 13 (17.33%)*
Atrial fibrillation	10 (62.50%)	13 (100%)
Valvular heart disease	15 (93.75%)	8 (61.53%)
IHD	9 (56.25%)	9 (69.23%)
PFO	2 (12.50%)	1 (7.70%)
Infective endocarditis	2 (12.50%)	1 (7.70%)

Table 7: Distribution of dietary habits of patients in young and old groups

Dietary habits	*Young group (N = 75)*		*Old group (N = 75)*		*Total (N = 150)*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Nonvegetarian	12	16.00	19	25.33	31	20.67
Vegetarian	63	84.00	56	74.67	119	79.33
Total	75	100.00	75	100.00	150	100.00

Ischemic stroke in younger adults is far less common than that among older adults, yet the underlying pathogenesis and risk factors are more diverse. As per a study, the mean age of those who have a stroke declined by 2 years, while the proportion of stroke among those 20–54 years of age increased by approximately 50% from 12.9 to 18.6%.[5] Approximately, 10–15% of all strokes occur in adults aged 18–50 years. This study allowed us to study risk factors related to ischemic stroke in more detail.[9]

Age and Sex

In this study, the mean age (in years) of the study population in the young stroke group was 41.64 (SD 8.847), while in the old stroke group it was 65.81 (SD 9.007). Females had a slightly higher mean age than males in both groups. A recent meta-analysis of 19 studies that reported on sex-specific stroke incidence among young adults found that there were 44% more women ≤35 years old with ischemic strokes than men, which is similar to what was found in our study. Young women are at a disproportionately increased risk of ischemic strokes compared with their male counterparts.[9] A better understanding of these sex differences is important to be able to implement strategies to prevent and treat strokes in this age-group more effectively.

Hypertension and Inadequate Physical Activity

In our study, hypertension was significantly higher in the older group (72%) compared to the younger group (38.67%), a finding consistent with previous literature. Studies like Maaijwee et al. (2014)[2] and George (2020)[5] corroborate that hypertension remains the leading risk factor for ischemic stroke, particularly in older adults. The Framingham Heart Study further emphasizes that hypertension's cumulative impact over time leads to greater risk in the elderly.

In the present study, the number of patients with inadequate physical activity was significantly higher in the old group as compared to the young group and was statistically significant ($p < 0.01$). Banerjee et al. (2005)[1] highlight a sedentary lifestyle as a critical contributor to stroke risk in the elderly. The strong statistical significance ($p < 0.001$) suggests that public health efforts must focus on promoting active lifestyles, especially in older populations.

Dyslipidemia and Diabetes

Contrary to the traditional belief that dyslipidemia primarily affects older patients, our study found significant dyslipidemia in both age-groups, with raised cholesterol and triglycerides observed in young (5.33%, 22.67%) and old patients (8%, 38.67%), respectively. This corroborates studies such as Putaala et al. (2012),[10] which reported abnormal lipid profiles even in young ischemic stroke patients, further supporting the need for early lifestyle interventions to manage cholesterol levels from a young age.

Diabetes was more prevalent in older patients (32%) than younger ones (16%), which is consistent with large epidemiological studies like George (2020).[5] The increasing incidence of diabetes in the elderly underscores the necessity for stringent blood sugar control as part of stroke prevention strategies.

Cardioembolic Stroke and Rheumatic Heart Disease

Cardioembolic stroke occurred at a similar frequency in both young (21.33%) and old (17.33%) patients in our study. This finding is consistent with those of Kittner et al. (1996),[11] who reported that cardioembolic strokes, often linked to conditions like atrial fibrillation and rheumatic heart disease, occur in both younger and older populations. However, we found that rheumatic heart disease was more frequent in the younger group, while atrial fibrillation was more common in the elderly. These findings highlight the need for thorough cardiac evaluations in both age-groups, including the use of Holter monitoring, particularly in older patients where atrial fibrillation is often underdiagnosed.

Homocysteine and Vitamin B_{12} Deficiency

There was a good number of patients who had low serum vitamin B_{12} and high serum homocysteine levels in both the old as well as the young age-group in the present

study. Thus, low serum vitamin B_{12} and high serum homocysteine levels, which are traditionally regarded as risk factors in the young, seem to be important risk factors in old stroke patients as well, and so their serum levels should be investigated routinely in all stroke patients irrespective of age. This is in line with findings from Subha et al. (2015),[4] where both young and old stroke patients exhibited elevated homocysteine levels. These results emphasize the need for routine testing of homocysteine and vitamin B_{12} levels, irrespective of patient age, particularly in populations with high rates of vegetarianism like India, where dietary B_{12} intake may be low.

Nontraditional Risk Factors: Venereal Disease Research Laboratory, Antinuclear Antibody, and Antiphospholipid Antibody

Our study found that positive VDRL, ANA, and APLA markers, traditionally associated with younger stroke patients, also showed elevated trends in older patients. While positive ANA was seen more frequently in young patients (6.67%) compared to old (2.67%), these findings suggest that autoimmune and infectious markers should not be overlooked in older patients, contrary to conventional beliefs. Similar results have been reported in Dominguez et al. (2018),[6] who found that older stroke patients may also present with elevated autoimmune markers, necessitating more comprehensive screening.

Large Artery Atherosclerosis and Small Vessel Occlusion

In our study, large artery atherosclerosis and small vessel occlusion were more frequent in older patients (29.33 and 28%, respectively), consistent with the findings of Feigin (2007)[8] and Yahya et al. (2020),[7] which show that these pathologies are more common as age progresses due to chronic vascular changes. In contrast, strokes of undetermined cause were more common in younger patients, underscoring the need for advanced diagnostic approaches in young stroke patients where traditional risk factors are absent.

Comparative Findings and Clinical Implications

Comparative studies like that of Maaijwee et al. (2014)[2] emphasize similar conclusions, particularly regarding the rising stroke rates among young adults and the increasing prevalence of traditional cardiovascular risk factors in this age-group. The similarities between our findings and international data suggest that global stroke prevention strategies must adapt to address the rising burden of stroke in young adults.

In conclusion, while many traditional risk factors such as hypertension and diabetes remain more prominent in older patients, nontraditional factors such as dyslipidemia, homocysteine elevation, and autoimmune markers affect both age-groups significantly, contrary to the belief of their affecting only young patients. These findings underscore the importance of tailored, age-specific stroke prevention strategies incorporating comprehensive risk factor assessment, lifestyle modification, thorough evaluation of stroke to prevent devastating recurrence, and early intervention.

Conclusion

Cardioembolic stroke was found equally in the old and young groups. The number of patients with rheumatic heart disease was comparatively higher in the young group, while atrial fibrillation was higher in the old age-group, signifying the importance of detailed cardiac workup and Holter monitoring in the old age-group when indicated.

Large artery atherosclerotic disease and small vessel occlusion were more frequent in the old group, whereas stroke of undetermined cause and stroke of other determined cause were more prevalent in the young stroke group. Cardioembolic stroke was found equally in the young and old.

Raised serum homocysteine and low serum vitamin B_{12} were equally found in the young and old, which signifies the importance of their routine evaluation in stroke patients regardless of age, and appropriate supplementation of vitamin B_{12} in deficient patients. This holds special significance in the Indian setup, as the majority of the Indian population are vegetarian and dietary supplementation is low.

Dyslipidemia was found in the young, and positive VDRL in the old age-group, signifying the importance of keeping an open mind while evaluating all cases of stroke irrespective of age.

Antinuclear antibody, reactive VDRL, and positive APLA, traditionally regarded as risk factors in the young, were similarly found in the old age-group as well, signifying their evaluation in the old age-group when necessary.

Hypertension, diabetes mellitus, and inadequate physical activity were more significantly associated with the old group as compared to the young group.

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ORIGINAL ARTICLE

Empowering Communities, Transforming Education—Evaluating the Students Perceptions about Family Adoption Program in India: A Cross-sectional Study

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Abstract

Background: The Family Adoption Program (FAP) is an integral part of medical education aimed at fostering empathy and practical skills among medical students by exposing them to rural healthcare settings. This study assesses the perceptions and experiences of Bachelor of Medicine and Bachelor of Surgery (MBBS) students regarding the FAP, with a focus on their professional development and challenges encountered during the program.

Methods: A cross-sectional study was conducted using a predesigned and pretested questionnaire. The questionnaire link was distributed *via* WhatsApp to MBBS students from the 2021, 2022, and 2023 batches. The data collected included students' prior exposure to rural settings, perceived professional growth, and challenges faced during the program. Descriptive statistics were used to analyze the data.

Results: The study found that 63.8% of students had prior exposure to rural settings before joining MBBS, reflecting a diverse participant background. A majority (81.4%) believed that the FAP enhanced their ability to become empathetic and confident physicians. However, 44.9% of students reported communication barriers, and 35.8% faced difficulties in gaining trust and cooperation from family members, highlighting key challenges in the program.

Conclusion: The FAP is valued for its role in developing empathy and confidence among medical students, though communication and trust-building remain significant challenges. Addressing these issues could further enhance the program's effectiveness.

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Introduction

India's healthcare landscape presents a complex picture. While significant advancements have been made in recent years, a persistent disparity exists in access to quality healthcare between urban and rural areas.[1] This disparity is often attributed to the uneven distribution of medical professionals and healthcare facilities. Medical graduates, primarily trained in urban settings with a focus on clinical knowledge, may lack the necessary practical skills and understanding of the social determinants of health prevalent in rural communities.[2] This knowledge-practice gap translates to challenges in addressing the specific needs of underserved populations and delivering holistic healthcare.

The Family Adoption Program (FAP) emerges as a promising initiative to bridge this gap and equip medical undergraduates with essential skills beyond the realm of clinical medicine. Launched by the Medical Council of India (MCI), now replaced by the National Medical Commission (NMC), FAP aims to create a longitudinal engagement between medical undergraduates and families residing in underserved communities.[3] This paper delves into the rationale behind FAP, its core components, and the challenges associated with its implementation. It further explores strategies to overcome these obstacles and maximize the program's effectiveness.

Methodology

Study Design

A cross-sectional study aimed to know the perceptions and experiences of medical students involved in the FAP at BLDE DU Shri B M Patil Medical College, Hospital and Research Centre, Vijayapura, Karnataka. The study was conducted in November 2023.

Participants

The targeted population for this study included all Bachelor of Medicine and Bachelor of Surgery (MBBS) students involved in the FAP at BLDE DU Shri B M Patil Medical College, Hospital and Research Centre, Vijayapura. This potentially included medical undergraduates participating in the program, and the total sample collected for this study was 539.

Data Collection

A pretested questionnaire was developed and deployed for this study using Google Forms. The content of the pretest focused on capturing students' perceptions about FAP's effectiveness, including benefits and challenges experienced, and also specific aspects of the program (e.g., student–family interactions, faculty support). The pretest was circulated *via* WhatsApp. This approach aimed to maximize participation.

Statistical Analysis

As this was a cross-sectional study, the data collected were analyzed using descriptive statistics to provide a comprehensive overview of the students' perceptions and experiences. SPSS version 23 was employed for data analysis. The data were examined through the calculation of frequencies and percentages, which allowed for the summarization of key variables and trends within the dataset.

Results

The Figure 1 illustrates the distribution of participants according to their MBBS batch year, highlighting the representation from the 2021, 2022, and 2023 cohorts. The 2023 batch had the highest participation, accounting for 36.7% of the total respondents, indicating strong engagement from the most recent group of students. This is followed by the 2022 batch, which made up 33.9% of the participants, showing a substantial contribution from this cohort as well. The 2021 batch, while representing the smallest portion, still constituted a significant 29.4% of the

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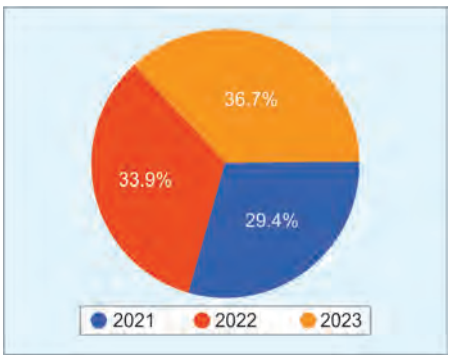

Fig. 1: Distribution according to MBBS batch

Table 1: Demographic details of study subjects and their opinion

Study variable	*Frequency (f)*	*Percentage (%)*
Gender		
Female	292	54.2
Male	247	45.8
Exposed to rural setting before joining MBBS		
No	195	36.2
Yes	344	63.8
Interacted with public before the initiation of FAP		
No	206	38.2
Yes	333	61.8
Felt to become complete physician with empathy and confidence in the future		
Maybe	88	16.3
No	12	2.2
Yes	439	81.4
Is there any communication barrier		
No	297	55.1
Yes	242	44.9
Difficulty in gaining the trust and cooperation of family members		
No	346	64.2
Yes	193	35.8
Good insight into the patients living condition		
Maybe	141	26.2
No	39	7.2
Yes	359	66.6
Motivate the students for the kind of career they have to prepare for		
No	26	4.8
Yes	513	95.2

respondents. This distribution reflects a fairly even participation across the three batches, with a slight predominance from the newer students, suggesting a consistent interest and involvement in the FAP across different academic years.

The demographic characteristics and perceptions of the study participants in Table 1 provide valuable insights into the impact of the FAP on medical students. The study involved a relatively balanced gender distribution, with 54.2% female and 45.8% male participants. A significant majority (63.8%) had prior exposure to rural settings before joining the MBBS program, suggesting a diverse background among the students. Furthermore, 61.8% had interacted with the public before the FAP, indicating that many students had some level of prior experience in public engagement. The program was perceived positively, with 81.4% of students believing it would help them become empathetic and confident physicians. However, nearly half of the participants (44.9%) reported facing communication barriers, highlighting a critical area for improvement. Additionally, 35.8% of students experienced difficulties in gaining the trust and cooperation of family members, reflecting the complexities of building trust in healthcare settings. Despite these challenges, 66.6% of students felt that the FAP provided good insight into patients' living conditions, and an overwhelming 95.2% reported that the program motivated them for their future careers. These findings underscore the program's overall effectiveness while also identifying key areas where further support is needed to enhance student experiences.

Discussion

The findings of the present study provide valuable insights into the experiences and perceptions of medical students participating in the FAP. A significant portion of students, approximately 36.2%, had not been exposed to a rural setting nor interacted with a rural community prior to this first visit. The lack of prior experience underscores the importance of programs like the FAP in bridging the gap between medical students and rural communities, thereby enhancing their understanding and preparedness to serve in diverse healthcare settings.[4]

One of the primary challenges encountered in our study was the presence of communication barriers and the difficulty in gaining the trust of family members, a concern that is echoed in several other studies. Patil et al. reported that one of the common constraints in the implementation of field programs is the level of cooperation from the public.[5] This finding is consistent with our study, where 35.8% of students reported difficulties in earning the trust and cooperation of the families they were assigned to. The challenges related to communication and trust-building highlight the need for targeted training and support for students to better equip them to handle these critical aspects of rural healthcare practice.

Despite these challenges, the overall perception of the FAP was overwhelmingly positive, with 81.4% of students in our study viewing the program favorably. This is in line with the findings of Landge et al., where 80% of students expressed a similarly positive perception.[6] The high level of approval indicates that the FAP is successfully meeting its objectives of fostering professional growth and enhancing students' understanding of rural health dynamics.

Moreover, the levels of family cooperation and trust were generally strong, with 66.6% of students in our study reporting a positive experience in this regard. However, this figure is somewhat lower compared to the study by Vairavasolai et al., where 88% of students reported high levels of cooperation and trust from the families.[7] This discrepancy may reflect variations in the implementation of the program, the specific rural settings involved, or the differing levels of prior exposure and experience among the student cohorts.

This cross-sectional study has some inherent limitations. Our study can only

provide a snapshot of perceptions and experiences at a specific point in time. The data are collected in one college only, potentially introducing selection bias into the sample. The findings of this study may not be generalizable to other medical colleges or FAP implementations due to the specific context of BLDE DU Shri BM Patil Medical College, Hospital and Research Centre.

Conclusion

The present study highlights the crucial role of the FAP in bridging the gap between medical students and rural communities. The FAP serves as an effective tool for enriching medical students' education by providing them with essential exposure to rural healthcare dynamics. To further enhance the program's effectiveness, future efforts should focus on addressing communication barriers and building trust, ensuring that students are better equipped to navigate the complexities of rural healthcare practice.

The students strongly believe that this FAP will not only make healthcare more accessible to the rural population but also help create a generation of doctors who are well aware of the challenges faced by rural communities. They have expressed that the program would improve healthcare delivery and enable them to become leaders within these communities. The FAP for MBBS students in India has the potential to significantly increase community engagement and improve healthcare outcomes in remote areas.

Ethical Considerations

Informed consent was obtained from all students before answering the questionnaire. Assurance of participant confidentiality was given to emphasize that data will be anonymized during analysis and reporting.

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ORIGINAL ARTICLE

Investigating Neurocognitive Functions in People Living with Human Immunodeficiency Virus: A Cross-sectional Study from an Indian Tertiary Health Care Institution

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Abstract

Introduction: Human immunodeficiency virus (HIV)-associated neurocognitive deficits (HAND) distress a substantial proportion of people living with HIV (PLHIV). The present research intends to examine the neurocognitive functions in PLHIV, compared to healthy volunteers.

Materials and methods: About 48 HIV patients were recruited from one tertiary health care center, while 24 matched healthy volunteers were enrolled as controls from the community. Neurocognitive functions were assessed using the Hindi Mental Status Examination (HMSE), Addenbrooke's Cognitive Examination (ACE)-III, and International HIV Dementia Scale (IHDS) questionnaires, along with the computer-based color-word Stroop cognitive task.

Results: The total HMSE scores ($p = 0.0047$), IHDS scores ($p = 0.0002$), and ACE-III scores ($p < 0.0001$) were statistically lower in PLHIV, compared to controls. The specific domain scores of ACE-III in PLHIV were also statistically lower compared to the control group, with greater differences seen in memory ($p < 0.0001$) and language ($p = 0.0012$) domains. Similarly, higher reaction time was seen in PLHIV in comparison with the control group ($p < 0.0001$) during Stroop cognitive task performance, while a statistically significant difference in accuracy was not observed among groups. Further, among PLHIV, reaction time had a significant positive correlation with years since diagnosis of HIV infection ($p = 0.006$, $r = 0.39$, Spearman correlation).

Conclusion: Observations demonstrate neurocognitive deficits in PLHIV across multiple domains. Our study, therefore, offers insights into the neurocognitive manifestations of HIV infection, which could facilitate tailored preventive and therapeutic interventions by healthcare providers to enhance the overall quality of life for PLHIV.

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Introduction

Human immunodeficiency virus (HIV) lingers to pose noteworthy medical challenges worldwide, distressing millions of people globally.[1] Although much progress has been made in the management of acquired immunodeficiency syndrome (AIDS) through combination antiretroviral therapy (cART), neurological complications remain a critical concern.[2] Despite advances in the treatment, HIV-associated neurocognitive deficits (HAND) distress a substantial proportion of people living with HIV (PLHIV).[2] HAND involves a range of cognitive disturbances extending from mild to severe, with varying deficit patterns in attention, memory, executive function, and motor skills.[3] These disturbances not only compromise everyday functioning but also contribute to social, occupational, and economic disparities among affected individuals. The occurrence of HAND remains high in certain geographical areas, in spite of suppressive cART, with a worldwide average prevalence of 50.41%, and 52.03% in the Indian subcontinent, as reported in 2022.[4]

While the etiology of neurocognitive difficulties in HIV remains multifactorial, several key factors have been implicated in their pathogenesis. The direct neurotoxic effects of the virus, chronic inflammation, immune activation, and the neurotoxicity of antiretroviral medications are among the primary contributors to neurocognitive impairment in PLHIV.[5,6] Additionally, comorbid conditions such as substance abuse, psychiatric disorders, and opportunistic infections further exacerbate cognitive dysfunction in this population.[7] Furthermore, sociodemographic factors, including socioeconomic status, education level, and access to healthcare, also demonstrate a substantial role in shaping the neurocognitive profile in PLHIV.[8] HAND has also been associated with improper adherence to treatment, which undermines the control of viral load, eventually leading to poorer living standards. Despite the growing recognition of neurocognitive difficulties in HIV, many questions remain unanswered regarding the precise mechanisms underlying these deficits and their impact on clinical outcomes.[2,9,10] Moreover, there is a paucity of published literature comparing the neurocognitive profiles of PLHIV to those of demographically matched healthy controls. Such comparative studies are indispensable for disentangling the specific effects of HIV on neurocognitive function from confounding influencers like age, education, and clinical comorbidities.

Therefore, this study was aimed at evaluating the neurocognitive functions in patients with HIV undergoing cART, in comparison with matched healthy volunteers. By employing a battery of questionnaire-based assessments and neuropsychological tests, we attempted to characterize the cognitive difficulties in PLHIV in terms of the specific domains of impairment. Additionally, we have explored the potential correlation between neurocognitive and clinicodemographic factors among PLHIV.

Materials and Methods

After obtaining the Institutional Ethical Clearance (Ref. No. IECPG-222/24.03.2022, RT-13/27.04.2022), a cross-sectional study design was employed for the evaluation of neurocognitive deficits in PLHIV, in comparison with healthy volunteers. The diagrammatic illustration of the protocol is depicted in Figure 1. The research was carried out at the ART Clinic of the Department of

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Medicine at the All India Institute of Medical Sciences (AIIMS), New Delhi.

Study Participants and Study Setting

About 75 participants of both genders were enlisted in the current study. Of them, 50 participants were seropositive for HIV and were recruited from the ART clinic of the Department of Medicine at the AIIMS, New Delhi. The remaining 25 participants were healthy controls and were enrolled through community advertisements. Both controls and patients were matched for educational status, gender, and age. The clinicodemographic details of the study participants are represented in Table 1. Participants below the age of 18 years or >40 years, as well as those with a history of neuropsychiatric/neurodegenerative disorders or addiction/substance abuse, were not included in the study. All the patients were undergoing antiretroviral therapy as per the national HIV program guidelines, with the fixed-dose combination of lamivudine (300 mg) + dolutegravir (50 mg) + tenofovir (300 mg). After obtaining informed consent, the patients and the controls were designated as group I and group II, respectively, and were subjected to neurocognitive assessment. Two of the 50 patients and one of the 25 controls were not included in the study, as they were unable to complete the total trials of the Stroop cognitive task. Data from the remaining 48 patients and 24 controls were compiled for analysis.

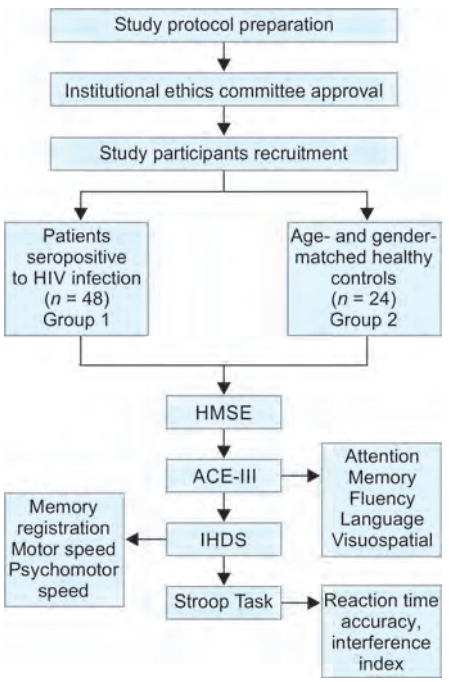

Fig. 1: Flowchart describing the study protocol. After ethical approval, patients seropositive to HIV infection and healthy volunteers (controls), in the age-group of 18–40 years were recruited. The study participants were subjected to subjective and objective neurocognitive assessments using the HMSE and ACE-III, IHDS as well as Stroop cognitive task, respectively

Neurocognitive Assessment

Neurocognitive functions of the study participants were evaluated using questionnaires and neuropsychological tests. For questionnaire-based assessment, the Hindi Mental Status Examination (HMSE), the Addenbrooke's Cognitive Examination (ACE)-III, and the International HIV Dementia Scale (IHDS) were employed, and for neuropsychological tests, the color-word Stroop cognitive task was administered, designed using Psychopy version 3.0 software. The total time for the neurocognitive assessment per participant was around 30–45 minutes.

Questionnaire-based Evaluation

The HMSE was employed in our study for subjective neurocognitive evaluation. The HMSE was chosen for our study, as it was better suited for neurocognitive testing in our setting, considering the largely Hindi-speaking Indian population attending the AIIMS ART clinic, with a high sensitivity (0.81) and specificity (0.60).[11] The maximum possible score is 31, and a score below 23 is used as the cutoff for cognitive dysfunction or dementia. The HMSE consists of 23 items evaluating the orientation to time (questions 1–5), place (questions 6–10), registration (question 11), attention (question 12), recall (questions 13–15), naming (questions 16–18), repetition (question 19), following commands (questions 20–21), sentences (question 22), and copying (question 23).[12]

The IHDS assesses memory, motor speed, and psychomotor operations.[13] The IHDS involves three tests, namely: four-item recall at 2 minutes, timed alternating hand sequence test, and timed finger tapping. Points are awarded based on the number of accurate responses out of 4, with a maximum score of 12. Prompting with semantic clues was allowed if the patient failed to recall the words initially, with a half-point awarded for every correctly recalled word with prompting. An abnormal score was considered as ≤10, as per earlier validation in PLHIV.[13]

The ACE-III, which was primarily utilized to distinguish between different types of dementia, is also employed as an objective neurocognitive screening tool.[14] Accessible to healthcare professionals, the ACE evaluates key cognitive functions and typically takes 15–20 minutes for its administration. With 100 as the maximum score, it assesses visuospatial abilities, attention, memory, language, orientation, and fluency. In our current study, both English and Hindi versions of the ACE-III questionnaire were used as per requirement.

Color-word Stroop Cognitive Task

The color-word Stroop cognitive task, an executive function task, comprises presentation of words that name a color that might or might not be displayed in the matching color, thereby generating interference in the second case. Facilitation trials are those where the words (green, blue, and red) name the same color in which they are printed, while interference

Table 1: Clinical and sociodemographic characteristics of the study participants

	Patients	*Controls*
Mean ± SEM age in years	29.58 ± 6.006	28.60 ± 4.260
Male:female	37:11	8:12
Educational status		
(i) Graduate	47.92%	100%
(ii) Secondary school	45.83%	0%
(iii) Primary school	6.25%	0%
Marital status		
(i) Married	77.08%	10%
(ii) Unmarried	22.92%	90%
Median (IQR) values of hemoglobin (gm/dL)	13.40 (12.00–14.70)	11.80 (10.80–13.60)
Median (IQR) years since diagnosis	5.31 (2.01–7.82)	Not applicable
Median (IQR) years of antiretroviral therapy	4.00 (1.63–8.75)	Not applicable
Median (IQR) values of CD4 count (cells/mm^3)	462.00 (371.80–599.80)	Not applicable

trials are those where the colors and words are incongruent with each other. Further, neutral trials are those with random words other than "green," "blue," and "red," printed in any of the three colors. Data from the Stroop cognitive task were collected in terms of accuracy and reaction time.[15] Participants were exposed to 120 trials, out of which 32 were facilitation trials, 44 were interference trials, and 44 were neutral trials. The trial structure is shown in Figure 2. A trial began with the stimulus cue, which was a word printed in any of the three colors (green, blue, red). The stimulus prompt was presented for 2000 ms, succeeded by a blank screen for 1000 ms, during which time the subjects had to press a keyboard button to input a response. The subject had to press "1" if the color of the word displayed is "green," press "2" if it is "blue," and press "3" for "red," notwithstanding the meaning of the words that were displayed.

Statistical Analyses

Analysis for statistical significance was done using GraphPad Prism 10 software, and the *p*-value of <0.05 was considered significant. Data were found to be non-normally distributed by means of the Shapiro–Wilk test and were compared between individual groups using the Mann–Whitney test. Correlation analysis between two variables was done using Spearman correlation.

Results

Clinical and Sociodemographic Characteristics of Participants

Data from 48 PLHIV and 24 healthy volunteers (controls) were included for analysis. Concerning age, the PLHIV exhibited a mean ± SEM age (years) of 29.58 ± 6.006, which was not statistically different (Table 1; $p > 0.05$, Mann–Whitney test] in comparison with controls (28.60 ± 4.260). Regarding educational status, it was observed that 93.75% of PLHIV and 100% of controls had attained above secondary school education. Further, in terms of marital status, a higher proportion of PLHIV (77.08%) were married compared to controls. The median [interquartile range (IQR)] values of hemoglobin (gm/dL) were not significantly different ($p > 0.05$, Mann–Whitney test; Table 1) between PLHIV and controls.

Among PLHIV, the median (IQR) years since diagnosis of HIV were 5.31 (2.01–7.82), while the years of cART were 4.00 (1.63–8.75). Moreover, the PLHIV had median (IQR) values of CD4 count (cells/mm^3) of 462.00 (371.80–599.80), which showed positive correlation with the time since diagnosis ($p = 0.012$, $r = 0.35$, Spearman correlation) and with years of cART ($p = 0.017$, $r = 0.23$, Spearman correlation). The clinical and sociodemographic features of the subjects are depicted in Table 1.

Neurocognitive Decline in Questionnaire-based Assessments

Hindi Mental Status Examination

People living with HIV had significantly lower (−4.00) median (IQR) HMSE scores in comparison with the controls (Table 2; $p = 0.0047$, Mann–Whitney test]. A substantial proportion of PLHIV scored zero in the items evaluating repetition (23%), recall (18%), copying (12%), sentences (8%), and orientation to time (6%). Further, the scores of the PLHIV in these domains were significantly lower in comparison with the controls ($p < 0.05$, Mann–Whitney test). In addition, scores of PLHIV in items evaluating orientation to place, registration, attention, and naming were not significantly different in comparison with the controls ($p > 0.05$, Mann–Whitney test).

International Human Immunodeficiency Virus Dementia Scale

People living with HIV had significantly lower (−2.00) median (IQR) total IHDS score in comparison with controls ($p = 0.0002$, Mann–Whitney test; Table 2). Further, individual domain scores of psychomotor speed and memory recall were significantly lower in PLHIV in comparison with the control group ($p < 0.0001$, Mann–Whitney test). However, individual domain scores of motor speed were not significantly different among PLHIV and controls ($p > 0.05$, Mann–Whitney test).

Addenbrooke's Cognitive Examination-III

People living with HIV had significantly lower (−11.00) median (IQR) total ACE-III score in comparison with controls ($p < 0.0001$, Mann–Whitney test; Table 2). The specific domain scores of the PLHIV, in addition, were significantly lower in comparison with controls ($p < 0.05$, Mann–Whitney test; Table 2), with maximum differences of −4.00 and −3.00

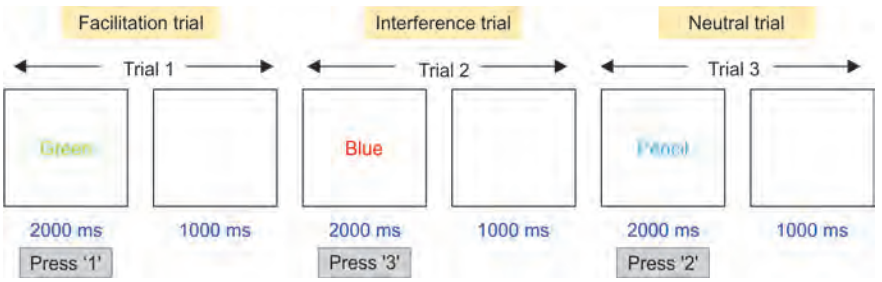

Fig. 2: Schematic representation of the trial structure of color-word Stroop cognitive task used for objective neurocognitive assessment. A trial began with the stimulus cue which was a word printed in any of the three colors (green, blue, red). The stimulus cue was displayed for 2000 ms, which was followed by a blank screen for 1000 ms, during which the participants had to input a response through the keyboard. This was followed by the next trial. The subject had to press "1" if the color of the word displayed is "green", press "2" if it is "blue", and press "3" for "red," notwithstanding the meaning of the words that were displayed

Table 2: Median (IQR) scores of the cognitive assessment using HMSE ACE-III questionnaires and IHDS

Questionnaires/scales		*Patients*	*Controls*	*p-value*
Total HMSE score		27.00* (25.00–29.00)	31.00 (30.00–31.00)	0.0047
ACE-III	Total	87.00* (81.00–91.00)	98.00 (98.00–99.00)	<0.0001
	Attention	17.00* (14.00–18.00)	18.00 (18.00–18.00)	<0.0001
	Fluency	10.00* (7.25–12.00)	12.50 (12.00–13.00)	<0.0001
	Memory	22.00* (17.00–23.00)	26.00 (25.00–26.00)	<0.0001
	Language	23.00* (22.00–24.00)	26.00 (25.00–26.00)	0.0012
	Visuospatial	14.00* (14.00–15.00)	16.00 (16.00–16.00)	<0.0001
Total IHDS score		10.00* (8.00–12.00)	12.00 (11.00–12.00)	0.0002

*Significant difference in the scores as compared to the control group ($p < 0.05$, Mann–Whitney test)

seen in memory and language domains, respectively. The fluency and visuospatial scores of the PLHIV were also significantly lower as compared to controls ($p < 0.0001$, Mann–Whitney test; Table 2). The attention domain was least affected in PLHIV, with a difference of –1.00 compared to the controls.

Neurocognitive Assessment using Color-word Stroop Cognitive Task

People living with HIV had significantly higher (+0.293 seconds) median (IQR) overall reaction time in comparison with controls ($p < 0.0001$, Mann–Whitney test; Table 3). Further, median (IQR) reaction time of the interference, facilitation, and neutral trials were also significantly higher in the PLHIV in comparison with controls ($p < 0.0001$, Mann–Whitney test; Table 3), with differences of +0.242, +0.228, and +0.265 seconds, respectively. Similarly, reaction time of the correct and incorrect trials were also significantly higher in PLHIV in comparison with the controls ($p < 0.05$, Mann–Whitney test/unpaired *t*-test; Table 3). Differences in the reaction time between the patient and control groups among the correct trials (+0.289 seconds) was higher than that of the incorrect trials (+0.252 seconds). The median (IQR) of the interference index was lower (–1.455%) in PLHIV, in comparison with controls ($p = 0.0700$, Mann–Whitney test; Table 3).

