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Death and Dying in India: Circa 2018: What the Conscientious Physician Needs to Know

RD Gursahani¹, SV Khadilkar²

The Indian constitution gives us liberty. The concept of liberty has long standing origins and privacy and autonomy are the major personal attributes of liberty. In two recent judgments, the Supreme Court of India has affirmed our constitutional right to both.¹,² Autonomy here refers to the patient’s right and responsibility to choose, refuse or otherwise make their own decisions about their medical treatment. Such autonomy implies that the health care provider’s duty is limited to educating them about available choices and their consequences. In the Western tradition, this right to autonomy is absolute and may even supersede the physician’s duty of beneficence (do good) and non-maleficence (do no harm) in select situations.³ The ancient Indian tradition, however, refers to the term ‘Swa-dharma’ which suggests that our autonomy is conditional or negotiable and factors in the social identity as well.⁴ Thus, liberty and patient autonomy are important concepts for physicians to understand, appreciate and incorporate in their practice. As we in India are living longer, the issues of later years of life, particularly of dying and death are assuming importance and in general, the society and physicians find themselves unprepared to tackle them. Therein is the importance of the living will and advance care plans.

The reach and implications of living will is important to understand. The very recent Supreme Court judgment² of 9 March, 2018 has confirmed the validity and enforceability of duly executed living wills and advanced care plans in India. This concept was first propounded in 1969 by Louis Kutzner, an American human and civil rights advocate.⁵ As life support systems prolonged existence and death was ‘medicalized’ the common man found himself losing control over the decision making process. Increasing awareness of the consumer rights helped the movement to take back the control over one’s last days. As the movement gathered pace, state after state in America passed legislation in favour of living will/advance care plan until finally the US Congress passed the US Patient Self-Determination Act. This act requires all federally funded medical facilities to ask patients if they have or would like to complete LW/ACP, at admission. Thus Americans have almost four decades of experience in regularly utilizing these documents.

The scene in India is beginning to change only recently and the concept of ‘good death’ is gradually taking roots. Last year, the Economist magazine⁶ carried this line on its cover: “Dying is inevitable, a bad death is not!” Too many Indians die badly as confirmed by two Quality of Death reports⁷ in 2010 and 2015. So, what is Good Death?⁸ This concept can be divided into three components. First is the knowledge of when death is approaching and what can be expected. Goodbyes can then be said and a life review completed. This emotional closure is known to lead to a peaceful passing. But the required clarity of communication is not a part of routine in India and the public awareness of these issues is only recently emerging. Too often we are told by families not to tell the patient about their prognosis. While the relatives mean well, this infringes the autonomy of the patient and also is an act of medical omission.⁹ Natural variations of length of survival also handicap the medical judgement and this is one more reason why doctors do not initiate the discussion about death issues. However, it is relatively easy to identify the subset of our patients who have a greater than 50% risk of passing away within one year.¹⁰ It is our duty to initiate conversations about death and dying with patients or families in this situation. These discussions will help the family and the patient to handle the eventuality with maturity.

Second component of a good death is to have control over one’s last days with dignity and privacy. Worldwide the vast majority of people would prefer to die in their own homes, surrounded by their loved ones.¹¹ Very few knowingly accept death in a noisy and chaotic hospital ICU, with painful interventions and surrounded by unfamiliar faces and yet that is the reality for most of us today. Since one may not be in a position to communicate coherently towards the end, living wills and advance care plans are required. These may need to be supported by the discretionary power of another person, usually but not necessarily a relative. This individual acts as the Health Care Power-of-Attorney who can interact with the medical team. All of this is now possible for Indian citizens. But it requires the medical practitioner to be aware of his ethical duties in an evolving legal framework. Withholding and withdrawing futile life-sustaining treatments is the norm worldwide. This needs to be systematically incorporated in our country. Doing right can never be illegal and we have adequate constitutional and legal protection for doing so.¹²

Thirdly and above all, a good death requires control of the many symptoms that bedevil the dying process. Their frequency and severity are largely similar regardless of diagnosis. All of us need to be aware of the basic principles of palliative medicine, a new speciality with a minute presence in India¹³. Currently it is limited to looking after oncology patients and exists in the large cities only. But it is heartening for physicians to know

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that training programs in palliative care are being scaled up in India, with online and clinical components. These are targeted at physicians with clinical experience who are motivated to take up this challenging field. In addition to symptom control, palliative medicine training focuses on communication skills for essential and difficult conversations.

We, the conscientious physicians of India now need to appreciate a very important fact that the Supreme Court has made it possible for all of us to follow our dharma in a legally systematized manner when faced with a dying patient. This dharma includes continuing to care when cure is no longer possible and handing over to the other side with grace and dignity.

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EDITORIAL

Vivax Malaria: Benign No More

Niteen D Karnik¹, Dhirendra S Yadav²

Malaria still remains an important cause of multisystem organ failure (MSOF) needing ICU care in tropical and developing countries. The 2016 global estimate of malaria was 216 million cases.¹ Ninety percent of these were recorded in WHO African region followed by 7% and 1% respectively in South-East and Eastern Mediterranean regions. A 18% global reduction in malaria incidence is documented; the figures being 76/1000 population in 2010 and 63/1000 in 2016. The Indian data on malaria compiled by National Vector Borne Disease Control Programme (NVBDCP) showed 1.09 million cases in 2016 and 0.67 million in 2017 (till September). The incidence of falciparum malaria was 65.53 and 65.32 percent respectively in 2016 and 2017.² The 2017 World Malaria Report revealed a high percentage of vivax malaria in WHO regions of the Americas, South-East Asia and Eastern Mediterranean (64, >30 and 40 percent respectively). The global deaths still remain high despite advent of artemisinin based combination therapy (ACT); the figures being 4.46 and 4.45 lakhs in 2015 and 2016 respectively.¹

Emergence of Vivax Malaria

Saravu.et.al. in a study of 922 patients of malaria in Manipal, Karnataka (2014) showed plasmodium vivax as predominant species (63.4%) vs plasmodium falciparum (34.4%) with mortality of 0.34% and 2.21% respectively. The predictors of mortality were acute respiratory distress syndrome (ARDS) in vivax malaria and MSOF in falciparum malaria.³ A study of 50 pediatric plasmodium vivax malaria patients from Mumbai by Kumari M and Ghildiyal R (2014) showed 20% needing ICU care with 4% mortality.⁴

Vivax is now reported with increasing prevalence even in Africa. A recent 2016 Ethiopian study by Geleta G and Ketema T in 263 children with malaria showed a complication rate of 23% (46/200) for falciparum malaria. The corresponding figures for vivax and mixed malaria were 31% (9/29) and 29.4% (10/34) respectively.⁵

Malaria - Disease of Complications

These include cerebral malaria, normocytic anemia, hypoglycaemia, metabolic acidosis, acute renal failure and fluid disturbances. Acute pulmonary edema/ARDS, septicaemia with algid malaria and coagulation abnormalities contribute to morbidity and mortality.

The clinical indicators of poor prognosis are deep coma, convulsions, papilledema, decerebrate/deccorticate rigidity or opisthotonus, circulatory collapse, renal failure, ARDS and metabolic acidosis. The laboratory indicators are hyperparasitaemia (>5%), peripheral schizontaemia, PCV <15%, haemoglobin<5gm/dl, RBS <40 mg/dl, BUN >60 mg/dl, creatinine >3 mg/dl, SGOT,SGPT>120 IU/L and high venous lactate >5 mmol/l.⁶

The complications in vivax malaria were outlined in a study of 102 severe plasmodium vivax malaria patients by Patil.et.al (2015). They showed MSOF rate of 43.1% with high rates of haemotological, renal and hepatic dysfunction (89.2, 34.3 and 21.6 percent respectively). The comparative rates of cerebral malaria and ARDS were much lower (7.8 and 2 percent). The mortality rate was 6.9%.⁷

In a study of 539 adult severe malaria patients by Kochar.et.al (2014), 40.26% had MSOF. The risk was greatest with mixed malaria [90.9%,(40/44)], followed by 37.6%, (103/274) and 33.5%, (74/221) respectively for falciparum and vivax mono infection.⁸

In this issue of journal Trivedi et.al have discussed malaria in Intensive care focusing on patients requiring ICU admission.⁹ They have enrolled 100 adult confirmed malaria (70 P.Vivax, 18 P.Falciparum and 12 mixed) patients requiring ICU admission and having SOFA score of 4 or above. Mortality was 21% which was more in vivax (16/70, 22.9%) and mixed (4/12, 33.3%) compared to falciparum (1/18, 5.6%). Mean pulse, respiratory rate, PT-INR and SOFA score was higher and mean BP, GCS, HCO3 and Pao2/Fio2 ratio was significantly lower in expired patients. Respiratory involvement (ARDS) was more in vivax, whereas renal involvement and coagulation derangement was common in falciparum/mixed malaria patients. ARDS, hypotension, lower GCS score, metabolic acidosis and high SOFA score were predictors of mortality.⁹

This study highlights the emerging role of vivax in causing complicated malaria needing intensive care in India. Permanent neurological, hepatic or renal sequelae were not seen in survivors. 10% of survivors of pediatric complicated malaria have neurological sequelae in form of cerebellar ataxia, hemiparesis, speech disorders, hyponotonia or spasticity. The use of SOFA score in critically ill malaria patients was validated in this study. The only limitation of the study was admission bias in favor of malaria with ARDS for ventilator support. Due to resource restricted setting of a tertiary referral centre, all complicated malaria patients could not be admitted in the MICU.

Around 50 million women are estimated to be exposed to the risk of malaria in pregnancy annually¹⁰ especially in 1st and 2nd trimester. The ability of infested erythrocytes to sequester in placenta leads to placental malaria with high infant morbidity and mortality.¹¹ None of the 32 female patients in this study were pregnant.

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Has Advent of Artesunate Improved the Morbidity and Mortality of Malaria?

If 2 drugs with different mode of action and pattern of resistance are used, the pre-parasite probability of developing resistance to both drugs is the product of their individual pre-parasite probabilities. So if pre-parasite probability of developing resistance to artemisinin and mefloquine or lumefantrine is 1 in 10,12 then probability of spontaneous resistance with Artemisinin based combination therapy (ACT) would be every 1 in 1024/parasite. The estimated number of malarial parasites in world is 10.20 This makes resistance to ACT’s virtually impossible - once in 10,000 years!!.12

Complications in malaria however have not reduced to a significant extent despite ACT. Some of possible reasons are:-

1. Incomplete coverage: Patients receive antimalarial monotherapy instead of ACT.
2. Substandard drugs.
3. Incomplete and inadequate adherence to antimalarial regimen especially in hyperparasitic patients; vomiting may be contributory.
4. Treatment may be started late. Delay of even 48hours can produce a strong proinflammatory cytokine storm leading to NO induced endothelial damage.
5. Once Systemic Inflammatory Response Syndrome (SIRS) occurs, it may increase despite ACT.

Trivedi et al’s article outlined the mechanisms of organ dysfunction in complicated malaria and also the possible reasons for changing clinical profile of vivax malaria. The pharmacological hallmark of artemisinin derivatives is a rapid clearance of parasitaemia (24-48 hours). Does this provoke an intense cytokine storm? ARDS has been noticed to occur even during or after clearance of parasitaemia. Animal studies of anti-inflammatory and immunomodulatory effects of artemisinin derivatives allay this fear.13

**ARDS and MOSF-Genetic Predisposition and Biomarkers**

Genetic susceptibility plays a key role in ARDS pathogenesis especially genes encoding Angiotensin Converting Enzyme(ACE), Interleukin-10, Tumor Necrosis Factor-α (TNF) and Vascular Endothelial Growth Factor (VEGF).14 ACE has been associated with overall susceptibility to ARDS and the ACE-2 protein is the receptor for the Severe acute respiratory syndrome (SARS) coronavirus. Experimentally induced lung injury from SARS CoV can be attenuated by blocking the RAAS pathway.14 Similar sites may exist for malaria antigen. Some persons may have multiple genetic variants that modify the risk and outcome of ARDS and MOSF after exposure to infections like malaria, leptospirosis and dengue. This may explain the occurrence of malaria complications in the destined few.