The median (IQR) of the overall accuracy (%) as well as the individual accuracies of interference, facilitation, and neutral trials were not statistically different between the PLHIV and controls ($p > 0.05$, Mann–Whitney test; Table 4).

Analysis of Correlation among Parameters of Neurocognitive Assessment

People living with HIV demonstrated significant negative correlation between the time since diagnosis of HIV and the total HMSE scores ($p = 0.012$, $r = -0.36$, Spearman correlation), language ACE-III scores ($p = 0.023$, $r = -0.33$, Spearman correlation), visuospatial ACE-III scores ($p = 0.003$, $r = -0.42$, Spearman correlation), overall accuracy ($p = 0.016$, $r = -0.35$, Spearman correlation), and significant positive correlation with the overall reaction time ($p = 0.006$, $r = 0.39$, Spearman correlation). The total HMSE scores exhibited positive correlation with attention ACE-III scores ($p = 0.048$, $r = 0.29$, Spearman correlation), and negatively correlated with the overall reaction time ($p = 0.006$, $r = -0.39$, Spearman correlation). Similarly, the accuracy of facilitation trials showed positive correlation with the total ACE-III score ($p = 0.045$, $r = 0.29$, Spearman correlation). Further, the total IHDS scores showed significant positive correlation with fluency ($p = 0.009$, $r = 0.37$, Spearman correlation), and memory ($p = 0.009$, $r = 0.38$, Spearman correlation) subdomains of ACE-III.

Among the controls, the total HMSE scores exhibited significant positive correlation with the overall accuracy ($p = 0.013$, $r = 0.54$, Spearman correlation), and with the attention ($p = 0.013$, $r = 0.55$, Spearman correlation) and visuospatial ($p = 0.013$, $r = 0.55$, Spearman correlation) ACE-III scores. In addition, the memory ACE-III scores showed negative correlation with the overall reaction time ($p = 0.022$, $r = -0.51$, Spearman correlation).

Table 3: Median (IQR) values of reaction time assessed using color-word Stroop cognitive task

Reaction time (sec)	*Patients*	*Controls*	*p-value*
Overall	1.105* (0.899–1.213)	0.812 (0.793–0.903)	<0.0001
Interference trials	1.107* (0.966–1.259)	0.865 (0.820–0.979)	<0.0001
Facilitation trials	1.051* (0.883–1.138)	0.823 (0.734–0.841)	<0.0001
Neutral trials	1.083* (0.912–1.229)	0.818 (0.764–0.862)	<0.0001
Correct trials	1.096* (0.916–1.212)	0.807 (0.788–0.894)	<0.0001
Incorrect trials	1.136# (0.949–1.271)	0.884 (0.837–0.959)	0.0133
Stroop facilitation interference index (%)	7.763 (1.569–14.620)	9.218 (1.482–22.290)	0.0700

*Significant difference in the scores as compared to the control group ($p < 0.05$, Mann–Whitney test); #Significant difference in the scores as compared to the control group ($p < 0.05$, unpaired *t*-test)

Table 4: Median (IQR) values of accuracy and interference indices assessed using color-word Stroop cognitive task

Accuracy (%)	*Patients*	*Controls*	*p-value*
Overall	90.78 (67.63–96.53)	90.00 (88.52–92.48)	0.6521
Interference trials	89.01 (41.66–95.65)	89.08 (86.57–91.10)	0.5137
Facilitation trials	96.29 (84.68–99.22)	90.53 (87.20–94.30)	0.139
Neutral trials	94.87 (85.91–97.61)	90.61 (88.29–95.00)	0.1909

*Significant difference in the scores as compared to the control group ($p < 0.05$, Mann–Whitney test)

Discussion

Human immunodeficiency virus, upon infection, can infiltrate the central nervous system and replicate within cells of the immune system located in the brain parenchyma. This continual viral replication, coupled with the inflammation and host immune response, contributes to the onset of HAND.[2,9,10] Over the last 20 years, the commencement of cART has steered a substantial decrease in AIDS-related mortality rates. Consequently, PLHIV undergoing cART now stand to achieve life expectancies nearly on par with the general population. This has resulted in an increase in the proportion of PLHIV reporting cognitive difficulties during their lifespan, presenting as various forms of cognitive impairments such as decreased attention span, memory issues, slower processing speed, and difficulties in executive function.[16,17]

Human immunodeficiency virus-associated neurocognitive deficits involves a range of neurocognitive impairments, manifesting as HIV-associated dementia (HAD), mild neurocognitive disorder (MND), and asymptomatic neurocognitive impairment (ANI). In the era before cART, HAD was the most widespread form of HAND and frequently led to lethal outcomes. The extensive acceptance of cART has significantly reduced the occurrence of HAD; however, ANI and MND still remain a significant source of morbidity. Estimates suggest that 15–55% of HIV-positive individuals experience some form of HAND, a rate similar to that before the cART era. Notably, most cases

today represent milder forms of HAND. Consequently, the prevalence of ANI has risen, constituting about 70% of all HAND cases. HAND profoundly affects quality of life, reducing productive lifespan by roughly 10–15 years. The occurrence of HAND typically peaks during young adulthood and continues to rise into late adolescence, which in fact is the productive phase of life. The effectiveness of cART is also compromised by the increasing risk of HAND due to loss of treatment adherence, impacting the overall well-being of PLHIV.[18,19] Despite the growing recognition of neurocognitive difficulties in HIV, many questions remain unanswered regarding the precise mechanisms underlying these deficits and their impact on clinical outcomes.[2,9,10] Moreover, published information is scarce comparing the neurocognitive profiles of PLHIV to those of demographically matched healthy controls. Such comparative studies are indispensable for unraveling the specific effects of HIV on neuropsychological functions, apart from confounders like age, education, and clinical comorbidities.

In this study, neurocognitive impairments in PLHIV were evaluated using both questionnaires and a computer-based color-word Stroop cognitive task and compared with healthy volunteers. Results indicated that PLHIV exhibited notably lower scores on the HMSE questionnaire compared to controls. In particular, a significant proportion of the PLHIV scored lower in the items evaluating repetition, recall, copying, sentences, and orientation to time. Further, the scores of the PLHIV in the items evaluating orientation to place, registration, attention, and naming were not statistically different in comparison with the controls. In agreement with our observations, an Indian study reported lower scores on mental status examination in PLHIV as compared with healthy controls.[20] These cognitive disturbances were associated with difficulties in concentration, slower thought processes, forgetfulness, and changes in behavior.[21] Some studies also reported that PLHIV find it challenging to stay focused or follow conversations.[22] These deficits typically originate from subcortical areas initially, which means that language-related impairments such as aphasia, agraphia, and alexia are relatively preserved.

In our study, the total score in the ACE-III questionnaire of the PLHIV was significantly lower in comparison with the control group. The individual domain scores of PLHIV, in addition, were statistically lower in comparison with the control group, with greater differences seen in the memory and language domains, respectively. The fluency and visuospatial scores of the PLHIV were also lower in comparison with the control group. The attention domain was least affected in PLHIV compared to the controls. Our observations that the maximum score differences between PLHIV and controls were seen in the memory and language domains were consistent with studies reported in the literature.[23–25] Using the ACE questionnaire, it was reported that visuospatial abilities, memory, and verbal fluency were the largely affected domains.[26] In our study, the total IHDS scores of the PLHIV were lower in comparison with the control group. Further, the individual domains of psychomotor speed and memory recall were mostly affected in PLHIV in comparison with controls, which was in congruence with the literature.[26]

Computerized neurocognitive tests evaluating attention, visuospatial memory, and executive functions demonstrated that performance on PLHIV was considerably impaired on tests of executive function, but their visual memory remained uncompromised. This observation strengthens the proposition that fronto-striatal dysfunction probably occurs in PLHIV.[27] Memory decline among asymptomatic PLHIV, along with the presence of psychomotor slowing and impaired attention, is correlated with the decline in CD4+ T lymphocyte levels, making the latter a robust determining factor of neurocognitive disturbances in PLHIV.[28] The neurocognitive profile of PLHIV differed from healthy controls in the domains of phonemic fluency, verbal learning, and verbal working memory.[29]

In our study, the reaction time of PLHIV on the Stroop cognitive task was significantly longer than those of controls. Consistent with our findings, studies in recent years that have used reaction time tasks to evaluate PLHIV have reported that HIV leads to a milder grade of neurocognitive slowness that is likely to deteriorate with increasing disease duration and severity.[30,31] Further, PLHIV exhibited slower performance than the healthy group on both paper–pencil and computerized Stroop cognitive tasks. Significant interference was evident in the paper–pencil Stroop task rather than the computer-based Stroop task. These deficits were attributed to HIV-induced fronto-striatal dysfunction and dopaminergic alterations.[32,33] On further analyses, it was observed that the reaction time of incorrect trials was greater than that of the correct trials in both patient and control groups. It was also observed that in the PLHIV, though the interference trial reaction time was less than the facilitation trial reaction time, the accuracy of interference trials was significantly lower than that of the facilitation trials. This was in contrast to the control group, who took a longer time to respond in interference trials with better accuracy as compared to the PLHIV.

Among PLHIV, there was a significant negative correlation between the duration since HIV diagnosis and questionnaire scores, and a positive correlation with overall reaction time, which was in agreement with observations in the literature.[33] Further, the total HMSE scores showed a positive correlation with attention ACE-III scores and were negatively correlated with the overall reaction time. Similarly, the accuracy of facilitation trials had a significant positive correlation with the overall ACE-III score. Likewise, total IHDS scores showed a significant positive correlation with fluency and memory subdomains of ACE-III. These observations validate that PLHIV experience cognitive difficulties across different domains, which are correlated with the performance in the Stroop cognitive task.

Strengths and Limitations

Considering the cons, the present study is the assessment of HAND in demographically diverse PLHIV, taking into account the variations in education, age, gender, and socioeconomic status. Conducted within a tertiary healthcare setting, the findings hold potential for broader applicability across other institutions as well. Furthermore, the study employed a comprehensive approach by evaluating neurocognitive functions through both questionnaires and objective tests, with comparisons made against age- and gender-matched healthy controls. Such insights could aid in predicting and detecting cognitive decline early, thereby potentially mitigating its hostile consequences on quality of life and significantly improving the living standards of HIV survivors.

While the current study offers valuable insights into HAND, employment of a prospective design, as opposed to a cross-sectional design, would have been more appropriate for understanding the progression trajectories of these cognitive difficulties. Additionally, investigation utilizing neuroimaging techniques and animal models could help delineate the specific factors contributing to the higher incidence of cognitive impairment in PLHIV.

Conclusion

The present research reveals the occurrence of neurocognitive deficits in PLHIV in comparison with healthy volunteers. PLHIV had significantly lower HMSE, ACE-III, and IHDS scores as compared to the controls. Further, the Stroop cognitive task reaction time of the PLHIV was higher in comparison

with the controls. In addition, in the PLHIV, the years since diagnosis of HIV infection had significant negative and positive correlation with the questionnaire scores and the overall reaction time, respectively. Thus, our research enriches comprehension of the neurocognitive impacts of HIV infection across multiple cognitive domains. This insight will enable healthcare professionals to customize interventions to suit the unique requirements of PLHIV, consequently enhancing treatment adherence, functional outcomes, and overall standard of living.

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ORIGINAL ARTICLE

Sustained Glycemic Control and Improved Well-being on Early Induction of Triple Drug Therapy in Newly Diagnosed Type 2 Diabetes Mellitus Patients with HbA1c ≥9%: A Prospective, Cross-sectional, and Observational Study

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Abstract

Introduction: To study outcomes of the triple-drug therapy in newly diagnosed type 2 diabetes mellitus (T2DM) [glycated hemoglobin (HbA1c) ≥9%] with respect to change in HbA1c, low-density lipoprotein (LDL) levels, weight, waist circumference, variation in drug dosages, hypoglycemic events, patient response of well-being, and corresponding result satisfaction.

Materials and methods: It was a prospective, observational study conducted from 1st June 2018 to 31st May 2019 at Indira Gandhi Medical College and Hospital, Shimla, a tertiary care hospital in Himachal Pradesh. During the initial 3 months, patients were treated with triple-drug [oral hypoglycemic agents (OHAs)] therapy and then switched over to dual or single therapy (OHAs) depending on the HbA1c levels and were followed up for 1 year.

Observations: A total of 137 participants completed the study period. At baseline, the mean values of fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), HbA1c, and LDL were 218.4 ± 36 mg/dL, 343.94 ± 60 mg/dL, 10.5 ± 1.42%, and 120.34 ± 30.99 mg/dL, respectively. At the end of 12 weeks, the mean values of FPG, PPPG, HbA1c, and LDL were reduced to 123 ± 16 mg/dL, 164 ± 30 mg/dL, 8.14 ± 0.97%, and 109.04 ± 28.28 mg/dL, respectively. The differences were highly significant statistically when compared with the baseline observations. At the end of the study (52 weeks), the mean values of FPG, PPPG, HbA1c, and LDL were 96 ± 10 mg/dL, 146 ± 16 mg/dL, 6.14 ± 0.43%, and 90.55 ± 28.14 mg/dL. Reductions in values were statistically significant when compared with both the baseline and 12-week values.

Conclusion: Early induction of combination therapy with glimepiride, metformin, and pioglitazone results in more desirable outcomes in terms of greater reduction in HbA1c level and lower incidence of hypoglycemia as compared to the conventional add-on therapy.

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Introduction

Diabetes mellitus is a metabolic syndrome characterized by an increase in blood glucose level (hyperglycemia).[1] Abrupt increase in blood glucose level and deficiency of insulin may result in many hyperglycemia-related symptoms, metabolic decompensation, and hospitalization. Chronic hyperglycemia is responsible for diabetes-related microvascular complications such as retinopathy, nephropathy, and neuropathy, as well as macrovascular complications like cardiovascular events and stroke.[1] Prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly, and presently 287 million people are affected with it globally. It is projected that 592 million people will be affected with T2DM by 2035. India has emerged as a center for T2DM in the Southeast Asia region, having >69 million people affected with diabetes, which is expected to affect nearly 101 million people by 2035.[1,2] A population-based study, conducted by "The National Urban Diabetes Society" (NUDS) in a few metropolitan cities of India, revealed that the age-standardized prevalence of T2DM was 12.1%. Further, it was reported that the prevalence was higher in the southern part of India (13.5% in Chennai, 12.4% in Bengaluru, and 16.6% in Hyderabad) than in eastern India (Kolkata, 11.7%), northern India (New Delhi, 11.6%), and western India (Mumbai, 9.3%).[3] The management of T2DM with regard to targeted glycated hemoglobin (HbA1c) and internationally recommended clinical guidelines for individualized approach is relatively difficult.[4]

Recent treatment guidelines given by the American Diabetes Association (ADA) (2019)[5] and the European Association for the Study of Diabetes recommend an individualized approach in selecting the appropriate drug for the treatment of T2DM. This includes consideration of efficacy of the drug and other patient factors such as: (1) important comorbidities such as atherosclerotic cardiovascular disease, chronic kidney disease, and heart failure; (2) hypoglycemia events; (3) body weight; (4) various side effects; (5) economy; and (6) patient's choice. The various treatment guidelines have considered metformin as the first-line pharmacological measure in the treatment of T2DM unless contraindicated. If desired glycemia is not achieved, dual therapy with metformin and sulfonylureas has been advocated by many international guidelines.[4] Even the triple-drug therapy has been instituted recently, which provided a significantly better and clinically relevant reduction in HbA1c when compared to dual therapy. Significant reduction in HbA1c, optimum body weight, and reduced incidence of hypoglycemia were major outcomes in the triple therapy.[4]

The ADA showed that triple-drug combinations had better outcomes in HbA1c, glucose metabolism, lipid levels, hypoglycemic events, body weight, and urine albumin as compared to dual therapy.[6] In contrast to the currently recommended sequential add-on therapy, we planned to assess the efficacy and safety of a triple-drug combination of metformin, glimepiride, and pioglitazone, initiated at earlier stages during the management of newly diagnosed T2DM patients.

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Aims and Objectives

To study the outcomes of triple-drug therapy in newly diagnosed T2DM (HbA1c ≥9%) with respect to change in HbA1c, low-density lipoprotein (LDL) levels, weight, waist circumference, variation in drug dosages, hypoglycemic events, patient response of well-being, and corresponding result satisfaction.

Materials and Methods

Patient Population

About 137 newly diagnosed T2DM patients who attended the outpatient department of the tertiary care hospital in the Department of Medicine at Indira Gandhi Medical College and Hospital, Shimla, were enrolled. The patients were enrolled according to the following inclusion criteria—aged between 20 and 80 years, patients willing to give informed consent, HbA1c ≥9%, and no treatment with insulin or oral agents for the recent 6 months. Patients were excluded if they had T1DM, secondary diabetes (chronic pancreatitis, drugs, Cushing's disease, pituitary, and thyroid disorders), presented with acute illness [acute fever, urinary tract infection (UTI), diabetic ketoacidosis (DKA), severe hypertension (HTN), congestive heart failure, short-term marked hyperglycemia, rigorous exercises], were younger than 20 years, had contraindications to metformin, sulfonylurea, and thiazolidinediones, or were pregnant or lactating women. Criteria delineated by the WHO were used for the diagnosis of T2DM, that is, a random plasma glucose concentration ≥200 mg/dL with symptoms of hyperglycemia, fasting plasma glucose (FPG) ≥126 mg/dL, or 2-hour postprandial plasma glucose (PPPG) ≥200 mg/dL during an oral glucose tolerance test with 75 gm oral glucose. This study was approved by the Institutional Ethics Committee. All patients were put on triple drug therapy, that is, metformin (1,000 mg) BD, sulfonylurea glimepiride (2 mg) OD, and thiazolidinediones (pioglitazone 15 mg) OD. Modification of treatment was done based on the glycemic levels of the patient during follow-up.

Study Design

It was a prospective and observational study.

Study Duration

It was conducted from 1st June 2018 to 31st May 2019.

Data Collection

After enrollment, a detailed history was recorded, followed by a general physical and systemic examination of the study participants. The various anthropometric variables, such as weight, height, waist, and body mass index (BMI), were recorded for all the study participants. FPG, PPPG, HbA1c, and blood pressure were recorded for every subject. Routine blood investigations, such as complete hemogram, liver function tests, kidney function tests, and lipid profile, were conducted. Where indicated, specific tests, such as chest X-ray and thyroid function tests, were performed. Contact details of the patients were noted, and all the participants were advised to report for follow-up at 3-month intervals. During their enrollment in the study, patients were warned about the symptoms of hypoglycemia. They were also educated about the use of corrective measures in case of hypoglycemia. Patients and their attendants were advised to contact the treating physician in case of severe symptoms of hypoglycemia. The study participants were followed up at 3, 6, 9, and 12 months. FPG, PPPG, HbA1c, weight, and waist were recorded at every visit. Symptoms of minor as well as major hypoglycemia, if any, were noted. Any episode of hospitalization and subjective feelings of well-being were also recorded.

Statistical Analysis

The categorical variables were analyzed using descriptive statistics and frequency percentages. The mean value and standard deviations were measured for quantitative data. In our study, we used Pearson's Chi-squared test and one-way ANOVA or paired *t*-test for analyzing qualitative data. A *p*-value < 0.05 was considered statistically significant. We used the statistical software IBM SPSS Statistics for Windows, version 21.0.

Results

Out of 137 participants in our study, the number of males was 77 (56.2%) and females were 60 (43.8%). Among all patients, 92 (67.2%) patients belonged to rural areas, and 45 (32.8%) belonged to urban areas. Among male patients, 27 (93.1%) were farmers, 21 (95.5%) were employees, and 29 (87.9%) belonged to different occupations. In the female patient group, 2 (6.9%) were farmers, 1 (4.5%) was an employee, 53 (88.3%) were housewives, and 4 (12.1%) belonged to other occupations. Out of 137 patients, 20 (20.4%) were smokers and 36 (26.3%) were alcoholics, whereas 58 (42.3%) patients had a positive family history of T2DM, of which the mother was predominantly affected. Further, 21 (15.3%) patients presented with HTN, and it was also observed that 6 (4.4%) of them had findings of diabetic retinopathy (grade 1/2) as well. In this study, the most common presenting complaint was osmotic features, which were seen in 83 (60.6%) patients, followed by complaints of easy fatigability/lethargy, which were seen in 21 (15.3%) patients; 16 (11.6%) patients presented for routine checkup; 7 (5.1%) patients were planned for surgery; 5 (3.7%) patients presented with vulvovaginitis; and 5 (3.7%) patients presented with skin lesions (Fig. 1). At baseline, the mean FPG was found to be 218 ± 36.9 mg/dL; among males, it was 218.40 ± 36.93 mg/dL, and among females, it was 209.22 ± 47.66 mg/dL. The mean PPPG was 343.94 ± 60.84 mg/dL, which was 343.93 ± 60.85 mg/dL among males and 342.12 ± 69.05 mg/dL among females. The mean HbA1c at baseline was recorded as 10.51% (±1.42), which was 9.47% (±1.56) in males and 11.55% (±1.28) in females. At baseline, the mean LDL level of all patients was 120.34 ± 30.99 mg/dL; it was 123.47 (±34.65) mg/dL in males and 116.33 (±25.26) mg/dL in female patients. The mean weight and mean waist circumference of all the patients enrolled were 68.50 (±8.01) kg and 91.04 (±8.85) cm, respectively (Table 1).

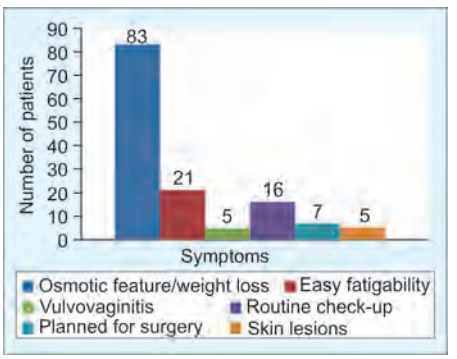

Fig. 1: Presenting symptoms (*n* = 137)

Table 1: Demographic profile and baseline clinical parameters (*n* = 137)

Variables	*Male*	*Female*	*Total*
Age (years)	49.48 (±8.26)	50.23 (±7.98)	49.81 (±8.12)
Weight (kg)	70.86 (±7.33)	65.47 (±7.88)	68.5 (±8.01)
Waist (cm)	90.62 (±6.95)	91.57 (±10.84)	91.04 (±8.85)
BMI (kg/m^2)	25.05 (±2.59)	24.20 (±2.75)	25.05 (±2.59)
FPG (mg/dL)	218.40 (±36.93)	209.22 (±47.66)	218.4 (±36.93)
PPPG (mg/dL)	343.94 (±60.85)	342.12 (±69.05)	343.94 (±60.84)
HbA1c (%)	9.47 (±1.56)	11.55 (±1.28)	10.51 (±1.42)
LDL (mg/dL)	123.47 (±34.65)	116.33 (±25.26)	120.34 (±30.90)

All patients were put on triple-drug therapy as per the protocol.

First Follow-up Visit at 3 Months

At the end of 3 months, FPG levels of study participants ranged from 84 to 195 mg/dL, with a mean of 123 ± 16 mg/dL. The PPPG levels ranged from 116 to 257 mg/dL, with a mean of 164 ± 30 mg/dL, and HbA1c ranged from 5.4 to 12.1%, with a mean HbA1c of 8.14 ± 0.97%. The LDL level ranged from 45 to 221 mg/dL, with a mean of 109.04 ± 28.28 mg/dL (Table 2). The reduction in the mean FPG, PPPG, HbA1c, and LDL levels was highly significant at 3 months of follow-up ($p < 0.001$) (Fig. 2). There was no noticeable change in weight and waist circumference at 3 months when compared with baseline. Out of 137, 109 (79.6%) patients were put on a triple-drug combination with reduced-dose glimepiride (1 mg) OD + metformin (1,000 mg) BD + pioglitazone (15 mg) OD, whereas 21 (15.3%) were kept on the same original drug combination. Further, four (2.9%) were prescribed dual-drug therapy of pioglitazone (15 mg) OD + metformin (1,000 mg) BD or glimepiride (1 mg) OD + metformin (1,000 mg) BD, and the remaining three (2.2%) were prescribed single therapy, metformin (1,000 mg) BD (Table 3). Only three minor events of hypoglycemia were recorded, for which patients had taken self-remedy in the form of sugar at home, and no major adverse events were documented.

Follow-up Results at 12 Months

At 12 months, it was found that FPG ranged from 81 to 146 mg/dL with a mean of 96 ± 10 mg/dL, PPPG ranged from 118 to 167 mg/dL with a mean of 146 ± 16 mg/dL, and the HbA1c ranged from 5.2 to 8.5% with a mean of 6.14 ± 0.43%. The LDL level ranged from 38 to 201 mg/dL with a mean of 90.55 ± 28.14 mg/dL (Table 2). Decreased mean values in all three parameters (FPG, PPPG, and HbA1c) were significant at 12 months when compared with baseline levels (Fig. 2). There was an average 860 gm increase in the body weight of study participants from 68.5 to 69.36 kg and an average 0.62 cm increase in waist circumference of the participants from 91.04 to 91.66 cm when compared with baseline. Based on clinical response, all patients were assessed for continuation or modification of further treatment. At the end of the study, 94 (68.6%) patients who had HbA1c <7–6% were prescribed dual drug therapy of glimepiride (1 mg) OD + metformin (1,000 mg) BD or pioglitazone (15 mg) OD + metformin (1,000 mg) BD. About 40 (29.2%) patients who had HbA1c <6% (better glycemic index) were prescribed single therapy of metformin (1,000 mg) BD. However, three (2.2%) patients were kept on triple drug therapy with reduced doses, such as glimepiride (1 mg) OD + metformin (1,000 mg) BD + pioglitazone (15 mg) OD; these patients had HbA1c ≥7 and <9% (Table 3). Among all study participants, there were 9.48 episodes/patient of hypoglycemia. However, all the hypoglycemia events were minor. Out of 137 patients, 117 (85.4%) were satisfied with their treatment, and there was improvement in their quality of life with the ongoing treatment. The patients were relieved from osmotic symptoms, and they felt more energetic; together, it was considered the "feel-good phenomenon." Thus, at the end of 12 months, the majority of patients were on dual-drug or single-drug regimens, while only a few needed triple-drug regimens.

Table 2: Comparison of clinical parameters at baseline, 3 months, and 12 months

Variable	*Baseline*	*3 months*	*12 months*
FPG (mg/dL)	218.40 (±36.93)	123 (±16)	96 (±10)
PPPG (mg/dL)	343.94 (±60.85)	164 (±30)	146 (±16)
HbA1c (%)	9.47 (±1.56)	8.14 (±0.97)	6.14 (±0.43)
LDL (mg/dL)	123.47 (±34.65)	109.04 (±28.28)	90.55 (±28.14)

Discussion

There are many options available for triple drug combinations in newly diagnosed T2DM (HbA1c ≥9%). Large numbers of patients with a high glycemic index (HbA1c ≥9%) are usually put on a combination of metformin, sulfonylurea, and insulin. However, due to the high cost of insulin, fear of injections, and increased risk of hypoglycemic events, compliance with such treatments is low. Sodium-glucose co-transporter 2 inhibitors (SGLT2-i) and glucagon-like peptide-1 (GLP-1) agonists can be added as the third drug with the dual combination of metformin and sulfonylureas, as these two different classes of drugs tend to have good HbA1c, cardiovascular, and renal outcomes. Unfortunately, due to their high costs, they also present affordability issues in our clinical setup. Thus, in our study, we used a combination of metformin, sulfonylureas, and thiazolidinedione, which resulted in significant reductions in HbA1c and LDL levels (bad cholesterol) without significant gains in weight and waist circumference. The added advantage of these three drugs in combination is that each drug targets a different pathophysiology of T2DM simultaneously, complementing each other's mechanism of action, which results in a greater reduction in HbA1c and a decreased incidence of micro/macrovascular adverse events. In

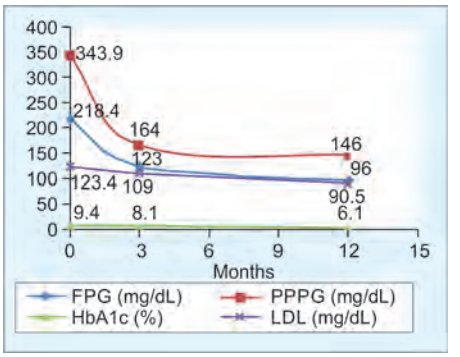

Fig. 2: Progressive decline in level of clinical parameters from baseline to end of treatment

Table 3: Cross tabulation between different time periods and variation in drug dosage

Time	*Variation in drug-dosage*									
	Triple drug therapy (A1c ≥9%)		*Triple drug therapy with reduced dosage (A1c ≥7 to <9%)*		*Dual drug therapy (A1c <7 to ≥6%)*		*Single drug therapy (A1c <6%)*		*Total*	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Baseline	137	100.0	0	0.0	0	0.0	0	0.0	137	100.0
3rd month	21	15.3	109	79.6	4	2.9	3	2.2	137	100.0
6th month	1	0.7	65	47.4	70	51.1	1	0.7	137	100.0
9th month	0	0.0	29	21.2	90	65.7	18	13.1	137	100.0
12th month	0	0.0	3	2.2	94	68.6	40	29.2	137	100.0

Chi-square value = 910.129; *p*-value < 0.001, significant; A1c = HbA1c

this study, we summarize the outcome of triple drug therapy used in newly diagnosed T2DM patients (HbA1c ≥9%) with respect to parameters such as changes in HbA1c level, lipid level (LDL), weight, waist circumference, hypoglycemic events, variation in drug dosages, changes in lifestyle and behavioral modification, patient well-being during the treatment, and corresponding result satisfaction. The age distribution in our study was from 20 to 80 years, with a mean age of 49.85 ± 8.12. The mean age among males was found to be 49.48 ± 8.26, and among females, it was 50.23 ± 7.99. These findings were comparable with the NHANES survey,[7] which reported that the mean age at diagnosis of T2DM in the United States decreased from 52 years (1988–1994) to 47 years (1999–2000). A cross-sectional study by Morkos et al.[8] demonstrated the mean age of patients as 49 ± 11.3 years. In our study, the mean BMI was 24.79 kg/m^2, with 25.05 ± 2.59 kg/m^2 among males and 24.2 ± 2.75 kg/m^2 among females. The Mayega and Rutebemberwa[9] study demonstrated the mean BMI of newly diagnosed diabetes patients as 24.7 (median 24; range 13.3–44.6), which was in concordance with our study. In our study, out of 137 patients, 92 (67.2%) were from rural backgrounds. In a cross-sectional study by Aung et al., the age-standardized prevalence of diabetes was much higher in the urban population (12.1%) than in the rural population (7.1%).[10] Educational status of the population had a noticeable impact on the prevalence of diabetes. Even in urban areas, the prevalence of T2DM was higher in populations with low education standards when compared with those with higher education levels. In rural areas, physical inactivity, lower intake of fruits and vegetables, and obesity culminated in a higher prevalence of DM than in those who were more physically active, took care of their diet, and managed their weight. The majority of the population in Himachal Pradesh belongs to rural areas (90%), so the chances of T2DM are higher in rural backgrounds. An increase in the prevalence of T2DM in rural populations could be the result of a lack of awareness and low education standards, which lead to ignorance of the symptoms and signs of T2DM.

Out of 137 patients, 58 (42.3%) had a positive family history of T2DM. These findings differ from the Mayega and Rutebemberwa study,[9] which reported only 20% of newly diagnosed diabetes patients with a family history of diabetes. In our study, 21 (15.3%) patients presented with a positive history of HTN. In Mayega and Rutebemberwa's study,[9] about 48% of newly diagnosed diabetes patients had high blood pressure at the time of enrollment. In the Venugopal and Mohammed study,[11] the prevalence of HTN was noted in 64 (25.6%) patients. Priya et al.[12] observed HTN in 42.7% of the patients. In a study by Ramachandran,[13] 38% of study subjects were hypertensive.

In our study, the most common presenting complaints were osmotic features seen in 83 (60.6%) patients, followed by others (Fig. 1). These were not consistent with the findings of a case series reported by Mayega and Rutebemberwa,[9] which stated increased urination as the most common symptom at presentation. It was followed by frequent drinking/thirst (79%) and easy fatigability (51%). Others had symptoms like blurred vision (38%), excessive sweating (27%), joint pains (22%), numbness (21%), and headache (21%). We observed a steady decline in the levels of the mean FPG, PPPG, and HbA1c from baseline to 12 months (Table 2 and Fig. 2). Thus, it was analyzed that the triple-drug combination of metformin, sulfonylureas, and thiazolidinedione was clinically effective in reducing HbA1c to a significant level. These observations were in concordance with a study done by Downes et al.,[4] which stated that all classes of drugs, in combination with metformin and sulfonylureas, provided a clinically relevant and statistically significant (>0.3%, >3.3 mmol/mol) decrease in HbA1c when compared to metformin and sulfonylureas dual therapy. Similar results were found in a multicentric study conducted by Meshram et al.[14] to determine the efficacy and safety of the triple-drug combination of glimepiride 2 mg, pioglitazone 15 mg, and metformin 500 mg for 2 months in 101 patients with T2DM. It was concluded that the goals recommended by the ADA can be achieved with the triple-drug combination. It was seen that after 2 months, the mean HbA1c, which was 10.32% at baseline, significantly reduced to 7.54% at the end of the study. The bad cholesterol (LDL) was shown to be reduced in our study from baseline 120.34 to 90.55 mg/dL at the end of the study; the reduction in mean value was statistically significant. Similar results were seen in the Meshram et al.,[14] which reported a significant reduction in levels of triglycerides, LDL, and total cholesterol with the triple-drug combination. In our study, there was no significantly documented hypoglycemic event (only 13 minor events), which is contrary to the study Downes et al.,[4] as this study was associated with major hypoglycemic events. In our study, none of the patients required hospitalization due to hypoglycemia. There was no case of poor tolerability to drugs reported as evaluated by patients as well as the investigator. No significant change in weight and waist circumference was observed in our study, as low-dose pioglitazone 15 mg was used. Also, the weight-gaining effect of thiazolidinedione might have been neutralized by metformin. These findings were consistent with the findings of the Praveen et al. study,[15] which stated that there was no significant increase in weight throughout the study period with the triple-drug combination therapy.

On having good compliance with the initial triple drug therapy of metformin, glimepiride, and pioglitazone, subsequent follow-up visits resulted in reduced doses of drugs due to significant reduction in HbA1c and better glycemic control. Due to better glycemic control, there was a reduction in both microvascular and macrovascular adverse events. The patient response, showing well-being and satisfactory results, was obtained in this study. All the subjects had satisfactory to very good improvement, assessed on the "Global Assessment of Efficacy of Treatment," evaluated by both the physician and patients at the 3rd and 12th months. Our study's observation could have been a step toward recommending the initiation of the triple drug combination of metformin, glimepiride, and pioglitazone in the treatment of newly diagnosed T2DM patients. However, stepwise add-on therapy is the existing recommendation for treating such patients. A longer-duration study within a multiethnic group may be needed to validate the observation in our study. It is also concluded that pharmacoeconomic studies of antidiabetic drugs should not be limited to the cost of drugs; emphasis should be given to other beneficial metabolic effects, such as a low risk of hypoglycemia, weight loss, and reduction of cardiovascular disease risk factors. Otherwise, these modalities may increase the overall cost of management in T2DM patients.

Conclusion

It is concluded that early induction of combination therapy with glimepiride, metformin, and pioglitazone results in a greater reduction of HbA1c levels with a lower incidence of hypoglycemia compared to the currently recommended add-on therapy with conventional agents, such as sulfonylureas and insulin. However, more studies with long-term follow-up are required to validate the favorable outcome of triple drug therapy in the management of newly diagnosed T2DM patients.

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ORIGINAL ARTICLE

Plasmodium vivax Malaria Presenting with Acute Respiratory Distress Syndrome: A Case Series

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Abstract

Plasmodium vivax, traditionally considered a benign cause of malaria, is increasingly being recognized for causing severe complications, including acute respiratory distress syndrome (ARDS), renal dysfunction, and multiorgan dysfunction syndrome. This case series highlights the presentation and outcomes of ARDS associated with *P. vivax* infection. This series reports five cases of *P. vivax* malaria complicated by ARDS, admitted to the Department of Medicine, Atal Bihari Vajpayee Institute of Medical Sciences and Dr Ram Manohar Lohia Hospital, New Delhi. Each patient underwent comprehensive clinical evaluation, laboratory investigations, and imaging studies. The management protocol included antimalarial therapy, supportive care, and critical care interventions as necessary. This case series underscores the potential severity of *P. vivax* infections, challenging the notion of its benign nature. The occurrence of ARDS in these patients emphasizes the need for heightened clinical vigilance and robust management strategies in treating *P. vivax* malaria. Further research is essential to elucidate the mechanisms underlying severe complications in *P. vivax* malaria and to improve patient outcomes.

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Introduction

Malaria is a parasitic infection transmitted by the *Anopheles* mosquito that leads to acute, life-threatening disease and poses a significant global health threat. Two billion people risk contracting malaria annually, including those in 90 endemic countries and 125 million travelers.[1] The incubation period, and therefore the time to symptom development, varies by species: 8–11 days for *Plasmodium falciparum*, 8–17 days for *Plasmodium vivax*, 10–17 days for *Plasmodium ovale*, 18–40 days for *Plasmodium malariae* (though possibly up to several years), and 9–12 days for *Plasmodium knowlesi*.[1] Here, our focus will be on *P. vivax* malaria and its complications.

Classic clinical signs and symptoms of malaria include fever, headache, nausea, vomiting, body aches, anemia, and jaundice. Cerebral malaria, renal dysfunction, severe anemia, acute respiratory distress syndrome (ARDS), shock, hemoglobinuria, thrombocytopenia, hypoglycemia, and multiple organ involvement are the major reported complications of *P. falciparum* in India as well as in other countries. Due to the parasite life cycle, patients with *P. vivax* malaria tend to have paroxysmal fevers approximately every 42–56 hours.[2] Unlike *P. falciparum*, *P. vivax* (also known as benign tertian malaria) does not tend to cause sequestration; therefore, multiorgan failure is rare. However, there are numerous case reports of severe *P. vivax* malaria during last two decades.[2,3]

Acute respiratory distress syndrome occurs in patients as a result of a secondary host immune response to parasitemia. The host response may reach full strength at lower parasitemia in *P. vivax* or *P. ovale*, than in *P. falciparum* malaria.[2,4]

Here, we are reporting a series of five cases in which ARDS complicates *P. vivax* infection:

Case 1

A 41-year-old male without any known comorbidities or relevant past history had fever for 8 days, shortness of breath for 5 days, one episode of melena 4 days ago, and abdominal distension for 4 days. General examination showed a blood pressure (BP) of 110/70, pulse of 92 beats per minute (bpm), and respiratory rate of 40/minute. Respiratory examination revealed bilateral axillary, infra-axillary, and infra-scapular fine inspiratory crepitations. Initial blood gas revealed potential of hydrogen (pH) 7.397, pO_2 39.7 mm Hg, partial pressure of carbon dioxide (pCO_2) 59.5 mm Hg, bicarbonate (HCO_3) 32.5 mmol/L, and partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio of 66 mm Hg. The patient was intubated in view of poor sensorium and respiratory distress. Laboratory investigations showed hemoglobin (Hb) 9.3 gm/dL, total leukocyte count (TLC) 12,000/mm^3, platelets 30,000/mm^3, urea 38 mg/dL, creatinine 1.0 mg/dL, aspartate aminotransferase (AST) 42 U/L, alanine aminotransferase (ALT) 43 U/L, sodium (Na) 138 mmol/L, and potassium (K) 3.72 mmol/L. Chest X-ray showed bilateral middle and lower zone alveolar-interstitial infiltrates (Fig. 1). Rapid diagnostic test came out positive for *P. vivax* and negative for *P. falciparum*. Thin blood smear examination demonstrated trophozoites and gametocytes of *P. vivax* (Fig. 2). The patient was managed in critical care settings with intravenous (IV) antibiotics, IV artesunate, IV steroids, and appropriate fluid resuscitation. Other tropical fever investigations for dengue, scrub typhus, leptospira, and chikungunya came out negative. Cerebrospinal fluid (CSF) studies were sent, which came out normal. Contrast-enhanced computed tomography (CECT) abdomen revealed multiple infarcts in the spleen, kidneys, and brain, a finding not seen before with *P. vivax* infection. Despite

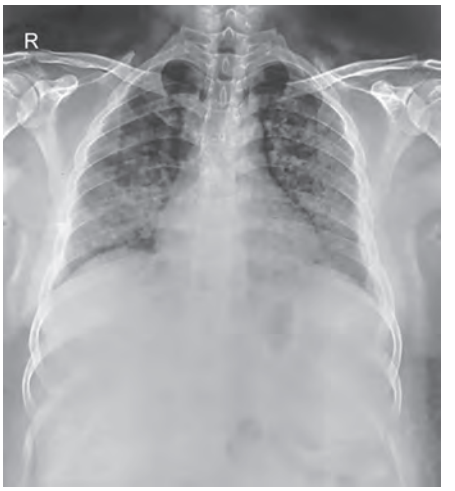

Fig. 1: Chest X-ray showing bilateral lower and middle zone alveolar-interstitial infiltrates

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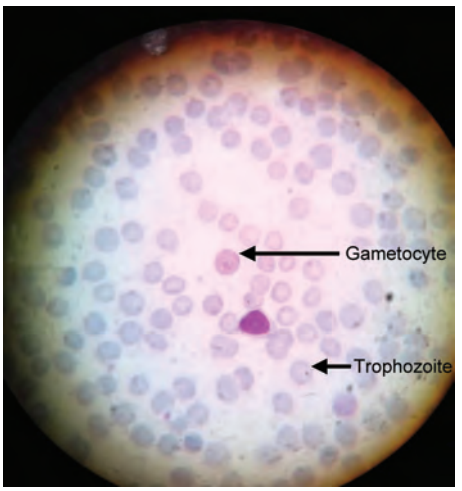

Fig. 2: Thin blood smear showing trophozoites and gametocytes of *P. vivax*

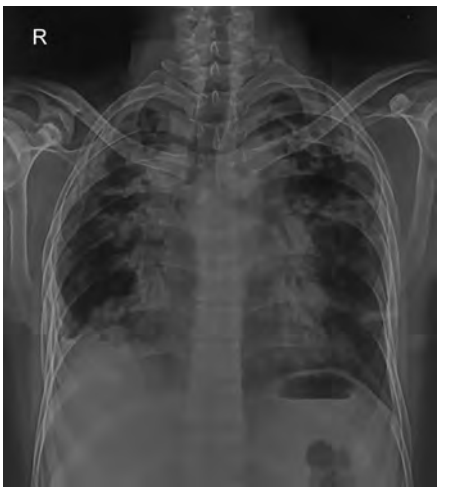

Fig. 3: Bilateral upper and middle zone fibrotic lesions (posttubercular) with bilateral lower zone alveolar-interstitial infiltrates on chest X-ray

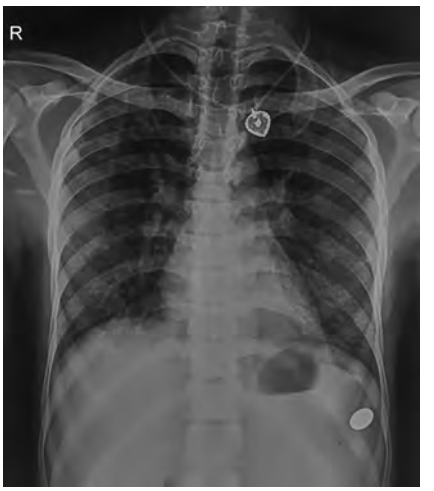

Fig. 5: Left mid and lower zone interstitial infiltrates on the chest X-ray

our best efforts, the patient couldn't be saved and succumbed to the illness after 20 days.

Case 2

A 35-year-old male with a past history of pulmonary tuberculosis had fever for 8 days, shortness of breath for 2 days, and altered sensorium for 2 days. General physical examination revealed BP 118/70 mm Hg, pulse 94 bpm, and respiratory rate of 36/minute. Respiratory examination showed bilateral coarse inspiratory crepitations all over the lung field. Blood gas showed pH 7.4, pO_2 159 mm Hg, pCO_2 40.2 mm Hg, HCO_3 22.8 mmol/L on 15 L/minute O_2 *via* nonrebreather mask (NRBM), and PaO_2/FiO_2 177 mm Hg. The patient was shifted to a critical care setting and first managed with noninvasive ventilation (NIV); however, the patient was intubated in view of respiratory distress and poor sensorium. Laboratory investigations showed Hb 10.7 gm/dL, TLC 17,350/mm^3, platelets 55,000/mm^3, urea 259 mg/dL, creatinine 5.3 mg/dL, AST 133 U/L, ALT 51 U/L, bilirubin (direct) 7.59 mg/dL, bilirubin (indirect) 4.58 mg/dL, Na 129 mmol/L, and K 5.22 mmol/L. Chest X-ray showed bilateral fibrotic lesions with fluffy opacities, which were suggestive of ARDS (Fig. 3). Thin smear showed trophozoites and gametocytes of *P. vivax* (Fig. 4). Rapid diagnostic test was positive for *P. vivax*, and *P. falciparum* was negative. Tests for other tropical fevers, including dengue, chikungunya, enteric fever, scrub typhus, and leptospira, were negative. Ultrasonography (USG) whole abdomen showed kidney sizes to be normal with raised cortical echogenicity. CSF studies were found to be normal. The patient was given renal replacement therapy (RRT) for acute kidney injury (AKI) and managed with appropriate IV antibiotics, IV steroids, IV artesunate, and appropriate fluid resuscitation.

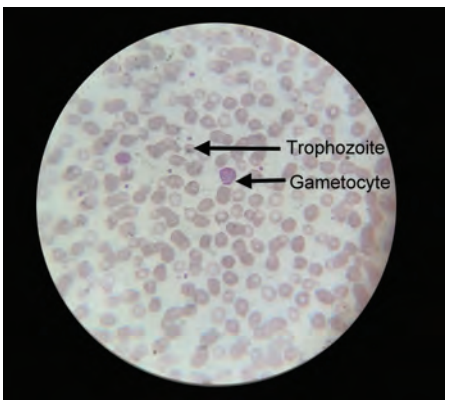

Fig. 4: Thin smear showing trophozoites and gametocytes of *P. vivax*

The patient, however, couldn't be saved and died after a week.

Case 3

A 20-year-old male with no known comorbidities and no significant past history has had fever for 5 days, abdominal pain for 5 days, shortness of breath for 3 days, and one episode of melena 3 days ago. General physical examination revealed BP 120/68 mm Hg, pulse 120 bpm, respiratory rate 38/minute. Respiratory examination showed bilateral fine inspiratory crepitations in the basal regions. Initial blood gas showed pH 7.507, pCO_2 30.6 mm Hg, pO_2 41.3 mm Hg, HCO_3 24.5 mmol/L on 10 L/minute O_2 *via* NRBM. PaO_2/FIO_2 69 mm Hg. The patient was shifted to a critical care setting and managed with high-flow nasal cannula (HFNC). Laboratory investigations showed Hb 11.7 gm/dL, TLC 1,480/mm^3, platelets 52,000/mm^3, urea 15 mg/dL, creatinine 0.9 mg/dL, and normal liver function tests (LFTs). Na was 132 mmol/L, and K was 3.8 mmol/L. Chest X-ray showed bilateral diffuse interstitial

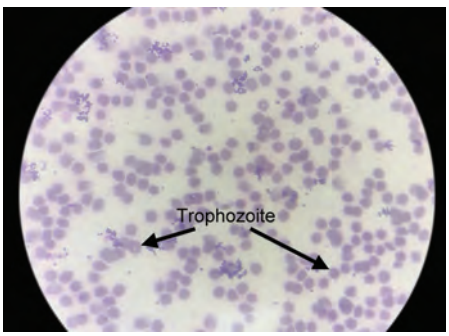

Fig. 6: Thin blood smear showing trophozoites of *P. vivax*

opacities (Fig. 5). Malaria rapid diagnostic test was positive for *P. vivax*, *P. falciparum* was negative. This was confirmed by thin blood smear demonstrating trophozoites of *P. vivax* (Fig. 6). Other tropical fever tests, such as dengue, chikungunya, enteric fever, scrub typhus, and leptospira, were negative. No other source of fever could be identified. The patient was started on IV antibiotics, IV artesunate, IV steroids, and appropriate fluid resuscitation. The patient's condition improved, and oxygen support was later de-escalated to NRBM. After 14 days, the patient was shifted to the general ward and later discharged.

Case 4

A 26-year-old female without any prior known comorbidities or any significant past history had complaints of headache for 5 days, fever and malaise for 4 days, and shortness of breath for 1 day. General physical examination showed BP 114/70 mm Hg, pulse 115 bpm, respiratory rate of 34/minute. Respiratory system examination showed bilateral fine inspiratory crepitations all over the lung field. The patient was initially put on NRBM at 12 L/minute. However, she was not able

to maintain oxygen saturation. She was shifted to a critical care setting and put on HFNC at flow rate of 30 L/minute with 50% FiO_2. Initial blood gas analysis showed pH 7.51, pCO_2 24.6 mm Hg, pO_2 63.8 mm Hg, and HCO_3 22.4 mmol/L. PaO_2/FiO_2 was calculated to be 127.6 mm Hg. Laboratory investigations showed Hb 13.5 gm/dL, TLC 5,600/mm^3, platelets 1,00,000/mm^3, urea 33 mg/dL, creatinine 0.6 mg/dL, normal LFTs, Na 136 mmol/L, and K 4.3 mmol/L. Chest X-ray showed bilateral diffuse infiltrates (Fig. 7). Malaria rapid card test was positive for *P. vivax* only. This was confirmed by thin blood smears showing the trophozoites of *P. vivax* (Fig. 8). Dengue, chikungunya, enteric fever, scrub typhus, and leptospira tests were negative. Other foci of infection were ruled out. The patient was started on IV artesunate, IV steroids, IV antibiotics, and appropriate fluid resuscitation. The patient responded well to the treatment, and the oxygen requirement was gradually reduced. The patient was shifted to NRBM. The patient was shifted to the general ward after 11 days and later discharged.

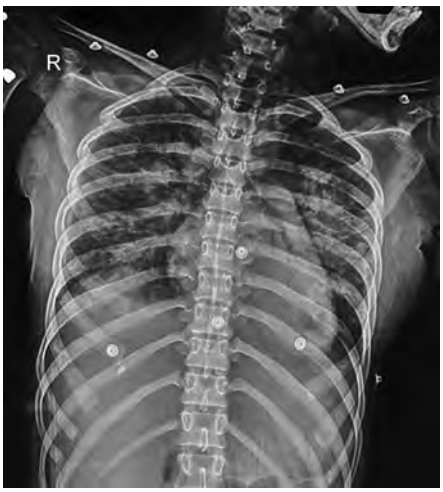

Fig. 7: Chest X-ray showing bilateral alveolar-interstitial infiltrates

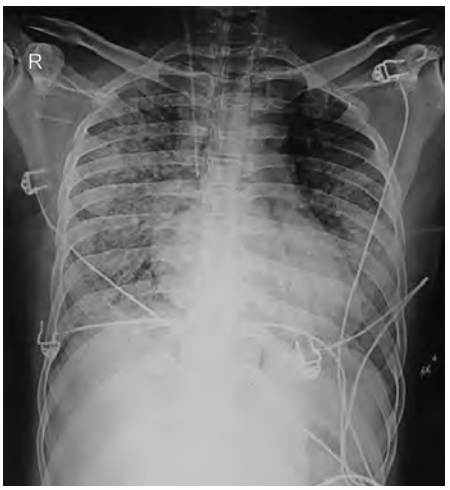

Fig. 9: Chest X-ray showing bilateral alveolar-interstitial infiltration with an almost white-out lung on the right side

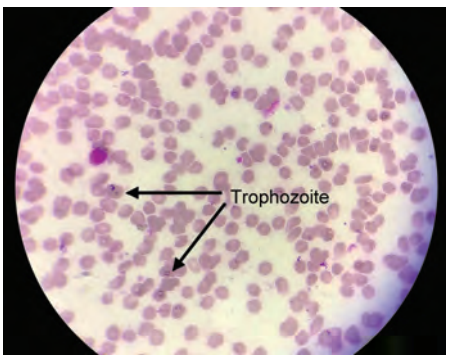

Fig. 8: Thin blood smear showing trophozoites of *P. vivax*

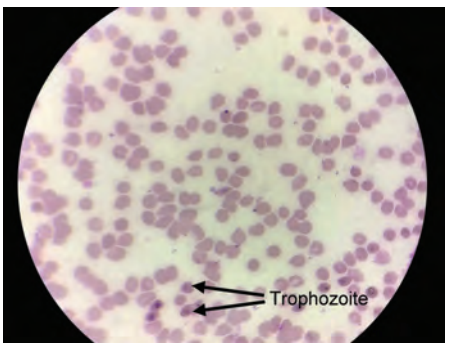

Fig. 10: Thin blood smear showing trophozoites of *P. vivax*

Case 5

A 21-year-old male with no known comorbidities had complaints of fever for 5 days, headache for 5 days, and shortness of breath for 2 days. General physical examination showed BP 120/80 mm Hg, pulse 120 bpm, and respiratory rate of 42/minute. Respiratory system examination revealed bilateral fine inspiratory crepitations present all over the lung fields. The patient was shifted to a critical care setting and was put on HFNC at 40 L/minute with 60% FiO_2. A blood gas analysis was done, which showed pH 7.54, pCO_2 22.4 mm Hg, pO_2 62.1 mm Hg, and HCO_3 24.2 mmol/L. PaO_2/FiO_2 was calculated to be 103.5 mm Hg. Routine laboratory investigations showed Hb 13.2 gm/dL, TLC 6,300/mm^3, platelets 80,000/mm^3, urea 23 mg/dL, creatinine 0.8 mg/dL, LFTs were normal, Na 137 mmol/L, K 4.5 mmol/L. Chest X-ray showed bilateral (right more than left) diffuse opacities (Fig. 9). Malaria rapid card test was positive for *P. vivax*, and this was confirmed by using thin blood smears demonstrating trophozoites of *P. vivax* (Fig. 10). *P. falciparum*, dengue, chikungunya, enteric fever, scrub typhus, and leptospira tests were negative. No other foci of infection were found. The patient was started on IV artesunate, IV steroids, IV antibiotics, and appropriate fluid resuscitation. The treatment yielded positive results, the oxygen requirement reduced, and it was gradually de-escalated to room air over the course of 10 days. The patient was then shifted to the general ward and later discharged (Table 1).

Discussion

The global burden of *P. vivax* infection is estimated to be approximately 70–80 million cases annually.[5] India is a country with a significant burden.

Severe malaria is usually associated with *P. falciparum*, whereas *P. vivax* infection is usually considered benign. This assumption is now being challanged as more and more cases of severe malaria due to *P. vivax* are being reported.

The incidence of ARDS in *P. vivax* infection was found to be around 3–7%, with mortality

Table 1: Summary

Serial no.	*Age/sex*	*Symptoms*	*Signs*	*Other features*
1.	41/M	Fever, shortness of breath, abdominal distension	Bilateral axillary, infra-axillary, and infra-scapular fine inspiratory crepitations	Multiple infarcts in spleen, kidneys and brain, melena
2.	35/M	Fever, shortness of breath, altered sensorium	Bilateral coarse inspiratory crepitations all over lung field	AKI, melena, altered sensorium
3.	20/M	Fever, pain abdomen, shortness of breath	Bilateral fine inspiratory crepitations in basal region	Melena
4.	26/F	Headache, fever, malaise, shortness of breath	Bilateral fine inspiratory crepitations all over lung field	None
5.	21/M	Fever, headache, shortness of breath	Bilateral fine inspiratory crepitations all over lung field	None

rates being as high as 50%.[6] The exact mechanism for the development of ARDS in *P. vivax* infection is not known. However, it may be attributed to leukocyte aggregation during febrile paroxysms, which is mediated by parasite-derived lipids along with host cytokines.[7] This activation may lead to increased alveolar permeability, which is widely accepted to be the main cause of ARDS.[8]

Acute respiratory distress syndrome is associated with a more systemic inflammatory response involving activation of neutrophils and cytokines, along with alveolar epithelial inflammation. The frequent onset of ARDS after starting antimalarial treatment may reflect a posttreatment exacerbation of the inflammatory response mediated by pro-inflammatory cytokine release. Thus, the parasite probably triggers a hyperimmune response with resultant lung injury.

A few studies highlighting severe *P. vivax* infection have been done in India. A study by Yadav et al.[9] explored the incidence of ARDS in children with *vivax* malaria. Over a year, 112 children with acute febrile illness were examined. Findings showed that 42.9% of ARDS cases were due to *vivax* malaria, challenging the notion that only *falciparum* malaria causes severe complications. Clinical differences included higher liver enzyme levels in *vivax* cases.

The case series by Aashish and Manigandan[10] highlighted the severe complications of *P. vivax* malaria. Through three detailed cases, the authors illustrated that *P. vivax* can lead to severe manifestations similar to *P. falciparum*, including renal dysfunction, hepatic dysfunction, thrombocytopenia, hypoglycemia, and shock.

The study titled "Severe *vivax* malaria trends in the last two years: a study from a tertiary care center, Delhi, India" by Matlani et al.[11] conducted between June 2017 and December 2018, examined the severity and complications of *P. vivax* malaria in 205 patients. Of these, 177 had *P. vivax* infections, with 32.7% showing severe complications such as severe anemia, jaundice, and significant bleeding.

The study by Anvikar et al.[12] explored the severe clinical manifestations of *P. vivax* malaria, challenging its historical benign perception. Conducted over a year at the Civil Hospital in Ahmedabad, it revealed that severe *P. vivax* cases outnumbered severe *P. falciparum* cases, predominantly affecting adults. Common complications included jaundice and thrombocytopenia, with jaundice being exclusive to *P. vivax* cases.

The study "Clinical profile and severity of *Plasmodium vivax* and *falciparum* malaria in hospitalized children from North India" by Badugu et al.[13] highlighted the severe manifestations of malaria in children in the state of Uttar Pradesh, India. The study enrolled 100 children with confirmed malaria diagnoses over a period of 1 year. The results showed that 59% of severe cases were due to *P. vivax*. Severe anemia, jaundice, and impaired renal function were common complications.

In our case series, other complications seen were multifocal infarcts, AKI, possible gastrointestinal bleed, and encephalopathy, apart from ARDS.

Conclusion

The presumed notion of *P. vivax* malaria being a benign disease is slowly being changed with increase in reported cases of severe malaria and ARDS associated with *P. vivax*. This should be kept in mind during the management of *P. vivax* infection. It may be wise to say that benign tertian malaria is no longer benign.

Further studies are required to fully understand the mechanism, role of cytokines, and burden of severe malaria with *P. vivax* in India as well as globally.

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UPDATE ARTICLE

Guillain–Barré Syndrome in India: A Call for Learning and Cohesive Action

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Abstract

In January 2025, a Guillain–Barré syndrome (GBS) outbreak was reported in Pune, which quickly spread to other states of India. Though GBS is a rare immune-mediated polyradiculoneuropathy, it is the most common cause of acute flaccid paralysis globally. Initially described in 1859, knowledge on pathophysiology, disease spectrum, and management has evolved with time. GBS typically develops postinfection, with symptoms emerging within 6 weeks of the infectious trigger. Clinically, GBS commonly presents with bilateral flaccid weakness, often following a monophasic course. However, multiple clinical variants and atypical presentations often lead to delay in diagnosis. Diagnosis of GBS is primarily clinical, with cerebrospinal fluid (CSF) analysis and electrodiagnostic tests having a supportive role. The concept of "time is nerve" should be rooted in practice, and immunomodulatory therapy either as intravenous immune globulin (IVIg) or plasma exchange should be initiated at the earliest. Monitoring for respiratory and autonomic function is critical in management, with specific clinical parameters guiding intensive care unit (ICU) transfer. Overall, holistic and multidisciplinary supportive care is key to reduce patient morbidity and mortality. Stakeholder involvement at multiple levels, including community participation, will be key for effective preventive and curative strategies at local and national level.

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As we Indians cheerfully ushered in the new year, a rare but distressing disease seemingly emerged in the vibrant city of Pune in January 2025. Guillain–Barré syndrome (GBS) quickly emerged as an outbreak and spread to other states, with 214 cases reported at the time of writing this article. New cases continue to emerge with significant morbidity and potential mortality implications. This necessitates rekindling our understanding of GBS in a nutshell to ensure optimal patient outcomes.

Brief History of 165 Years

Guillain–Barré syndrome is an immune-mediated polyradiculoneuropathy which, though rare, is the most common cause of acute flaccid paralysis worldwide.[1,2] In 1859, Landry first described 10 cases of acute ascending paralysis, which laid a fulcrum for the 1916 seminal paper by Guillain, Barré, and Strohl on GBS.[3] Since then, strides have been made in our understanding of the disease from etiopathogenesis to management. Studies published in 1978 and 1993 demonstrated that glucocorticoids were ineffective in the management of GBS.[4,5] Notably, only in 2007, evidence informed practice that only intravenous immune globulin (IVIg) or plasma exchange (PLEX) hastened recovery, while also reaffirming that corticosteroids showed no benefits.[3,6]

Etiopathogenesis

Guillain–Barré syndrome is caused by an aberrant immune response (usually triggered by a preceding infection) in which autoantibodies are directed against neuronal gangliosides, thereby disrupting the peripheral nervous system.[1] Two-thirds of GBS patients report symptoms of an infection within 6 weeks before GBS symptoms. Temporal association has been established with 6 pathogens—*Campylobacter jejuni*, Zika virus, *Cytomegalovirus*, *Mycoplasma pneumoniae*, Epstein–Barr virus, and hepatitis E virus.[7] In a recently published Indian study, Nagubadi and colleagues reported 0.6% incidence of GBS in a cohort of COVID-19 cases admitted to their tertiary care center.[8] Notably, absence of symptoms suggestive of infection should not be an exclusion for GBS, since infections can be subclinical. Also, older influenza vaccines (1976 swine influenza vaccine) and a few immune-biologicals (based on case series) have also been implicated.[7] Intriguingly, although GBS is labeled as an inflammatory neuropathy, it is still unclear if the main driver is auto-inflammation (aberrant innate immunity driven) or true autoimmunity (aberrant adaptive immunity driven). Notably, GBS displays a male gender predominance, lack of association with other autoimmune diseases, lack of association with specific human leukocyte antigens, self-resolving generally monophasic course, and lack of response to glucocorticoids—all of which clearly earmark it as different from that of a typical autoimmune disease.[1]

Clinical Course and Subtypes

Clinical course is typically monophasic and follows three phases: the progressive phase, which lasts <4 weeks; the plateau phase, where clinical severity and symptoms achieve a plateau; and the recovery phase, which may last weeks to years.[1,9] A prospective study showed that 14% of GBS patients had moderate to severe disability at the end of 10 years after the initial event.[10] From an electrophysiological perspective, GBS was earlier classified as demyelinating or axonal subtypes. However, mixed (axonal-demyelinating), equivocal, and even normal (especially in early disease phase) patterns are commonly seen in nerve conduction studies (NCS).[1] Based on electrophysiological features, GBS has been classified into three major subtypes, namely acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN). However, in the current era, classification into these subtypes is neither helpful in early diagnosis nor does it have any additive value in management of GBS.[11]

Clinical Manifestations and Variants

Patients who have rapidly progressive, bilateral, flaccid weakness of legs and/or arms without central nervous system (CNS) involvement should be suspected to have GBS.[7] The heterogeneity of results seen in NCS seems to also mirror a similar

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trend of heterogeneity seen with clinical manifestations, often resulting in diagnostic delays.[1,7] Many patients, when probed, will reveal a history suggestive of an infection in the 6 weeks prior to the start of GBS symptoms.[7] Multiple clinical variants may present as shown in Figure 1 and Table 1. Among them, sensorimotor GBS (30–85%) and motor GBS (5–25%) are common presentations.[7,11] Typically, the classical presentation of sensorimotor and motor GBS is progressive, flaccid limb paresis with areflexia. Sensory loss occurs in motor-sensory GBS but not in pure motor GBS.[1] Bladder or bowel involvement and heart rate fluctuations may occur, thereby suggesting dysautonomia.[1,11] In severe cases, respiratory failure may occur due to involvement of diaphragm (predominantly), intercostals, and abdominal muscles.[12] Most patients usually experience their peak level of disability within 2 weeks. If patients reach their peak disability within 24 hours of onset or later than 4 weeks, alternate diagnoses should be taken into consideration.[11] Neuropathic pain may be reported as part of sensory nerve involvement.[1,11]

Guillain–Barré syndrome disability scale (GBS-DS) is an easy, validated, and useful clinical tool that can be performed at the patient's bedside. It ranges from a functional score of 0 (healthy) to 6 (death). This tool can be used to document the clinical course of the disease and guide therapy decisions.[1,3,4,7,11] This GBS-DS score is elaborated in Table 2.

Diagnosis

Clinical: Diagnosis of GBS is mainly clinical, and hence the prudent need for good history taking and clinical examination. Ancillary investigations, for example, cerebrospinal fluid (CSF) analysis and electrodiagnostic tests, are primarily supportive.[7]

Sensorimotor and motor GBS are considered typical GBS. Key features that are required to diagnose the classical sensorimotor or motor variants of GBS are[1,11]:

- Progressive weakness of legs and arms.
- Absent or decreased tendon reflexes in affected limbs.
- Progressive worsening within 4 weeks.