Increased levels of biomarkers like IL-6, angiopeitin 2 have been associated with adverse outcomes in ARDS and these may be under genetic control.14 The success of human mesenchymal stem cells in ex vivo human lungs injured with live bacteria opens exciting avenues for future treatment of ARDS due to tropical infections.15

**References**

Mortality in Malaria: Intensive Care (MIMIC)

Trupti Trivedi1*, Poonam Bajaj2, Nivedita Moulick3, Namita Padwal4

Abstract

Background: While global incidence of malaria has fallen in last decade, it continues to be an important cause of mortality and morbidity in acutely ill febrile patients. Many patients with complicated malaria require ICU care. In past it was believed that vivax is a benign form of malaria, but now all complications of malaria are reported in vivax.

Aims and Objectives:
1. To find out proportion of patients with plasmodium vivax and plasmodium falciparum malaria requiring treatment in Medical ICU.
2. To compare clinical profile and severity of illness in these patients.
3. To study treatment received including organ support requirement in these patients and compare outcome in patients with vivax and falciparum malaria.

Results: During study period total 932 patients were diagnosed as confirmed malaria (601 vivax, 240 falciparum and 91 mixed) and 107 (vivax 74, falciparum 20, mixed 13) required ICU admission. Common symptoms observed apart from fever were, oliguria (48), dyspnea (41), bleeding (29), hemoptysis (15) and petechial rash (13). Mean BUN and creatinine and PT INR of falciparum/mixed malaria patients was significantly higher and HCO3 and pH significantly lower than vivax patients. But PaO2/FiO2 of vivax patient was significantly lower as compared falciparum/mixed patients. There was no significant difference between two groups with regards to requirement of supportive treatment like inotropes (11/70 vs 5/30, p=0.858), mechanical ventilation (28/70 vs 7/30, p=0.17), platelet transfusion (24/70 vs 9/30, p=0.853) and renal replacement therapy (5/70 vs 3/30 p=0.936). Out of 100 patients, 21 patients expired. Mortality in mixed malaria group (4/12, 33.3%) and vivax group (16/70, 22.9%) was more as compared to falciparum/mixed patients. There was no significant difference between two groups with regards to requirement of supportive treatment like inotropes (11/70 vs 5/30, p=0.858), mechanical ventilation (28/70 vs 7/30, p=0.17), platelet transfusion (24/70 vs 9/30, p=0.853) and renal replacement therapy (5/70 vs 3/30 p=0.936).

Conclusions: Incidence of Plasmodium vivax malaria is higher compared to falciparum malaria in hospitalized patients and higher percentage of these need ICU care. Most common complications of malaria are thrombocytopenia followed by renal failure, hepatic dysfunction, ARDS, shock and cerebral dysfunction respectively. Mortality was higher in vivax and mixed malaria compared to falciparum. Higher SOFA score (Sequential organ failure assessment score), lower GCS score (Glasgow coma scale), hypotension, ARDS and metabolic acidosis are predictors of mortality.

Introduction

Malaria is one of the most common causes of deaths from infectious diseases in India and continues to cause significant economical burden. Global incidence of malaria seems to have peaked in 2003 at 232 million cases and has since fallen by about 29% to 165 million new cases in 2013. Plasmodium falciparum is considered to be the main cause of severe and fatal disease, responsible for major complications like cerebral malaria, acute respiratory distress syndrome, hepatic and renal failure, severe acidosis, severe hemolysis and anemia. There were substantial explanations to support the benign nature of vivax malaria till 20th century like low parasite biomass, increased deformability parasitized RBCs and relative paucity of parasite sequestration compared to P. falciparum. There has been remarkable increase in case reports, series and studies describing severe and fatal disease with vivax malaria recently. All complications like coma, renal failure, hepatic failure, acute respiratory distress syndrome (ARDS), acidosis, bleeding, shock, multi-organ dysfunction have been recognized in vivax malaria. Now with more sensitive and specific molecular diagnostics and PCR studies, vivax mono-infection is being reliably diagnosed and dilemma of mixed infection causing complications has been removed. A combination of microcirculatory occlusion, cytokine activation, and nitric oxide-mediated changes in vascular tone are believed to cause organ dysfunction that characterizes severe malaria. This can occur in many different organs, a feature that can partly explain the complexity of the clinical manifestations occurring in severe malaria. Another observation made over last few years is that the pattern of complications associated malaria is changing. Hence this study was undertaken to estimate the incidence of severe vivax malaria requiring ICU admission compared to falciparum and mixed malaria and to compare various clinical, and laboratory parameters between vivax and falciparum malaria and determine factors associated with risk of mortality.

Aims and Objectives

1. To find out proportion of patients with plasmodium vivax and plasmodium falciparum malaria requiring treatment in Medical ICU.
2. To compare clinical profile and severity of illness in these patients.

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Annexure 1: SOFA SCORE for assessment of severity of disease

<table>
<thead>
<tr>
<th>SOFA score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration PaO2/FIO2 (mmHg)</td>
<td>&gt;400</td>
<td>&lt;400</td>
<td>221-301</td>
<td>142-220</td>
<td>&lt;100</td>
</tr>
<tr>
<td>SaO2/FIO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;67</td>
</tr>
<tr>
<td>Coagulation Platelets x 1000/mm³</td>
<td>&gt;150</td>
<td>&lt;150</td>
<td>100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Liver serum bilirubin</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-5.9</td>
<td>6.0-11.9</td>
<td>&gt;12.0</td>
</tr>
<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypotension</td>
<td>MAP &lt;70</td>
<td>Dopamine ≤5 or dobutamine (any)</td>
<td>Dopamine &gt;5 or norepinephrine ≤0.1</td>
<td>Dopamine &gt;15 or norepinephrine &gt;0.1</td>
</tr>
<tr>
<td>CNS Glasgow Coma Score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Renal Creatinine (mg/dL) or urine output (mL/d)</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-3.4</td>
<td>3.5-4.9 or &lt;500</td>
<td>5.0 or &lt;200</td>
</tr>
</tbody>
</table>

3. To study treatment received including organ support requirement in these patients and compare outcome in patients with vivax and falciparum malaria.

Material and Methods

It was an observational study in medical ICU (MICU) of a tertiary care centre in Mumbai. All patients admitted to hospital with confirmed malaria (smear and/or rapid test) were screened and those admitted to MICU following were included.

Inclusion Criteria

1. All patients with age >12 years in ICU with confirmed malaria by peripheral smear or rapid antigen test and giving valid consent.

2. Sequential Organ Failure Assessment (SOFA) score of equal to or more than 4 on admission to MICU.

Exclusion Criteria

1. Patients having other concomitant cause for acute febrile illnesses (AII) like dengue, leptospirosis, enteric fever, scrub typhus or viral hepatitis.

2. Patients with pre-existing severe end stage disease like chronic kidney disease (CKD), advanced AIDS, end stage liver disease and terminal malignancies.

Study Procedure

All indoor patients admitted to hospital over a period of 18 months with acute febrile (AII) illness were screened for presence of malaria by Peripheral Smear and/or rapid malaria antigen test. Patients requiring Medical ICU care and satisfying inclusion criteria were studied in details. Detailed history was taken which included history of presence, duration and pattern of fever, breathlessness, bleeding, oliguria, altered sensorium, convulsion and any other symptoms. Previous treatment with antimalarials and other supportive treatment were noted. Examination was performed with specific emphasis over blood pressure, respiratory rate, icterus, petechiae, hepatosplenomegaly and organ failure signs. Routine hematological and biochemical investigations were carried out which included complete blood count with peripheral smear, rapid malaria antigen test, liver function tests, renal function test, arterial blood gas analysis, chest X-ray and ECG. Tests to diagnose other causes for AII like dengue, enteric fever or leptospirosis were done. For dengue, NS1 antigen test was done if patient presented within 5 days of fever onset. Beyond that duration, dengue IgM and IgG antibody test was done. For leptospirosis, PCR (polymerase chain reaction) and leptospira IgM antibody tests were done. For enteric fever blood culture was done. Special tests like USG abdomen, CT, MRI, CSF examination, and 2D-ECHO were carried out when indicated. Patients disease severity index was calculated using SOFA score (annexure 1). Patients were followed up till hospital discharge or death. Primary end point was survival. Secondary end points were duration of hospital stay and requirement of supportive treatment like hemodialysis, ventilator, inotropes and blood component transfusions.

Statistical Analysis: data was analyzed Student’s t test for quantitative data. Chi square test and Fishers exact test were applied for qualitative data depending on sample size.

Results

During study period total 932 patients were diagnosed as confirmed malaria (601 vivax, 240 falciparum and 91 mixed) and 107 (vivax 74, falciparum 20, mixed 13) required ICU admission and had SOFA score of 4 or more. Of these 7 patients were excluded from the study as 2 had concomitant dengue (NS1 antigen positive), two had leptospiros (PCR test positive). One patient was suffering from terminal malignancy two were having underlying chronic kidney disease. Following this exclusion, remaining 100 patients were studied in detail further. Out of these 100 patients, 32 were malaria positive by smear only, 28 were positive by rapid malaria test and 40 were positive by both.

Their demographic data is shown in Table 1. Age of patients ranged from 15 - 73 years with average a 36.61 years in falciparum group which was comparable with 33.17 and 34.29 years in mixed and vivax group. Out of all 100 patients, 68 patients were male and 32 were female. Three patients were pregnant (2 vivax positive and one falciparum). As there were very few patients in falciparum group and sizable number of patients in mixed group, both are considered together henceforth in analysis for statistical purpose.

As shown in Table 2 common symptoms observed were fever (100) followed by oliguria (48), dyspnea (41), bleeding (29), hemoptysis (15) and petechial rash (13). There was no significant difference between symptoms of vivax and Falciparum/mixed malaria. As shown in Table 3, respiratory rate of patients in vivax group at presentation was significantly more as compared to falci/mixed group. Mean BP was lower in vivax group than in Falcic/mixed group but the difference was statistically not significant. SOFA score was similar between the two groups (vivax 9.6, falciparum/mixed 9.87 p=0.729). As shown in Table 4 complications noted were thrombocytopenia followed by renal involvement, hepatic involvement, ARDS, hypotension, anemia and cerebral malaria respectively. There was no significant difference between two groups with regards to these complications. As shown in Table 5, Mean BUN and creatinine and PT
Table 1: Demographical data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Falciparum (n=18)</th>
<th>Mixed Malaria (n=12)</th>
<th>Vivax (n=70)</th>
<th>Total (n=100)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>36.61±9.34</td>
<td>33.17±13.84</td>
<td>34.29±13.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>23 – 56</td>
<td>17 – 57</td>
<td>15 – 73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (66.7)</td>
<td>09 (75.0)</td>
<td>47 (68.1)</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>06 (33.3)</td>
<td>03 (25.0)</td>
<td>23 (31.9)</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

*By Student ‘t’ Test; P Not Significant; # by Chi-square Test; P Not Significant

Table 2: Comparison of symptoms in Vivax and Falciparum/mixed Malaria in ICU

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Vivax (n=70)</th>
<th>Falc/Mixed (n=30)</th>
<th>Total (n=100)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>70(100%)</td>
<td>30(100%)</td>
<td>100(100%)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>32(45%)</td>
<td>9(30%)</td>
<td>41(41%)</td>
<td>0.214</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>12(17%)</td>
<td>3(10%)</td>
<td>15(15%)</td>
<td>0.541</td>
</tr>
<tr>
<td>Bleeding</td>
<td>20(28%)</td>
<td>9(30%)</td>
<td>29(29%)</td>
<td>0.923</td>
</tr>
<tr>
<td>Rash</td>
<td>9(12%)</td>
<td>4(13%)</td>
<td>13(13%)</td>
<td>0.795</td>
</tr>
<tr>
<td>Oliguria</td>
<td>30(42%)</td>
<td>18(60%)</td>
<td>48(48%)</td>
<td>0.176</td>
</tr>
</tbody>
</table>

@By Student ‘t’ Test; P Not Significant; # by Chi-square Test; P Not Significant

Table 3: Comparison of examination findings in Vivax and Falciparum/mixed Malaria in ICU

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Vivax (Mean±SD)</th>
<th>Falc/Mixed (Mean±SD)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse</td>
<td>88.45±13.36</td>
<td>84.43±10.95</td>
<td>0.15</td>
</tr>
<tr>
<td>Mean BP</td>
<td>71.75±14.57</td>
<td>77.36±20.75</td>
<td>0.126</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>26.21±9.72</td>
<td>22±7.09</td>
<td>0.035</td>
</tr>
<tr>
<td>GCS</td>
<td>13.95±1.91</td>
<td>14.03±2.24</td>
<td>0.856</td>
</tr>
<tr>
<td>SOFA</td>
<td>9.6±3.69</td>
<td>9.87±3.23</td>
<td>0.729</td>
</tr>
</tbody>
</table>

*By Student t test

Table 4: Comparison of complications Vivax and Falciparum/mixed Malaria in ICU

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Vivax (n=70)</th>
<th>Falc/Mixed (n=30)</th>
<th>Total (n=100)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension (mean BP&lt;70 mmHg)</td>
<td>25(35.7%)</td>
<td>7(23.3%)</td>
<td>32(32%)</td>
<td>0.326</td>
</tr>
<tr>
<td>Tachypnea (Respi rate&gt;20)</td>
<td>37(52.8%)</td>
<td>9(30%)</td>
<td>46(46%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Cerebral malaria (GCS&lt;10)</td>
<td>4(5.7%)</td>
<td>3(10%)</td>
<td>7(7%)</td>
<td>0.732</td>
</tr>
<tr>
<td>Anaemia (Hb&lt;12 for males &amp; &lt;11 for females)</td>
<td>18(25.7%)</td>
<td>28(26%)</td>
<td>46(46%)</td>
<td>0.881</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet&lt;1.5 L)</td>
<td>70(100%)</td>
<td>29(96.6)</td>
<td>99(99%)</td>
<td>0.661</td>
</tr>
<tr>
<td>Renal involvement (creatinine &gt;1.5mg%)</td>
<td>50(71.4%)</td>
<td>26(86.6)</td>
<td>76(76%)</td>
<td>0.168</td>
</tr>
<tr>
<td>Hepatic involvement (total bilirubin &gt;2mg %)</td>
<td>43(61.4%)</td>
<td>24(80%)</td>
<td>67(67%)</td>
<td>0.115</td>
</tr>
<tr>
<td>ARDS (PaO2/FiO2&lt;300)</td>
<td>32(45.7%)</td>
<td>7(23.3%)</td>
<td>39(39%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

(Chi square test)

INR of falciparum/mixed malaria patients was significantly higher and HCO3 and pH significantly lower than vivax patients. But PaO2/FiO2 of vivax patient was significantly lower as compared falciparum/mixed patients. There was no significant difference between two groups with regards to mean Hemoglobin, platelet count, liver function test (SGOT, SGPT, total bilirubin) and random blood glucose value on admission. There was no significant difference between two groups with regards to requirement of supportive treatment like inotropes (11/70 vs 5/30, p=0.858), mechanical ventilation (28/70 vs 7/30, p=0.17), platelet transfusion (24/70 vs 9/30, p=0.853) and renal replacement therapy (5/70 vs 3/30 p=0.936).

Out of 100 patients, 21 patients expired. Mortality in mixed malaria group (4/12, 33.3%) and vivax group (16/70, 22.9%) was more as compared to falciparum group (1/18, 5.6%, p<0.05). As shown in Table 6 Mean pulse, respiratory rate, PT-INR and SOFA score was significantly higher and mean BP, GCS, HCO3 and PaO2/FiO2 was significantly lower in patients who expired. As shown in Table 7 dyspnea, hemoptysis, bleeding, hypotension, tachypnea and X-ray infiltration of ARDS were significantly more in patients who...
succumbed. However presence of oliguria, anemia, thrombocytopenia, renal and hepatic involvement did not have significant impact on survival. As shown in Figure 1, mortality of patients increased with increase in number of organ dysfunction (p<0.0001). Duration of ICU stay in survived patients varied from 2 to 23 days. Hypotension (13/39 vs 7/40), renal involvement (32/39 vs 27/40) and hepatic involvement (30/39 vs 25/40) was more in survived patients whose ICU stay was of more than 4 days. But this difference was statistically not significant. Initial SOFA score was more in survived patients whose stay in ICU was more than 4 days (9.28 vs 7.98, p=0.026).

Out of 35 patients who required mechanical ventilation, 4 patients suffered from VAP (Ventilator Associated Pneumonia). Five patients out of 100 patients developed catheter associated urinary tract infection. These patients were treated with appropriate antibiotics. There was no long term morbidity in any the form of permanent neurological, hepatic or renal sequel in any of the survived patients. One of the expired patients underwent autopsy. His lung showed remarkable changes of ARDS like thick hyaline membrane, inflammatory cells and destruction of alveolar spaces as shown in Figure 2.

Discussion

P. vivax malaria is now increasingly associated with severe disease and high case fatality. The exact cause of changes in the clinical profile of vivax malaria is uncertain. Genetic alterations of the parasite or vector or chloroquine resistance may be responsible. It was previously believed that the severe disease with vivax malaria is actually caused by co-infection of vivax and falciparum and while schizonts of P. vivax are detected in venous blood in contrast those of P. falciparum remain undetected as they are found in the capillaries of internal organs. However with availability of the recently developed tests of malarial antigen and the nucleic acid amplification technique it has become evident that vivax mono-infection can be a cause of severe malaria and death. In present study mixed infections were identified by peripheral smear and rapid malaria test. In 2009 Kocher et al reported series of 11 cases of severe vivax malaria from Bikaner. They used antigen and PCR test to exclude falciparum co-infection. In present study there were more hospital admissions with vivax as compared to falciparum malaria. This is concordant with the fact that in India and other Southeast Asian countries, incidence of vivax malaria is on rise. In Africa also where falciparum is much more common, vivax is emerging as a major type of malaria with complications. A similar study of clinical profile of malaria in 314 patients, done in a tertiary referral centre in South Canara, plasmodium vivax was the major parasite type (52.54%), followed by P. falciparum (33.75%), and followed by mixed malarial infection (13.69%) which matches with the pattern observed in present study. Study from a tertiary care hospital in Mumbai also showed higher incidence of severe vivax malaria than falciparum and mixed malaria.

Most of the patients were in the age group of 21-30 years. This finding matches observations in a study done in South Canara (Karnataka) aimed at studying the demographic profile of malaria. Majority of their patients were males between the age group of 15 and 40 years. The factors responsible for this pattern include outdoor work and outdoor sleeping habits in young males and other socioeconomic and cultural factors. There was no significant difference between symptoms of vivax and Falciparum/ mixed malaria in this study. It is difficult to differentiate various types of acute undifferentiated fevers in tropics based on clinical presentation alone- an enlarged liver and spleen could be found in malaria, dengue, typhoid fever and leptospirosis. Similarly, headache, neck stiffness and other signs of meningeal inflammation-traditionally associated with meningitis, lack accuracy for ruling in or ruling out meningitis. Thrombocytopenia, renal failure and liver dysfunction were common complications. Only one third of patients with thrombocytopenia required platelet transfusions as they were administered only in case of clinical bleeding or severe thrombocytopenia with platelet count <10000/cmm. Only 7.14% patients with renal failure required renal replacement therapy. Mean BUN and creatinine value was significantly more in falciparum patients as compared to vivax patients which was similar to what has been observed in another study from Mumbai. Hepatic involvement was not significantly different in vivax and falciparum/mixed malaria. Cerebral malaria was found in 7% of patients with higher incidence in falciparum/ mixed malaria (10%), but the difference was not statistically significant. Cerebral malaria was much less as compared to 40% incidence in a similar study done in an ICU at tertiary care hospital in Mumbai in 2002. A study by Tjitra in Southeast Asia showed severe anaemia as the most common complication but there were no such patients in present study. The prevalence of ARDS was comparable in both the groups but the mean
value of PaO2/FiO2 was significantly less in P. vivax compared to falciparum malaria as compared to vivax malaria.11 All these complication patterns clearly shows that over a decade, cerebral malaria and severe anaemia have remarkably decreased while ARDS and renal, hepatic dysfunction are increasing in severe malaria. Reasons for this changing pattern of complications can be change in virulence or genetics of the parasite or early use of faster acting anti-malarial drugs16 or a combination of multiple factors. Recent analysis suggests that severe malarial anemia, severe thrombocytopenia, pulmonary distress, cerebral syndromes (ranging from seizures to coma), and hepatic and renal dysfunction dominated reported syndromes in patients with a diagnosis of P. vivax infection and classified as having severe disease. Severe ill patients with a diagnosis of P. falciparum infection have the same syndromes but are more likely to present with two or more of these.17 A recent retrospective study concluded that anemia, hepato-renal dysfunctions were equally frequent in vivax malaria and it can no longer be considered as benign infection.18

In our study the overall mortality was 21% and P. vivax and mixed malaria had higher mortality than falciparum malaria, which was in contrast to an observational study done at another tertiary care hospital in Mumbai19 where mortality was significantly lower in vivax malaria (1.77%) than in falciparum (9.71%) and mixed malaria (10.29%). However that study was on all hospitalized patients and present study was in ICU patients. A study from Orissa found that there were 4 independent risk factors for a patient of developing complicated malaria-no fever on presentation, high parasite count, mono infection with falciparum, and longer fever to treatment interval.19 Predictors of mortality in our study were higher SOFA, lower GCS, hypotension, metabolic acidosis and ARDS irrespective of species of malaria. A study by V.B. Kute in Ahmedabad concluded that Mortality in malaria was associated with higher APACHE II, SOFA, MODS, GCS scores and requirement of inotrope, and ventilator support.20

There are important limitations of present study. As during monsoon season there is a surge of admission of patients with acute febrile illness and there are large number of patient needing ICU care. But there are constraints due to limited number of ICU beds, hence all cases of severe malaria needing ICU care cannot be shifted to ICU and many of them are continued to be managed in the general wards. Those who require mechanical ventilation and inotropic support are given preference over patients with other organ involvement for ICU care. Due to this reason, pattern of organ involvement and mortality of severe malaria patients in our ICU cohort cannot be directly extrapolated to pattern of complications in overall severe malaria cases admitted to the hospital.

Conclusions

Incidence of Plasmodium vivax malaria is higher compared to falciparum malaria in hospitalized patients and higher percentage of these need ICU care.

Young males are most vulnerable in suffering from complicated malaria. Oliguria, dyspnea, bleeding and hemoptysis are common presenting symptoms in both vivax and falciparum malaria in ICU.

Most common complications of malaria are thrombocytopenia followed by renal failure, hepatic dysfunction, ARDS, shock and cerebral dysfunction respectively. Falciparum/mixed patients had more mean BUN and creatinine value and more metabolic acidosis as compared to vivax group. Mean PaO2/FiO2 was less in vivax malaria as compared to falciparum/ mixed malaria. Organ support requirements like mechanical ventilation, platelet transfusion, renal replacement therapy and inotropic support were similar between plasmodium vivax and falciparum/ mixed patients.

Overall mortality in our study was 21% in ICU patients with complicated malaria. Mortality was higher in vivax and mixed malaria compared to falciparum. Higher SOFA score (Sequential organ failure assessment score), lower GCS score (Glasgow coma scale), hypotension, ARDS and metabolic acidosis are predictors of mortality.

References

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Implications for Diagnosis and Treatment of Infective Endocarditis: Eight year Experience of an Infectious Disease Team in a Private Tertiary Care Centre

Rajeev Soman†, Neha Gupta§, Piyush Chaudhari†, Ayesha Sunavala§, Anjali Shetty§, Camilla Rodrigues§

Abstract

**Background:** The profile of Infective endocarditis (IE) has been evolving continuously. Like other infectious Diseases (ID) syndromes, IE has not escaped from antibiotic resistance issues. The aim of this study was to determine the implications for diagnosis and treatment by studying the clinical profile and outcome of patients admitted with IE in a tertiary care centre in Mumbai during the period from 2007-2015.

**Methods:** 53 patients having definite or possible IE as per Modified Duke’s Criteria (MDC), that were referred to the ID division, were included in this study.

**Results:** 44 (83%) patients had definite IE and 9 (17%) patients had possible IE. 77.4% of the patients were above 40 years of age. 3 patients presented as eutermic IE. Vegetations were not seen on transthoracic echocardiography (TTE) in 3 patients and were seen only on transesophageal echocardiography (TEE). 15 patients had prosthetic valve IE. 7 patients had rheumatic heart disease. 3 patients had bicuspid aortic valve and 4 had ventricular septal defect (VSD). The rest had no apparent underlying heart disease (45.3%).