Considering varied and atypical presentations as discussed above, some clinical variants and

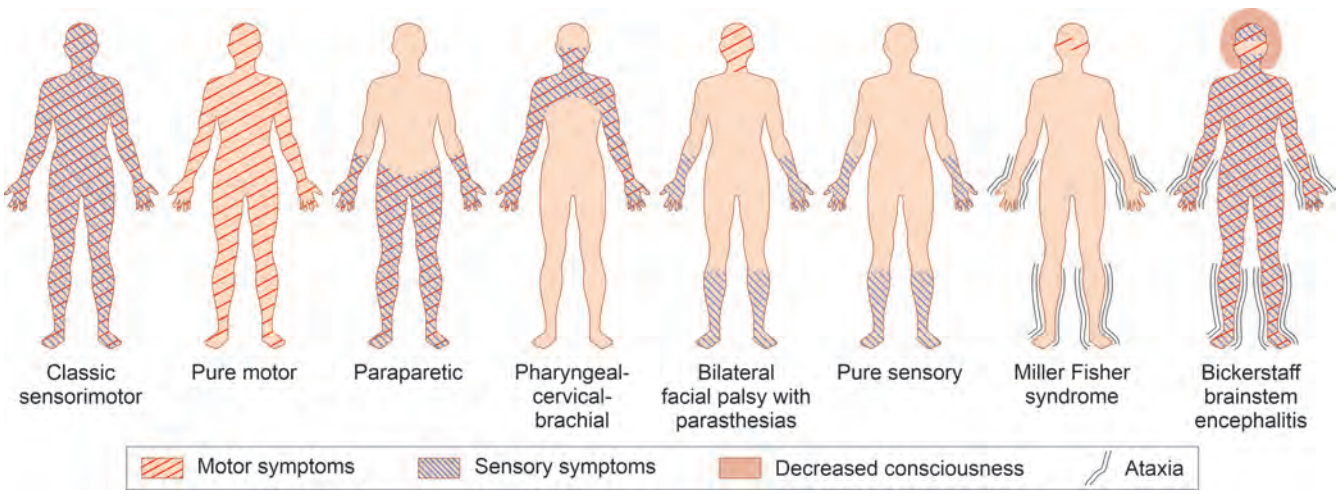

Fig. 1: Clinical variants of GBS; GBS can manifest in a variety of clinical variants. Classic sensorimotor GBS is rapidly progressive symmetrical weakness and sensory signs with absent or reduced tendon reflexes, usually reaching nadir within 2 weeks. Pure motor GBS presents without sensory signs, while pure sensory GBS (rare) patients do not exhibit motor signs. Pharyngeal-cervical and brachial GBS presents with weakness in these muscle groups without lower limb weakness. A subset may also manifest with bilateral facial nerve palsy with paresthesias. Miller Fisher syndrome (MFS) classically manifests as a triad of ophthalmoplegia, ataxia, and areflexia. However, incomplete forms with isolated ataxia (acute ataxic neuropathy) or ophthalmoplegia (acute ophthalmoplegia) can occur. Fifteen percent of MFS patients may have overlaps with classical sensorimotor GBS. Patients with Bickerstaff brainstem encephalitis manifest with ophthalmoplegia, ataxia, areflexia, pyramidal tract signs, and impaired consciousness, often overlapping with sensorimotor GBS (image reproduced from Leonhard et al., 2019)[7]

Table 1: Types and clinical features of different clinical variants of GBS (adapted from Leonard et al.)[7]

Variant (% frequency)	*Clinical features*
Sensorimotor (30–85%)	Rapidly progressive symmetrical weakness and sensory signs, absent or reduced tendon reflexes, usually reaching nadir within 2 weeks
Pure motor (5–70%)	Motor weakness without sensory signs
Paraparetic (5–10%)	Paresis restricted to the legs
Pharyngeal-cervical-brachial (<5%)	Weakness of pharyngeal, cervical and brachial muscles without lower limb weakness
Bilateral facial palsy with paresthesias (<5%)	Bilateral facial weakness, paresthesias and reduced reflexes
Pure sensory (<1%)	Acute or subacute sensory neuropathy without other deficits
Miller Fisher syndrome (5–25%)	Ophthalmoplegia, ataxia and areflexia. Incomplete forms with isolated ataxia (acute ataxic neuropathy) or ophthalmoplegia (acute ophthalmoplegia) can occur. Overlaps with classical sensorimotor GBS in an estimated 15% of patients
Bickerstaff brainstem encephalitis	Ophthalmoplegia, ataxia, areflexia, pyramidal tract signs and impaired consciousness, often overlapping with sensorimotor GBS

Table 2: GBS disability scale (GBS-DS)

Score	*Description*
0	Healthy
1	Minor symptoms but capable of running or manual work
2	Able to walk 10 metres or more without assistance but incapable of running or manual work
3	Able to walk 10 metres or more across an open space but only with help (stick, appliance, or support)
4	Bedridden or chairbound
5	Requiring assisted ventilation (for any part of the day or night)
6	Dead

Table 3: Key features of GBS noted in electrodiagnostic tests[11]

*High sensitivity (but low specificity)**	*High specificity (but low to moderate sensitivity)$*	*In suspected MFS*
• Sensory and/or motor conduction abnormalities consistent with a polyneuropathy • Absent H-reflexes# • Facial nerve direct responses showing either increased distal motor latency or decreased CMAP amplitude • Blink responses either absent or showing prolonged ipsilateral R1 and R2 responses and contralateral R2 response	• Sural sparing pattern, that is, abnormal median or ulnar nerve SNAP with normal sural nerve SNAP after excluding carpal tunnel syndrome • Indirect discharges (often multiple and resembling A-waves and distinct from F-waves) • Distal CMAP duration prolongation >8.5 millisecond (time from onset of first negative deflection to return to baseline of last negative deflection, using a filter bandpass of 2 Hz–10 kHz)	• Sural-sparing pattern • Any sensory and motor conduction abnormalities consistent with polyneuropathy

*In suspected GBS patients examined within the 1st week of onset, these features are supportive of diagnosis but do not exclude GBS mimics; #Presence of H-reflexes makes GBS diagnosis less likely; $Diagnosis is well supported by these features; CMAP, compound muscle action potential; SNAP, sensory nerve action potential

Table 4: Features that support or are inconsistent with diagnosis of sensorimotor or motor GBS (Adapted from van Doorn et al.)[11]

Features that support GBS	*Features inconsistent with GBS*
• Relative symmetry • Relatively mild or absent sensory symptoms and signs • Cranial nerve involvement (especially bilateral facial palsy) • Autonomic dysfunction • Respiratory insufficiency (due to muscle weakness) • Pain (muscular or radicular in back or limb) • Recent history of infection (<6 weeks) Laboratory findings that support diagnosis • CSF: increased protein (however, normal CSF protein levels do not exclude diagnosis); WBC usually <5 × 10^6/L, that is, albumino-cytological dissociation[9] • Blood: anti-GQ1b antibodies usually present in Miller Fisher syndrome (approximately 90% patients)[9] • Electrodiagnosis: NCS consistent with polyneuropathy (note: NCS may be normal during early stage of disease)	• Asymmetric weakness (marked and persistent) • Severe respiratory dysfunction at onset with mild limb weakness • Predominant sensory signs at onset (paresthesias often occur) with mild weakness • Fever at onset • Sensory level or extensor plantar responses • Hyperreflexia (initial hyperreflexia does not exclude GBS) • Bladder or bowel dysfunction (does not exclude GBS) • Abdominal pain or vomiting • Nystagmus • Alteration of consciousness (except in BBE) • Abnormal routine blood tests • CSF: >50 × 10^6/L mononuclear or PMN cells • No further worsening after 24 hours • Continued worsening >4 weeks or ≥3 TRFs (consider A-CIDP)

A-CIDP, acute-onset chronic inflammatory demyelinating polyneuropathy; BBE, Bickerstaff's brainstem encephalitis; CSF, cerebrospinal fluid; NCS, nerve conduction studies; PMN, polymorphonuclear; TRF, treatment-related fluctuations; WBC, white blood cell

Miller Fisher syndrome (MFS) do not satiate the above requirements for GBS.[11,13]

Basic blood tests: Complete blood count, electrolytes, glucose, kidney, and liver function tests may aid in excluding other causes of acute flaccid paralysis or confounding factors. Further specific tests (including imaging studies) may be conducted based on suspected differential diagnosis.[11]

Cerebrospinal fluid analysis: It is especially useful if diagnosis is uncertain.[11] The classic finding in CSF analysis is albumin-cytological dissociation, that is, elevated CSF protein level in the face of normal CSF leukocyte count. However, CSF protein levels may be normal in up to 50% of patients in the 1st week and up to 30% of patients in the 2nd week. Hence, normal CSF protein levels should not be considered a hallmark to exclude GBS. CSF pleiocytosis >50 cells/μL warrants suspicion for infections, inflammatory diseases of the spinal cord, or leptomeningeal malignancy.[7]

Electrodiagnostic tests: They are not required for diagnosis, but if done, may increase diagnostic certainty (especially in atypical presentation).[7,11] They may show features of sensorimotor polyradiculoneuropathy or polyneuropathy. Notably, they might be normal if conducted within 1 week of symptom onset or in patients with initial proximal weakness, slow progression, mild disease, or some clinical variants.[7] In such scenarios, conducting a second electrodiagnostic test later in the disease course may be useful.[11] Hence, within the 1st week, diagnosis by clinical criteria may be more reliable than relying on electrodiagnostic tests.[14] Table 3 summarizes key features noted in electrodiagnostic studies.

Antibodies: Testing for antiganglioside antibodies is not required in most patients with typical sensorimotor GBS. However, GQ1b antibody should be checked if Miller Fisher syndrome is suspected.[11] Antibodies to nodal and paranodal antigens may be tested in patients who relapse, continue to progress, or exhibit poor treatment response.[1]

Neuroimaging: Magnetic resonance imaging (MRI) and ultrasonography (USG) of nerve roots and peripheral nerves is an emerging area of interest.[1] MRI frequently shows nerve root enhancement, a nonspecific finding.[1,11] Whole spine MRI with contrast may assist in excluding differential diagnoses like transverse myelitis, spinal cord tumors, and cord compression.[11] USG of peripheral nerves may reveal enlarged cervical nerve roots in the early phase of the disease, which may aid with early diagnosis. However, it has still not been validated for GBS diagnosis.[7]

Features which either support the diagnosis of sensorimotor or motor GBS or are inconsistent with it are tabulated in Table 4.[11]

Differential diagnosis: Clinicians must also be aware of major differential diagnoses of GBS at the level of the brain, spinal cord, nerve (and nerve roots), neuromuscular junction, and muscle. Key differential diagnosis considerations have been illustrated in Figure 2.[1,7,15]

Red Flag Signs and Monitoring—The Eyes See What the Mind Knows

All patients with GBS in the progressive phase should be monitored for respiratory and autonomic function. One fifth of patients may develop respiratory muscle weakness and subsequent respiratory failure, even without symptoms of dyspnea.[1,7] Bulbar weakness may cause upper airway obstruction, thereby necessitating intubation. Similarly, one fourth of patients may have dysautonomia, which can cause heart rate variability and circulatory collapse.[1] Hence, in all suspected GBS cases (in the progressive phase), it is recommended that the following parameters be monitored frequently[1,11]:

- Single breath count (SBC): SBC <20 indicates need for ICU transfer.[11]
- Forced vital capacity (FVC): Test every 4 hours. If FVC reduction >30% in 24 hours, transfer to ICU. A 50% decline in 24 hours indicates need for mechanical ventilation (MV). Consider elective MV also if FVC <20 mL/kg.[1,11]
- Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP): Can be measured if facilities are feasible. MEP <30 cm H_2O or MIP <40 cm H_2O warrants need for elective MV.[7]
- Heart rate and blood pressure.[1]

Other important clinical risk factors which may predict need for MV include[11]:

- Admission within 7 days of symptom onset.
- Inability to cough.
- GBS-DS grade >4.
- Inability to lift arm above horizontal level.
- Neck flexion weakness.
- Abnormal liver function at admission.

Recently, the modified Erasmus respiratory insufficiency score (mEGRIS) has emerged as a useful, validated tool for predicting respiratory failure in GBS patients within 2 months of symptom onset. The score considers four main parameters, with the risk of requiring MV being higher in patients with bulbar disease, rapid disease progression, and weakness of neck flexion and hip flexion.[11,15,16]

Treatment

The only proven disease-modifying therapies for GBS are intravenous IVIg and plasma exchange (PLEX).[1,3,4,7,11] Both IVIg and PLEX exert benefits by acting against the immune dysregulation in GBS, thereby preventing further neural damage and promoting functional recovery. As a corollary, these agents will be less useful if started during the nadir phase or recovery phase after the immune-mediated damage has already reached its zenith.[15] A recently published Indian study by Salagre and colleagues also showed that early initiation of immunomodulator therapy was associated with a reduced probability of requiring MV.[17] Hence, the concept of "time is nerve" should be rooted in clinical practice with the idea to initiate IVIg or PLEX therapy as early as feasible.[1,15] Clinical trials have demonstrated best results with IVIg if administered within 2 weeks and PLEX done within 4 weeks of weakness onset.[7,18,19] However, many authorities have extrapolated the benefits of IVIg even up to 4 weeks from disease onset.[11,15] Notably, based on current evidence, glucocorticoids offer no therapeutic benefits in GBS.[11,20] Also, there is no role in combining IVIg with PLEX, since evidence has not demonstrated any benefits of doing the same.[11,21]

Whom and how to treat: Decision to initiate treatment depends on clinical severity, time from onset of weakness, and rate of disease progression.[1,11] Patients who are unable to independently walk for 10 metres (GBS-DS ≥3) and are within 4 weeks of weakness onset require treatment with either IVIg or PLEX. Additionally, even patients who are still able to walk independently for >10 m (GBS-DS ≤2) but have either rapidly progressing disease, swallowing problems, or are at high risk of requiring MV should also be treated with either IVIg or PLEX. Additionally, in patients with milder form of GBS who are able to independently walk but unable to run (GBS-DS ≤2), treatment with IVIg or PLEX should be considered if within 2 weeks of weakness onset.[1] Hence, in the vast majority of GBS patients, treatment should be initiated as soon as feasible after

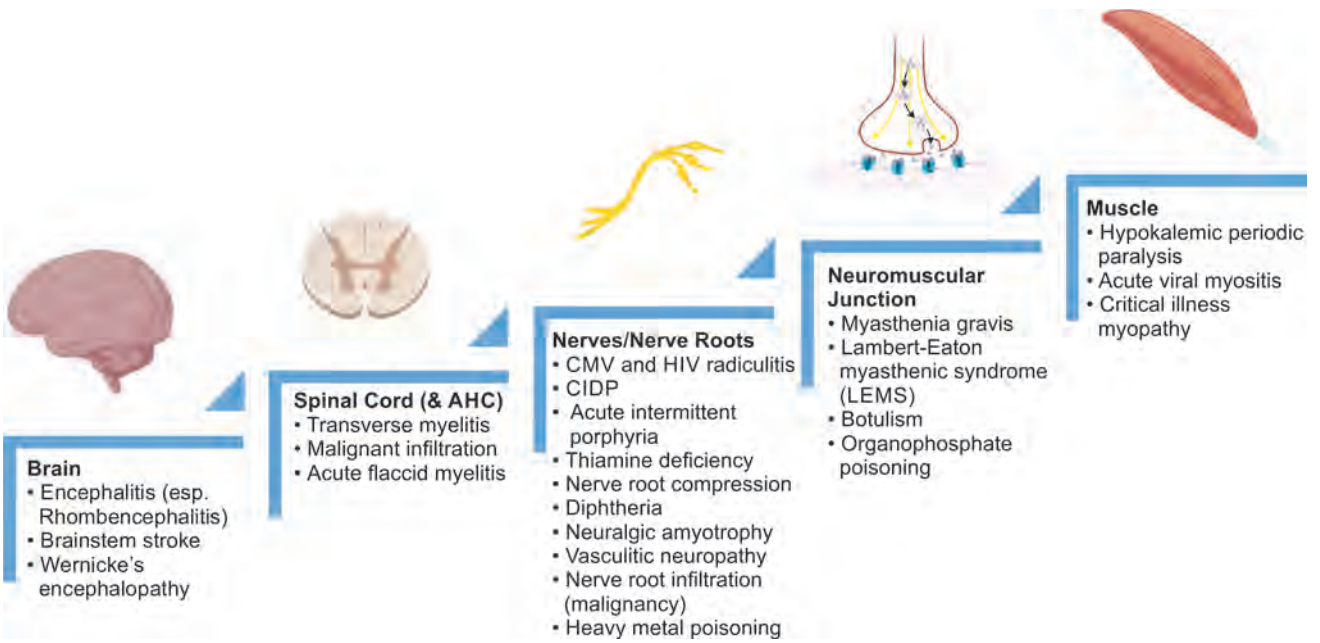

Fig. 2: Differential diagnosis of GBS: AHC, Anterior Horn Cell; CMV, Cytomegalovirus; HIV, Human Immunodeficiency virus; CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; ^Acute Flaccid Myelitis for example as a result of polio, enterovirus D68 or A71, West Nile virus, Japanese encephalitis virus or rabies virus

Table 5: Suggested collective action for/at various levels

Level	*Suggested measures*
For community	• Education on preventive measures • Education on recognizing signs and symptoms in patients
For/at primary care physician	• Upgradation of knowledge • Have "low-threshold" of suspicion for GBS diagnosis
For/at referral medical center	• Clear protocols from admission to discharge • Integrated multidisciplinary approach • Provide/maintain adequate supply of IVIg
At governmental level	• Creation of National GBS Registry • Diarrhea surveillance • Provide "Free of Cost" IVIg for GBS patients nationally • Provide free/economical healthcare for ventilator-dependent patients • Set up rehabilitation clinics for long-term care of GBS patients
At global level	• Data sharing across countries • Call for targeted research and drug development

diagnosis.[22] The dose of IVIg is 0.4 gm/kg/day administered daily for 5 days (i.e., 2 gm/kg administered over 5 days).[7] Similarly, in case of PLEX, 4–5 exchanges (with removal of 12–15 L of plasma) over 1–2 weeks is the standard of treatment for most pati ents.[1,11,15] Potential contraindications to PLEX are hemodynamic instability, while contraindications to IVIg are IgA deficiency and/or previous severe allergic responses.[1]

Supportive care: Supportive care for deep vein thrombosis prophylaxis, nutrition, fluids, chest physiotherapy, frequent turning and skin care (to prevent bedsores), daily range-of-motion exercises (to prevent joint contractures), prevention and treatment of constipation, treatment of neuropathic pain, etc., is vital for patient well-being and recovery.[1,22] Tracheostomy should be considered in patients who have been intubated for >2 weeks.[22]

Potential therapies and future trends: Small-volume plasma exchange (SVPE) involves repeated removal of small volumes of plasma over several days and may potentially serve as a low-cost alternative to PLEX in resource-crunched settings. However, randomized controlled trials will be needed to prove its efficacy and safety.[15] Complement inhibition seems to be an upcoming investigational strategy for GBS.[15] Eculizumab (monoclonal antibody against C5) did not meet the primary endpoint in its phase 2 trial.[23] Further clinical trials may shed light on its utility.[15] ANX005 (monoclonal antibody against C1q) had shown preliminary positive evidence; however, phase 3 trial (NCT04701164) results have yet to be published.[24] Imlifidase, an IgG-degrading enzyme, is also under investigation for management of GBS.[15]

Nearly 85% of GBS patients achieve complete functional recovery in a year (though areflexia and fatigue may persist).[22]

Health for All—A Call for Collective Action

While we have discussed the disease and its management in a nutshell, preventing it should be of prime importance. Community education by governmental and private stakeholders should focus on aspects such as boiling water before consumption, washing vegetables and fruits thoroughly, avoiding raw or undercooked meat, and handwashing with soap and water prior to handling food and after using the toilet. Community education on recognizing signs and symptoms of GBS so that such patients can receive timely medical care is important. Mass media campaigns *via* print and electronic media can help take this message to a large scale. Within the medical fraternity, primary care physicians must be updated or trained to diagnose and refer GBS patients to designated centers for streamlined treatment. Centers treating GBS must have clear protocols in place to streamline care from admission to discharge. Also, a multidisciplinary approach should be implemented to prevent or treat any complications due to GBS. At the governmental level, a registry of GBS cases must be created, and "diarrhea surveillance" can be planned. Live tracking of case counts should be available in the public domain regarding number of suspected cases, confirmed cases, patients requiring ventilatory support, discharged cases, and number of deaths. Quality IVIg should be made available free of cost for GBS patients across the country. For long-term care of patients, subsidized rehabilitation clinics must be set up. Globally, there is a need for transparent data sharing and research on drug development for GBS. Table 5 summarizes these points.

Conclusion

The GBS outbreak in India needs to be tackled prudently at all levels. Being vigilant and taking measures at all levels—be it community, physician, institutional, governmental, or even global—will be a cornerstone for our collective success. Preventive health measures like boiling drinking water, handwashing prior to meals and after using toilets, washing fruits and vegetables, and avoiding raw or undercooked food (especially meat) should be emphasized at the community level. Community education on GBS can also aid by ensuring that patients seek timely medical care for best patient outcomes.

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REVIEW ARTICLE

Melioidosis: An Indian Perspective

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Abstract

Melioidosis is caused by *Burkholderia pseudomallei* and is found in soil and water in tropical and subtropical regions of the world. The bacterium is capable of evading the host's immune system, leading to the development of acute, subacute, or chronic invasive infections or potentially entering a latent state that may persist for an extended period.

The true burden of melioidosis is vastly underestimated. Hot and humid climates with extreme weather conditions and rainy seasons are linked to increased melioidosis cases. Rice fields, building construction workers working on the muddy soil, and barefoot walkers in the endemic areas acquire infection *via* inadvertent inhalation or inoculation. Over 80% of patients diagnosed with melioidosis exhibit associated comorbid conditions predisposing them to infections.

The disease mostly mimics tuberculosis of any organ. The blood or abscess fluid culture continues to serve as the cornerstone of diagnosis. Intravenous therapy for 4 weeks (from 2 to 8 weeks) or until culture conversion is essential for individuals presenting with concurrent bacteremia and bilateral or unilateral multi-lobar pneumonia. The prolonged oral eradication therapy is also essential after intravenous therapy to prevent relapse. The overall mortality is very high due to delays in diagnosis and appropriate treatment, particularly in resource-poor areas.

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Introduction

Melioidosis is an enigmatic tropical infectious disease caused by *Burkholderia pseudomallei*, a Gram-negative environmental saprophytic bacterium of soil and water origin. This disease was first identified by Whitmore and Krishnaswami in 1912 after observing a series of cases of cavitating pneumonia in Burma. In 1950, the first case of melioidosis was documented in Australia; the patient unfortunately succumbed to septicemia in Townsville.[1] Mortality varies depending on the severity and can be up to 90% without early laboratory diagnosis and timely institution of appropriate antimicrobial therapy. The Centers for Disease Control (CDC) has classified the bacterium as a tier-1 select agent because of its virulence, pathogenic potential, and restricted antimicrobial therapy.[2]

Microbiology

B. pseudomallei is a Gram-negative soil-dwelling bacterium, a strict aerobe, oxidase-positive, and motile. *B. pseudomallei* shares similarities with members of the *Pseudomonas* genus and was previously, in 1992, known as *Pseudomonas pseudomallei*.[3,4] Later, it was classified in 1992 under a new genus nomenclature. Recent research using advanced techniques such as whole-genome sequencing and phylogeographic analysis indicates that ancestral strains of the organism originally emerged in Australia and subsequently spread through Asia and underwent further evolution and dissemination across the tropical regions of the world.[5] *B. pseudomallei* is a highly robust environmental organism that can withstand extreme temperatures and resist antiseptics and antibacterial solutions.[1] This intracellular pathogen adopts various strategies to survive within the cells of the host's immune system, promoting bacterial spread and biofilm formation.[3,4]

Epidemiology and Risk Factors

Melioidosis is well-documented in Northern Australia, Coastal India, and Northeastern Thailand.[6] However, there is significant underdiagnosis and underreporting of infections throughout developing countries in tropical and subtropical Southeast Asia, as well as the coastal and subcoastal areas of India, Sri Lanka, and Bangladesh.[4] There has been a significant rise in isolated incidents reported in various regions, including South America, parts of Central America and Africa, the Middle East, the Caribbean, and the Indian Ocean (such as Mauritius).[4] As of 2019, the estimated global burden of the disease was 4.64 million disability-adjusted life-years (DALY), which may be an underestimated value. The region of South Asia contributes maximally and represents 44% of the total global burden.[5,7] In India, there have been numerous case series of melioidosis diagnosed; however, these cases likely represent just a small fraction of the overall prevalence.[8] The limited availability of standardized diagnostic tests and lack of awareness have resulted in clinical and laboratory errors in accurately identifying this condition. The presence of biogeographic and genetic diversity among bacteria in South Asia, alongside variations in the prevalence of certain genetic markers, prompts intriguing inquiries into the epidemiology of *B. pseudomallei*.[9]

Melioidosis occurs in individuals of all age-groups, with a higher occurrence in adults aged between 40 and 60 years.[4] The severity of the disease is influenced by various factors, such as the individual's health status, the route of acquiring infection, the infection load, and specific strain virulence. Previous studies conducted in Australia and Thailand have identified several potential risk factors for melioidosis, including conditions such as diabetes mellitus, excessive alcohol consumption, and chronic kidney and lung disease. Additionally, individuals with higher levels of exposure to soil or mud, with abrasions and inhalation of contaminated soil dust, are also at increased risk.[10,11] People with damaged skin, old abrasions, and increased exposure to soil and water in areas where the disease is prevalent, such as indigenous and construction workers, agricultural workers, and ecotourists,[6] are at higher risk of infection. The risk of developing melioidosis among American soldiers after returning from Vietnam due to the activation of *B. pseudomallei* from latency over the years is widely acknowledged and has been commonly referred to as "The Vietnam time-bomb."[12] Statistical analysis has shown a strong correlation between melioidosis cases and monthly rainfall, with nearly 81% of cases occurring during the rainy season in Australia.[13] The primary modality of transmission is through the skin after barefoot contact with muddy soils or stagnant water.[4]

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It has been observed that this element is commonly found in conjunction with both clay and sandy soils. Research indicates that *B. pseudomallei* thrives in layers of compacted silt sediment with optimal levels of porosity and permeability.[14] It is hypothesized that the bacterium emerges to the surface as the groundwater level increases in the soil, experiencing growth during periods of heavy rainfall.[14,15] Consequently, most cases in regions where the bacterium is prevalent occur during the wet season. The impact of iron levels on *B. pseudomallei* growth is influenced by factors such as bioavailability, oxidation state, and other physicochemical properties.[14] In certain circumstances, such as heavy rainfall or severe storms, transmission can also occur through aerosols or aspiration events (e.g., near drowning), which results in reduced incubation periods and higher virulence, manifesting as severe pneumonia, septic shock, and fatality.[6,11,13] Ingestion of unchlorinated potable water in some endemic areas can also lead to melioidosis.[13,16] Although rare, additional methods of transmission, such as zoonotic transmission, transmission *via* the breast milk of lactating mothers with mastitis, and coitus injury, have been documented. Nosocomial outbreaks are infrequently documented.[11,13]

Pathogenesis

Depending on the mode of entry, the organism initially infiltrates the epithelial cells of the mucosal surface or damaged surface of the skin before spreading to different cell types. Various adhesins facilitate the process of entry. Once attached and taken up by the cells, intracellular invasion and subsequent survival are crucial in developing the disease. Various variable virulence factors, for example, *Burkholderia* intracellular motility factor (Bim), filamentous hemagglutinin B (FhaB), and lipopolysaccharide (LPS) genotypes, enable the bacterium to attach, invade, and replicate in the host cells, with the ability to survive intracellularly as a crucial mechanism for evading the host's defenses.[15] The enzymes that neutralize reactive oxygen species can delay the apoptosis of polymorphonuclear cells and promote bacterial survival.

Upon escaping from the phagosomes and entering the host cell's cytosol, the bacterium triggers actin polymerization and moves throughout the cell, eventually spreading to neighboring cells. The dissemination of the bacteria to various sites from a primary focus of respiratory melioidosis is chiefly driven by capsular polysaccharide (CPS), which hinders opsonization and allows the organism to persist in the bloodstream, increasing its capacity to infect internal organs.

The organism demonstrates resistance to innate immune response elements and can survive within the lysosomes of neutrophils and macrophages. However, interferon-γ can enhance the macrophages' ability to eliminate the organism. These characteristics contribute to the early dissemination of the infection through the bloodstream. Antibodies do not protect this organism, and compromised cell-mediated immunity (such as in individuals with HIV infection) does not seem to increase susceptibility to the infection.[17]

Moreover, there are strong indications that factors such as climate change, extreme weather conditions, and other human-influenced drivers will lead to a rise in melioidosis cases worldwide.[18]

Immunity and Pathology

The involvement of cellular adaptive immunity in response to *B. pseudomallei* has been documented. Individuals who succumbed to melioidosis exhibited reduced *B. pseudomallei*-specific CD4+ IFN-γ T-cell and CD8+ IFN-γ T-cell responses compared to those who survived the infection.[19] In autopsy cases, findings revealed acute (Table 1) necrotizing inflammation characterized by focal or diffuse areas with a mix of neutrophils, macrophages, lymphocytes, and "giant cells."

The diagnosis of fatal melioidosis is characterized by necrotizing and suppurative inflammation, typically lacking multinucleated giant cell formation. Involvement of the gastric and mediastinal areas suggests that ingestion and inhalation may be potential routes of infection. The use of CPS staining has been helpful in aiding the establishment of a histopathological diagnosis.[21] The potential link between melioidosis and the rise in global usage of immunosuppressive drugs, as well as the prevalence of diabetes and chronic kidney disease, underscores the significance of adopting a "One Health" approach. This is particularly crucial considering the susceptibility of animals to melioidosis and its connection to international trade.

Clinical Features

The clinical manifestations of melioidosis closely resemble those of several other diseases: community-acquired pneumonia with multiorgan abscess formation, variable course of multiorgan involvement, and sepsis. This similarity often mimics tuberculosis and other similar conditions like infective endocarditis. Because of this, melioidosis is referred to as the "great mimicker." On average, the incubation period is around 9 days (varies from 1 to 21 days), although symptoms can develop more rapidly (within 24 hours) after inhaling or aspirating the bacteria. In cases of acute melioidosis, sepsis syndrome is frequently observed, with >50% of patients showing signs of bacteremia upon presentation and 20% developing septic shock. A wide range of clinical presentations of melioidosis is observed, which can be attributed to factors such as bacterial inoculating concentration, mode of acquisition, host susceptibility factors, and potentially varying virulence of infecting *B. pseudomallei* strains.[15,22] The most common form of acute infection in adults is pulmonary involvement, accounting for over half of the cases, while pneumonia is less common, occurring in approximately 20% of pediatric cases. It is worth noting that children are more susceptible to skin involvement, with a much higher prevalence compared to adults. Cutaneous melioidosis often manifests as a solitary lesion, indicating the infection's entry point. Additionally, visceral abscesses frequently involve abdominal organs like the spleen, liver, adrenals, and kidneys. It has been observed that up to 20% of males in Australia experience prostatic abscesses.

Encephalomyelitis is an uncommon yet potentially severe complication that is more frequently observed than reported, accounting for over 4% of cases. Numerous small intracerebral abscesses are commonly found in these instances, with the brainstem often affected.

Distant organ involvement usually results from spreading bacteria through the bloodstream. Osteomyelitis and septic arthritis can also occur due to penetrating injuries or the dissemination of bacteria through the bloodstream. Melioidosis may also present with rare clinical manifestations such as mycotic aneurysms, pericarditis, mediastinal masses, and scrotal abscesses. Some of the different systemic involvement is shown in Figure 1.

Most patients typically experience acute melioidosis after recently being infected, but approximately 11% of cases present with chronic melioidosis, lasting for a period longer than 2 months. Constitutional symptoms often accompany this form of the disease and frequently appear as infiltrates in the upper lobe. A small percentage, about 4% of cases, may experience reactivation of the latent disease in the lungs, sometimes even several decades after the initial infection. Furthermore, relapse or recrudescence of the primary infection is possible.

Table 1: Spectrum of clinical features of melioidosis depending of the organ involvement (including acute infection, chronic infection, and reactivation of dormant cases)

Spectrum of clinical features of melioidosis	
Asymptomatic seroconversion	Seroconversion, variously defined based on indirect hemagglutination titer ≥1:20 is stated to be the most common event following environmental exposure in endemic areas[1]
Acute melioidosis (approximately 85% of total cases)	Variable and short incubation period, ranging from 1 to 21 days. Symptoms appear early in cases of inhalation or aspiration.[1,13‡] Common during the rainy season and after extreme weather events
	Defined by the duration of symptom <2 months.[1] Up to half of the cases develop acute bacteremic melioidosis and about 20% progress to septic shock[6]
Pulmonary infection	Mostly seen in adults; less in pediatric ages (<20%)[6,10]
	Diverse radiologic presentations: consolidation with multilobar pneumonic infiltrates, cavitation with extensive pleuro-parenchymal involvement.[10] Rapidly progressing dypnea, fever, and cough
Cutaneous infection	More commonly seen in the pediatric age-group
	Typically, single lesions may be seen at the site of inoculation[1]
Dissemination of infection	Nonpulmonary parenchymal visceral abscesses are frequently observed in organs such as the spleen, liver, and kidney[6]
	Splenic, hepatic, renal, and prostatic abscess are common (18%[1]; Fig. 1)[§] Parotid infection is rare but common in new geographical areas[□]
Central nervous system involvement and infection	Intracerebral abscesses (usually multiple and small) as a result of hematogenous spread[1,3]
	Trigeminal nucleus involvement and extension along the corticospinal tract. Encephalomyelitis[#]: typically, symptoms related to the brainstem[8]
Bone and joint infection	Approximately 4% of cases show bone and joint involvement, whether through direct extension or hematogenous spread[6]
Other (rare)	IgG4 disease, mediastinal masses, pericardial infection, thyroid, and scrotal abscesses.[1,5] In prolonged cases, simultaneous multiorgan involvement
Chronic melioidosis (11%)	If symptoms continue over the duration >2 months
	Slow disease progression, the outcome is often better than acute-onsetmelioidosis[6]
Pulmonary infection	Fever and cough often manifest as aggressive pneumonia and hemoptysis or mimic tuberculosis[6,10]
	Upper lobe patchy consolidation and infiltrates are not like tuberculosis, but other lobes are commonly involved, as seen in chest radiography.[6,10] Mediastinal lymphadenopathy is also associated with lung involvement
Cutaneous infection	Chronic nonhealing skin wound, frequently unresponsive to repeated rounds of antibiotic treatment[5]
Reactivation of dormant cases (4%)	Typically present as a fresh case of pulmonary infection and may not progress rapidly toward septicemia[6]
	The latent period may range up to 24 years, potentially extending up to 62 years in a case from Australia[1,5,6]
Modifiable risk factors	Concurrent infections: viral infections like HIV, influenza, and other infections like scrub typhus, bacterial sepsis[1]
	Known risk factors for disease include immunosuppression and diabetes mellitus. Prolonged glucocorticoid use, heavy alcohol consumption, barefoot exposure to soil (rainy season), sickle cell anemia/hemoglobinopathies, chronic heart diseases, chronic renal disease and/or renal or ureteric stone, parenchymal lung disease, chronic granulomatous disease, pulmonary hemosiderosis, and systemic lupus erythematous (SLE) disease[1]

Besides conventional risk factors, the risk of infection in the hospital setting may include medical conditions such as malignancy, iron overload, and tuberculosis.[10,20] [‡]Incubation periods of 1 day have been occasionally reported[1,3,4]; [§]prostatic abscess is reported mostly in Australia but uncommonly reported in Thailand[1,3,4]; [□]suppurative parotitis is reported in 40% of cases in the pediatric age-group in Thailand and Cambodia[1]; [#]encephalomyelitis encompasses a wide range of clinical manifestations but mostly presents as inflammation of the brainstem. Key clinical characteristics include cranial nerve dysfunction (particularly nerves VI and VII), unilateral weakness in the limbs caused by upper motor neuron impairment, signs of cerebellar dysfunction, and bulbar palsy or weakness in the lower limbs.[1] Encephalomyelitis is more and more reported in India[1]

Diagnosis

Melioidosis presents a diagnostic challenge as it cannot be distinguished solely based on clinical or radiological characteristics from other common community-acquired infections. Melioidosis is often misdiagnosed due to its diverse and nonspecific clinical symptoms, lack of knowledge about the disease, and the incorrect identification of *B. pseudomallei*, especially in less experienced setups of microbiology. Acute infections are frequently mistaken for rapidly progressive community-acquired pneumonia with cavitation, septic shock, or disseminated disease. On the contrary, chronic lung infections often present similarly to pulmonary tuberculosis. Diagnostic and clinical clues for suspecting acute melioidosis (Table 2).