41 patients (77.3%) had culture-positive IE and 12 patients (22.6%) had culture-negative IE. *Streptococcus* spp. was found in 14 (26.4%) patients, *Enterococcus* spp. in 9 patients (17%). Other organisms isolated were methicillin-sensitive *S. aureus* (3), Methicillin Resistant *S. aureus* (1), *Eikenella corrodens* (1), *B. cepacia* (2), *Salmonella Typhi* (1), *P. aeruginosa* (1), *M. abscessus* (2) and other rapidly growing mycobacteria (RGM) (5), *Candida parapsilosis* (1), *Candida pelliculosa* (1) and *Aspergillus fumigatus* (1). Notably there was only one case of MRSA.

Among the *Streptococcus* spp., Penicillin MIC testing was done in 11 cases of the 14 cases of Strep spp. 3 of them showed intermediate resistance and 2 were resistant. Among enterococcal IE, 3 had high level aminoglycoside resistance (HLAR) and 2 had β-lactamase producing enterococci with HLAR and 1 had Vancomycin resistance. These were successfully treated with combinations of Ampicillin with Ceftriaxone, Ampicillin-Sulbactam with Imipenem and Daptomycin respectively. The only case of MRSA prosthetic valve endocarditis was successfully treated with Vancomycin and Rifampicin in addition to surgery. Surgery for IE was performed in 26 out of 53 (49%) patients. Early valve surgery (within 15 days of hospital admission) was performed in 6 of these 26 patients.

**Conclusion**

There is a change in the spectrum and antimicrobial susceptibility of organisms causing IE. We encountered several difficulties with the use of the MDC as 43.5% patients had no predisposing factors for IE and blood cultures were negative in

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22.6% cases. In our study, PVE was the most common predisposing condition for IE. VGS followed by enterococci were found to be the commonest cause for IE in our setting. Both organisms show variable drug resist patterns. MRSA was isolated in 1 patient only. Thus vancomycin may not be required as empiric treatment in our setting. This is important from the perspective of antimicrobial stewardship. Good infection control practices are essential to prevent nosocomial IE due to pathogens such as non-tuberculous mycobacteria (NTM). Important changes in the disease characteristic, treatment, and outcome are noted. Surgery, whenever indicated, helps in improving outcome in these patients thus reiterating the need for a team approach for optimal management of this complex, challenging condition.

for IE, indication and timing for surgery, and clinical outcome of IE were recorded.

**Results**

44 patients were diagnosed to have definitive IE and 9 patients had possible IE as per the Modified Duke’s criteria. 77.4% patients were above 40 yrs of age (Figure 1). There were total 5 cases of right sided IE. Among them 3 had VSD, 1 was following central venous line insertion and 1 patient had SLE. Prosthetic valve (n=15) was a more common risk factor for IE than RHD (n=7) in our study (Figure 2).

The commonest symptoms and signs observed were fever, shortness of breath, weight loss, and pallor. Three patients presented as euthermic IE – one was an immunocompetent patient (n=1), one was a chronic kidney disease patient (n=1) and the third patient had systemic lupus erythematosis (SLE) with *Aspergillus* IE (n=1).

Vegetations were not seen on TTE in 3 patients and were seen only on TEE.

**Blood Cultures were positive in 41 of the 53 patients with IE.** 12 cases had culture- negative IE. All the culture-negative IE patients had received prior antibiotic therapy. One culture-negative IE was diagnosed as *Aspergillus fumigatus* on valve culture and histopathology.

Viridans Group of streptococci (VGS) was the most common organism isolated followed by enterococci (Figure 3). Among the Streptococcus spp., penicillin minimum inhibitory concentration (MIC) were interpreted as per the American Heart Association (AHA) criteria in 11/14 cases. 3 of them had intermediate susceptibility and 2 were resistant. Among enterococcal IE, 3 had high level aminoglycoside resistance (HLAR), 2 had β-lactamase producing enterococci with HLAR and 1 had Vancomycin resistance (Table 1). These were successfully treated with combinations of Ampicillin with Ceftriaxone, Ampicillin-Sulbactam with Imipenem and Daptomycin respectively (Table 2).

The only case of MRSA prosthetic

---

**Table 1: Antibiotic susceptibility of GPC isolated**

<table>
<thead>
<tr>
<th>Organism isolated</th>
<th>Total</th>
<th>Ampicillin</th>
<th>Cefoxitin</th>
<th>Amoxyclav</th>
<th>Ceftriaxone</th>
<th>Gentamicin</th>
<th>Imipenem</th>
<th>Ciprofloxacin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGS</td>
<td>14</td>
<td>*</td>
<td>-</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Enterococci</td>
<td>9</td>
<td>55</td>
<td>-</td>
<td>67</td>
<td>0</td>
<td>55</td>
<td>100</td>
<td>0</td>
<td>89</td>
</tr>
<tr>
<td>MSSA</td>
<td>3</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>MRSA</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

*For VGS IE-Penicillin MICs are recommended.

**Table 2: Antibiotics used for the treatment of enterococcal IE (n=9)**

<table>
<thead>
<tr>
<th>Antibiotic resistance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin and Gentamicin sensitive (n=2)</td>
<td>Ampicillin and Gentamicin</td>
</tr>
<tr>
<td>HLAR (n=3)</td>
<td>Ampicillin and Ceftriaxone</td>
</tr>
<tr>
<td>Ampicillin resistant (β-lactamase producing enterococci) with HLAR (n=2)</td>
<td>Ampicillin–sulbactam and Imipenem*</td>
</tr>
<tr>
<td>Ampicillin and Gentamicin sensitive (n=1)</td>
<td>Ampicillin and Imipenem due to risk of gentamicin nephrotoxicity</td>
</tr>
<tr>
<td>Vancomycin resistant (n=1)</td>
<td>Daptomycin</td>
</tr>
</tbody>
</table>

Good outcome was observed in 42 of the 53 patients (79%). Among those who underwent surgery 2 (7.7%) patients had poor outcome out of 26, whereas among medically managed patients 9 (33.33%) out of 27 patients had poor outcome. In-hospital mortality was seen in 4 patients (3 RGM IE and 1 Culture negative endocarditis).

We found a change in spectrum and antimicrobial susceptibility of organisms causing IE. Important changes in the disease characteristics, treatment, and outcome are noted. *Streptococcus* spp. is the commonest cause for IE in our study. Increasing antibiotic resistance may have implications for empiric therapy of culture-negative IE. Also, infection control measures need to be emphasized for preventing nosocomial IE.
valve endocarditis was successfully treated with Vancomycin and Rifampicin. Gentamicin was avoided due to compromised renal function.

Stent related IE due to rapidly growing Mycobacteria (RGM) IE was identified in 5 patients whereas I had *Pseudomonas aeruginosa* after coronary angioplasty. Two patients had RGM IE after coronary angiography. In both of them the coronary angiography was normal. The case of stent related *P. aeruginosa* IE had resistance to aminoglycosides, carbapenems and all beta lactams except Ceftazidime with intermediate susceptibility to Ciprofloxacin. The patient was managed successfully with a combination of Colistin, Ceftazidime and Ciprofloxacin in addition to surgery. Among patients with RGM IE, 3 patients succumbed to the disease during hospitalization, 3 succumbed post discharge and 1 was successfully managed with combination of surgical and medical treatment.

There was 1 patient who had multiple episodes of IE. The patient was receiving hemodialysis through AV fistula from the same dialysis unit highlighting the role of poor infection control practices leading to increase in episodes of nosocomial IE that we found in our study. This particular patient also had differences in susceptibility of Enterococcal species isolated between the 2 episodes of Enterococcal IE whereas 3rd episode was with Methicillin Resistant Staphylococcus Epidermidis (MRSE). She also had multiple CNS septic emboli causing varying degrees of neurological deficits leading to a poor outcome.

There were 3 cases of Fungal IE. 1 was *A. fumigatus* in an SLE patient, 1 was *C. parapsilosis* and 1 *C. pelliculosa* in patients with prosthetic valve surgery. 2 of 3 patients died after being discharged from hospital.

Surgery for IE was performed in 49% patients with IE (n=26). Most common indication for surgery was refractory heart failure (Figure 4). Early valve surgery (within 15 days of hospital admission) was performed in 6 of these 26 patients.

Clinical cure was observed in 42 of the 53 patients (79%). Among those who underwent surgery 24/26 patients were cured, whereas among medically managed patients only 18/27 patients were cured. In-hospital mortality was seen in 4/44 patients (3 RGM IE and 1 Culture negative endocarditis). 2 patients who had fungal IE died post discharge, increasing the total mortality to 6/44 (13.6%) patients.

**Discussion**

In the present study most patients (>77%) were over 40 years of age. In our country, younger patients (mean age-25 yrs) were earlier reported to be more commonly affected with IE while our results are comparable to data reported by developed countries.

We encountered several difficulties with the use of the Modified Duke’s Criteria. Blood cultures were negative in 22.6% cases. However, most of these patients were on antibiotics. Vegetations were not seen on TTE in 3 patients in whom TEE was required. 43.5% of our patients had no predisposing condition as per the Duke’s criteria. Although bicuspid aortic valve is not included as a predisposing condition for IE, we found 3 patients who had bicuspid aortic valve as the only cardiac defect. The use of PET scan for diagnosis of IE was not explored in our study, both due to issues of cost and as it is an evolving recommendation during the study period.

In this study 52.8% of patients had no underlying cardiac risk factors. Amongst those who had risk factors, prosthetic valve IE (28.3%) was more common. RHD was the most common underlying risk factor for IE (present in 46.9% patients) in earlier studies.²³

Left-sided IE is still more common than the right-sided IE as earlier reported. In the present study (VSD and nosocomial procedures such as central venous catheter insertion) are the common causes of right-sided IE where as puerperal sepsis and septic abortion were the commonest causes in earlier studies.⁴

VGS is the most common cause of IE in our study.⁵ Entercoccal IE appears to be increasing in frequency (17% vs 8% reported by Garg et al)⁶ - more common in elderly pts, associated UTI. Only 1 methicillin-resistant *S. aureus* IE was found during this study period. This microbiological profile has implications on the empirical antibiotic therapy for IE and hence empirical vancomycin for all patients is perhaps not indicated for IE in our setting.

Also, an emerging resistance is noted among a few organisms causing IE. VGS resistance pattern has not been reported in any Indian series previously. Enterococci exhibit various resistance mechanisms including high level aminoglycoside resistance (HLAR) and β-lactamase production.

More patients were managed surgically (49%) vs 23% in earlier reported studies.

IE is associated with high mortality. Patients with heart failure, periannular complications and IE due to *S. aureus* the mortality reaches 79%. Mortality from IE in this study was found to be 21%. This may be attributed to the increase in RGM and fungal IE which had uniformly dismal outcome with only 1 patient with RGM and fungal IE each surviving from our study population.
RGM IE is unusual but at present but it may be observed more in the future because of the increasing use of non-reusable devices in the developing world.7

In our study patients managed with surgery in addition to optimum medical treatment had better outcomes than those managed medically alone. This result may be skewed due to survivor selection bias due to selection bias in choosing patients who undergo surgery. High risk patients, but only those who are suitable surgical candidates are chosen for surgery. This bias may favour the perceived benefit of surgery.

This study has limitations. These findings may pertain to a private tertiary care hospital. The epidemiology and resistance patterns may vary in different settings. We recognize that similar facilities for management may not be available and clinicians may have to manage in different ways to suit patient preferences, affordability, available local expertise etc. However, our results show that a team approach is beneficial to optimize the outcome for this complex, challenging condition.

Conclusions

There is a change in spectrum and antimicrobial susceptibility of organisms causing IE. Identifying the organism is the key. In our study, PVE was the most common predisposing condition for IE. 43.5% patients had no predisposing factors for IE as per the MDC. Blood cultures were negative in 22.6% cases. Hence, there are difficulties in applying MDC for diagnosis in our setting.

VGS is still the most common cause for IE but VGS are not uniformly sensitive to penicillin and penicillin MICs are needed. Enterococci exhibit various resistance mechanisms including HLA and β-lactamase production. β-lactamase production needs to be ruled out by nitrocephin disc even if enterococci is ampicillin sensitive in case of IE. Thus, combination of ampicillin-sulbactam and ceftriaxone and ampicillin-sulbactam with imipenem have potential role in the treatment. This will avoid the use of vancomycin for ampicillin resistant β-lactamase producing enterococci. Also MRSA was isolated in 1 patient only. Thus vancomycin may not be required as empiric treatment in our setting. This is important from the perspective of antimicrobial stewardship.

In view of nosocomial IE, due to difficult pathogens such as NTM, infection control practices should be given far more importance than at present.

Important changes in the disease characteristic, treatment, and outcome are noted. Surgery, whenever indicated, helps in improving outcome in these patients thus reiterating the need for a team approach for optimal management of this complex, challenging condition.

References

Seroprevalence of Anti-Citrullinated Protein Antibodies (ACPA) in Patients with Rheumatic Diseases other than Rheumatoid Arthritis

Renu Saigal*, Surendra Singh Bhakal, Laxmikant Goyal, Akhil D Goel

Abstract

Objective: To evaluate the prevalence of anti-citrullinated protein antibodies (ACPA) in patients with a variety of rheumatic diseases other than rheumatoid arthritis (RA).

Methods: 144 cases of rheumatic diseases other than rheumatoid arthritis (RA) over a period of 1 year were recruited after consenting and followed up for 2 years. Their serum samples were tested for ACPA.

Result: ACPA seropositivity of 9.03% was observed in rheumatic diseases other than RA.

Conclusion: Whether ACPA seropositivity in non-RA rheumatic diseases indicates a false positive result or an overlap RA syndrome is a mystery yet unsolved. Long term follow ups of these patients will be required to understand the course of rheumatic diseases in relation to ACPA.

Introduction

ACPA have demonstrated their usefulness for the diagnosis of RA. However these antibodies have also been found positive in rheumatic diseases other than RA like Systemic Lupus Erythematosus (SLE),[1] Psoriatic arthritis,[2] Juvenile idiopathic arthritis (JIA),[3] Idiopathic Inflammatory myositis (IIM),[4] Systemic sclerosis (SSc),[5] Primary Sjogren’s syndrome (PSS) and others.

Very few studies have reported the seroprevalence of ACPA in rheumatic diseases other than RA as incidence of ACPA in other rheumatic diseases is low but needs to be evaluated in further studies.

Aim of our study was to find out seroprevalence of ACPA in rheumatic diseases other than RA.

Material and Methods

All the patients with rheumatic diseases attending the Rheumatology Clinic at a Medical College Hospital in North India from June 2011 to May 2012 were screened and followed up for two year. We categorized patients in different rheumatic diseases according to American College of Rheumatology classification criteria.

Patients with RA at first visit or on follow up were excluded. We, thus, recruited 144 patients of rheumatic diseases other than RA and followed them up for 2 years. Well-informed and written consent was obtained from each recruited patient. Necessary approval was obtained from the ethics committee of institution.

Clinical assessment: Detailed history and physical examination was done thoroughly. Laboratory Evaluation: Fasting venous samples of the patients were taken for Glucose, kidney and liver function tests, ESR, C-reactive protein (CRP) and ACPA. Patients were further investigated for any complications indicated clinically or by initial investigations. ESR and CRP were measured using Westergren method and Nephelometry respectively. Serum ACPA levels was measured by an ELISA test system for the quantitative measurement of IgG class ACPA in human serum or plasma with positive cut off value ≥ 20 U/ml.

Results

Out of the 144 patients of rheumatic disease, 90 (62.5%) were females. Systemic Lupus Erythematosus (SLE) 65 (45.1%) cases, 47 (32.6%) cases of Spondyloarthritides (SpA), 10 (6.9%) of SSc, 4 (2.8%) of PSS and 18 (12.5%) patients were of other rheumatic diseases [one case of Antiphospholipid Antibody Syndrome (APS), 1 case of Adult Onset Still Disease (AOSD), 3 cases of Enthesitis- related Arthritis (ERA), 2 cases of Henoch Schonlein Purpura (HSP), 3 cases of Juvenile Idiopathic Arthritis (JIA), 4 cases of Mixed Connective Tissue Disease (MCTD), 3 cases of IIM and 1 case of Relapsing polychondritis] (Figure 1).

Thirteen (9.03%) patients were positive for ACPA and 131 (90.97%) were negative. Out of 13 ACPA positive patients 6 were of SLE, 3 of SpA, 2 of SSc, 1 of PSS and 1 of HSP (Figure 2, Table 1).

Discussion

Enzyme Peptidyl Arginine Deiminase (PAD) converts Arginine to Citrulline on peptide proteins. This is a post-translational modification changing biochemical properties of proteins. Citrullination is predominantly observed in proteins like cytokeratin, filaggrin, vimentin, α and β fibrin, α-enolase, and peptides of collagens I
and II. Antibodies recognizing these citrullinated peptides are known as anti-citrullinated protein antibodies (ACPAs). ACPAs are locally produced by synovial B cells and therefore contribute to the inflammatory and destructive processes in the RA. ACPAs are present early in the course of the RA and may precede the clinical onset.

ACPA has 95% specificity and 75% sensitivity for RA. RA should be differentiated from other rheumatic diseases as early initiation of treatment leads to better prognosis. Such high specificity should be evaluated in patients with suspected rheumatic diseases. In our study, patients with inflammatory rheumatic diseases excluding RA, were taken as study population.

We observed a seroprevalence of 9.03% of ACPA in rheumatic disease other than RA. This is in concordance with the few studies where seroprevalence was 9.8% and 10% respectively. We found prevalence of ACPA in SLE 9.23% which was higher than one study of 7% but lower than another study of 17%.

Among ACPA positive SLE patients one patient with titre >300 U/ml presented with symmetric polyarthritis for 1 year along with characteristic SLE manifestations. Another patient with titre >300 U/ml presented with SLE class 4 nephritis and vasculitis without arthralgia. One more patient with titres of ACPA equal to 51.6 U/ml was diagnosed as cutaneous lupus with inflammatory bowel disease (celiac disease) on routine follow up this patient developed symmetric polyarthritis however, patient was RF negative and on routine follow up did not show any radiological erosions.

In our study we observed a seroprevalence of 6.38% of ACPA in SpA. One patient of undifferentiated SpA had titre of 49.2 U/ml while 2 other ACPA positive patients one was diagnosed as Ankylosing Spondylitis and other patient with chronic ReA and they had ACPA titers of 243.6 u/ml and 58.71 u/ml respectively but in both these patients there was no hand joint involvement. We observed a seropositivity of 20% of ACPA in Systemic Sclerosis (SSc), which is higher than the other studies. This can be explained by small number of SSc patients in our study. Y. Morita et al recommended that ACPA titres should be measured in SSc patients suffering from joint involvement so that SSc-RA overlap patients may be diagnosed early. So ACPA may play important role to differentiate SSc from SSc –RA overlap.

One patient of PSS which was ACPA positive was 41 years female present with bilateral parotid enlargement, dry eyes and dry mouth with background history of Raynaud’s phenomenon (RP) and arthralgia for 1 year. She had high titre ACPA positive (62.90 u/ml) as well as high titer anti Ro/SSA antibody positive (99.92 u/ml). In our study ACPA positive patient had RP while G J Tobo´n et al found that 2 out of 5 ACPA positive patients had RP. It is possible that marked B-lymphocyte hyper-reactivity which is a characteristic of primary Sjogren’s syndrome may explain the presence of ACPA.

The possibility that patients with ACPA positivity could be prone to develop RA in future cannot be ruled out, warranting regular follow up. We followed our patients for 2 years. All the ACPA positive patients on follow up were found to have no erosions and these were fitting in the diagnostic criteria of that particular rheumatic disease. One of the 13 ACPA positive patients in our study developed symmetric polyarthritis resembling RA on routine follow-up but she did not have radiological erosions. So the term “false positive” cannot be applied in this patient and these patients need continuous follow up for development of erosions when these patients may be put under overlap syndromes or pure RA.

**Conclusion**

In our study 13 patients were ACPA positive among 144 patients with inflammatory rheumatic diseases other than RA.
than RA. So prevalence of ACPA was 9.03%. Out of these 13 seropositive patients, one developed symmetric polyarthritis resembling RA on routine follow-up of 2 years. Term “false positive” cannot be strictly applied to these patients of non-RA rheumatic diseases, as ACPA is known to antedate RA by many years and these patients need follow up.

References

Office Bearers of Andhra Pradesh Chapter of API (APAPI)
for the Year 2017-2018
Chairman: Dr. Y.V.S. Prabhakar; Chairman Elect: Dr. Alladi Mohan; Hon. Secretary: Dr. K.S.R. Swamy; Hon. Treasurer: Dr. C.S.S. Sarma
Nerve Conduction Abnormalities in Pre-Diabetics and Asymptomatic Diabetics

SH Talib1*, Gaurav Punde2, RK Dase3

Abstract

Aim: To determine the electrophysiological abnormalities in pre-diabetics and/or asymptomatic diabetics and analyse the role of nerve conduction for recognizing distal symmetric polyneuropathy.

Material and Methods: A total of 180 subjects were categorized as: Group A: healthy Subjects (n=60), Group B Pre-diabetics (IFG +IGT, n=60) and Group C: Asymptomatic type 2 diabetics (n=60)

Results: Electrophysiological studies revealed that amplitude of B/L Sural SNAP and tibial CMAP was significantly lower in affected pre-diabetics and asymptomatic diabetics. The presence of significant f wave latency was also noted in both these groups, more among asymptomatic diabetics. The observations on distal latency and nerve conduction velocity of sensory and motor nerves were statistically nonsignificant.

Conclusion: Sensory nerve abnormality was more obvious than motor nerve abnormality in the pre-diabetic subjects. The changes in amplitude of motor nerve abnormality was observed late in course of disease i.e. in asymptomatic diabetic group than pre-diabetics. The amplitude of sensory nerve action potential and F wave latency parameters were the most sensitive measures of peripheral neuropathy in early diabetics in our study.

Introduction

Commonly used concept of diabetic neuropathy is the presence of symptoms and/or signs of peripheral nerve dysfunctions in persons with diabetes/near diabetes after exclusion of other causes.¹ The neuropathy progresses from functional to structural changes in due course of time. The commonly observed neuropathy in diabetics is distal symmetrical polyneuropathy (DPN) and has a prevalence of about 50%.² The presence of neuropathy in diabetics and/or pre-diabetics is associated with considerable morbidity, mortality and diminished quality of life. The peripheral neuropathy is a complication in approximately 50% of patients with diabetes/near diabetes revealing that remaining 50% of patients with peripheral neuropathy may not have symptoms. The axons are affected in a length dependent manner and this centripetal pattern of axonal degeneration is fundamental to the clinical presentation and investigative tools.³ Timely identification of loss of protective sensations may allow preventive interventions.

Optimal glycemic control is the only available measure with proven efficacy in preventing progression of peripheral neuropathy, provided measures are instituted at an early stage, least the condition becomes poorly reversible or even irreversible.

The nerve conduction studies are electro-diagnostic tests which are used to evaluate the ability of the electrical conduction of the motor and sensory nerves. Diabetic peripheral neuropathy is associated with changes in both, nerve conduction velocity and amplitude.⁴ Nerve conduction studies are most objective, accurate and reliable for detecting DPN and most useful tool for evaluating disease progression. In our study we studied electrophysiological changes for evidence of peripheral neuropathy in pre-diabetics, asymptomatic diabetics and healthy controls.

Material and Methods

Study design: cross sectional study
Study duration: 24 months
Sample size and Inclusion criteria: Total 180 cases divided into three groups
Group A- Healthy participants between age 20-70 years of both genders who on clinical evaluation are not suffering from diabetes, any acute or chronic ailments, on any medications which could influence NCS (n=60).
Group B- men and women aged 20-70 years having established diagnosis of prediabetes with or without signs of peripheral neuropathy (n=60)
Group C- men and women aged 20-70 years with asymptomatic type 2 diabetes with or without clinical evidence of neuropathy (n=60).

Exclusion Criteria
- Patients who deny consent to be a part of study.
- Previous diagnosis of any systemic/infective/toxic/genetic/metabolic/inflammatory diseases related to polyneuropathy.
- Patients consuming medications (phenytoin, Antiretroviral, Antitubercular) including diuretics and vitamins.
- Alcoholic patients.
- Patients of chronic Kidney Disease.
- Hyperthyroid or Hypothyroid patients.