The culture of *B. pseudomallei* from clinical specimens is essential for diagnosis. It grows slowly on standard blood culture media and MacConkey agar. Ordinarily, the identification of bacteria using conventional biochemical identification processes is also unreliable. This often leads to misidentification as *Pseudomonas* or other species of *Burkholderia*, especially outside endemic areas. To improve isolation, nonsterile specimens should be inoculated onto selective media such as Ashdown's agar, which helps detect colonies. In some cases, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) systems with extended database libraries can identify

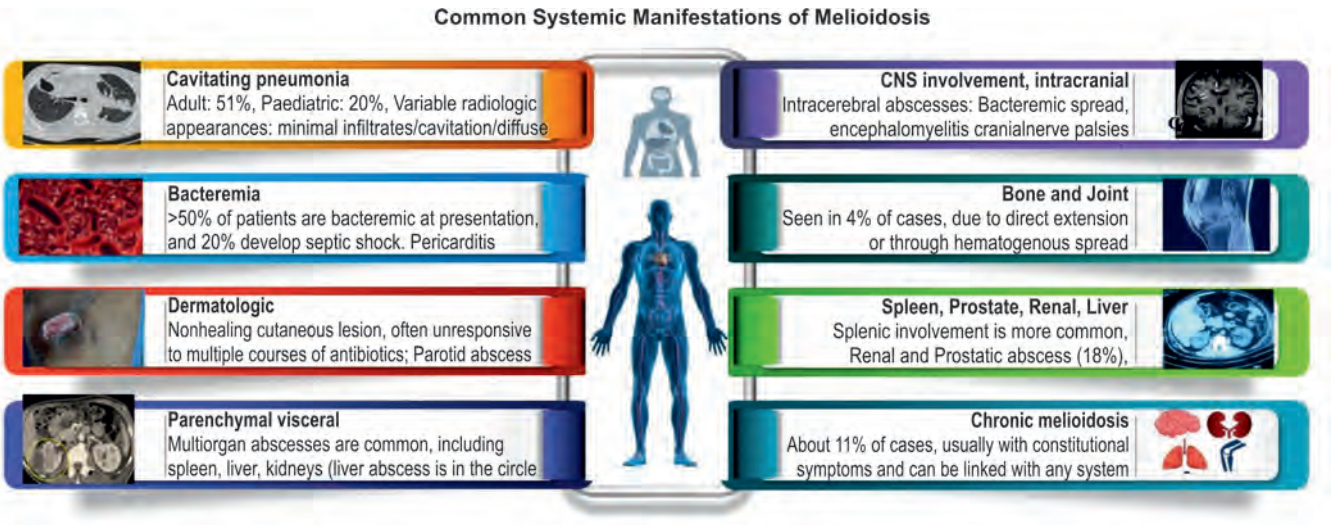

Fig. 1: Common clinical and radiological manifestation involving different organs, including acute and chronic melioidosis

Table 2: Diagnostic and clinical clues for suspecting acute melioidosis

When to suspect acute melioidosis
• Potential exposure to dust during extreme weather conditions, soil, mud, or water while walking barefoot in a contaminated endemic area
• A patient with immunocompromised or uncontrolled diabetes mellitus
• A patient presenting with a persistent high-grade fever of unknown origin or diagnosed as gram-negative bacteria but resistant to aminoglycoside, polymyxin B, or colistin
• Progressive pneumonia showing rapid deterioration on chest radiograph, exhibiting resistance to standard antibiotic treatment protocols
• Presence of multiple abscesses and multisystemic/visceral involvement, such as in the liver and/or spleen

B. *pseudomallei* when available quickly. When appropriate spectra are incorporated, MALDI-TOF MS demonstrates an ultimate level of sensitivity and specificity, approaching 100% accuracy.[23]

Serologic assays are adjuncts to a symptomatic patient's diagnosis and are usually used to determine seroprevalence in an area. Serology studies indicate that most infections are asymptomatic, and the percentage of persons exposed to and developing latent infections remains uncertain. Frequent exposure to *Burkholderia* leads to measurable levels of specific antibodies in the bloodstream, yet these antibodies may not provide protection.[24,25] Indirect hemagglutination assay (IHA) presents challenges in accurately diagnosing acute melioidosis within endemic regions because of mass seropositivity, has limited practical utility in a clinical setting due to prevalent background antibody positivity in the areas affected by the disease, and the occurrence of false negative results during its early stages. A lateral flow immunoassay displays potential in Thailand; however, its availability is currently lacking in India.

Management

Prompt and proactive intervention can greatly increase survival rates. The management of acute melioidosis typically involves urgent evaluation, resuscitation, and transfer to a hospital for inpatient care. However, primary care physicians also play a crucial role, especially in rural areas, in assessing patients at the early stages, recognizing the disease, and stabilizing the patient. There is a need to collect samples like blood cultures and start treatment with antibiotics promptly, followed by appropriate transfer. In some cases, localized infections can be managed in the community. The recommended antimicrobial treatment for melioidosis is outlined in (Table 3). After observing a reasonable clinical response with a recommended duration of treatment and culture negativity, parenteral antimicrobial therapy may be considered on a daycare basis, even during the intensive phase of treatment, requiring oversight from a primary care physician. Once the intensive therapy is completed, it is important to manage the antibiotic treatment to ensure adherence, minimize the risk of side effects, and identify any early signs of treatment failure.

Newer Drugs

Cefiderocol has demonstrated significant potency *in vitro* against primary clinical isolates of *B. pseudomallei*. This compound holds promise for the potential treatment of melioidosis in regions where the disease is endemic and warrants clinical trials for the drug.[27] Levonadifloxacin, a novel benzoquinolizine-fluoroquinolone, has demonstrated a promising bactericidal effect in *in vitro* time-kill assays and is awaiting clinical trial.[28] Different organ involvement requires longer treatment (Table 4) and organ-specific recommended duration of treatment of antibiotics as intensive phase and eradication phase.

Guidelines for Therapy

2020 revised Darwin melioidosis guideline (Tables 3 and 4).[26]

Prognosis

The mortality rate for acute melioidosis ranges up to 90%, although it mainly varies from 20 to 50% in different settings globally. In limited-resource settings with a lack of proper diagnostic and intensive care unit facilities, the mortality rate is very high. Good clinical clues, early diagnosis, appropriate use of antibiotics, and comorbidities all contribute to the outcome of the disease. Management of the comorbidities is crucial in addition to appropriate antimicrobial management, primarily in adults rather than children. The data from Thailand indicates that there are several independent risk factors associated with death and treatment failure in melioidosis. These include bacteremia, respiratory failure, renal

Table 3: Antibiotic management of melioidosis including intensive phase therapy, antimicrobial treatment option, length of treatment, adjunctive treatment, eradication therapy, management of relapse, and recrudescence

Management of melioidosis	
Intensive phase therapy	Intensive therapy is aimed and must be started as early as possible to stop organ damage and abolish high bacterial loads and septicaemia[9,11]
Antimicrobial treatment option	Ceftazidime: intravenous 50 mg/kg to 2 gm, 6-hourly. Continuous IV infusion 6 gm/day may be given[9,11,†]
	Meropenem: IV 25 mg/kg to 1 gm, 8 hourly, IV 50 mg/kg up to 2 gm, 8 hourly for CNS melioidosis[9,11]
Length of treatment	Intravenous treatment at least for 2 weeks for isolated pulmonary cases/cutaneous disease/bacteraemia without identifiable focus[9,11]
	Intravenous treatment for 4–8 weeks in cases of septicemic pneumonia/septicemia/clinical deterioration/ complicated pneumonia. 8 weeks IV therapy for deep-seated abscess, bone or joint infection, CNS disease[9,11]
Adjunctive treatment	Surgical drainage for deep abscesses, which are less responsive to antibiotics[11]
Eradication therapy	Oral therapy at least 3–6 months to be started just after IV therapy to avert relapse, evaluated as per initial clinical response[11]
	Oral TMP-SMX 320/1600 mg bid, monotherapy[9,11]
	Doxycycline may be used of TMP-SMX intolerance or, hematological issues, other adverse drug reaction[9]
	Amoxicillin/clavulanic acid is reserved as the third line, given an association with treatment failure and relapse[11]
Relapse and recrudescence	Recrudescence: defined as "the development of clinical illness during the oral eradication phase with a concurrent new culture of *B. pseudomallei* in a clinical specimen"[26] Recurrence is defined as "the development of clinical illness after the oral eradication phase, with a new culture of *B. pseudomallei* in a clinical specimen." Recurrence can be either a relapse with a previous genotype or a new *B. pseudomallei* with a different genotype.[26] It can be due to inadequate dose/duration of antibiotics, noncompliance/ nonadherence, or persistent infection
Management of relapse	Evaluation of the cause of relapse[11] Repeat the antimicrobial susceptibility testing carefully[11] Restarting the antibiotic as per susceptibility and reintroducing the intensive phase of the recommended treatment[11]

Table 4: Different organ involvement and organ specific recommended duration of treatment of antibiotics as intensive phase and eradication phase

Antibiotic duration determining focus	*Minimum intensive duration weeks*[a]	*Eradication phase duration months*[f]
Skin abscess	2	3
Bacteremia with no focus	2	3
Unilateral unilobar pneumonia without lymphadenopathy[b], ICU admission, and with negative blood cultures	2	3
Multilobar unilateral or bilateral pneumonia without lymphadenopathy[b], ICU admission, and with negative blood cultures OR Unilateral unilobar pneumonia without lymphadenopathy[b], ICU admission, but with positive blood cultures	3	3
Pneumonia with either lymphadenopathy[b] or ICU admission OR Multilobar unilateral or bilateral pneumonia with positive blood cultures	4[d]	4
Deep-seated collection[c]	4	3
Central nervous system infection	8	6
Arterial infection[e]	8[d]	6[g]

[a]Clinical judgment to guide prolongation of intensive phase if the improvement is slow or if blood cultures remain positive at 7 days; [b]defined as enlargement of any hilar or mediastinal lymph node to >10 mm diameter; [c]defined as abscess anywhere other than skin, lungs, bone, CNS, or vasculature. Septic arthritis is considered a deep-seated collection; [d]intensive phase duration is timed from the date of the most recent drainage or resection where culture of the drainage specimen or resected material grew *B. pseudomallei* or where no specimen was sent for culture; the clock is not reset if the specimen is culture-negative; [e]most commonly presenting as mycotic aneurysm; [f]if concurrent oral therapy is not indicated in the intensive phase, oral eradication therapy to commence at the start of the final week of planned intensive intravenous therapy, with the timing of eradication duration commencing from the day after the last intravenous therapy; [g]life-long suppressive antibiotic therapy may be required following vascular prosthetic surgery; (reproduced with permission under Creative Commons Attribution license (CC BY), from PLOS Neglected Tropical Diseases, https://doi.org/10.1371/journal.pntd.0008659)[26]

failure, and being over the age of 50. Similar findings have been observed in Australian data. The challenges of recognizing and diagnosing melioidosis in India and South Asia are meticulously discussed and highlight the obstacles faced in clinical identification and laboratory testing. The complexities of addressing these challenges and establishing successful prevention programs are also emphasized.[29]

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REVIEW ARTICLE

Montelukast: A Scientific and Legal Review

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Abstract

Montelukast, a potent and selective cysteinyl leukotriene receptor 1 (CysLT1) antagonist, has played a transformative role in the management of asthma and allergic rhinitis. By attenuating leukotriene-driven inflammation, bronchoconstriction, and airway hyperresponsiveness, it has offered clinicians a reliable once-daily oral therapy that enhances patient adherence and symptom control. However, its clinical trajectory has become increasingly complex considering growing concerns over neuropsychiatric adverse effects, including anxiety, depression, sleep disturbances, and suicidal ideation, particularly in children and adolescents. These associations have prompted significant regulatory responses, including boxed warnings, updated prescribing information, and calls for heightened clinical vigilance. As a result, there is a renewed emphasis on thorough patient counseling, informed consent, and close monitoring of mental health symptoms during treatment. From a scientific standpoint, the precise mechanisms underlying montelukast's central nervous system (CNS) effects remain under investigation, with current research pointing toward its influence on neuroinflammatory pathways and neurotransmitter modulation. Navigating the dual narrative of montelukast—as both a highly effective respiratory therapy and a potential contributor to serious neuropsychiatric outcomes—requires a cautious, evidence-based, and patient-centered approach that integrates clinical efficacy with ethical responsibility.

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Introduction

Montelukast, an esteemed member of the pharmacological armamentarium for asthma and allergic rhinitis, has emerged as a pivotal therapeutic agent since its introduction in the late 1990s. As a selective antagonist of the cysteinyl leukotriene receptor 1 (CysLT1), montelukast intervenes in the intricate cascade of inflammatory processes that characterize these respiratory ailments. By modulating the activity of leukotrienes—potent mediators of bronchoconstriction, mucus secretion, and vascular permeability—montelukast affords clinicians an innovative approach to ameliorating airway hyperreactivity and enhancing the quality of life for patients beset by chronic respiratory disorders.

The Pharmacological Paradigm Shift

Historically, the management of asthma predominantly relied upon bronchodilators and corticosteroids, agents that primarily target the symptoms rather than the underlying inflammatory etiology of the disease. The advent of montelukast represented a paradigm shift in this therapeutic landscape, emphasizing a more holistic approach to asthma management by directly addressing the inflammatory milieu. Its efficacy in both pediatric and adult populations has been substantiated through numerous clinical trials, culminating in its endorsement by various global health authorities, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[1]

Clinical Applications and Versatility

Montelukast's therapeutic applications extend beyond asthma management to include seasonal and perennial allergic rhinitis and exercise-induced bronchoconstriction, thereby cementing its status as a versatile agent in the realm of respiratory medicine. The drug's ability to alleviate the multifaceted symptoms associated with allergic rhinitis—such as nasal congestion, sneezing, and ocular irritation—further underscores its clinical utility.[1] Notably, the pharmacokinetics of montelukast facilitate once-daily dosing, enhancing patient adherence and promoting a seamless integration into daily therapeutic regimens.

The Emergence of Neuropsychiatric Concerns

Despite its therapeutic benefits, the safety profile of montelukast has come under increasing scrutiny, particularly regarding its association with neuropsychiatric side effects. Reports documenting alterations in mood, behavior, and cognitive function have proliferated, leading to heightened vigilance among healthcare providers.[2] The potential for adverse neuropsychiatric outcomes, including depression, anxiety, and suicidal ideation, has prompted regulatory agencies to issue safety communications and revise product labeling to reflect these risks.[3] Such developments necessitate a nuanced understanding of montelukast's risk–benefit profile, particularly in vulnerable populations, including children and adolescents, who may be at heightened risk for these adverse effects.

History of Montelukast

Inception and Development

Montelukast was developed by Merck & Co., Inc., as part of an extensive effort to explore the therapeutic potential of leukotriene receptor antagonists in the late 20th century. The impetus for this exploration emerged from the recognition of leukotrienes—potent inflammatory mediators derived from arachidonic acid—as critical players in the pathophysiology of asthma and allergic rhinitis. The initial identification of leukotrienes in the 1970s and 1980s highlighted their roles in bronchoconstriction, airway inflammation, and increased mucus production.[4]

The discovery of leukotrienes laid the groundwork for the development of montelukast, which was conceived as a targeted intervention to block the action of these mediators at the CysLT1. In the early 1990s, Merck conducted extensive preclinical studies that demonstrated the efficacy of montelukast in mitigating bronchoconstriction and inflammatory responses in animal models of asthma.[5]

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Clinical Trials and Approval

Montelukast underwent rigorous clinical evaluation in the 1990s, culminating in a series of Phase II and Phase III trials that assessed its safety and efficacy in both adult and pediatric populations. A pivotal study published in 1999 in the *New England Journal of Medicine* demonstrated that montelukast significantly reduced asthma symptoms and the need for rescue medication compared to placebo.[6] This trial was instrumental in establishing montelukast's role as a foundational therapy for asthma management.

In 1998, the US FDA granted approval for montelukast as a once-daily oral treatment for asthma in patients aged 6 years and older.[7] The approval marked a significant milestone in the pharmacotherapy of asthma, as montelukast offered a novel mechanism of action that diverged from traditional therapies such as bronchodilators and corticosteroids.

Expanded Indications

Following its initial approval for asthma, montelukast quickly garnered attention for its efficacy in treating allergic rhinitis and exercise-induced bronchoconstriction. In 2000, the FDA expanded its indications to include the management of seasonal and perennial allergic rhinitis, further solidifying its position as a versatile therapeutic agent.[8] This versatility was reinforced by subsequent studies that showcased montelukast's effectiveness in alleviating nasal symptoms and improving overall quality of life for patients with allergic rhinitis.[8]

Neuropsychiatric Concerns and Regulatory Actions

Despite its widespread use and favorable safety profile, montelukast's history took a concerning turn in the 2000s as reports of neuropsychiatric side effects began to surface. In 2009, the FDA mandated a label revision for montelukast to include warnings about potential adverse neuropsychiatric effects, including mood changes, anxiety, and suicidal thoughts.[3] This regulatory action was prompted by an increasing number of case reports documenting these adverse effects, particularly among pediatric patients.

The emergence of these safety concerns led to further scrutiny and investigations by regulatory agencies worldwide. In 2010, the EMA conducted a review of montelukast's safety profile and similarly recommended the inclusion of warnings related to neuropsychiatric events.[3] The ongoing discourse surrounding these safety concerns has catalyzed a reevaluation of montelukast's risk–benefit profile, particularly in populations at risk for mental health issues.

Mechanism of Action of Montelukast

Montelukast operates through a highly specific and targeted mechanism, acting as a selective antagonist of the CysLT1. This receptor is integral to the inflammatory pathways implicated in asthma and allergic rhinitis, making its blockade a strategic therapeutic target. Below, the mechanism is dissected into several critical components, elucidating the biochemical and physiological effects of montelukast.

Leukotriene Pathway Overview

The leukotriene biosynthesis pathway initiates with the enzymatic release of arachidonic acid from membrane phospholipids by phospholipase A2. This arachidonic acid is subsequently metabolized by lipoxygenase enzymes, predominantly lipoxygenase-5 (5-LOX), leading to the formation of various leukotrienes, notably leukotriene C_4 (LTC_4), D_4 (LTD_4), and E_4 (LTE_4).[9] These cysteinyl leukotrienes (CysLTs) are potent mediators of inflammation, contributing to bronchoconstriction, increased vascular permeability, mucus secretion, and recruitment of inflammatory cells to the airway tissues.

Cysteinyl Leukotriene Receptor 1

The CysLT1 receptor is a G-protein-coupled receptor (GPCR) found in various tissues, including airway smooth muscle cells, endothelial cells, and inflammatory cells.[10] Upon activation by cysteinyl leukotrienes, CysLT1 triggers a cascade of intracellular signaling pathways. Notably, its activation leads to the mobilization of intracellular calcium stores and the activation of phospholipase C (PLC), resulting in the formation of inositol trisphosphate (IP_3) and diacylglycerol (DAG). This signaling ultimately promotes bronchoconstriction and exacerbates the inflammatory response, contributing to the pathophysiology of asthma and allergic reactions.

Mechanism of Montelukast

Montelukast selectively binds to the CysLT1 receptor, inhibiting the binding of leukotrienes such as LTD_4. This blockade prevents the downstream signaling effects typically induced by leukotriene receptor activation. The resultant pharmacological effects can be summarized as follows:

- Bronchodilation: By inhibiting the action of LTD_4, montelukast alleviates bronchoconstriction, promoting bronchodilation and improving airflow in patients with asthma. This action is particularly relevant during acute exacerbations when leukotriene levels are elevated.
- Reduction of inflammation: Montelukast diminishes the recruitment and activation of eosinophils and other inflammatory cells within the airways. By attenuating the leukotriene-mediated inflammatory cascade, montelukast contributes to a decrease in airway inflammation, which is a hallmark of asthma pathology.
- Mucus secretion modulation: Montelukast's antagonism of CysLT1 reduces mucus hypersecretion, a common symptom in asthmatic patients. This effect aids in improving respiratory function and alleviating symptoms such as wheezing and shortness of breath.[11]
- Vascular permeability: By preventing CysLT1 receptor activation, montelukast also mitigates increased vascular permeability associated with asthma exacerbations, thereby decreasing edema and mucosal swelling in the airways

Clinical Implications

The clinical ramifications of montelukast's mechanism are profound. Its ability to target a key pathway in asthma pathophysiology enables it to serve not only as an adjunctive therapy in patients inadequately controlled by inhaled corticosteroids but also as a monotherapy for certain patients with mild to moderate asthma. Additionally, its efficacy in managing exercise-induced bronchoconstriction highlights its utility in a broad spectrum of allergic conditions.

Pharmacokinetics and Dosing

Montelukast demonstrates favorable pharmacokinetic properties, with a bioavailability of approximately 64% and peak plasma concentrations occurring about 3–4 hours postadministration. The drug's long half-life allows for once-daily dosing, enhancing patient adherence to treatment regimens. It is primarily metabolized by cytochrome P450 enzymes (CYP3A4, CYP2C9), with renal excretion being the principal route of elimination.

Neuropsychiatric Mechanism of Action of Montelukast

Montelukast, as a CysLT1 antagonist, primarily targets the inflammatory

pathways associated with asthma and allergic rhinitis. However, an emerging body of evidence has linked montelukast to various neuropsychiatric side effects, raising concerns about its safety profile, especially in vulnerable populations such as children and those with preexisting mental health conditions. Understanding the neuropsychiatric mechanisms associated with montelukast involves examining its pharmacodynamics, receptor interactions, and resultant biochemical pathways.

Interaction with Central Nervous System Receptors

Montelukast's primary action is on peripheral CysLT1 receptors; however, its ability to cross the blood–brain barrier (BBB) suggests potential central nervous system (CNS) effects. The extent of this penetration allows montelukast to interact with CysLT1 receptors in the brain, particularly in regions involved in mood regulation and cognitive function.[12] The modulation of these receptors can lead to alterations in neurotransmitter systems and neuronal excitability.

Influence on Neurotransmitter Systems

Neurotransmitters, such as serotonin (5-HT), dopamine (DA), and norepinephrine (NE), are critical to mood and behavior regulation. Recent studies suggest that leukotrienes may influence the metabolism of these neurotransmitters, potentially exacerbating mood disorders when their actions are inhibited by montelukast. Specifically:

- Serotonin: Research indicates that leukotriene receptors can modulate serotonin levels. Inhibition of leukotrienes by montelukast might disrupt the serotonergic pathways, leading to mood alterations, anxiety, or depressive symptoms.[13]
- Dopamine and norepinephrine: Similarly, alterations in dopamine and norepinephrine signaling pathways may result from montelukast's effects on leukotriene metabolism, potentially contributing to symptoms such as restlessness, agitation, or psychosis.[13]

Activation of Inflammatory Pathways in the Central Nervous System

Leukotrienes are not only peripheral mediators of inflammation but are also implicated in neuroinflammatory processes. Inflammatory cytokines, which can be modulated by leukotriene signaling, have been associated with various neuropsychiatric disorders, including depression and anxiety. The blockade of leukotriene receptors by montelukast may inadvertently lead to dysregulation of inflammatory pathways in the CNS.[14,15] For instance, the balance between pro-inflammatory and anti-inflammatory cytokines could shift, contributing to neuroinflammation and resultant neuropsychiatric symptoms.

Neurochemical Studies

Emerging neurochemical studies are examining the effects of montelukast on brain-derived neurotrophic factor (BDNF) and other neuroprotective molecules. BDNF plays a crucial role in neuronal survival, synaptic plasticity, and mood regulation. Alterations in BDNF levels due to montelukast administration could contribute to mood dysregulation and cognitive impairments.[16] Understanding these interactions is vital for elucidating the full spectrum of montelukast's neuropsychiatric effects.

Uses of Montelukast

Montelukast is a widely utilized leukotriene receptor antagonist with a primary focus on the management of asthma and allergic conditions. Its therapeutic applications extend beyond these approved indications, encompassing various off-label uses. Below, the uses of montelukast are delineated in detail.

Approved Indications

Asthma Management

Montelukast is primarily indicated for the prophylaxis and chronic treatment of asthma in adults and children aged 12 months and older. It plays a pivotal role in managing persistent asthma by[17,18]:

- Reducing symptoms: Montelukast has been shown to decrease daytime and nighttime asthma symptoms, improving overall quality of life.
- Improving lung function: Regular administration of montelukast can enhance lung function as measured by forced expiratory volume (FEV_1).
- Decreasing exacerbations: It reduces the frequency of asthma exacerbations, which are often precipitated by exercise, allergens, or respiratory infections.

Allergic Rhinitis

Montelukast is approved for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients aged 2 years and older. Its utility in allergic rhinitis includes:

- Symptom relief: Montelukast alleviates nasal congestion, sneezing, itching, and runny nose, providing effective control of allergic symptoms.[19]
- Improvement of quality of life: By managing allergy symptoms, montelukast enhances patients' daily functioning and overall quality of life (Table 1).

Exercise-induced Bronchoconstriction

Montelukast is indicated for the prevention of exercise-induced bronchoconstriction in patients aged 6 years and older. It is particularly beneficial for:

- Preventing bronchospasm: Administering montelukast at least 2 hours before exercise can significantly reduce the incidence of exercise-induced asthma symptoms, allowing for improved exercise tolerance.[20,21]

Various Society-based Guidelines on Use of Montelukast for Asthma and Allergic Rhinitis[22–28]

Off-Label Uses

In addition to its approved indications, montelukast has been employed off-label for various conditions, supported by anecdotal evidence and clinical observations.

Chronic Urticaria

Montelukast has been used in the management of chronic urticaria, particularly when standard antihistamines fail to provide adequate relief. Its anti-inflammatory properties may contribute to reducing the severity and frequency of urticarial flares.[29]

Aspirin-exacerbated Respiratory Disease

Montelukast has been explored as a therapeutic option for patients with AERD, characterized by asthma, nasal polyps, and hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). It may help in mitigating symptoms and improving respiratory function in this patient population.[30]

Sleep Disorders

Some studies have investigated the potential benefits of montelukast in patients with sleep disorders, including obstructive sleep apnea (OSA) and insomnia. While the data is limited, its anti-inflammatory effects may positively impact upper airway patency and overall sleep quality.[31]

Autism Spectrum Disorder

There is emerging interest in the use of montelukast in managing behavioral symptoms in children with ASD, particularly in addressing irritability and mood dysregulation. Animal studies have shown potential.[32]

Cystic Fibrosis

Montelukast has been studied for its potential benefits in patients with cystic fibrosis, particularly in managing pulmonary inflammation and enhancing lung function. Although the evidence is preliminary, it suggests a role in adjunctive therapy for this complex condition.[33]

Additional Considerations

Dosing and Administration

Montelukast is available in various formulations, including chewable tablets, oral granules, and film-coated tablets, allowing for flexible dosing based on patient age and preference. The typical dosage is as follows:

- Asthma and EIB: 10 mg once daily for adults and children aged 15 years and older; 5 mg for children aged 6–14 years; 4 mg for children aged 2–5 years; and 4 mg once daily for children aged 6 months to 2 years.
- Allergic rhinitis: Same dosing as asthma, with administration generally recommended in the evening.

Safety Profile

Montelukast is generally well tolerated, but it is essential for clinicians to monitor patients for potential neuropsychiatric side effects, particularly in children and adolescents. Commonly reported side effects include gastrointestinal disturbances, headache, and, as previously discussed, mood changes.

Case Reports of Neuropsychiatric Side Effects Associated with Montelukast

Montelukast, while widely prescribed for asthma and allergic conditions, has been linked to various neuropsychiatric side effects, prompting clinical concern. Here, we present several key case reports that illustrate the spectrum of these adverse effects (Table 2).[34]

Legal Issues and Ongoing Controversy Surrounding Montelukast

Below, we outline the key legal issues, provide a timeline of events, and quote pertinent court rulings.

Table 1: Neuropsychiatric mechanisms of montelukast—overview of its impact on CNS receptors, neurotransmitter systems, and inflammatory pathways

Guideline	*Allergic rhinitis*	*Montelukast use in asthma*	*Special considerations*
GINA 2024	Recommended as an adjunct for allergic rhinitis associated with asthma	Adjunct to ICS in mild persistent asthma and aspirin-sensitive asthma	Not first-line therapy; preferred in patients with concurrent allergic rhinitis
Indian 2015 Guidelines	Montelukast effective as an add-on therapy for allergic rhinitis, particularly in patients who fail to respond to antihistamines	Recommended for long-term control in mild-to-moderate persistent asthma, as an alternative to ICS or as an add-on to ICS	Emphasis on the use in patients with concomitant asthma and allergic rhinitis
NHLBI 2020	Recommended as an add-on therapy for allergic rhinitis with asthma	Effective as add-on therapy in moderate-to-severe persistent asthma, and in aspirin-sensitive asthma	Used in asthma patients with allergic rhinitis to address both conditions
ERS 2023	Not specifically mentioned in allergic rhinitis management	Montelukast is recommended as an add-on therapy for poorly controlled asthma, especially in AERD and exercise-induced bronchoconstriction	Montelukast may improve lung function and is useful in managing asthma with concurrent allergic conditions
Japanese 2021 Guidelines	Recommended as second-line therapy after antihistamines for allergic rhinitis	Frequently used in mild-to-moderate asthma in children	Recognized for safe profile in pediatric populations
ARIA 2023	Effective in reducing nasal symptoms in allergic rhinitis	Used for asthma control particularly when allergic rhinitis coexists	Beneficial in patients with asthma and allergic rhinitis
NICE Guidelines	Recommended as an add-on therapy for allergic rhinitis, especially in those with asthma	Suggested for asthma patients with allergic rhinitis to improve symptom control and reduce exacerbation risks	Emphasizes an integrated management strategy to address both asthma and allergic rhinitis for improved patient outcomes

Table 2: Approved and off-label uses of montelukast—indications, mechanisms, and clinical evidence

Case number	*Details*	*Symptoms*	*Outcome*
1	12-year-old girl developed severe depression shortly after starting montelukast	Persistent sadness, social withdrawal	Symptoms resolved after discontinuation
2	15-year-old boy experienced suicidal ideation and ultimately committed suicide after 3 months on montelukast	Irritability, suicidal thoughts	Immediate psychiatric intervention; drug discontinued
3	8-year-old girl showed behavioral changes, including increased aggression	Hyperactivity, aggression toward peers	Improvement in behavior after stopping the medication
4	30-year-old woman reported heightened anxiety and mood swings after treatment	Anxiety, irritability, mood instability	Symptoms improved following discontinuation
5	72-year-old man exhibited delirium after initiating montelukast for COPD	Confusion, disorientation	Cognitive function improved after cessation

Key Legal Issues

Neuropsychiatric Side Effects

The primary legal issue revolves around the alleged neuropsychiatric side effects associated with montelukast, including depression, suicidal ideation, and aggressive behavior. Plaintiffs have argued that:

- Inadequate warnings: Manufacturers, including Merck & Co., are accused of failing to provide adequate warnings regarding these risks in the drug's labeling and promotional materials.
- Negligence: Legal actions often cite negligence, asserting that the pharmaceutical company did not conduct sufficient safety evaluations or adequately communicate the potential risks associated with montelukast.
- Product liability: Plaintiffs have filed product liability claims, arguing that montelukast is defectively designed due to its unforeseen neuropsychiatric effects, which were not disclosed to healthcare providers or patients.

Regulatory Scrutiny

Regulatory agencies, including the US FDA, have faced pressure to reassess the safety profile of montelukast. Concerns raised by patients, parents, and healthcare providers have led to calls for:

- Label revisions: Advocacy for updates to the drug's labeling to include prominent warnings about neuropsychiatric risks.
- Postmarketing surveillance: Increased monitoring of adverse events related to montelukast usage.

Timeline of Events

2000: Food and Drug Administration Approval

Montelukast received FDA approval for asthma management, with initial indications limited to respiratory conditions.

2008: Initial Reports of Neuropsychiatric Side Effects

Reports began to emerge linking montelukast to neuropsychiatric side effects, leading to increasing awareness among healthcare professionals and patients.

2010: Food and Drug Administration Safety Communication

The FDA issued a safety communication highlighting potential neuropsychiatric side effects associated with montelukast. The communication advised healthcare providers to be vigilant about these risks, particularly in pediatric populations.

2012: First Lawsuits Filed

Plaintiffs began filing lawsuits against Merck, alleging negligence and inadequate warnings regarding neuropsychiatric risks. One notable case involved a 10-year-old boy who developed suicidal ideation after starting montelukast therapy.

2018: Expanded Warning Labels

In response to ongoing litigation and mounting evidence, the FDA mandated expanded warning labels for montelukast, emphasizing the risk of neuropsychiatric events and advising prescribers to closely monitor patients.

2020: Class Action Lawsuit

A class action lawsuit was filed, consolidating multiple claims regarding the lack of adequate warnings. The plaintiffs argued, "Had the manufacturer provided sufficient information regarding the neuropsychiatric risks, many individuals would have chosen alternative therapies."

2021: Ongoing Legal Proceedings

As of 2021, numerous lawsuits remained pending, with plaintiffs continuing to present evidence of adverse neuropsychiatric effects. Courts have increasingly scrutinized the adequacy of manufacturer warnings and their implications for patient safety.

The legal status surrounding Merck & Co.'s drug Singulair (montelukast) is a complex and ongoing saga, with over multiple lawsuits alleging that the company failed to properly warn users of the drug's severe neuropsychiatric side effects. These cases are significant not only due to the volume of plaintiffs but also because of the substantial harm linked to the drug. The FDA tallied 82 suicides linked to Singulair[35] and its generic versions reported to its adverse-event database since 1998. Only 64 of the reports provided an age; of those, 31 involved someone 19 or younger. These lawsuits have primarily been consolidated into multidistrict litigation (MDL), offering a more streamlined legal process. However, Merck's defense, particularly through the use of the preemption doctrine, has significantly shielded the company from liability.

Multidistrict Litigation and Lawsuit Consolidation

Due to the growing number of lawsuits against Merck, a multidistrict litigation (MDL) was formed in August 2022.[36] The MDL consolidates federal cases filed across the country, all of which accuse Merck of failing to properly warn consumers of Singulair's risks. The MDL allows for streamlined pretrial processes, including discovery and the possible emergence of bellwether trials—a method that tests a few select cases to gauge how juries might react to the overall evidence.

In the consolidated lawsuits, plaintiffs argue that Merck knew about the drug's neuropsychiatric risks long before the FDA required the boxed warning. Internal documents allegedly show that Merck had been aware of these concerns for years but did not act swiftly enough to update Singulair's label or communicate these risks to the public.

Preemption Doctrine: Merck's Legal Shield

A significant legal obstacle for the plaintiffs has been the use of the preemption doctrine. Preemption occurs when federal law overrides or preempts state laws, preventing state-level claims from proceeding. In the case of Singulair, this defense has become central to Merck's strategy, particularly regarding the lawsuits involving generic versions of the drug.

Preemption was strengthened in two US Supreme Court rulings in 2011 and 2013, which found that generic drug manufacturers could not be held liable for design defects or failure-to-warn claims because federal law requires generics to carry the same labels as the original branded drug. As a result, lawsuits involving generic forms of Singulair, which make up the majority of montelukast prescriptions in the US, have largely been blocked by preemption defenses.

For instance, in the tragic case of Nicholas England, a healthy 22-year-old man who took a generic version of Singulair and committed suicide,[35] his parents' lawsuit against both Merck and the generic manufacturer was dismissed due to preemption. The court ruled that since the generic manufacturer was legally bound to use Merck's original labeling, which had FDA approval, neither the generic manufacturer nor Merck could be held liable under federal law for the claims of failure to warn. This defense has proven to be a substantial legal barrier for many families seeking justice for their loved ones (Table 3).

The Toll: 82 Suicides and Beyond

As the litigation moves forward, one of the most harrowing aspects of the lawsuits involves the 82 suicide cases linked to

Table 3: Reported neuropsychiatric side effects of montelukast—case reports and adverse event data

Events	*Time on drug*
15-year-old male completed suicide. Approximately 2 weeks prior to death, the patient started montelukast to treat allergic rhinitis. The parents noted increasing anxiousness, agitation, insomnia, mood swings, and muscle aches. Subsequently, around the time of his death, the patient became angry, irritable, had difficulty sleeping, feelings of hopelessness, and poor energy level. Symptoms worsened over the course of 1 to 2 days while on treatment. He had outbursts of anger. All of these behaviors were uncharacteristic. No concomitants, no psychiatric history, or depression. Hanged himself	17 days
17-year-old female completed suicide. Physician father reported no signs of depression; she was a happy girl, active in school. Concomitant budesonide, occasional use of inhaler. Coroner listed cause of death as "suicide due to depression"	>5.5 years
22-year-old male completed suicide. Physician initially stated the patient did not have any psychiatric history or history of depression, and the patient did not state he was depressed, nor did he appear depressed. In follow-up, the physician reported questionable depression; no further information was provided. Concomitants included albuterol (rarely, for exercise), fluticasone, topical acne medications, and allergy shots	6 months
17-year-old male completed suicide; history of moodiness and suicidal ideation while on montelukast. Psychiatric evaluation found him to be depressed, but parents did not start him on medication. Montelukast prescription lapsed. He was put back on montelukast at age 15 when he switched doctors. Moodiness returned. Parents attributed it to "teenage years." Report states moodiness correlated with montelukast (as if bipolar)	>7 years, not continuous
63-year-old female completed suicide. Was treated with montelukast for allergies for 2.5 months. Prior to her suicide, she became easily annoyed, frustrated, and depressed. No concomitants	2.5 months
41-year-old male with asthma and allergies was switched to montelukast for 2 weeks when he committed suicide. History also included acid reflux. Montelukast was the only recent medication switch. Experienced extreme depression in the last 2 weeks of his life, cold sweats, palpitations, and a vacant or exhausted look.	2 weeks
15-year-old male completed suicide. Described as a "fun-loving kid," he took montelukast as needed for asthma and had been on and off the medication for 26 months. Experienced severe leg cramps, headaches, sleeplessness, followed by sleeping for 18 hours, and occasional moodiness. Restarted montelukast in the month of the suicide and was emotional at times. No suicide note	26 months, on and off

Singulair in the US, a figure cited in court filings and reported widely in the media.[35] Plaintiffs argue that these deaths, as well as numerous other instances of attempted suicides, severe depression, and mood disturbances, could have been prevented had Merck acted more responsibly.

Critics claim that internal Merck documents reveal that the company was aware of the risks but did not take adequate steps to either update the label or alert the medical community to the potential dangers. This alleged delay in warning, they argue, is directly responsible for the harm caused to Singulair users.

Conclusion

The legal battle over Singulair and its neuropsychiatric side effects, including 82 suicides, underscores the challenges consumers face when trying to hold pharmaceutical companies accountable. The formation of the MDL has consolidated hundreds of lawsuits, but Merck's reliance on the preemption defense has significantly shielded the company from liability. As bellwether trials approach and the MDL process unfolds, the future of this litigation will be crucial in determining how much responsibility Merck will ultimately bear for the harm caused by Singulair, and how federal regulations will influence the balance between corporate liability and consumer safety in the pharmaceutical industry.

Countries That have Issued Warnings or Banned Montelukast

United States

Regulatory body: US FDA.

Action: The FDA has issued multiple safety communications regarding montelukast since 2010. In March 2020, the FDA expanded its warnings to emphasize the risk of serious neuropsychiatric events, particularly in pediatric patients.

Details: The FDA's communication advised healthcare providers to monitor patients closely for behavioral changes, anxiety, and mood disorders. The updated labeling was meant to inform prescribers and patients about potential risks, especially among those with a history of psychiatric disorders.[3]

Canada

Regulatory body: Health Canada.

Action: In 2019, Health Canada issued a warning regarding montelukast, advising that the medication may lead to neuropsychiatric events such as depression, anxiety, and suicidal thoughts.

Details: Health Canada recommended that healthcare providers assess the risks and benefits of montelukast before prescribing it, especially to children and adolescents. The warning included guidance for monitoring patients and considering alternative therapies when appropriate.[37]

European Union

Regulatory body: EMA.

Action: In 2019, the EMA conducted a review of montelukast and recommended updates to the product information to include warnings about the risk of neuropsychiatric effects.

Details: The review emphasized that while montelukast remains an important treatment option for asthma and allergic rhinitis, the benefits must be weighed against the potential risks. The EMA urged healthcare professionals to inform patients of these risks and advised monitoring for mood changes.[38]

Australia

Regulatory body: Therapeutic Goods Administration (TGA).

Action: The TGA issued a safety alert in 2020 regarding montelukast, highlighting the association between the drug and neuropsychiatric effects, including depression and suicidal thoughts.

Details: The TGA advised healthcare professionals to reconsider the use of montelukast in patients with a history of psychiatric disorders and recommended monitoring for any behavioral changes. Patients were also encouraged to report any adverse effects.[39]

New Zealand

Regulatory body: Medsafe (New Zealand Medicines and Medical Devices Safety Authority).

Table 4: Regulatory actions on montelukast—warnings and bans issued by different countries

Characteristic	*Seratrodast*	*Montelukast*
Drug class	Thromboxane A2 receptor antagonist	Leukotriene receptor antagonist (LTRA)
Mechanism of action	Inhibits thromboxane A2, reducing bronchoconstriction and inflammation	Blocks leukotriene D4 (LTD4) from binding to its receptor, reducing inflammation and bronchoconstriction
Primary indications	Asthma management (chronic treatment)	Asthma prophylaxis, allergic rhinitis, exercise-induced bronchoconstriction
Additional uses	Anti-inflammatory effects, potential cardiovascular benefits	Allergic rhinitis, prevention of exercise-induced asthma
Neuropsychiatric risks	Less reported neuropsychiatric issues	Associated with neuropsychiatric events such as mood changes, depression, suicidal thoughts (FDA warning)
Efficacy	Primarily effective in mild to moderate asthma	Effective for chronic asthma and allergic rhinitis
Side effects	Headache, nausea, liver enzyme elevation	Headache, abdominal pain, neuropsychiatric events, sleep disturbances
Administration	Oral tablets	Oral tablets or chewable tablets
Regulatory approvals	Approved in Japan and select countries for asthma	Globally approved (USA, EU, Canada, Australia, etc.) for asthma and allergies
Metabolism	Hepatically metabolized (CVP enzymes)	Primarily metabolized by liver (CYP3A4 and CVP2C9)
Contraindications	Severe liver dysfunction	Hypersensitivity to montelukast or its components
Dosing	80 mg/day	10 mg/day for asthma, lower doses for allergic rhinitis

Action: In 2021, Medsafe updated its recommendations for montelukast, advising on the potential for neuropsychiatric side effects.

Details: The updated guidance included recommendations for healthcare providers to inform patients about the risks and to monitor for any adverse psychological symptoms. The information was aimed at ensuring informed consent prior to prescribing montelukast.[40]

Singapore

Regulatory body: Health Sciences Authority (HSA).

Action: In 2020, the HSA issued a safety advisory about the use of montelukast, citing potential neuropsychiatric events.

Details: The advisory included recommendations for prescribers to assess the risks versus benefits before prescribing montelukast, especially in children. The HSA emphasized the need for ongoing patient monitoring.[41]

Seratrodast Vs Montelukast: Can Seratrodast be an Alternative?

Montelukast and seratrodast both significantly differ in their mechanisms of action and side effect profiles.

Montelukast is a leukotriene receptor antagonist (LTRA) that blocks the action of leukotriene D_4, a substance in the body that causes inflammation and bronchoconstriction. It is commonly prescribed for asthma control and the management of allergic rhinitis. Despite its effectiveness, montelukast has been associated with neuropsychiatric side effects, including mood changes and suicidal thoughts, prompting safety warnings from regulatory bodies like the FDA.

Seratrodast, on the other hand, is a thromboxane A_2 receptor antagonist. It inhibits the action of thromboxane A_2, which is involved in promoting bronchoconstriction and inflammation. While it shares a similar indication for asthma management, it has been shown to have a different side effect profile, with fewer reports of neuropsychiatric issues. However, it is primarily approved in Japan and certain other regions, making its availability limited compared to montelukast (Table 4).

For comparison purposes, we need more trials to ascertain the suitability of seratrodast over montelukast.[42]

Summary

Montelukast, a cysteinyl leukotriene receptor antagonist, is primarily used to manage asthma and allergic rhinitis. Approved in the late 1990s, it represented a significant breakthrough in addressing airway inflammation, shifting treatment paradigms from merely targeting symptoms to addressing underlying inflammatory processes. Montelukast has been well established in both pediatric and adult populations due to its efficacy in reducing bronchoconstriction, improving lung function, and decreasing asthma exacerbations. It is also used for conditions like exercise-induced bronchoconstriction, allergic rhinitis, and off-label for chronic urticaria and sleep disorders.

However, concerns emerged around its neuropsychiatric side effects, including anxiety, depression, and suicidal ideation, particularly in children. Regulatory agencies worldwide, including the US FDA, Health Canada, and the EMA, have issued warnings about these adverse effects.

Several case reports have documented severe neuropsychiatric symptoms in pediatric and adult patients on montelukast, leading to the discontinuation of the drug in some cases. Legal cases have surfaced globally, with plaintiffs alleging that Merck failed to provide adequate warnings about these risks. Court rulings in favor of plaintiffs have emphasized the need for pharmaceutical companies to prioritize transparent communication about drug risks.

Conclusion

Montelukast remains a cornerstone in the treatment of asthma and allergic rhinitis, offering relief to countless individuals struggling with respiratory ailments. However, its potential neuropsychiatric side effects—ranging from anxiety to suicidal ideation—have necessitated a revaluation of its safety profile. As these concerns come to light, it is imperative that both healthcare providers and patients navigate montelukast therapy with heightened awareness and caution. Balancing the drug's undeniable therapeutic benefits with the emerging risks is the key to ensuring patient safety.

Regulatory bodies worldwide, including India's Central Drugs Standard Control Organization (CDSCO), need to respond with advisories aimed at improving patient safety through informed prescribing and monitoring practices. In this evolving landscape, continuous research, patient education, and robust clinical vigilance will be essential to ensuring montelukast's safe and effective use in the years to come.

Recommendations

- Empower patients through education: Thorough education of patients and caregivers about montelukast's potential neuropsychiatric side effects is crucial. Providing clear, detailed information about risks such as anxiety, depression, and suicidal ideation will empower patients to identify early symptoms and seek timely medical intervention.
- Vigilant monitoring: Healthcare providers must adopt strict monitoring protocols, particularly for vulnerable populations such as children, adolescents, and individuals with a history of psychiatric conditions. Regular follow-ups should assess not only asthma control but also the patient's emotional and psychological well-being.
- Informed consent as a cornerstone: Prior to starting montelukast therapy, clinicians must ensure that patients and their caregivers are fully informed about both the benefits and risks of the drug. Informed consent should be comprehensive, covering potential neuropsychiatric side effects, so that patients can make educated decisions about their treatment.
- Restrict over-the-counter (OTC) availability: Making montelukast unavailable OTC is a necessary step to safeguard patients. It would allow for better patient selection, comprehensive risk assessment, and more rigorous monitoring, all of which are essential in preventing serious adverse events.
- Consideration of alternatives: If neuropsychiatric symptoms arise during treatment, healthcare professionals should consider alternative therapies. Whether adjusting the montelukast dosage or transitioning to a different treatment option, the mental health and overall safety of the patient should be prioritized.
- Encourage reporting of adverse effects: It is essential to encourage patients to report any adverse neuropsychiatric reactions, enabling early intervention. Prompt reporting of side effects helps prevent symptom escalation and ensures that necessary adjustments are made in treatment.
- Further research is critical: There remains a critical need for further research into the mechanisms underlying montelukast's neuropsychiatric side effects. Investigating these pathways will aid in developing strategies to mitigate risks and improve patient outcomes, ensuring that montelukast can continue to be safely prescribed.
- Collaborative approach to legal and ethical responsibilities: The legal controversies surrounding montelukast highlight the need for ethical transparency in pharmaceutical communications. Drug manufacturers, regulatory bodies, and healthcare institutions must collaborate to refine product labeling, ensuring that warnings about neuropsychiatric risks are clear and easily accessible to both healthcare providers and patients.
- Develop India-specific guidelines through broad consensus: Given the widespread use of montelukast in India and the emerging concerns surrounding its safety, there is an urgent need for India-specific guidelines. These guidelines should be developed through broad consensus within the pulmonology, pediatric, and general medical communities. A collaborative effort among these specialties would ensure that the unique needs of Indian patients are addressed, creating tailored protocols for prescribing, monitoring, and managing montelukast therapy.

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ANNOUNCEMENT

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SHORT COMMUNICATION

Online Mode of Tobacco Hazards Awareness for Capacity Building and Awareness Generation: A Promising Initiative in Addition to the Existing Tobacco Control Measures

Neeta Ghate*

Received: 18 January 2025; *Accepted:* 13 March 2025

Abstract

Our tobacco hazards awareness work in Mumbai since 2014 had to be stopped with the onset of the coronavirus disease 2019 (COVID-19) pandemic. There was a need to prioritize and strengthen tobacco cessation efforts and disseminate information in society and to medical professionals and healthcare workers to highlight such facilities. Hence, this online tobacco hazards awareness initiative was undertaken on various platforms for a diverse audience. This included:

1. Creating awareness in society about the hazards of tobacco and the facilities available for cessation through articles for online newspapers, online talks, blogs, videos for news channel websites, and interviews on television (TV) in Marathi.

2. Capacity building for:

a. Medical professionals by conducting lectures and presentations at medical conferences about the need to integrate tobacco control in healthcare delivery at all levels—to ask all adults about tobacco use in any form at each visit and document it. If using tobacco, advise, including elderly patients, to quit and share the toll-free quitline number or refer them. Address tobacco use in women and integrate tobacco cessation advice in antenatal care and preventing initiation of tobacco use by adolescents.

b. Government healthcare staff—doctors and healthcare workers.

c. Medical and dental undergraduate and postgraduate students through talks.

3. An online school-based tobacco hazards program was conducted.

Using the online mode, dissemination of this information was possible across various regions of India.

In addition to existing tobacco control initiatives, the online mode of creating awareness about incorporating tobacco control at all levels of healthcare delivery needs consideration for capacity building and training of the healthcare workforce. Tobacco control modules must be included in graduate and postgraduate medical training curricula across all specialties.

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Sir,

Services for quitting tobacco include the toll-free National Tobacco Quitline (1800 112 356), which provides counseling in English, Hindi, and regional languages. Total 16 languages and free Tobacco Cessation Clinics with a list accessible on ntcp.nhp.gov.in (National Tobacco Control Program).

Our tobacco (smoking and smokeless (unburnt tobacco such as chewing tobacco—twice the prevalence of smoking))[1] hazards awareness work in Mumbai since 2014, including a school-based tobacco hazards awareness program to prevent the initiation of tobacco use, had to be stopped with the onset of the coronavirus disease 2019 (COVID-19) pandemic.

There was a need to prioritize and strengthen tobacco cessation efforts and disseminate information in society and to medical professionals and healthcare workers to highlight such facilities. With the increased use of mobile phones, many people can avail themselves of such facilities if information is widely disseminated, including in regional languages.

Hence, this online tobacco hazards awareness initiative was undertaken on various platforms for a diverse audience.

This included:

1. Creating awareness in society about the hazards of tobacco and the facilities available for cessation through articles for online newspapers, online talks, blogs, videos for news channel websites, and interviews on television (TV) in Marathi.

2. Capacity building

a. For medical professionals by conducting lectures and presentations at medical conferences about:

i. The need to integrate tobacco control in healthcare delivery at all levels—to ask all adults about tobacco use in any form at each visit and document it. If using tobacco, advise, including elderly patients, to quit and share the toll-free quitline number or refer them.

ii. Tobacco use in women[2] and the integration of tobacco cessation advice in antenatal care,[3] where counseling is the mainstay of tobacco cessation for pregnant women.

iii. Preventing the initiation of tobacco use by adolescents.

These presentations were delivered at medical conferences for doctors of various specialties, including primary care physicians, obstetricians, gynecologists, physicians, ears, nose, and throat (ENT) surgeons, and pediatricians at local, national, and international levels.

b. Talks for the government health workforce—doctors and healthcare workers, including nurses, ASHAs, and Anganwadi workers of Mumbai and Kalyan Dombivli Municipal Corporations.

i. It was emphasized that in tobacco users, in addition to tobacco quitting advice, an oral cavity examination[4,5] must be conducted to rule out suspicious lesions, with referrals to specialist centers if necessary.

Feedback was appreciative of the initiative.

c. Talks for medical and dental students and faculty in Pune and Sikkim.

d. Lecture for postgraduate students of DNB ENT from all over India—this was probably the first time that tobacco use prevention was included in postgraduate teaching.

3. Online school-based tobacco hazards program was conducted.

Consultant ENT Surgeon, Dr Mendadkar's Children Hospital; Founder Trustee and President, Association for Tobacco Use Hazards Awareness and Preventive Measures (ATHAPM), Mumbai, Maharashtra, India; *Corresponding Author

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Feedback from teachers *via* Google Forms was appreciative of both the content and the online mode.

Some of this work was mentioned in mass media.

Using the online mode, dissemination of this information was possible across various regions of India.

Recommendations

In addition to the existing tobacco control initiatives, the online mode of creating awareness about incorporating tobacco control at all levels of healthcare delivery needs consideration for capacity building and training of the healthcare workforce. Tobacco control modules must be included in graduate and postgraduate medical training curricula across all specialties.

This paper was selected for presentation and presented as a Practitioner's Case Study at the XIX International Conference on Public Policy and Management at the Centre for Public Policy (CPP) of the Indian Institute of Management Bangalore (IIMB) August 2024.

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CASE REPORT

Long-term Exposure to Complementary and Alternative Medicine Leads to Neural Epidermal Growth Factor-like 1 Membranous Nephropathy

Sangeetha Priya[1*], Arivazhagan S[2], Dilip Kumar[3]

Received: 17 September 2024; *Accepted:* 23 October 2024

Abstract

Introduction: Membranous nephropathy is a type of glomerular disease which results in nephrotic syndrome that can be seen in adults. In most cases of membranous nephropathy, the target antigen has been phospholipase A2 receptor (PLA2R). In recent times, another antigen named neural epidermal growth factor-like 1 (NELL-1) has been labeled. We present a case report of NELL-1-positive membranous nephropathy due to intake of complementary and alternative medication, mercury being the possible content.

Methods: A case report—50-year-old female, brought to emergency department with breathing difficulty, bilateral swelling of legs, and reduced urine output for 3 days. Patient had periorbital edema, facial puffiness, and bilateral limb edema on examination. Family members revealed a past history of rheumatoid arthritis for which she is on complementary and alternative medication.

Vitals—blood pressure (BP)—70/50 mm Hg, in view of shock, patient was started on inotropes at emergency medical department (EMD). On evaluation, her complete blood count showed anemia, neutrophilic leukocytosis, erythrocyte sedimentation rate (ESR) was high. Serum electrolytes showed hyponatremia. Urine complete showed albuminuria with high urine spot protein–creatinine ratio (PCR). Renal function test showed increase in creatinine level which rapidly worsened on serial monitoring. Liver function test showed severe hypoalbuminemia with albumin-globulin (AG) reversal. Lipid profile showed high cholesterol, triglyceridemia, with increased low-density lipoprotein (LDL). Serum electrophoresis showed hypoalbuminemia with relative increase in alpha 2 fraction, suggestive of nephrotic syndrome.

In view of shock and hypotension, adrenal insufficiency was considered and patient was started on steroids. With the clinical presentation and laboratory parameters, the differential diagnoses considered here were membranous nephropathy, minimal change disease, and focal segmental glomerulosclerosis.

So, we proceeded with renal biopsy after optimizing her renal parameters, and it was reported as membranous nephropathy and acute interstitial nephritis. Antigen panel for membranous nephropathy was sent and came out to be NELL-1-positive. She was started on IV pulse steroid therapy.

Results: In our case report, we conclude that NELL-1 has been shown to cause a rare form of membranous nephropathy when negative for PLA2R and thrombospondin type 1 domain containing 7A (THSD7A). Our possible explanation is mercury-induced membranous nephropathy.

Conclusion: Our patient was started on pulse steroids and slowly tapered. Her renal parameters gradually improved. Since everything resolved without any active intervention for rheumatoid arthritis, thereby eliminating the inciting agent.

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Outcome and Follow-up

The patient improved gradually and returned to daily activities. Her renal parameters were normalized (Table 1).

Discussion

Membranous nephropathy (Figure. 1) is a type of glomerular disease characterized by deposition of immune complexes along the glomerular basement membrane.[1] Generally, thrombospondin type 1 domain containing 7A (THSD7A) and phospholipase A2 receptor (PLA2R) are target antigens in 5 and 70% of primary nephropathy cases, respectively. In all other remaining cases, the target antigens would be unknown. Neural epidermal growth factor-like 1 (NELL-1) is a gene named after its similarity to a gene *Nel* that is strongly expressed in neural tissue, encoding a protein with epidermal growth factor-like (EGF-like) repeats. In the kidney, NELL-1 expression is higher in tubules.[2] This autoantigen is associated with both primary and secondary membranous nephropathy. It is described with autoimmune diseases, malignancy, traditional indigenous medicines, and lipoic acid.[3]

The most common renal manifestation attributable to mercury toxicity is membranous nephropathy.[4] In the largest series of NELL-1 membranous nephropathy reported, in 33% of patients malignancy was identified, compared to 11% of THSD7A membranous nephropathy and 4% of PLA2R membranous nephropathy.[5] The most common non-PLA2R membranous antigen reported to date is NELL-1, and the only membranous antigen that has been associated with segmental membranous nephropathy is NELL-1.[5]

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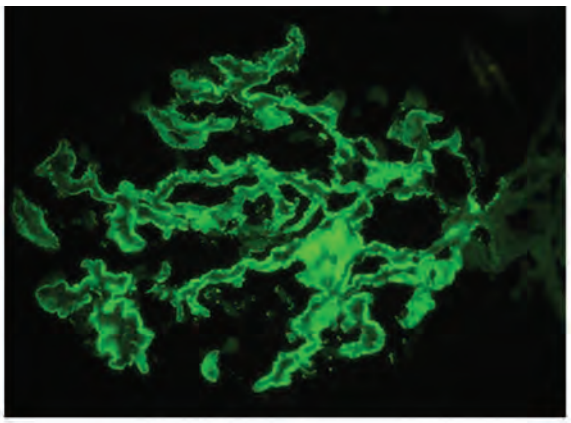

SURGICAL PATHOLOGY REPORT @

SLIDE NO	:	B/14565/23
SPECIMEN	:	Renal biopsy for Target antigen (five antigens) staining
CLINICAL HISTORY	:	Nephrotic syndrome. Anti PLA2R - negative, h/o Siddha medications+
GROSS	:	Received 1 paraffin block labelled as 6900
MICROSCOPY	:	1. PLA2R - Negative / not over expressed in glomeruli
		2. THSD7A (thrombospondin) - Negative in glomeruli
		3. NELL1 - 1+ segmental granular staining along glomerular capillaries.
		4. Semaphorin 3b (Sema 3b) - Negative in glomeruli
		5. Exostosin 1 (EXT-1) - Negative in glomeruli

Fig. 1: Renal biopsy showing membranous nephropathy under immunofluorescence

Table 1: Laboratory parameters

Parameters	*Reference range*	*Patients result*
Hemoglobin	12–15 gm/dL	8.7 gm/dL
White blood count	4–10 × 10^3/µL	17.65 (*N*—75.3)
Platelet count	150–400 × 10^3/µL	476 × 10^3/µL
Erythrocyte sedimentation rate	3–10 mm	120 mm
Liver function test	T. bilirubin—0.2–1 mg/dL SGOT—5–38/µL SGPT—5–41/µL	T. bilirubin—0.2 mg/dL SGOT—18 SGPT—8
Serology for HIV, anti-HCV and HBSAG (by ELISA)		Negative
Urine complete		Protein—3+, blood—3+
Lipid profile	Cholesterol	468
	Triglycerides	287
	LDL—low density lipoprotein	386
Rheumatoid factor	0–20 IU/mL	<20
Anti-CCP	Negative	
C3 level	88–201 mg/dL	84.8 mg/dL
C4 level		36.9 mg/dL
Serum protein electrophoresis		Hypoalbuminemia with relative increase in alpha 2 fraction—S/O nephrotic syndrome

Parameters	*Reference range*	*Day 1*	*Day 18*	*Postdialysis*	*On follow-up*
Creatinine	0.8–1.25 mg/dL	1.25	6.21	4.85	0.85
Spot urine PCR	0–0.3	22.06		2.35	0.41

Anti-CCP, anticyclic citrullinated peptide; CAM, complementary and alternative medication; EGF-like repeats, epidermal growth factor-like repeats; MN, membranous nephropathy; Urine PCR, protein–creatinine ratio

CASE REPORT

Unilateral Vocal Cord Palsy as Presenting Feature of Amyotrophic Lateral Sclerosis

Koushik Ramachandra[1*], Amruth Reddy Narayana[2], Anusha Induraj[3], Rohit Pai[4]

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative pathology marked by the degeneration of upper and lower motor neurons, resulting in muscle weakness and atrophy, impairing motor function. Bulbar-onset ALS is a distinct clinical subtype, with initial involvement of bulbar motor neurons, often causing severe speech and swallowing difficulties. Despite its impact, bulbar-onset ALS, especially with rare symptoms like unilateral vocal cord palsy (UVCP), lacks extensive research. Here, we detail the case of a 79-year-old nonambulatory diabetic male with a 1-year history of hoarseness of voice, diagnosed with bulbar-onset ALS with UVCP. This underscores the importance of recognizing unusual presentations of ALS, particularly in geriatric populations, urging tailored medical evaluations for optimal care and improved outcomes in this challenging neurological condition.

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder marked by upper and lower motor neuron degeneration in the brain and spinal cord, causing muscle wasting.[1] Bulbar-onset ALS is a rare variant, more prevalent in the elderly, with symptoms like dysarthria, dysphagia, and voice hoarseness. It has a shorter median survival (27 vs 41 months) and is associated with neurocognitive decline and sudden death.[2] While bilateral vocal cord palsy occurs in up to 30% of cases, unilateral vocal cord palsy (UVCP) is rare.[3,4] We aim to highlight the underexplored topic of UVCP in ALS for better recognition and management.

Case Description

A 79-year-old nonambulatory male, a known case of type 2 diabetes mellitus for the past 30 years, presented to the outpatient department with a 1-year history of hoarseness of voice. Initially, his symptoms began with dysarthria, progressively worsening to include difficulties with articulation and swallowing. Remarkably, the patient disclosed experiencing gradual limb weakness, a symptom previously attributed to age-related decline, leading to no specific prior medical evaluation.

Physical examination revealed multiple fasciculations and severe wasting throughout the body. The Department of Otorhinolaryngology was consulted to assess the hoarseness, and a video laryngoscopy identified unilateral adductor palsy of the vocal cord. Subsequent magnetic resonance imaging (MRI) imaging, aimed at excluding structural abnormalities, revealed age-related cerebral atrophy. Given the constellation of symptoms, including dysphonia, limb weakness, and fasciculations, a diagnosis of motor neuron disease (MND) was suspected. Electromyography confirmed denervation changes, with fasciculations observed in muscles innervated by bulbar, cervical, thoracic, and lumbar nerve systems, strongly indicative of MND. Further diagnostic workup through nerve conduction studies revealed symmetric sensorimotor demyelinating polyneuropathy with predominant lower limb involvement, likely related to long-standing diabetes. Electromyography (EMG) findings are described in Table 1.

Treatment was commenced with oral riluzole 50 mg twice daily, aimed at slowing disease progression, supplemented by intravenous administration of edaravone 60 mg for 7 consecutive days each month.

The patient received comprehensive counseling regarding the progressive nature of the illness and its implications. Prognostic discussions were conducted, emphasizing the importance of supportive care in managing symptoms and optimizing quality of life.

This case presents a unique aspect of ALS, occurring in a geriatric patient beyond the commonly reported age of onset, highlighting the importance of recognizing atypical presentations and promptly initiating appropriate management strategies.

Discussion

Bulbar-onset ALS represents a distinct clinical phenotype characterized by the predominant involvement of bulbar motor neurons. Pathological changes in the corticobulbar brainstem and cranial nerve branches lead to laryngopharyngeal paresis, causing symptoms such as dysarthria, dysphonia, and dysphagia.[5]

Bulbar-onset ALS constitutes approximately 25–30% of all ALS cases, with a median survival of 2–3 years from symptom onset.[6,7] While ALS typically affects individuals between the ages of 40 and 70, the case presented here highlights the diagnostic challenges posed by an atypical age of onset and the overlap of symptoms with age-related conditions.

Early recognition of bulbar-onset ALS enables timely intervention and improves outcomes. Clinical evaluation, EMG, and neuroimaging play pivotal roles in diagnosis. A video laryngoscopy, as performed in this case, is instrumental in confirming UVCP, a rare presenting feature of bulbar involvement in ALS. Accompanying characteristic denervation changes in muscles innervated by bulbar nerve systems helped confirm the diagnosis. Nerve conduction studies often demonstrate evidence of sensorimotor demyelinating polyneuropathy, reflecting the widespread neurodegenerative process in ALS.[8]

Management of bulbar-onset ALS necessitates a multidisciplinary approach aimed at symptom alleviation and preservation of function. Speech therapy, nutritional support, and assistive devices are integral components of care, addressing dysarthria and dysphagia.[9] Pharmacological interventions, including riluzole and edaravone, may modestly prolong survival and slow disease progression.[10]

Despite therapeutic efforts, the prognosis of bulbar-onset ALS remains poor, as the involvement of critical structures is associated with rapid respiratory decline and shortened

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Table 1: EMG findings

Muscle	*Side*	*IA*	*Fibs.*	*Pos. wave*	*Fas.*	*Myotonic discharge*	*Normal MUP*	*Recruitment*
Paraspinal thoracic	Left	+	–	–	3+	–	–	–
Deltoid	Left	+	–	–	3+	–	Normal	Complete
Abductor pollicis brevis	Left	+	+	–	3+	–	Normal	Incomplete
1st dorsal interosseous	Left	+	–	–	3+	–	Normal	Complete
Biceps brachii	Left	+	–	–	3+	–	Normal	Incomplete
Vastus lateralis	Left	+	–	–	3+	–	Normal	Incomplete
Tibialis anterior	Left	+	+	–	3+	–	Normal	Incomplete
Genioglossus	Left	+	–	–	3+	–	–	–

Fas., Fasiculations; Fibs., Fibrillation potential; IA, Insertional activity; MUP, Motor unit potential; Pos. wave, Positive sharp wave

survival compared to limb-onset ALS. Palliative care and advanced directives are crucial for ensuring patient-centered care and dignity throughout the disease trajectory.[11]

Conclusion

This case underscores the diagnostic and therapeutic complexities associated with a rare presenting feature of bulbar-onset ALS. By raising awareness of its distinctive features and challenges, healthcare providers can enhance diagnostic accuracy, optimize management strategies, and improve overall outcomes for patients living with this devastating neurological condition.

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CASE REPORT

Amebic Liver Abscess with Inferior Vena Cava Thrombosis—Case Report and Review of Literature

Arti Yadav[1], Sourav Kumar[2], Sagar Sindagi Mallappa[3], Kritirupa Sarkar[4], Priya Bansal[5], Anupam Prakash[6*], Anil Gurtoo[7]

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Abstract

The clinical evolution and resolution of amebic liver abscess (ALA) is usually unremarkable. However, factors such as malnutrition, alcoholism, and smoking increase the risk of complications that may be seen with ALA. We present a case of inferior vena cava thrombosis as a complication of ALA. Timely anticoagulation therapy along with antibiotics was given which led to rapid resolution of symptoms.

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Introduction

In India, amoebiasis is endemic, and the gastrointestinal tract is the most commonly affected system. Amebic liver abscess (ALA) is the most common extraintestinal manifestation of invasive amoebiasis. It is seen in 3–9% of cases. As per a World Health Organization report, amoebiasis accounts for approximately 1,00,000 deaths each year, mostly from ALA. The disease usually affects adult males.[1] The patients present with fever, pain in the abdomen, fatigue, and loss of appetite. About 20–40% of ALA patients present with complications such as rupture, ascites, multiple organ dysfunction, hydrothorax/pyothorax, or biliary communication with jaundice.[2] Risk factors associated with complications include older age, leukocytosis, hypoalbuminemia, hyponatremia, chronic alcoholism, and smoking. We describe a case of ALA with thrombosis of the inferior vena cava (IVC), which is a rare association but timely diagnosis and intervention can prevent catastrophic consequences.