¹Professor and Head of Medicine, ²Chief Post Graduate Resident in Medicine, Dept. of Medicine, ³Asso. Prof., Dept. of Community Medicine, MGM Medical College, Aurangabad, Maharashtra, ⁴Corresponding Author
Received: 07.11.2016; Accepted: 21.12.2017
The criteria of ADA 2014, has not changed in 2016.

- Patients of macrocytic hypochromic anaemia
- Skin lesions or swellings that would interfere with NCS
- Patients who were critically ill that they cannot be transferred for performance of nerve conduction study
- Patients Having Malignancy
- Trauma to lower limbs of any kind

Statistical analysis: Statistical analysis was done by using SPSS version 20th. All parameters are expressed in mean ± SD. For comparison of Quantitative data of three groups, ANOVA was applied, Tukey Post Hoc test was also used for comparison of two groups. For Comparison of Healthy and Pre-diabetics / asymptomatic diabetics subjects unpaired t-test was applied. Chi-square test was also used to check significance association between different groups and outcome of different variables. P-value was checked at 5 % level of significance.

Results

In the present study, we compared changes in NCS parameters in both prediabetes (Group B) and asymptomatic diabetes group (Group C) with healthy controls (Group A). We extended our analysis for Group D comprising Pre + asymptomatic diabetics. The study was undertaken for analyzing distal latency, Amplitude, velocity and F wave latency in various studied groups as described below in Tables 2-5.

Similarly, the amplitude of motor Tibial nerve is noted significantly abnormal in asymptomatic diabetics (A vs C) and combined pre + asymptomatic diabetics (A vs D). However, the values are insignificant in pre-diabetic group (A vs B) when compared with healthy participants.

In the same table mean values of both sensory and motor amplitude seems within normal range because of "outlier phenomenon" observed in the study.

We found that total number of abnormal nerve conduction rate in prediabetic group was 30% (18/60) and in group C was 58.3% (35/60).

Discussion

Diabetic neuropathies are neuropathic disorders that are thought to result from diabetic microvascular injury involving small blood vessels that supply nerves in addition to microvascular condition that culminate in diabetic neuropathy and responsible for significant morbidity and mortality. The diabetic neuropathies are noticed clinically and on electromyographic studies in situations of pre-diabetics, asymptomatic diabetics and diabetic population. Three general types of diabetic neuropathies are described. They include sensory neuropathy also called peripheral neuropathy, motor neuropathy and autonomic neuropathy. A variety of evidence suggests neuropathy may occur early in diabetes. The neuropathy associated with IGT is clinically similar to early diabetic neuropathy, with preferential injury to small nerve fibers, resulting in pain and autonomic dysfunction. IGT and diabetic neuropathy patients share abnormal microvascular endothelial dysfunction. These impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) states, have a high risk of conversion to diabetes. Thus, early intervention and prompt management at pre-diabetic or early stages of diabetes before development of symptoms prevents further complications. Evaluation of neuropathies undertaken in this study by clinical Michigan criteria’s for examination and evaluation and by undertaking electrophysiologic measurements which are sensitive, specific and reproducible measures of the presence and severity of peripheral neuropathy, defining quantitative dysfunction. The role of NCS with MNSI in early detection of subclinical neuropathies makes NCS a suitable test for periodic evaluation of diabetic patients. The neurological parameters studied were nerve conduction velocity (NCV) expressed in meter per sec (m/S), distal latency (DL) expressed in millisecond (ms) and amplitude of Sensory Nerve Action Potential (SNAP) expressed in microvolt (µV) and compound muscle action potential (CMAP) expressed in millivolt (mV) and F wave latency of tibial nerve. In this study, total number of abnormal nerve conduction rate was 30% (18/60) in pre-diabetic group and 58.3% (35/60) in

<p>| Table 1: Subjects of study were enrolled and categorized on the basis of ADA 2014 criteria* |</p>
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Fasting plasma glucose</th>
<th>2-hour OGTT</th>
<th>HbA1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;100 mg/dl (5.6 mmol/l)</td>
<td>&lt;140 mg/dl (7.8 mmol/l)</td>
<td>&lt;5.7%</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>100–125 mg/dl (5.6–6.9 mmol/l)</td>
<td>140–199 mg/dl (7.8–11.0 mmol/l)</td>
<td>5.7–6.4%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥126 mg/dl (7.0 mmol/l)</td>
<td>≥200 mg/dl (11.1 mmol/l)</td>
<td>≥6.5%</td>
</tr>
</tbody>
</table>

*The criteria of ADA 2014, has not changed in 2016.

<p>| Table 2: Distal latency of Sural (DSL) and Tibial nerve (DML) in group A, B, C and D |</p>
<table>
<thead>
<tr>
<th>Distal latency (milli sec)</th>
<th>Group A (n=60)</th>
<th>Group B (n=60)</th>
<th>Group C (n=60)</th>
<th>Group D (n=120)</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sural nerve Rt</td>
<td>2.32±0.72</td>
<td>2.56±0.67</td>
<td>2.32±0.88</td>
<td>2.44±0.79</td>
<td>P=0.204  NS</td>
</tr>
<tr>
<td>Sural nerve Lt</td>
<td>2.50±0.64</td>
<td>2.61±0.65</td>
<td>2.50±0.91</td>
<td>2.56±0.79</td>
<td>P=0.427  NS</td>
</tr>
<tr>
<td>Tibial nerve Rt</td>
<td>3.52±0.95</td>
<td>3.45±0.92</td>
<td>3.65±1.02</td>
<td>3.55±0.97</td>
<td>P=0.204  NS</td>
</tr>
<tr>
<td>Tibial nerve Lt</td>
<td>3.49±1.03</td>
<td>3.50±1.05</td>
<td>3.61±1.15</td>
<td>3.56±1.10</td>
<td>P=1.00   NS</td>
</tr>
</tbody>
</table>

Above table shows that the Distal latency of B/L Sural and Tibial nerve is statistically nonsignificant in all groups when compared with control group.

<p>| Table 3: Conduction velocity of Sural and Tibial nerves in group A, B, C and D |</p>
<table>
<thead>
<tr>
<th>Conduction velocity (m/s)</th>
<th>Group A (n=60)</th>
<th>Group B (n=60)</th>
<th>Group C (n=60)</th>
<th>Group D (n=120)</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sural Nerve Rt</td>
<td>73.5±20.47</td>
<td>71.6±23.69</td>
<td>77.7±24.15</td>
<td>74.7±24.02</td>
<td>P=0.897  NS</td>
</tr>
<tr>
<td>Sural Nerve Lt</td>
<td>76.3±23.18</td>
<td>74.0±21.30</td>
<td>76.2±26.85</td>
<td>73.2±24.16</td>
<td>P=0.854  NS</td>
</tr>
<tr>
<td>Tibial Nerve Rt</td>
<td>64.3±23.07</td>
<td>70.9±54.49</td>
<td>63.4±45.86</td>
<td>66.7±50.26</td>
<td>P=0.767  NS</td>
</tr>
<tr>
<td>Tibial Nerve Lt</td>
<td>59.0±20.93</td>
<td>57.4±20.65</td>
<td>59.6±44.83</td>
<td>58.5±34.83</td>
<td>P=0.599  NS</td>
</tr>
</tbody>
</table>

Above table shows that the NCV of B/L Sural and Tibial nerve is statistically nonsignificant in all groups when compared with control group.
Involvement of motor nerves occur later than motor and autonomic. Extremities with sensory involvement are comparable to studies conducted by diabetic. 9

This study did not found any changes in motor nerve abnormality in the both groups. Sensory nerve action potential is statistically significantly abnormal in pre-diabetic (A vs B) and asymptomatic diabetic (A vs C) and highly significant in combined group (A vs D) when compared with healthy participants on either side. The sensory amplitude values are insignificant with group of pre-diabetic vs asymptomatic diabetes bilaterally (B vs C). Above table shows that the amplitude of sural SNAP is statistically significantly abnormal in pre-diabetic (A vs B) and asymptomatic diabetic (A vs C) and highly significant in group C. The amplitude of Sural SNAP, Tibial CMAP and f wave latency were found to be most sensitive parameter in detecting peripheral neuropathy in the studied groups. Sensory nerve abnormality was more obvious than motor nerve abnormality in the both groups. The amplitude study of sensory and motor component revealed that the onset of sensory component is earlier in pre-diabetics and marches forward when patient enters zone of asymptomatic diabetes indicating viability of axons damaged. The changes in motor nerve abnormality were noted late in course of disease i.e. in asymptomatic diabetic group. This study did not found any changes in distal latency and nerve conduction velocity of both sensory (Sural) and motor (Tibial) nerves on either side. In present study, the abnormality in f wave latency was found statistically significant (P≤0.0001) in both pre-diabetics and asymptomatic and this observation implies that F wave latency is an earlier and vital indicator for peripheral neuropathy where distal motor latency or nerve conduction velocities are not helpful. F-waves of the tibial nerves are the most sensitive measure to detect subclinical or overt diabetic. 7

Results of this study were comparable to studies conducted by various authors who had reported that DPN usually involve the distal lower extremities with sensory involvement greater than motor and autonomic. Involvement of motor nerves occur later in development of disease.

A study by Yunqian Zhang et al 2014 31 on Amplitude of sensory nerve action potential in early stage diabetic peripheral neuropathy of 500 cases correlates with our study which has shown the extent of impairment is more in lower extremity than upper and affection of sensory nerve is more than motor nerves. Therefore, nerve conduction especially amplitude of sensory nerve action potential detection, should be routinely examined.

A study by Im Sun et al 2012 11 also confirmed that the SNAP amplitude and also tibial CMAP amplitude were significantly smaller in cases of IGT as compared to healthy group. The findings which correlates with the present study.

A study by Soley Thrainsdottir et al 2009 12 found out that there was low sural nerve amplitude and conduction velocity in cases of impaired glucose tolerance as compared to the normal control group. The observation finding of low sural nerve amplitude correlates with the present study. We did not find any abnormality in nerve conduction velocity as described by Soley et al. The reason could be different methodologies adapted in the studies.

A study by Pan H et al 2014 8 in their study evaluated the sensitivity of electro physiologic assessments and compared F-waves and motor and sensory nerve conduction studies among patients with diabetes. They found that F-waves of the tibial and fibrilar nerves are the most sensitive measure to detect subclinical or overt diabetics which correlates with the present study.

A study by Sumner CJ et al 2003 13 in their study found that Patients with IGT had predominantly small fiber neuropathy, compared to patients with DM, who had more involvement of large nerve fibers. Thus they concluded that neuropathy is associated with IGT though it is milder than the neuropathy associated with DM which correlates with the present study.

Conclusion

The physiological properties of nerve and muscles are modified due to derangements of pathophysiological changes in diabetes mellitus. In our study results conclude that changes of diabetes peripheral neuropathy affected sensory as well motor nerves in both the limbs. Nerve conduction studies are useful aid in diagnosing, monitoring the development of early diabetic peripheral neuropathy when clinical parameters viz. history and clinical examination remains inconclusive. Though clinical examination and history components are essential in evaluation of diabetic peripheral neuropathy, electromyography and nerve conduction study are of paramount importance even in asymptomatic and pre-diabetes. Virtuosity of presence of diabetes mellitus per se is not that important than the presence of diabetic peripheral neuropathy (DPN). The DPN is significantly associated with higher dreaded complications like cerebrovascular stroke and cardiovascular morbidity and mortality. F wave latency measurement and sensory amplitude are of paramount importance especially in asymptomatic and pre-diabetic categories for, motor components abnormalities are observed late in course of the disease, revealed in this study.

References

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Clinical and Etiological Profile of Fever with Thrombocytopenia – A Tertiary Care Hospital Based Study

Kailash Chandra Saini\(^1\), RP Agrawal\(^2\)*, Surendra Kumar\(^3\), Pankaj Tantia\(^4\), Kunal Thakkar\(^1\), Aashish Kumar Sharma\(^1\)

Abstract

**Objectives:** Febrile thrombocytopenia is a condition commonly caused by infections. The present study is intended to know the underlying etiology of fever with thrombocytopenia, the various presentations and complications in our community.

**Material and Methods:** A cross-sectional epidemiological study was conducted including 1217 patients aged more than 14 years with fever and thrombocytopenia admitted in the medical wards from October 2013 to September 2014. Detailed clinical examination and routine investigations were done; specific investigations like blood culture, widal test, antigen test for malaria, IgM ELISA leptospiira, IgM ELISA dengue, bone marrow aspiration/biopsy etc. were done as and when indicated. The data are presented as percentage and numbers. Rates and ratios are computed.

**Results:** Infection was the commonest cause of thrombocytopenia and dengue was the commonest of the infections followed by malaria. Bleeding manifestations were seen in 42.7% of patients. 91.40% of patients with bleeding tendencies had petechiae/purpura as the commonest bleeding manifestation, followed by spontaneous bleeding in 57%. Spontaneous bleeding was noted when platelet counts were less than 20,000. Petechiae/Purpura were seen more commonly when platelet count was in the range of less than or equal to 50,000. Good recovery was noted in 95%, while 5% had mortality. Septicemia accounted for 85.24% of deaths followed by malaria (6.55%) and dengue (5%).

**Conclusion:** Fever with thrombocytopenia is an important clinical condition commonly caused by infections, particularly dengue and malaria. In majority of patients thrombocytopenia was transient and asymptomatic, but in significant number of cases there were bleeding manifestations. On treating the specific cause drastic improvement in platelet count was noted. Mortality in febrile thrombocytopenia is not directly associated with degree of thrombocytopenia but with concomitant involvement of other organs leading to multiorgan dysfunction.

Introduction

Fever is defined as an elevation of the body temperature above the normal circadian range, as the result of a change in the thermoregulatory center located in the anterior hypothalamus. A morning temperature of more than 37.2°C (98.9 °F) or evening temperature of more than 37.7°C (99.9°F) would define fever.\(^1\) Thrombocytopenia is defined as platelet count less than 150,000 /µl. This is due to decreased production, increased destruction (immunogenic and non-immunogenic) and increased sequestration in spleen.\(^2\)

At times, the fever course is prolonged and fever with thrombocytopenia narrows the differential diagnosis of the clinical entity. Septicemia, infections like malaria, dengue, leptospirosis, typhoid, human immunodeficiency virus (HIV) and miliary tuberculosis are some of the common causes of fever with thrombocytopenia.

Therefore, a well-organized systemic approach, carried out with an awareness of causes of fever with thrombocytopenia can shorten the duration of investigations and bring out the diagnosis.

**Material and Methods**

A cross-sectional epidemiological study was conducted including 1217 patients (age ≥14 years) admitted with fever and thrombocytopenia in the medical wards from October 2013 to September 2014 in the department of medicine, S.P. medical college & associated group of hospitals, Bikaner. We prospectively collected a series of 1217 patients of fever with thrombocytopenia.

**Inclusion Criteria**
- Age more than 14 years.
- Fever less than 15 days duration.
- Fever more than 100°F at least once a day.
- Platelet count less than 1, 50,000 /µl.

**Exclusion Criteria**
- Known patients of Primary Thrombocytopenia.
- Drug induced thrombocytopenia.
- Diagnosed cases of Thrombocytopenic purpura on treatment.
- Patients with thrombocytopenia already diagnosed to have hematological disorder / malignancy, on treatment with chemotherapy and other immunosuppressant.

The patients fulfilling the selection

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\(^1\)Sr. Registrar, \(^2\)Professor, \(^3\)Asso. Professor, \(^4\)Sr. Resident, S. P. Medical College and Associated Group of P.B.M. Hospitals, Bikaner, Rajasthan; \(^*\)Corresponding Author

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Out of 1217 cases of fever with thrombocytopenia, 858 were males and 359 were females. In this study 24% of the patients were in the range of 50,000 to 1,50,000 platelet counts, peripheral smear for malaria parasite, QBC for malaria parasite, bleeding time and clotting time, urine routine and microscopy, blood culture, urine culture, renal function tests, liver function tests, blood smear, blood agglutination test, leptospira, bone marrow examination etc. were done as and when indicated. Once the specific diagnosis was reached, a patient was treated for it specifically and symptomatically (mechanical ventilators, haemodialysis etc.). Platelet transfusions were done for bleeding complications. The patient was followed from the day of admission till their discharge from the hospital. The data are presented as percentage and numbers. Rates and ratios are computed. P value of less than 0.05 was considered as significant.

Observations

Out of 1217 cases of fever with thrombocytopenia, 858 were males and 359 were females. In this study 24% of the patients were in the range of 50,000 to 1,50,000 platelet counts, peripheral smear for malaria parasite, QBC for malaria parasite, bleeding time and clotting time, urine routine and microscopy, blood culture, urine culture, renal function tests, liver function tests, blood smear, blood agglutination test, leptospira, bone marrow examination etc. were done as and when indicated. Once the specific diagnosis was reached, a patient was treated for it specifically and symptomatically (mechanical ventilators, haemodialysis etc.). Platelet transfusions were done for bleeding complications. The patient was followed from the day of admission till their discharge from the hospital. The data are presented as percentage and numbers. Rates and ratios are computed. P value of less than 0.05 was considered as significant.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Numbers of patients (n=1217)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>572</td>
<td>47%</td>
</tr>
<tr>
<td>Malaria</td>
<td>243</td>
<td>20%</td>
</tr>
<tr>
<td>Unexplained</td>
<td>200</td>
<td>16.5%</td>
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<tr>
<td>Septicemia</td>
<td>128</td>
<td>10.5%</td>
</tr>
<tr>
<td>Dengue*Malaria</td>
<td>56</td>
<td>4.5%</td>
</tr>
<tr>
<td>Enteric fever</td>
<td>12</td>
<td>1%</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>6</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number of patients(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding PR</td>
<td>0.5%</td>
</tr>
<tr>
<td>Hematuration</td>
<td>1.5%</td>
</tr>
<tr>
<td>Menorrhagia</td>
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<tr>
<td>Hematemesis</td>
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<tr>
<td>Epistaxis</td>
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<tr>
<td>Bleeding gums</td>
<td>7.5%</td>
</tr>
<tr>
<td>Malena</td>
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</tr>
<tr>
<td>SC Haemorrhages</td>
<td>12.5%</td>
</tr>
<tr>
<td>Petechiae</td>
<td>38.45%</td>
</tr>
</tbody>
</table>

Fig. 1: Thrombocytopenia and bleeding tendencies

Fig. 2: Correlation of petechiae/purpura with thrombocytopenia

Fig. 3: Thrombocytopenia and bleeding symptoms

malena, 91(31.16%) cases had bleeding gums, 67(23%) cases had epistaxis, 55 (18.8%) cases had hematomesis, 24(8.2%) cases had menorrhagia, 18(6%) cases had hepatitis and 6 (2%) case had bleeding per rectum (Figure 3). Mixed infections with both dengue and malaria had highest bleeding tendency (57.14%). Among other causes, 55.3% cases of dengue, 35% cases of unexplained causes, 23.8% cases of septicemia, 27.12% cases of malaria had bleeding tendencies (Table 2). Generally, spontaneous bleeding was noted in platelet count < 20,000 but in some may be due to qualitative defects, it was seen in platelet count in the range of > 50,000/µl also. Some patients with platelet count of 10,000 did not have spontaneous bleeding (Figure 4).

Out of 1217 cases, 1156 cases had good recovery and 61 cases expired. Out of 61 cases of mortality, 52 (85.24%) were due to septicemia and was the common cause followed by malaria 4 (6.55%) cases, dengue 3 (5%) cases, leptospirosis 1 case and 1 case due to mixed infection with malaria and dengue (Table 3). In 61 mortality...
In our setup 95% of cases showed increasing trends in platelet count both at the time of discharge and

Discussion

In this study infection was the established diagnosis in 83.50% of the cases. Dengue (47%) was the commonest cause of fever with thrombocytopenia followed by malaria (20%), unexplained cause (16.5%), septicemia (10.5%), dengue+malaria (4.5%), enteric fever (15%), other causes (21%), enteric fever followed by dengue and malaria with 16, 15 and 10 cases respectively. In our study clinical manifestations of thrombocytopenia were there in 512 (42.7%) patients and petechiae/purpura (91.40%) was the commonest bleeding manifestation followed by spontaneous bleeding (57%). In some other similar study by Srinivas et al, Prithviraj patil et al malaria (54%) remained the most common cause followed by dengue (15%), other causes (21%), enteric fever (6%), septicemia (4%) (Table 4). This may be due to seasonal and geographical variation. Incidence and prevalence of various infections vary seasonally and geographically. Some infectious diseases occur cyclically. A Study conducted during epidemic of a disease shows high incidence of the same. Therefore, duration and time period of study conducted also affect the study results. Available resources also affect the diagnosis of a disease.

In most of the studies infections represented the most important cause of fever with thrombocytopenia with a relative frequency ranging from 68% - 100%. However, in a study by Nair PS, Jain A, Khanduri U, Kumar V et al, Prithviraj patil et al, petechiae/purpura (91.40%) was the commonest bleeding manifestation followed by spontaneous bleeding (57%). In some other similar study by Srinivas et al, Prithviraj patil et al, petechiae/purpura was also the commonest bleeding manifestation (73.9%),(63%) respectively followed by spontaneous bleeding (26.9%), (37%) respectively.

In a study conducted by Nair PS et al, out of 109 patients 45 patients had thrombocytopenic signs accounting for 41.3%. Out of 45 patients spontaneous bleeding was seen in 31 patients accounting for 69%, the commonest bleeding manifestation followed by petechiae/purpura accounting for (22.22%), because septicemia was the most common cause in their study which causes spontaneous bleeding more commonly than petechiae/purpura.

In septicemia there may be a striking propensity toward intravascular fibrin deposition, thrombosis (consumption coagulopathy) which causes increased spontaneous bleeding. Infectious disease causes thrombocytopenia by impaired platelet production and increased destruction and Petechiae/purpura is the earliest manifestations of thrombocytopenia. A platelet count of approximately 5000–10,000 is required to maintain vascular integrity in the microcirculation. When the count is markedly decreased, petechiae first appear in areas of increased venous pressure, the ankles and feet in an ambulatory patient. Wet purpuras, blood blisters are thought to denote an increased risk of life-threatening hemorrhage in the thrombocytopenic patient. Excessive bruising is seen in disorders of both platelet number and function.

In our study no. of cases having malaria, 4 patients required hemodialysis; of them 2 were expired and 2 were discharged. All 1156 cases, who had good recovery were followed up and their platelet count was repeated at the time of discharge.
in future follow up. While in Nair PS et al\(^5\) study during the course of follow up platelet count showed increasing trends accounting for 63.3% and continuously falling counts in 7.3% in their study, because septicemia was the most common cause of fever with thrombocytopenia in their study which has very high mortality, while infections were the most common cause in our study in which platelet count improved rapidly on treatment. Srinivas\(^3\) et al, Prithviraj patil\(^4\) et al, also found results consistent with our study.

In our study septicemia was the most common cause (85.24%) of death followed by malaria (6.55%) and dengue (5%). In the study of Prithviraj patil\(^4\) et al septicemia accounted for 60%, dengue accounted for 20% and other causes accounted for 20% of mortality. In the study of Srinivas\(^3\) et al septicemia accounted for 78% and dengue accounted for 22% of mortality. In conclusion septicemia was the major cause of mortality. The findings were consistent with existing literature. A study done on mortality in sepsis by Finfer S et al\(^7\) shows 37.5% mortality. Another study by Kirs-Maija et al\(^9\) shows 18.4% mortality by sepsis. Variations in the definition of severe sepsis can explain differences in mortality rates among septic patients.\(^9\)

Mortality depends on severity of disease, diagnosis made, available treatment and care, time of initiation of treatment and associated other medical illness. Mortality can be reduced by early and right diagnosis, timely and effective treatment and care. In future various pathological and microbiological imaging modalities should be needed for research and diagnosis of many viral hemorrhagic fevers.

**Limitation of Study**

There were a few limitations to our study. This was a single centre study. In our study in 200 out of 1217 patients, cause of thrombocytopenia remained undiagnosed, because we could not take follow up of such large number of patients and some required investigations were not available at our centre.