Case Description

A 25-year-old male with history of alcohol abuse for the last 5 years presented with continuous high-grade fever for 10 days (102°F), progressive abdominal distension, yellowish discoloration of eyes, nausea, and vomiting. There was no past history of jaundice, blood transfusion, tattooing, or high-risk behavior.

On examination, the patient's general condition was fair, and he was hemodynamically stable. Pulse rate was 96/minute, blood pressure was 112/68 mm Hg, SpO_2—99% on room air, respiratory rate was 22/minute, body mass index (BMI)—24.3 kg/m^2, well-built, normal body hair pattern. Icterus was present, with pedal edema and abdominal wall edema. Abdominal girth was 85 cm, and there was tender hepatomegaly (liver span 17 cm). Shifting dullness was also present. There were no peripheral signs suggestive of chronic liver disease. Other systems were normal.

A clinical diagnosis of liver abscess with jaundice was made. The cause of anasarca in the form of ascites, lower limb edema, and abdominal wall edema was not clinically obvious.

Blood parameters were suggestive of anemia (hemoglobin = 9.4 gm/dL), total leukocyte count = 23271 cells/dL, platelet count = 452000/dL. Liver function tests revealed hyperbilirubinemia (total bilirubin of 8.6 mg/dL, direct bilirubin 5.6 mg/dL), mild transaminitis with raised alkaline phosphatase [serum glutamic oxaloacetic transaminase (SGOT)/serum glutamic pyruvic transaminase (SGPT)/alkaline phosphatase were 378/239/584 U/L], and albumin = 2.6 gm/dL. There was hyponatremia (120 mEq/L). International normalized ratio (INR) was 1.89, D-dimer = 1619 ng/mL, lactate dehydrogenase = 409 U/L. On kidney function tests, there was evidence of acute kidney injury. Viral markers were nonreactive. Blood culture and urine culture were sterile. The patient tested positive for amoebic antibody by enzyme-linked immunosorbent assay (ELISA). Ascitic tap was transudative in nature.

Ultrasonography was suggestive of 520 cc liver abscess compressing the IVC (Fig. 1). There was evidence of a thrombus lodged in it below the level of the abscess, which was confirmed on contrast-enhanced computed tomography of the abdomen (Figs 2 and 3).

The patient was started on intravenous antibiotics, low molecular weight heparin, and other supportive management. Ultrasound-guided pigtail insertion was done and abscess drained. The pus was typical anchovy sauce-like and was sent for analysis. Over a duration of 10 days, the patient's fever subsided, appetite improved, vomiting resolved, and liver and kidney functions improved. The swelling of limbs also improved, probably a result

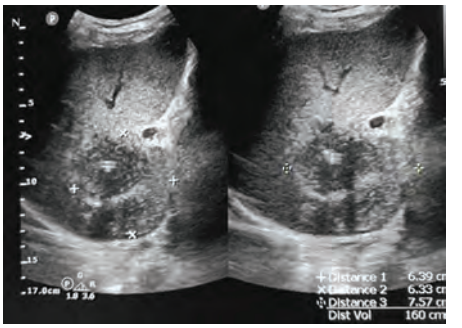

Fig. 1: Ultrasound showing residual liver abscess of size 160 cc with pigtail *in situ*

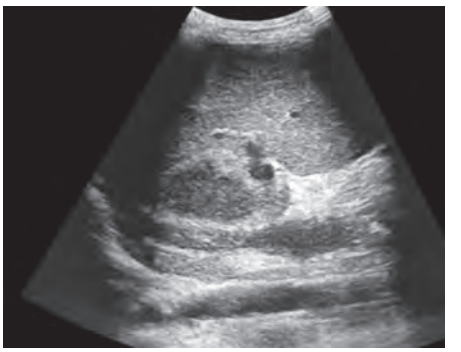

Fig. 2: Ultrasound showing liver abscess abutting the inferior vena cava with a thrombus of size 5.2 cm in it

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Table 1: Case reports of amebic liver abscess with inferior vena cava thrombosis

S. no.	*Author*	*Year of publication*	*Case summary*
1	Hodkinson et al.[4]	1988	50-year-old man with ALA and IVC thrombosis extending up to the right atrium
2	Sodhi et al.[5]	2008	57-year-old man with ALA with hepatic and IVC thrombosis
3	Ray et al.[6]	2012	47-year-old man with ALA and IVC thrombosis
4	Siddiqui et al.[7]	2013	2-year-old boy with ALA complicated by IVC thrombus extending up to the right atrium
5	Thati and Nagral[8]	2014	50-year-old man with ALA with thrombus in the right hepatic vein extending into the IVC, with pulmonary thromboembolism
6	McKenzie et al.[9]	2015	43-year-old man from West Africa with ALA with hepatic vein and IVC thrombosis and bilateral pulmonary emboli
7	Martin et al.[10]	2017	43-year-old Canadian man with ALA complicated by thrombosis in intrahepatic IVC, inferior right hepatic vein, iliac veins
8	Jain et al.[11]	2018	58-year-old male who presented with hemoptysis, had ALA complicated by IVC thrombosis progressing to pulmonary embolism
9	Jesrani et al.[12]	2020	26-year-old man with ALA complicated with IVC thrombosis and pulmonary thromboembolism

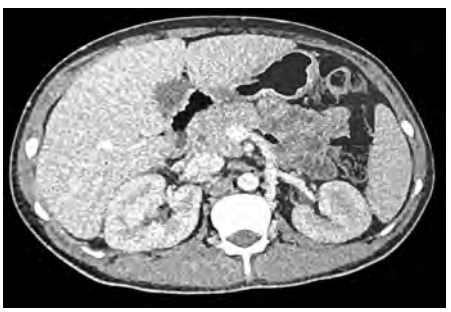

Fig. 3: Contrast-enhanced computed tomography (CECT) of the abdomen—intrahepatic inferior vena cava showing a filling defect with hepatic abscess in segment VIII

of improved patency of IVC following anticoagulation.

The patient was discharged on antibiotics and oral anticoagulant rivaroxaban.

Discussion

The commonly seen clinical course of ALA is uncomplicated, and patients present with chief complaints of fever, upper abdominal pain, and a poor appetite.[1] About 20–40% of ALA patients may present with complications such as pleural effusion, rupture of abscess into the pleural, pericardial and peritoneal cavity or into the bile ducts, and mechanical compression of the biliary tree or the IVC. Systemic complications include septic shock, acute kidney injury, and acute respiratory distress syndrome.[2]

Thrombotic complications are rare in patients with ALA, and vascular thrombosis has been reported in the hepatic vein and portal vein, and there may be extension into the IVC. Krishnan et al. presented a retrospective analysis of ALA following 95 autopsies.[3] Thrombosis of the IVC in combination with hepatic vein was seen in 8% of the cases, and in one case thrombosis was seen following rupture of the abscess into the IVC. Other than this study, only a few case reports have described IVC thrombosis with ALA and have been summarized in Table 1.

The exact pathogenesis of IVC thrombosis in association with ALA is not clearly understood. In a study by Muñoz and Salazar, it has been described how complement and coagulation systems act together and enhance each other's effects which is crucial for defense against infective agents.[13] Additionally, platelets contribute to the activation of complement through the phosphorylation of C3b, and thrombin triggers the release of P-selectin. Furthermore, impairment of fibrinolysis by complements occurs. Thus, both complement and coagulation system act in conjunction to augment each other's outcome, while also creating a procoagulant state. In a pediatric case reported by Siddiqui et al., it has been suggested that the inflammation in the wall of the hepatic abscess may lead to involvement and injury of the intima of hepatic vein or IVC, leading to thrombosis. The thrombosis may extend from hepatic vein to the IVC, and may reach up to the right atrium. Rupture of abscess into the IVC may also predispose to the thrombus formation. Mechanical compression of the IVC may also occur leading to stasis and thrombosis.[7] The latter was seen in our patient.

The management of liver abscess with IVC thrombosis mainly includes antibiotics and drainage of the abscess, and anticoagulation therapy may be needed to achieve complete resolution.

Conclusion

The physician should be aware of thrombotic complications of ALA. Timely recognition and intervention can avert life-threatening consequences associated with thromboembolism.

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CASE REPORT

A Rare Case of Axial Spondyloarthritis with IgA Vasculitis

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Received: 10 November 2024; *Accepted:* 30 November 2024

Abstract

Spondyloarthritis (SpA) is a chronic inflammatory disease characterized by axial, peripheral, and extra-musculoskeletal manifestations. Axial involvement manifests as sacroiliitis, spondylitis, and peripheral involvement in the form of arthritis, enthesitis, and dactylitis. The extra-musculoskeletal manifestations commonly include uveitis, inflammatory bowel disease, and psoriasis, in addition to rare manifestations such as aortitis, interstitial lung disease, immunoglobulin A (IgA) nephropathy, and renal amyloidosis. IgA vasculitis is an immune complex mediated vasculitis affecting small vessels with characteristic IgA deposition within the vessel walls. It primarily affects children and can affect adults in about 10% of cases. A 25-year-old male, diagnosed with nonradiographic axial SpA with bilateral sacroiliitis and enthesitis, presented with recurrent episodes of purpuric skin rash, abdominal pain, loose stools, and pedal edema. On evaluation, he had hypertension and nephritic-range proteinuria. Histopathology of skin lesions and renal biopsy revealed IgA deposits suggestive of IgA vasculitis. To date, only four case reports of SpA and IgA vasculitis have been described in the literature. In a patient with long-standing SpA, the possibility of IgA vasculitis should be considered.

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Introduction

Spondyloarthritis (SpA) is a chronic inflammatory disease characterized by axial, peripheral, and extra-musculoskeletal manifestations. Axial involvement manifests as sacroiliitis, spondylitis, and peripheral involvement in the form of arthritis, enthesitis, and dactylitis. The extra-musculoskeletal manifestations commonly include uveitis, inflammatory bowel disease, and psoriasis, in addition to rare manifestations such as aortitis, interstitial lung disease, immunoglobulin A (IgA) nephropathy, and renal amyloidosis.

Immunoglobulin A vasculitis is an immune complex mediated vasculitis affecting small vessels with characteristic IgA deposition within the vessel walls. It is characterized by a tetrad of purpuric skin rash, arthralgias, abdominal pain, and renal involvement. Children are primarily affected and typically have a good prognosis with a self-limiting course in about 90% of cases. About 10% of cases occur in adults, among whom renal involvement accounts for 40%, and 15% of adults have relapsing disease.

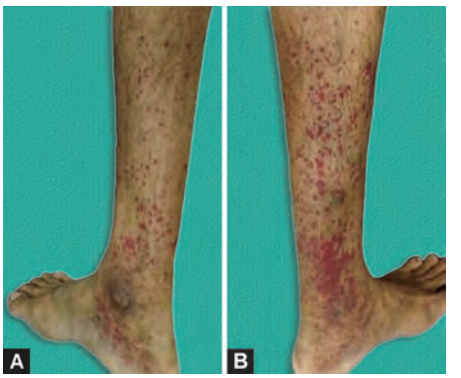
Here, we describe a case of a 25-year-old male, with nonradiographic axial SpA, presenting with IgA vasculitis. To date, only four such cases are reported in the literature having SpA associated with IgA vasculitis.

Case Description

A 25-year-old male had a medical history of inflammatory back pain from the age of 10 years, with alternating bilateral buttock pain and heel pain. He had no history of psoriasis, abdominal pain, diarrhea, or uveitis. No family history of SpA was present. He was using on-demand nonsteroidal anti-inflammatory drugs (NSAIDs) without any formal visit to a physician or rheumatologist.

Five years later, he developed colicky type of abdominal pain, periumbilical in location, which would aggravate post meal. He also reported increased stool frequency, with five to six episodes per day. Simultaneously, he developed painless nonpruritic reddish purpuric rash over both lower limbs, extending from distal feet to proximal thighs. The rash would worsen after prolonged walking. In addition, he had knee and ankle arthralgias. The rash, abdominal pain, and loose stools later improved spontaneously in 1 month duration.

Four years later, he had recurrence of purpuric skin rash over both lower limbs and periorbital swelling in the mornings. He was noted to have reddish purpuric rash distributed on both lower limbs (Figs 1A and B), pitting pedal edema, and had systemic hypertension. Musculoskeletal examination revealed tendoachilles enthesitis, lower limb arthritis of knees and ankles, and a positive Patrick's test (FABER test) bilaterally. In view of pedal edema and *de novo* systemic hypertension, a possibility of renal involvement in the form of glomerulonephritis was considered and appropriate work up was done. He was found to have nephritic range proteinuria of 1260 mg/24 hours. Histopathological examination of skin lesions showed evidence of IgA vasculitis. Renal biopsy was consistent with IgA nephropathy. He tested negative for antinuclear antibodies and antineutrophil cytoplasmic antibodies. Magnetic resonance imaging showed T2 STIR hyperintensities along iliac aspects of both sacroiliac joints, suggestive of active sacroiliitis (Figs 2A and B).



Figs 1A and B: Clinical images of the right and left legs with multiple petechiae and palpable purpura

A diagnosis of nonradiographic axial and peripheral SpA with IgA vasculitis and IgA nephropathy was made.

He had been initiated elsewhere on 1 mg/kg prednisolone equivalent oral glucocorticoids, angiotensin receptor blockers, along with conventional synthetic disease-modifying antirheumatic drugs (DMARDs) (sulfasalazine). Proteinuria had subsided over the course of time. Due to his poor drug compliance, he had recurrence of skin lesions 3 years after the second episode and persistent sacroiliitis with enthesitis. He was planned to be initiated on tumor necrosis factor (TNF) inhibitors because of active sacroiliitis and high disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) = 5.3]. However, the patient opted not to switch to TNF inhibitors and hence was continued on sulfasalazine 2 gm/day. Over the next 3 months, he had a 60% improvement in

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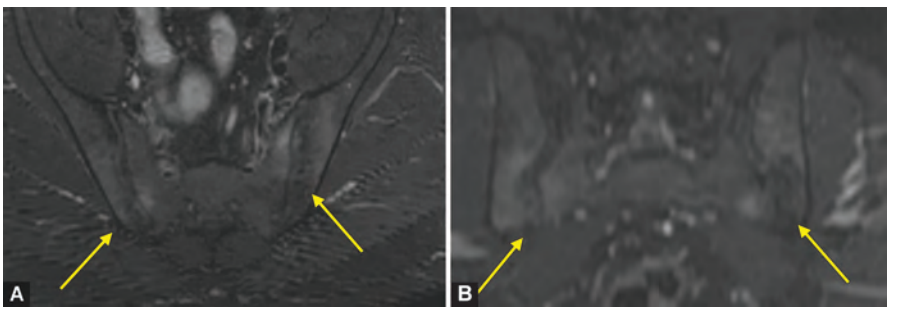

Figs 2A and B: (A) Coronal STIR images; (B) Axial STIR images of both sacroiliac joints showing hyperintensities (yellow arrows) of bilateral sacral and iliac aspects, suggestive of bilateral sacroiliitis

back pain, BASDAI = 2.6, with no recurrence of skin rash.

Discussion

Here, we describe a rare association of poorly controlled nonradiographic axial SpA with recurrent self-limiting episodes of IgA vasculitis and IgA nephropathy.

Immunoglobulin A nephropathy is a rare complication of seronegative SpA, principally seen in long-standing uncontrolled disease. Other causes of IgA nephropathy in relation to SpA include drugs such as NSAIDs and TNF inhibitors.[1] Our patient had not received TNF inhibitors and had been completely off NSAIDs for the prior 2 years, thus making NSAID-induced IgA vasculitis an unlikely etiology. There was no evidence of any secondary causes of IgA vasculitis such as infections or connective tissue disorders.

The role of the mucosal immune system of the gastrointestinal tract in the pathogenesis of SpA is well established.[2] In the setting of dysregulated mucosal immunity, peripheral B cells induce enhanced production of galactose-deficient IgA1 (Gd-IgA1). In Gd-IgA1, the abnormal glycosylation exposes galactose and *N*-acetylgalactosamine (GalNAc) residues, leading to neoepitope formation and autoantibody production against Gd-IgA1, culminating in the formation of circulating immune complexes. These immune complexes get deposited in the small vessels of the skin and the mesangium of the kidneys, further perpetuating the inflammatory process.[3]

In a study by Cowling et al., it was found that mean serum IgA levels were 38% higher in SpA patients compared to healthy controls. The IgA levels were elevated more in SpA patients with higher inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).[4] This increase in IgA levels may be because of altered mucosal immunity.

To date, only four cases have been reported of the association between IgA vasculitis and SpA. Beauvais et al. described two cases of long-standing SpA of 11 years disease duration presenting with cutaneous vasculitis and glomerulonephritis with IgA deposits. HLAB27 association was seen in one, and the other case had no such association. In addition, one of them also had digital ischemia.[5] John et al. described a young male presenting with concurrent HLA B27 positive ankylosing SpA, cutaneous vasculitis and nonspecific ileitis with a disease duration of 2 months.[6] Kamath et al. described a long-standing HLA B27 ankylosing spondylitis with disease duration of 7 years who presented with cutaneous vasculitis, gastrointestinal symptoms, arthritis and orchalgia.[7] None of these patients were on TNF inhibitors; however, some of them were using on-demand NSAIDs. Similar to the cases reported erstwhile in literature, our patient had a long disease duration of 15 years, but HLA B27 association was not detected.

Conclusion

In a patient with long-standing untreated axial SpA, the occurrence of uncommon manifestations is possible. In a patient with SpA presenting with purpuric skin lesions, proteinuria, and hypertension, coexisting IgA vasculitis should be considered.

Patient Consent Statement

The authors have obtained written informed consent from the patient for publication of the case report details and related images.

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CASE REPORT

Unveiling the Psychiatric and Neurological Manifestations of Idiopathic Hypoparathyroidism: A Case of Auditory Hallucinations and Seizure Disorder

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Received: 25 June 2024; *Accepted:* 07 December 2024

Abstract

Background: Idiopathic hypoparathyroidism (IHP) is a rare endocrine disorder characterized by hypocalcemia, leading to a diverse array of neurological and psychiatric manifestations. The emergence of psychiatric symptoms, particularly those that mirror primary psychiatric disorders, creates considerable difficulties in achieving a precise diagnosis and effective treatment.

Case description: A 35-year-old female patient was admitted with status epilepticus and a documented history of psychiatric illness. Initial investigations revealed hypocalcemia, hypomagnesemia, and hyperphosphatemia. A noncontrast computed tomography (CT) scan of the head showed striopallidodentate calcification, a characteristic finding in hypoparathyroidism. The patient reported persistent auditory hallucinations for the past 3 years, which were unresponsive to antipsychotic treatment. Additionally, she had a very low serum parathyroid hormone (PTH) level. Notably, the patient had no history of neck surgery, autoimmune disorders, cancers, radiation therapy, or infiltrative disorders such as hemochromatosis. There were no other congenital abnormalities or family history of similar illnesses. A diagnosis of IHP was established based on the patient's clinical symptoms and the results of the investigations. Calcium and magnesium supplements were started to correct the deficiencies of hypocalcemia and hypomagnesemia. Antiepileptic drugs were administered to control seizures. Despite the normalization of serum calcium levels, the patient's auditory hallucinations persisted, indicating a possible need for alternative therapeutic approaches.

Conclusion: This report emphasizes the need to consider IHP when diagnosing patients who present with ongoing psychiatric symptoms and seizures. The persistence of auditory hallucinations despite corrected hypocalcemia highlights the complexity of managing psychiatric manifestations in IHP. Early recognition and appropriate management of hypocalcemia are crucial for improving patient outcomes, although some psychiatric symptoms may remain refractory to conventional treatments.

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Introduction

Hypoparathyroidism results in hypocalcemia, which can present with a variety of symptoms. The history should emphasize eliciting symptoms and signs of neuromuscular irritability, including paresthesia in the fingertips, toes, and perioral area, irritability, fatigue, anxiety, mood swings, and personality changes.[1,2] Other potential symptoms encompass seizures, hoarseness of voice, wheezing, shortness of breath, muscle cramps, sweating, and biliary colicky pain.[1,2]

Moreover, hypomagnesemia, hypokalemia, and alkalosis (e.g., resulting from hyperventilation) can aggravate the clinical manifestations of hypocalcemia. During physical examination, patients commonly exhibit muscle cramps, with severe hypocalcemia potentially leading to the development of tetany. Neuromuscular irritability can be observed at the bedside by demonstrating the Chvostek and Trousseau signs.[1]

Extrapyramidal clinical features, such as parkinsonism, dystonia, hemiballismus, and oculogyric crises, can be seen in patients with idiopathic hypoparathyroidism (IHP).[3,4]

Spastic paraplegia, ataxia, dysphagia, and dysarthria have also been reported in connection with hypocalcemia associated with hypoparathyroidism. Severe hypocalcemia can cause raised intracranial pressure, which improves with the correction of calcium derangement.[1,5]

Patients with IHP have been documented to exhibit a range of psychiatric symptoms, including emotional instability, anxiety, depression, confusion, hallucinations, and even psychosis.[6,7] Normocalcemia corrects these conditions.

It has been estimated that at least 50% of the surgical cases of hypoparathyroidism have psychiatric manifestations, and the prevalence of psychiatric conditions is probably higher still in IHP.[8] Delirium is the most common clinical picture, while anxiety or depression is less common. Psychosis as the main presenting feature is uncommon and presents a diagnostic and therapeutic dilemma to psychiatrists.

Chronic hypocalcemia, associated with IHP, can also show clinical manifestations such as ocular cataracts, abnormal dentition, and dry, puffy, coarse skin, and nail changes (Beau's lines).[7,9,10]

Congestive heart failure and a prolonged QT interval on electrocardiogram (ECG) can be seen in severe hypocalcemia.[7,9] Correction of hypocalcemia reverses these cardiac effects of hypoparathyroidism.

Case Description

A 35-year-old female patient was admitted to us with status epilepticus, characterized by generalized tonic–clonic seizures.

During the physical examination, after stabilizing the patient in the emergency department, the Trousseau sign was noted during blood pressure monitoring, and the Chvostek sign was demonstrated.

The patient's vitals were stable except for tachypnea, which was later attributed to aspiration. Following seizure control, the patient was sent for a computed tomography (CT) scan of the head, which revealed striopallidodentate calcification (Figs 1 and 2).

Further inquiry into the patient's history revealed muscle spasms in both upper and lower limbs lasting 4–5 years, along with auditory hallucinations for the past 3 years. She also had a history of seizures for the past 1.5 years, for which she was receiving treatment.

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The addition of calcium and antiepileptics controlled the spasms and seizures. However, the auditory hallucinations were not controlled by antipsychotics. The patient reported hearing voices coming from her body, sometimes commenting on her activities. Despite these hallucinations, she had no disturbances in thought processes, was socially well-adjusted, took care of her baby, and interacted well with family members. However, she occasionally became agitated and violent due to the hallucinations.

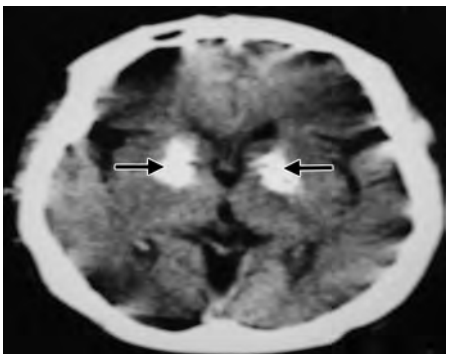

Fig. 1: Basal ganglia calcification. An axial noncontrast CT head scan demonstrating calcifications in the bilateral basal ganglia (indicated by black arrows)

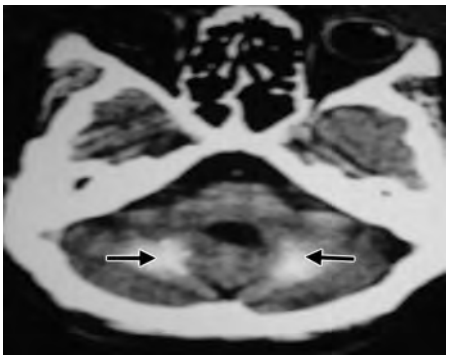

Fig. 2: Dentate nuclei calcification. An Axial noncontrast CT head scan illustrating calcifications in the bilateral cerebellar dentate nuclei (indicated by black arrows)

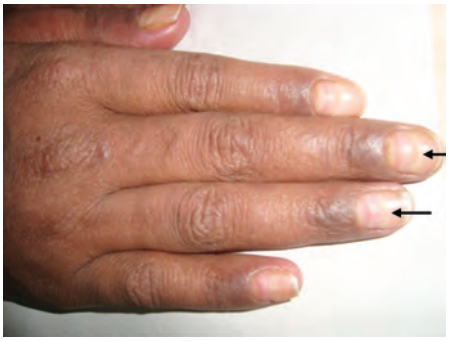

Fig. 3: Beau's line. The dorsal aspect of the hand exhibiting characteristic transverse indentations (Beau's lines) on the nail plate (indicated by a black arrows)

Laboratory results showed serum ionized calcium (iCa^{++}) of 3.68 mg/dL (normal level: 4.5–5.6 mg/dL) and total serum calcium of 7.2 mg/dL (normal level: 8.5–10.2 mg/dL). The patient's serum phosphate was 5.92 mg/dL (normal level: 2.5–4.5 mg/dL), serum magnesium (Mg^{++}) was 1.30 mg/dL (normal level: 1.8–2.6 mg/dL), and serum sodium/potassium (Na^{+}/K^{+}) levels were 133 mEq/dL (normal level: 135–145 mEq/dL) and 2.7 mEq/dL (normal level: 3.5–5.0 mg/dL), respectively. Serum parathyroid hormone (PTH) levels were sent and found to be low at 1.5 pg/dL (normal level: 15–68 pg/dL). These findings were indicative of hypoparathyroidism, which was later classified as idiopathic, given the absence of any surgical history or other identifiable causes.

On general examination, the patient exhibited Beau's lines (Fig. 3) and abnormal dentition, with no other congenital abnormalities. An X-ray of both hands showed no abnormalities in the shape or size of the phalanges. Cardiovascular and abdominal examinations were normal. Central nervous system examination revealed a Mini-mental State Examination (MMSE) score of 17, indicating moderate cognitive impairment.

There was no past history of neck surgery, autoimmune disorders, cancers, radiation therapy, or infiltrative disorders such as hemochromatosis. There was no family history of similar illness on pedigree analysis, further suggesting an idiopathic origin.

Upon discharge, the relevant laboratory investigations showed serum iCa^{++} of 4.36 mg/dL (normal level: 4.5–5.6 mg/dL) and total serum calcium of 8.4 mg/dL (normal level: 8.5–10.2 mg/dL). The patient's serum phosphate was 6.2 mg/dL (normal level: 2.5–4.5 mg/dL), and serum magnesium (Mg^{++}) was 1.90 mg/dL (normal level: 1.8–2.6 mg/dL).

A diagnosis of primary hypoparathyroidism (idiopathic) was made, and the patient was discharged with high doses of calcium and vitamin D supplementation, antiepileptics, and antipsychotics following psychiatric evaluation. On three consecutive follow-ups within 1.5 months, the patient reported no spasms or seizures. However, hallucinations persisted, and she did not respond to the combination therapy of antipsychotics prescribed by the psychiatrist. Despite the persistence of these auditory hallucinations, her overall quality of life improved, and she was able to resume her daily activities with less disruption.

Following, Table 1 shows investigations of patients on admission and discharge.

Table 1: Investigations of patients on admission and discharge

Parameters	*On admission*	*On discharge*
Hb%	7.3 gm/dL (normal level: 12–16 gm/dL)	8.9 gm/dL (normal level: 12–16 gm/dL)
TLC	9,000 (normal range: 4,000–11,000)	9,300 (normal range: 4,000–11,000)
DLC	P65L22E11 Normal range: P (40–60%), L (20–40%), M (2–8%), E (1–4%), B (0.5–1%)	P60L35E4 Normal range: P (40–60%), L (20–40%), M (2–8%), E (1–4%), B (0.5–1%)
Serum iCa^{++}	3.68 mg/dL (normal level: 4.5–5.6 mg/dL)	4.36 mg/dL (normal level: 4.5–5.6 mg/dL)
Total	7.2 mg/dL (normal level: 8.5–10.2 mg/dL)	8.4 mg/dL (normal level: 8.5–10.2 mg/dL)
Serum phosphate	5.90 mg/dL (normal level: 2.5–4.5 mg/dL)	6.2 mg/dL (normal level: 2.5–4.5 mg/dL)
LFT	WNL	WNL
RFT	WNL	WNL
Serum magnesium	1.30 mg/dL (normal level: 1.8–2.6 mg/dL)	1.90 mg/dL (normal level: 1.8–2.6 mg/dL)
Serum Na^{+}	133 mEq/dL (normal level: 135–145 mEq/dL)	132 mEq/dL (normal level: 135–145 mEq/dL)
Serum K^{+}	2.5 mEq/dL (normal level: 3.5–5.0 mg/dL)	3.1 mEq/dL (normal level: 3.5–5.0 mg/dL)
pH	7.47 (7.35–7.45)	7.43 (7.35–7.45)
CPK	1548 IU/L (normal level: 30–135 IU/L)	96 IU/l (normal level: 30–135 IU/L)
Serum PTH	1.5 pg/mL (normal level: 15–68 pg/mL)	

Discussion

Idiopathic hypoparathyroidism is an uncommon endocrine disorder characterized by insufficient secretion of PTH, leading to low calcium and elevated phosphate levels in the serum.[2,3] The clinical presentation can be diverse, ranging from mild neuromuscular irritability to severe, life-threatening conditions.[1,4] The following discussion highlights the pertinent findings and management strategies related to the presented case of IHP.

Pathophysiology

Parathyroid hormone plays a crucial role in calcium homeostasis by promoting calcium reabsorption in the kidneys, calcium release from bones, and the activation of vitamin D in the kidneys, which in turn enhances intestinal calcium absorption.[1,4] Deficiency or inactivity of PTH causes low serum calcium levels, manifesting as neuromuscular irritability, muscle cramps, tetany, and seizures.[1,2] Chronic hypocalcemia results from this deficiency, leading to complications such as basal ganglia calcifications. In our case, the prolonged history of muscle spasms in both upper and lower limbs is indicative of chronic hypocalcemia.[2,4]

Clinical Manifestations

The neurological symptoms of hypoparathyroidism are varied and can lead to a significant impairment in the patient's quality of life. Common manifestations include:

- Neuromuscular symptoms: Patients often present with clinical features such as muscle cramps, tetany, and carpopedal spasms due to increased neuromuscular excitability caused by hypocalcemia. The classic signs of Chvostek and Trousseau may be observed during physical examination.[1,9] Chvostek's sign is observed by percussing the facial nerve, resulting in the involuntary twitching of the facial muscles. Trousseau's sign is elicited by inflating a blood pressure cuff to a level above the systolic blood pressure for several minutes, inducing a carpal spasm. These signs are indicative of latent tetany and are highly specific for hypocalcemia.
- Neuropsychiatric symptoms: Hypocalcemia can cause various neuropsychiatric symptoms like irritability, anxiety, depression, and psychosis.[3,6] Auditory hallucinations are less common but are significant as they impact psychological health.[6] These symptoms can mimic primary psychiatric disorders, complicating diagnosis without thorough biochemical evaluation. Recognizing the interplay between hypocalcemia and psychiatric symptoms is crucial for optimal treatment in the context of IHP, ensuring comprehensive patient care.
- Seizures: Seizures are a severe manifestation of hypocalcemia, resulting from increased neuronal excitability.[1–4] They can range from minor focal seizures to generalized tonic–clonic seizures, requiring immediate correction of calcium levels.[1,11] Seizures are frequent in patients with IHP. A characteristic of seizures in hypocalcemia is resistance to anticonvulsant therapy.[12] Seizures initially decrease in frequency and finally cease when normal serum calcium levels are restored.[12] In our patient, seizures were controlled entirely after normalization of calcium and with the addition of antiepileptics.
- Extrapyramidal symptoms: Chronic hypocalcemia can lead to basal ganglia calcifications, resulting in movement disorders such as parkinsonism, choreoathetosis, and dystonia. These symptoms are due to the deposition of calcium salts in the brain, which alters basal ganglia function.[5,13] In this patient, bilateral basal ganglia and cerebellar dentate nuclei calcifications were seen on the CT head. The movement disorders associated with basal ganglia calcifications may include a spectrum ranging from mild tremors to severe dystonic posturing and chorea, significantly affecting the patient's motor function and quality of life.
- Cognitive impairment: Prolonged hypocalcemia can also affect cognitive function, leading to memory impairment, difficulty concentrating, and, in severe cases, dementia-like symptoms.[2,4] These cognitive changes can significantly affect daily functioning and quality of life.[12] Cognitive deficits can range from mild memory lapses and difficulty with complex tasks to severe impairments that mimic dementia.
- Autonomic dysfunction: Autonomic symptoms are less commonly reported, but some patients may experience symptoms such as palpitations, diaphoresis, and gastrointestinal disturbances, contributing to the overall symptom burden, which further complicates the clinical picture of hypoparathyroidism.[1]
- Dermatological manifestations: Chronic hypocalcemia can also lead to dermatological changes such as dry, coarse skin, brittle nails, and hair loss.[9] Due to calcium's impact on skin health, patients may also present with eczema or other skin conditions. While not life-threatening, these dermatological symptoms can greatly affect the patient's quality of life and self-esteem.
- Dental abnormalities: Hypoparathyroidism diagnosed in childhood can result in dental abnormalities, including enamel hypoplasia, delayed tooth eruption, and a higher propensity for dental caries.[7] These dental issues are due to the role of calcium in tooth development and maintenance.

Diagnostic Challenges

The diagnosis of IHP requires a thorough clinical evaluation and laboratory investigations. Key findings include hypocalcemia, hyperphosphatemia, and low or inappropriately normal levels of PTH. Neuroimaging studies, such as CT or magnetic resonance imaging (MRI), revealing characteristic basal ganglia calcifications, provide supportive evidence for the diagnosis. The occurrence of striopallidodentate calcifications in IHP is attributed to chronic hypocalcemia, hyperphosphatemia, poor calcium control, and elevated calcium-phosphate products.[14]

Several case reports have highlighted the diverse presentation of hypoparathyroidism. For instance, Sheldon et al. described a rare association between hypoparathyroidism and pseudotumor cerebri, suggesting that the neurological sequelae of hypoparathyroidism can be diverse and sometimes unexpected.[5] Similarly, the presence of psychosis in patients with hypoparathyroidism-induced hypocalcemia has been documented, underscoring the potential for psychiatric manifestations in these patients.[6]

In our case, the diagnosis of IHP was confirmed by the patient's typical clinical features, absence of family history, lack of other endocrinal deficiencies or congenital abnormalities, presence of hypocalcemia, hyperphosphatemia, low PTH levels, and a noncontrast CT scan of the head showing bilateral basal ganglia and cerebellar dentate nuclei calcifications.

The serum phosphate level was lower at admission compared to discharge, likely due to the intravenous use of dextrose, which reduced the level. After stopping intravenous dextrose, the serum phosphate level increased by the time of discharge. The patient exhibited respiratory alkalosis due to tachypnea (hyperventilation), which worsened the signs and symptoms of hypocalcemia. The cause of tachypnea was later determined to be due to aspiration caused by seizures.

Management

Managing IHP involves correcting hypocalcemia and keeping serum calcium

levels in the low-normal range. This is usually accomplished through the use of oral calcium supplements and active vitamin D forms like calcitriol. Thiazide diuretics may be used to reduce urinary calcium excretion in some cases. In patients with refractory hypocalcemia, recombinant PTH (teriparatide) has been used as an adjunct therapy.[2,7]

In this patient, a regimen of oral calcium and calcitriol was initiated, leading to symptomatic improvement. The use of calcitriol is particularly beneficial as it bypasses the need for renal conversion of vitamin D to its active form, which can be impaired in patients with hypoparathyroidism. Thiazide diuretics were considered to reduce renal calcium loss but were not needed due to adequate response to initial therapy.

Prognosis and Follow-up

Patients with IHP should be closely monitored for potential complications, including nephrocalcinosis and chronic kidney disease, which can result from prolonged hyperphosphatemia and calcium-phosphate imbalance. Regular follow-up visits should include an assessment of serum calcium, phosphate, renal function, urinary calcium excretion, and bone density to monitor for osteopenia or osteoporosis, which are common in the long-term management of hypoparathyroidism.[3,7] Additionally, patients should be educated about the symptoms of hypocalcemia and the importance of medication adherence to prevent acute hypocalcemic crises.[1,2]

In summary, IHP is a complex disorder with a wide spectrum of clinical manifestations. Early recognition and appropriate management are crucial to prevent complications and improve patient outcomes. Ongoing research and case reports continue to enhance our understanding of this condition, providing insights into its varied presentations and optimal management strategies.[1,2]

Conclusion

It is critically important to consider IHP in patients who present with persistent psychiatric symptoms and seizures. The patient's clinical presentation, characterized by generalized tonic–clonic seizures, muscle spasms, and auditory hallucinations, was indicative of severe hypocalcemia secondary to hypoparathyroidism. Despite appropriate correction of hypocalcemia and management of seizures, the persistence of auditory hallucinations highlights the complexity of psychiatric manifestations in IHP.

The detailed clinical history and thorough laboratory evaluation were pivotal in diagnosing IHP, particularly given the absence of surgical history or other identifiable causes of hypoparathyroidism. The findings of low serum calcium, phosphate imbalances, and diminished PTH levels were consistent with hypoparathyroidism, and the presence of basal ganglia calcifications further supported this diagnosis.

The patient's management involved a multidisciplinary approach, including adequate calcium and vitamin D supplementation to address hypocalcemia, antiepileptics for seizure control, and antipsychotics for psychiatric symptoms. While the somatic symptoms and seizures were well-controlled, the refractory nature of auditory hallucinations to standard antipsychotic treatment underscores the need for ongoing psychiatric support and potential exploration of alternative therapeutic strategies.

This case illustrates the need for heightened awareness and prompt intervention in managing IHP, emphasizing early recognition and appropriate treatment of hypocalcemia to prevent severe neuromuscular and psychiatric complications. Further research focused on individualized psychiatric interventions and comprehensive long-term management strategies is essential to improve the prognosis for patients with IHP. This case also underscores the crucial need for a holistic, patient-centered approach in the management of complex endocrine disorders that exhibit multifaceted clinical presentations.

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CASE REPORT

Interesting Case of Familial Partial Lipodystrophy Syndrome (Type 6) with *LIPE* Gene Defect: A Case Report

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Abstract

We report on an interesting case of familial partial lipodystrophy syndrome (type 6) due to a *LIPE* gene defect. Lipodystrophy syndromes are characterized by dysfunctional adipose tissue. While there are several types of lipodystrophies, this report is of a case of familial partial lipodystrophy with a *LIPE* gene mutation, which is very rare. Because the *LIPE* gene defect was of heterozygous nature, it presented in a milder clinical form. Thanks to genetic testing, we were able to clinch the diagnosis in this case. This case teaches us that we should have a high index of suspicion to pick up such rare cases and to offer genetic testing whenever indicated.

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Introduction

Lipodystrophy syndromes are ultrarare syndromes whose prevalence is 1.3–4.7 cases per million.[1] They can be either inherited or acquired due to dysfunction of the adipose tissue. These disorders can be classified as congenital or acquired lipodystrophy based on the degree of fat and further subclassified as congenital generalized or partial lipodystrophies and acquired generalized or partial lipodystrophies.[2,3] Congenital generalized lipodystrophies and familial partial lipodystrophies are the most common subtypes. Here, we elaborate on an interesting case of familial partial lipodystrophy with a *LIPE* gene mutation.

Case Description

Mrs S was diagnosed with diabetes at the age of 24 years in 2019 while undergoing investigations related to an ectopic pregnancy. Both parents, as well as three of her siblings, were detected with diabetes, one of whom died at the age of 45 years due to COVID-19. Grandparents were not detected to have diabetes. Mrs S was treated with a basal-bolus insulin regimen along with oral hypoglycemic agents. She came to our center in July 2024 with complaints of weight loss, increased frequency of thirst, and excess micturition, suggestive of uncontrolled blood sugar levels. On examination, there was mild acanthosis nigricans at the posterior aspect of the neck with no other clinical abnormalities. At our hospital, Mrs S was investigated and found to have a glycated hemoglobin (HbA1c) of 9.8%, fasting C-peptide levels of 0.84 pmol/mL, and stimulated C-peptide levels of 2.58 pmol/mL, indicating fairly good pancreatic beta-cell reserve. This, plus the fact that glutamic acid decarboxylase (GAD), islet antigen 2 (IA2) and zinc transporter antibodies were negative, ruled out type 1 diabetes. Triglyceride levels were also markedly elevated (416 mg/dL), and high-density lipoprotein (HDL) cholesterol was low (34 mg/dL). Ultrasound of the abdomen showed grade 2 fatty liver with a fatty pancreas. The clinical diagnosis suggested type 2 diabetes, and Mrs S was started on a sulfonylurea and metformin combination with basal insulin to correct the glucotoxicity. She was also given a dual peroxisome proliferator-activated receptor (PPAR) agonist, saroglitazar, for raised triglycerides. She responded well to the treatment, but there was weight gain. As she had a strong family history of diabetes and the age at onset of diabetes was below 30 years, a monogenic diabetes gene panel test was recommended. It was identified that she was harboring a heterozygous 19 base pair deletion (c.3203_3221del) in exon 10 of the *LIPE* gene (lipase E, hormone-sensitive type), which results in a frameshift and premature truncation of the protein 102 amino acids downstream to codon 1068 (p. Val1068GlyfsTer102), pathogenic for familial partial lipodystrophy 6 syndrome. The *LIPE* gene defect in the heterozygous state is a milder form, and hence the lipodystrophy was not pronounced in Mrs S. However, the elevated triglycerides and low HDL levels, along with diabetes, are features of familial partial lipodystrophy with a *LIPE* gene defect.

Discussion

Familial partial lipodystrophy is characterized by fat loss, usually in the limbs or the gluteal regions, sparing the abdomen. This abnormality is typically detected around puberty.[3] The selective loss of adipose tissue is accompanied by multiple metabolic complications, ranging from insulin resistance and hypertension to derangements in lipid profile, especially severe hypertriglyceridemia, and accumulation of fat in the liver. In generalized lipodystrophy, where there is greater fat loss, these metabolic derangements are more severe compared to partial lipodystrophy. In female patients with lipodystrophy syndromes, polycystic ovarian disease and infertility are also common.[4]

There are seven subtypes of familial partial lipodystrophy due to mutations in genes like *LMNA*, *PPARG*, *PLIN1*, *CIDEC*, *LIPE*, *AKT2*, or *CAV1*. The two most common types of familial partial lipodystrophy are types 2 and 3, with mutations in *LMNA* and *PPARG*. Lipodystrophy is clinically characterized by partial or complete absence of adipose tissue and ectopic deposition of adipose tissue, typically characterized by thin upper and lower limbs with truncal obesity or deposition of adipose tissue in the neck, submental, supraclavicular regions, or on the face, giving a cushingoid appearance,[5,6] along with metabolic derangements as described earlier.[7] Since Mrs S had a heterozygous mutation of the *LIPE* gene, which is a milder form, there was only mild acanthosis nigricans and dyslipidemia, along with diabetes.

Diagnosis of lipodystrophy can be challenging. It requires strong clinical suspicion, physical examination, and

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body composition studies. There are no definite diagnostic criteria for lipodystrophy. However, skinfold studies or imaging by dual-energy X-ray absorptiometry (DEXA) or magnetic resonance imaging (MRI) can help us clinch the diagnosis.[8–11] In our case, the monogenic diabetes panel, which we perform in all atypical young patients with diabetes, helped us clinch the diagnosis as a mild heterozygous form of familial partial lipodystrophy syndrome (type 6).

Conclusion

Since lipodystrophies are very rare, they can be wrongly diagnosed as type 2 diabetes with elevated triglycerides and low HDL cholesterol, and hence missed.

This case report emphasizes the value of genetic testing in those with young-onset diabetes, particularly in those with atypical features.

Patient Consent Statement

The author(s) have obtained written informed consent from the patient for the publication of the case report details and related images.

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Electrocardiogram Changes in Subarachnoid Hemorrhage: A Pictorial Essay

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Subarachnoid hemorrhage (SAH) is known to be associated with electrocardiogram (ECG) changes in many cases.[1] In different studies, the prevalence of ECG changes post-SAH has been found to be very high, with some studies reporting even 100% association.[2] The exact etiology of these ECG changes is still debated, but autonomic dysfunction and/or hypothalamic stimulation are thought to be important factors.[1] We here present the description of sequential ECG changes in a patient of SAH.

A 45-year-old female presented with sudden onset unconsciousness of 2 hours' duration. At the emergency room (ER), the blood pressure was found to be 190/100 mm Hg. There was some neck rigidity, and Glasgow Coma Scale score was 5. Computed tomography (CT) scan of brain done at the emergency showed (Fig. 1) extensive SAH. ECG tracings were done for this patient on consecutive days. They are described below:

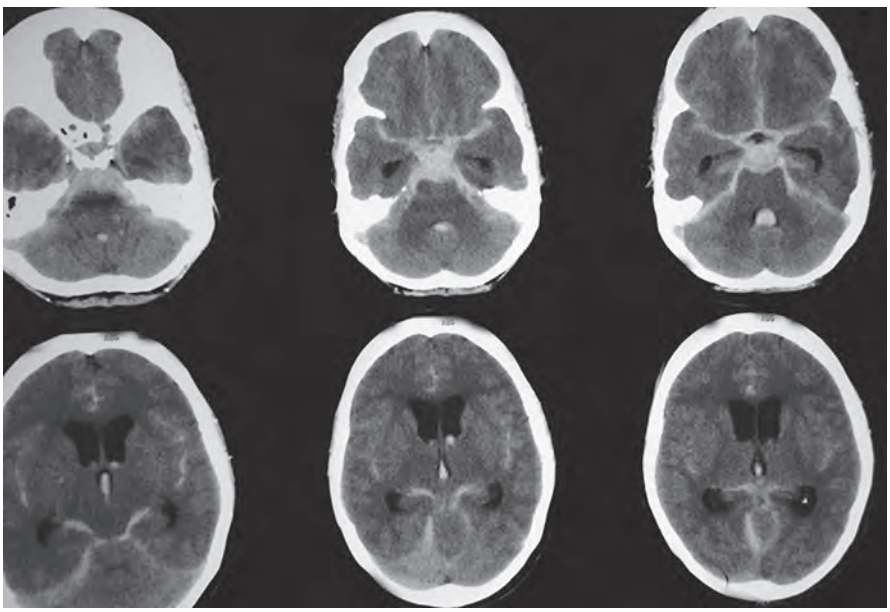

Fig. 1: Computed tomography scan of brain showing extensive SAH

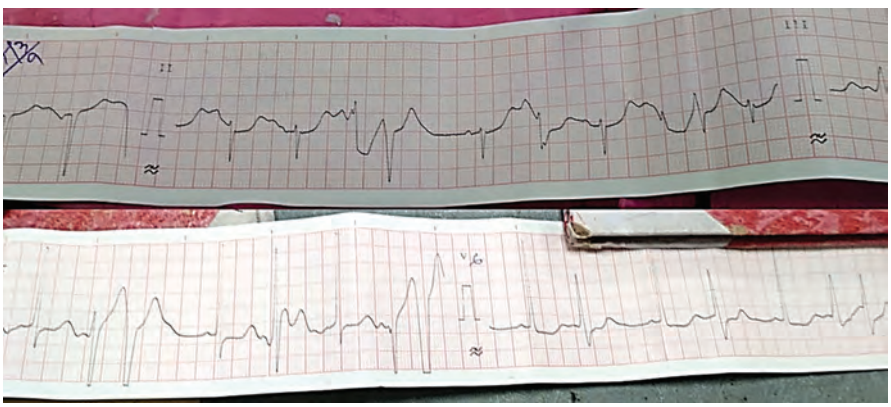

Fig. 2: Electrocardiogram: Day 1

Day 1: The rhythm was grossly irregular with multiple ventricular ectopics. The axis was rightward (Fig. 2).

Day 2: The rhythm reverted to normal sinus rhythm with bradycardia (rate = 60/minute). There was only occasional irregularity. There was prolonged QT interval (corrected QT = 720 milliseconds). There was ST depression and T inversion in all precordial leads (Fig. 3).

Day 3: The axis became normal. The rate was also normal (68/minute) and rhythm completely regular. ST-T changes in the precordial leads persisted. New prominent U waves were seen (Fig. 4). QT interval was 596 milliseconds.

Day 7: Axis normal. Rate = 90/minute. Rhythm regular. QT interval = 464 milliseconds. ST-T changes in right-sided precordial leads disappeared. The only ST-T changes were left ventricular hypertrophy (LVH) with strain pattern, probably due to preexisting hypertension (Fig. 5).

This pictorial essay depicts the various ECG changes in SAH. These changes, in isolation, can be quite confusing and may lead to inappropriate treatment decisions. For example, the ST-T changes from day 2 may lead to a diagnosis of myocardial infarction. In fact, there have been case reports of patients with SAH being misdiagnosed as acute coronary syndrome and treated for that diagnosis.[3]

The constellation of ECG changes in SAH is diverse. In a large study, the most prominent changes were those related to repolarization abnormalities like ST-T changes, U waves, and prolonged QTc.[4] These changes were found in our case. Like our case, cardiac arrhythmias

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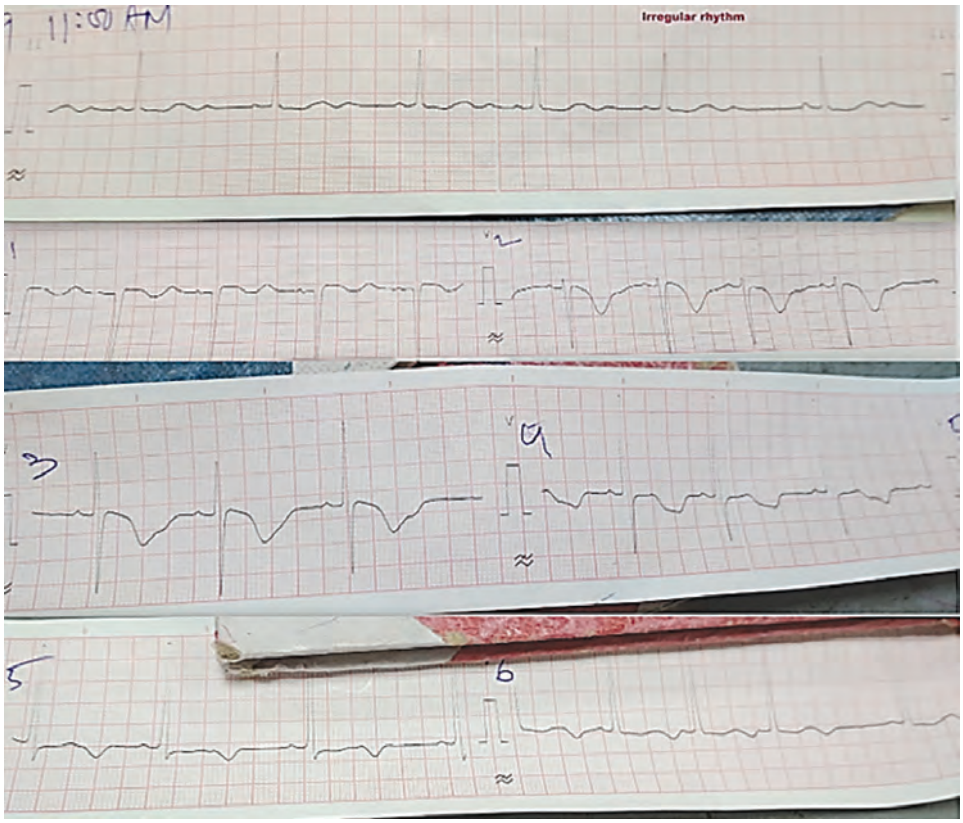

Fig. 3: Electrocardiogram changes: Day 2

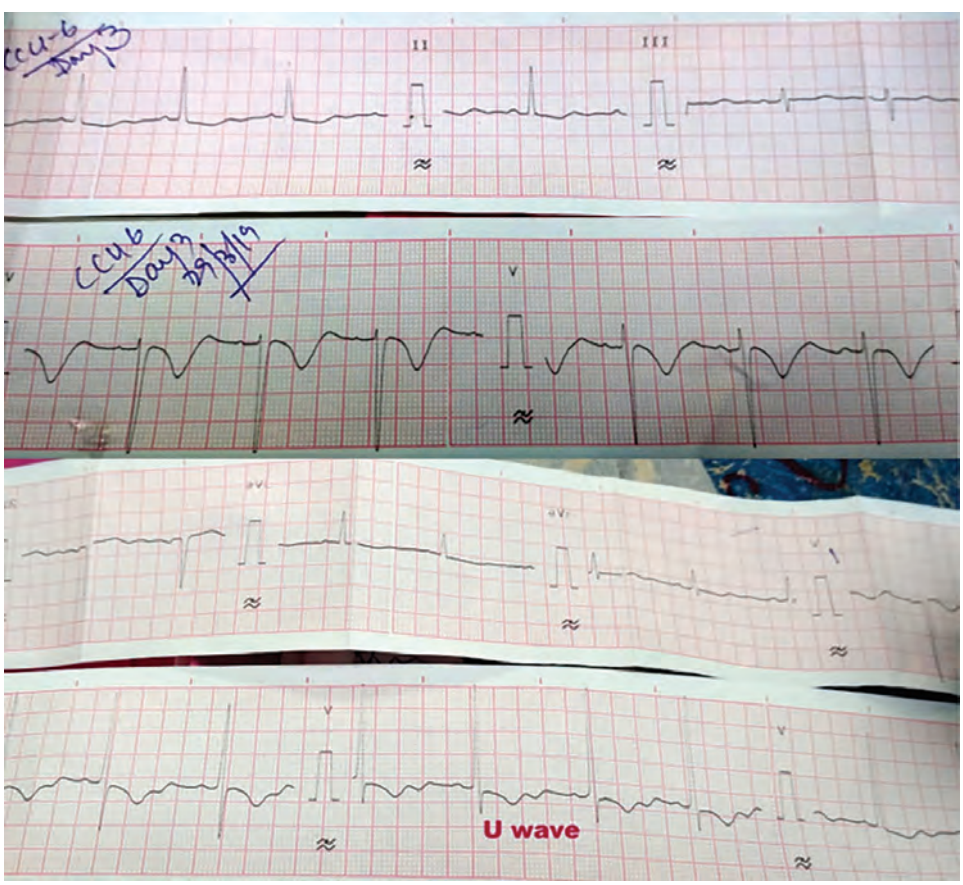

Fig. 4: Electrocardiogram: Day 3

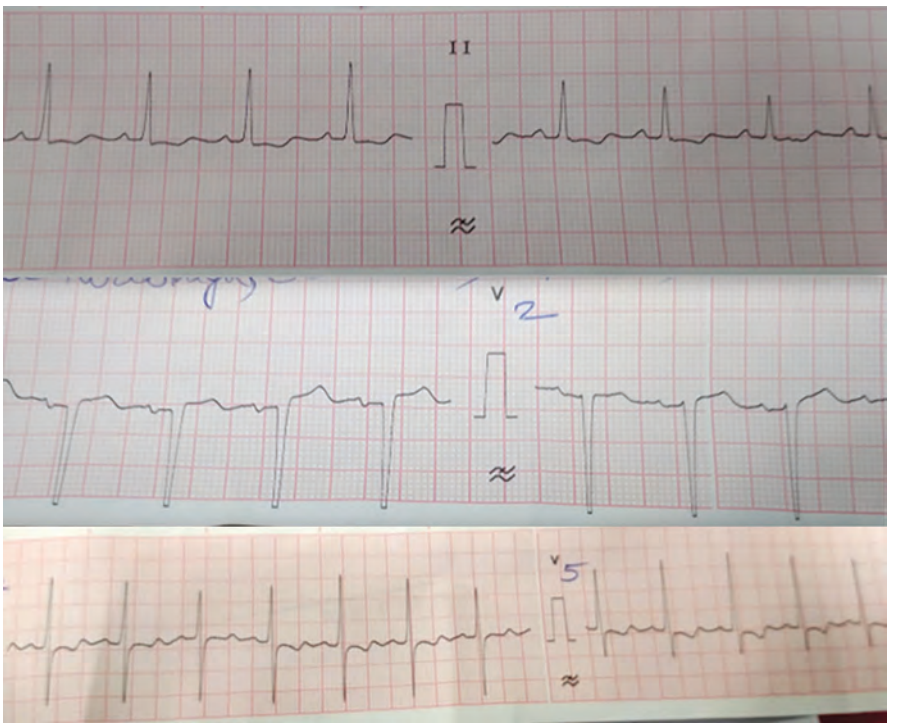

Fig. 5: Electrocardiogram changes: Day 7

like ectopic beats are also quite commonly reported.[1]

In many cases, these ECG changes revert to normal and cardiac function is unaffected. In our case too, the prominent changes were mostly reversed spontaneously by day 7.

We present this pictorial essay to sensitize clinicians to the varied ECG changes of SAH. In an unconscious patient with suggestive ECG abnormalities, there should be a low threshold for brain imaging to rule out probable cerebral causes of ECG anomalies.

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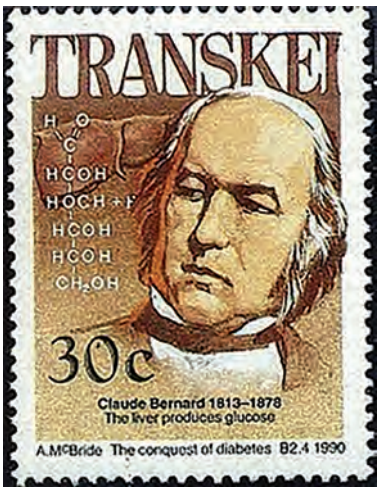
Otto Fritz Meyerhof and Muscle Biochemistry

JV Pai-Dhungat

Otto Warburg. Germany, 1983



Claude Bernard and glycogen molecule and liver. Transkei, 1990

Montreal Olympic, 1976. Muscle power in shot put. Dominica, 1976

Otto Fritz Meyerhof. Nicaragua, 1995

Otto Fritz Meyerhof (1884–1951) was born in Hanover, Germany. He graduated in medicine from Heidelberg University in 1909. He was interested in psychiatry at first, but a meeting with Otto Warburg drew him toward physiology and biochemistry. He joined the department of physiology at the University of Kiel in 1912 as an assistant and went on to the post of assistant professor of physiology in 1918. Meyerhof was interested in the mechanism by which the energy of foodstuffs is released and utilized by the body. He devoted himself to the biochemistry of muscle because energy in it is released as heat and mechanical action.

Claude Bernard (1813–1878) had isolated a starch-like substance in liver and muscles that he called glycogen a century back, and at Cambridge Gowland Hopkins proved that when muscle contracts under anaerobic conditions, lactic acid accumulates and the same lactic acid disappears when oxygen is supplied to it. Nothing was known of the chemical reactions involved for release of energy. No further work was done until Meyerhof entered the field at the end of World War I.

The method for estimating lactic acid in muscle was complex and required about a week to carry out; using a new rapid method devised by him, Meyerhof, in a series of careful experiments showed that there was a quantitative relationship between glycogen that disappeared and lactic acid that was formed. He also found that oxygen was not consumed during the process. What took place was anaerobic glycolysis. Meyerhof further observed that when muscle rested after work, some of the lactic acid was oxidized and molecular oxygen was then consumed to pay off the earlier "oxygen debt" as it was then called. The energy so developed made it possible for the major portion of lactic acid to be converted to glycogen. This became known as the Embden–Meyerhof pathway after him and his coworker in 1920. They established the cyclic character of energy transformations in the living cell.

In the physical field, Archibald Vivian Hill (1886–1977), about 1910, had been investigating the heat produced in muscle on contraction. Heat production was small, which was difficult to measure in the past. Hill made use of thermocouples, which swiftly and delicately recorded heat changes in the form of tiny electric current. He adapted himself for this purpose with great patience and ingenuity. Hill's results exactly matched with those of Meyerhof's. He showed that the heat was proportional to the work performed; he also demonstrated that about half the heat appeared during the anaerobic contraction phase, while the other half was evolved during the aerobic recovery phase. Hill concluded early in his work that not enough heat was evolved during the recovery period to account for the oxidation of all the lactic acid produced during contraction. Hopkins also had this important investigation checked at Cambridge, using the older method for estimating lactic acid. Meyerhof's results were fully confirmed.

The Nobel Prize in Physiology or Medicine 1922 was divided equally between Archibald Vivian Hill "for his discovery relating to the production of heat in the muscle" and Otto Fritz Meyerhof "for his discovery of the fixed relationship between the consumption of oxygen and the metabolism of lactic acid in the muscle."

Professor (Retired), Department of Medicine, Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital; Honorable Physician, Bhatia Hospital, Mumbai, Maharashtra, India

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Disseminated *Enterococcus* Infection: A Rare Cause of Lumbosacral Radiculopathy

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Sir,

Enterococcus, normal inhabitants of the large intestine of humans, have potential to cause varied infections, including infections of the urinary tract and central nervous system.

A 50-year-old, nondiabetic male presented with fever and low back pain radiating to both legs for 10 days, which increased with standing and forward bending, and was accompanied by numbness on the lateral parts of both legs, and had not undergone urethral instrumentation.

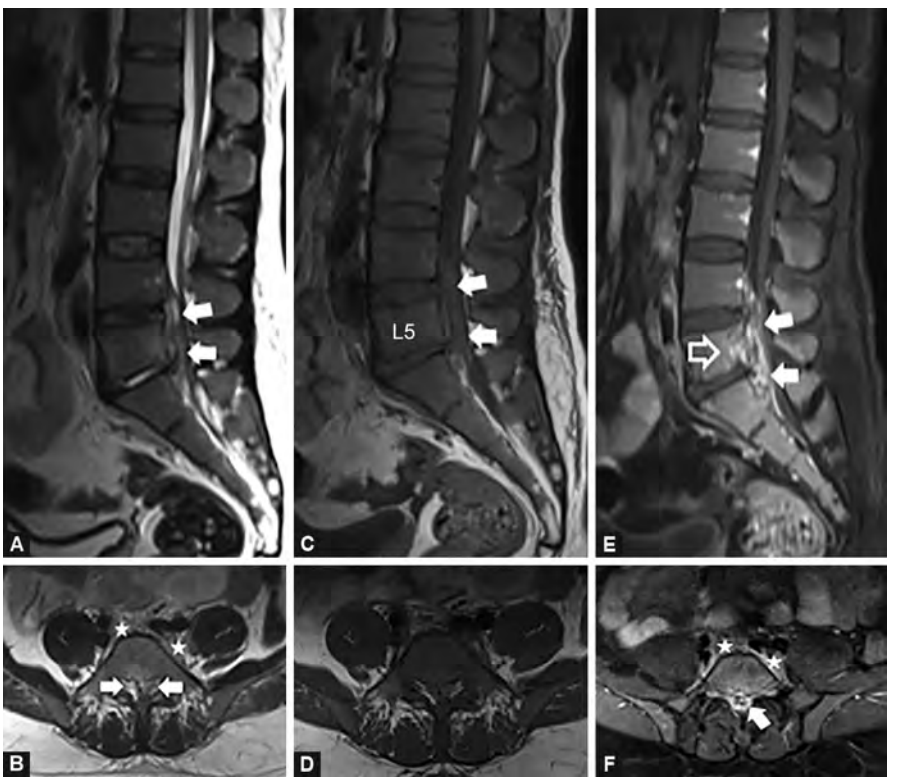
On examination, he was febrile with mild splenomegaly. Central nervous system examination revealed decreased power on flexion and extension in the left knee joint and ankle joint dorsiflexion (grade 4/5). Touch, pain, and temperature sensations were decreased on the lateral part of the legs and feet bilaterally. The rest of the examination was normal, and tenderness was present on the L5 vertebra.

Hemoglobin was 10.1 gm/dL, total leukocyte count 12,200/mm^3, platelets 92,800, ESR 70, and qCRP was 94.2 mg/L. Biochemical investigations were unremarkable. Urine microscopy showed 10–15 pus cells/HPF. Ultrasound of the abdomen and echocardiography were normal. Other investigations for tropical causes of fever were negative. Urine culture grew *Enterococcus* spp.

The magnetic resonance imaging (MRI) spine revealed a heterogeneously enhancing soft tissue in the anterior part of the spinal canal from L4 to S1 level, erosion and enhancement of the posterior body of the L5 vertebra (Figs 1A to F). The analysis of cerebrospinal fluid (CSF) showed protein 100 mg/dL, glucose 55 mg/dL, and a few Gram-positive cocci were seen. In CSF workup for tuberculosis, malignant cells were negative; however, CSF culture reported growth of *Enterococcus faecalis*. Echocardiography was normal. He was treated with inj. vancomycin for 2 weeks, and on discharge, linezolid was given for 3 more weeks. On follow-up after 1 month and 3 months after discharge, he was afebrile, back pain-free, jaundice disappeared, and weakness was fully recovered but with numbness on the dorsal part of the third to fifth toes of the left foot.

The meningitis due to *Enterococcus* remains an uncommon entity and involves patients with head trauma, shunt devices, or CSF leakage; however, occurrence as "spontaneous," secondary to enterococcal infections from endocarditis or pyelonephritis, has also been reported.[1]

The hematogenous route from a distant source or iatrogenic inoculation is the commonest route of spinal infection. The spondylodiscitis due to *Enterococcus* is infrequent.[2] A case of an anterior epidural inflammatory mass and lumbosacral involvement secondary to an infection of urinary origin due to *Enterococcus* was treated with antibiotic treatment.[3] The medical treatment with antibiotics in pyogenic spondylodiscitis is recommended, however, surgical intervention with antibiotics remains another option.[4]



Figs 1A to F: On contrast-enhanced MRI of the lumbosacral spine (A and B), sagittal and axial T2WI show an ill-defined, heterogeneously hyperintense signal intensity in lumbar epidural and pre/paravertebral soft tissue (A and B: solids arrows and asterisks, respectively), elucidating heterogeneous enhancement on postcontrast images suggestive of inflammatory changes (phlegmon) with necrotic areas (C and D: pre- and, E and F: postcontrast T1WI, solid arrows). Mildly enhancing heterogeneous T2 hyperintense signal is seen involving the L5 vertebra—more on posterior inferior aspect (C and E: pre- and postcontrast T1WI, open arrows) with T2 hyperintense but nonenhancing L5–S1 IVD, features suggestive of infective etiology with a possibility of atypical spondylitis

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ARBs: Which is the Best?

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Dear Sir,

We read the review article "Olmesartan: 360-degree Perspectives Befitting an Angiotensin Receptor Block" with interest and congratulate the authors.[1] We think the analysis focusing on only losartan, telmisartan,

and olmesartan will not help the readers to choose the angiotensin receptor block (ARB) in absence of discussion on other important ARBs like valsartan, candesartan, fimasartan, azilsartan, and irbesartan. We think evidence today fails to answer the question as to which ARB should be preferred in the management of hypertension (HTN), as presently all major guidelines discuss ARBs as a class of drugs for the management of HTN because of paucity of substantial direct comparative trials between different ARBs regarding their effects beyond blood pressure (BP) lowering. Existing evidence documents that ARBs differ from each other in various aspects of pharmacokinetics and cellular effects, and these differences influence their clinical efficacy, safety profile, and suitability for different patient populations. That is why the "best" ARB can vary depending on individual patient needs, health conditions, and specific treatment goals with each ARB having its strengths in different clinical situations.[2]

We suggest that a comparison of Olmesartan with other important ARBs like valsartan, candesartan, fimasartan, azilsartan, and irbesartan along with losartan and telmisartan, would have made the review article more rational and balanced and allowed clinicians to select the most appropriate ARB based on various aspects of pharmacokinetics, cellular effects, the individual patient's needs, comorbidities, treatment goals, and a step forward toward more personalized, precise treatments that can better address the complexities of HTN, its comorbidities, and associated risks. Next-generation ARBs are poised to revolutionize HTN therapy by offering more effective, safer, and more patient-friendly options, and still more evidence is needed to answer the question "which ARB is best."[3]

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