**References**

Clinical and Laboratory Profile of Dengue Fever in a North Indian Tertiary Hospital

MU Rabbani¹, Mohd. Aslam², MS Zaheer¹, Muhammad Uwais Ashraf²

Abstract

Objectives: The present study was done to ascertain the presentations of dengue fever in a North Indian tertiary care Hospital, and to compare the clinical and laboratory features among patients with and without warning signs in dengue fever.

Methods: A total of 600 patients of dengue admitted to medical wards were included in the study. A detailed history as well as a general and systemic clinical examination were carried out. Haematological profiles and biochemical investigations were done at the time of admission and were followed daily or at times twice a day. Signs of plasma leakage were assessed by chest radiograph and abdominal ultrasonography, serum albumin etc. Patients were classified as dengue fever without warning signs and with warning signs and laboratory diagnosis of dengue was established by demonstration of NS1 antigen and specific antibodies to dengue in serum.

Results: Of the 600 dengue positive patients, 421 (70.2%) were males and 179 (29.8%) were females. Mean age of the patients was 27.35±11.43 years. Among all patients of dengue, 21 (3.5%) presented with bleeding from any site. Out of these, only 7 of those presenting without warning signs had bleeding episodes whereas, 22 (34.3%) of patients presenting with warning signs had bleeding and this difference was statistically significant (p=0.01). Haematocrit was an important factor to predict severity of dengue. Whereas the mean haematocrit among all patients was 39.79±3.23%, it was 39.49±4.25% among those without warning signs and 42.22±3.54% among those with warning signs of dengue, and this was significant statistically, with a p-value of 0.002.

Conclusion: Early diagnosis, monitoring and prompt supportive management can reduce mortality in dengue. In the present study, it was found that newer signs and symptoms are emerging and may cause delay in the diagnosis. It was found that the mortality rate was significantly higher in patients of dengue with warning signs.

Introduction

Over the past few years, dengue has emerged as a serious public health concern especially in India. It is estimated that around 2.5 billion people, in urban areas of tropical countries, are at a risk of developing dengue infection.¹ Most of the cases of Dengue Fever are being reported from Southeast Asian and the western Pacific regions.² The emergence of dengue in India has gone into epidemic proportions and dengue outbreaks are frequently engulfing different parts of the country in both urban and rural populations.³-⁴ Dengue infections may vary from flu-like self-limiting illness to life-threatening dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) which can be fatal, if left untreated. The mortality rates with dengue have been reported to be as high as 20%.² In recent years some new presentations of dengue have been reported. Many atypical presentations have led to delayed suspicion and diagnosis of dengue. Some presentations have been completely different from any of the features of dengue described until now in literature.⁵⁻¹⁰ We conducted this study in the Department of Medicine, J N Medical College, AMU, Aligarh, from June to October 2013 to assess the clinical profile of patients diagnosed to have dengue fever as well as to compare the differences in clinical and laboratory parameters among patients of dengue with and without warning signs admitted in medicine wards.

Materials and Methods

A total of 600 patients of dengue admitted to medical wards were included in the study. An informed consent was taken from all the patients. A detailed history as well as a general and systemic clinical examination (including the tourniquet test) was recorded. Haematological profiles and biochemical investigations were done at the time of admission and were followed daily or at times twice a day. Signs of plasma leakage were assessed by chest radiograph and abdominal ultrasonography, serum albumin etc. Specific investigations were performed in patients who presented with neurological involvement (cerebrospinal fluid analysis, neuroimaging, electrodiagnostic studies or muscle biopsy) or hepatic failure (viral markers, peripheral smear and serology for plasmodium falciparum, typhoid fever and leptospirosis).

Patients were classified as dengue fever without warning signs and with warning signs and laboratory diagnosis of dengue was established by demonstration of NS1 antigen and specific antibodies to dengue in serum.

Statistical analysis

All data are described as means with standard deviations or numbers with percentages. Statistical analysis was
performed by Chi Square test done by using the Statistical Package for Social Sciences (SPSS 21) with p < 0.05 taken as statistically significant. Wicoxon’s signed rank test and ANOVA were also applied wherever applicable.

**Results**

It was a hospital based observational study conducted in a tertiary care hospital. A total of six hundred patients were included in the study. Of the 600 dengue positive patients, 421 (70.2%) were males and 179 (29.8%) were females. Mean age of the patients was 27.35±11.43 years. Of the total 600 patients 536 (89.33%) presented without warning signs and 64 (10.66%) presented with warning signs. Among the patients presenting with warning signs the mean age was 31.04±11.8 years which was slightly more than the mean age of patients presenting without warning signs (27.01±11.38 years), however this difference was not statistically significant (P=0.09). Out of all patients of dengue fever, 129 (21.5%) had vomiting, 46 (7.7%) had pain abdomen and 20 (3.3%) had a rash. 28 (4.7%) patients had a history of travel to endemic areas. 8 (1.3%) had a history of past dengue infection.

Among all patients of dengue, 21 (3.5%) presented with bleeding from any site. Out of these, only 7 of those presenting without warning signs had bleeding episodes whereas, 22 (34.3%) of patients presenting with warning signs had bleeding and this difference was statistically significant (P=0.01). 36 (6%) patients presented with shock or developed shock during the hospital stay, however as many as 26 (40.64%) of those with warning signs had shock (P=0.01). A total of 3 (0.5%) patients had pleural effusion, of which one had presented with warning signs. 21 (3.5%) patients had presented with ascites, of which, 6 (9.36%) had presented with warning signs (Table 1).

Of the total dengue patients, 159 (26.5%) had hepatitis. Among those without warning signs 126 (23.5%) had hepatitis, whereas among those with warning signs 33 (51.56%) had hepatitis. This difference was also statistically significant (P<0.001).

Whereas, the mean duration of hospital stay was 5.13±1.45 days among all patients of dengue, it was 4.93±1.34 days among those without warning signs and 6.76±1.2 days among those with warning signs. This difference was also statistically significant (p=0.002). Mortality was significantly increased among patients presenting with warning signs.

Among all the 600 patients of dengue, the mortality was 2.7% (Total 16 patients died during hospital stay), however only one (0.2%) of those presenting without warning signs died during treatment. However, of all the 64 patients presenting with warning signs, 15 (23.43%) died during hospital stay, and this was statistically significant (p=0.001).

Of all the 600 patients of dengue, 553 (92.2%) patients had NS1Ag positive. However, among the patients without warning signs of dengue, 499 (93.1%) had positive NS1Ag, while, among the patients with warning signs 54 (84.37%) had positive NS1Ag.

Among all the 600 patients suffering from dengue, IgM antibody was raised in 116 (19.3%) patients (P=0.012). However, it was raised in 95 (17.7%) and 21 (32.81%) patients with warning and without warning signs of dengue fever respectively.

Out of all the 600 patients of dengue, 95 (15.8%) patients had raised IgG antibody level (P=0.013), of which 79 (14.7%) and 16 (25%) patients had raised levels with and without warning signs respectively.

Mean lowest platelet count of all the patients was 46273.3±12432.55 (P=0.042). However among the patients with warning signs, it was 34221±17112 and among the patients without warning signs, it was 23656±14123.

Mean AST of all the 600 patients, was 28.68±11.11 U/L (P=0.011). It was 26.9±10.1 U/L in patients with warning signs while it was 31.17±14.3 U/L in patients without warning signs.

Of all the patients of dengue, mean ALT was 31.53±12.34 (P=0.021). It was found to be 26.94±10.1 and 568±23.4 in the patients with and without warning signs of dengue.

Mean alkaline phosphatase of all the patients of dengue was 9.73±2.11 U/L. However, in patients with warning signs of dengue, mean alkaline phosphatase was 9.37±1.22 U/L and in patients without warning signs, it was 9.4±3.6 U/L.

Mean serum bilirubin of all the patients suffering from dengue was 1.71±0.66 mg/dl. It was 1.01±0.22 mg/dl and 0.99±0.34 mg/dl in patients with and without warning signs of dengue respectively.

Mean serum albumin of all the 600 patients was found to be 3.82±0.74 mg/dl. However, among the patients with warning signs of dengue, it was 3.95±0.71 mg/dl and among the patients without warning sign signs, it was 3.41±0.83 mg/dl. Mean Prothrombin time was 14.3±1.55 seconds among all patients, whereas it was 13.65±3.33 seconds among patients without warning signs and 16.93±5.5 seconds among patients with warning signs, and this data was statistically significant with a p value of 0.01.

Haematocrit was an important factor to predict severity of dengue. Whereas the mean haematocrit among all patients was 39.79±3.23%, it was 39.49±4.25% among those without warning signs and 42.22±3.54% among those with warning signs of dengue, and this was significant statistically, with a p-value of 0.002 (Table 2).

**Discussion**

This was a hospital based observational study, where we tried to find out the clinical spectrum of dengue patients presenting to our hospital. We tried to find out the features more common in dengue with warning signs and predictors of complications in dengue patients as well. We have found that age group affected by dengue in the present study is lower than in other Indian studies.11 Fever, vomiting, hepatomegaly bleeding, thrombocytopenia, raised liver enzymes, deranged PT, hyponatremia, hypoalbuminemia, ascites and pleural effusion were the predominant clinical and laboratory findings in our patients and the same have also been reported in previous studies.11 The most common bleeding manifestation in our patients was epistaxis, which was in concert with that reported by Kulkarni et al.12 However, Agarwal et al have reported hematemesis as the most common manifestation.11

Average duration of fever in our patients was 4.63±2.01 days, similar to the study by Manjith et al. (4.9 days)13 and Ratageri et al. (5.4 days).14 Altered sensorium was present in nine patients and convulsions were present in five of these patients. Panchanoen has earlier reported altered sensorium (83.3%) as the most common neurological finding, followed by seizures (45.2).15
Dengue causes cerebral hypoperfusion due to shock, and there may be encephalitis/encephalopathy, hepatic dysfunction, metabolic derangements or acute disseminated encephalomyelitis which may lead to the neurological manifestations. Rarely, Guillain-Barré Syndrome (GBS) may also be a manifestation following dengue fever. Ultrasonography was helpful in the present study to detect ascites and pleural effusion in 21 and 3 patients, respectively. Ultrasonography has already been reported to have the highest sensitivity in detecting plasma leakage in dengue.7

A platelet count <50,000/mm³ in dengue has a six-fold higher mortality.18 In our study, there was no correlation between platelet counts and bleeding manifestations. Previous studies have reported similar findings,18 and this finding points towards the fact that bleeding in dengue is multifactorial. Various factors leading to bleeding in dengue, include thrombocytopenia, abnormal platelet function, prolongation of prothrombin time, fibrinogen consumption, etc.19 The average duration of hospital stay was longer in patients with warning signs. Patients with warning signs required more supportive therapy (blood products and inotropes), compared to those without warning signs.

Elevation in liver enzymes is a common finding in dengue infection20 and it was also noted in the current study. We found that, AST levels were equal to or greater than ALT levels. This feature has already been reported in previous studies.21 Acute hepatic failure, is a rare manifestation of severe dengue.22 It was found in four of our patients. Derangement in liver function may be found in dengue due to the direct effect of the virus on liver cells. Fulminant hepatic failure may occur secondary to acute severe hepatitis and massive necrosis of the liver, causing hepatic encephalopathy and even death.

The overall mortality was 2.7%, which is comparable with other previous studies conducted in India.11 Joshi et al have reported a mortality rate of 3.5%.23

Conclusion

Dengue is taking epidemic form in India. It is one of the common acute febrile illnesses seen in India like enteric fever, malaria, leptospirosis, and viral hepatitis. Symptoms like fever, vomiting, headache, and musculoskeletal pain, hemorrhagic rash, pleural effusion and ascites are commonly the presenting features of dengue fever. Laboratory findings may reveal hemoconcentration, elevated liver enzymes and thrombocytopenia. Early diagnosis, monitoring and prompt supportive management can reduce mortality in dengue. In the present study, it was found that newer signs and symptoms are emerging and may cause delay in the diagnosis.

It was found that the mortality rate was significantly higher in patients of dengue with warning signs.

References

Prognostic Significance of Inferior Vena Caval Diameter in Patients with Chronic Heart Failure

Sandip Ghosh1*, Biswajit Majumder2, Tapobrata Guharay2, Viral Tandel1, Sumana Gupta3, Sharmistha Chatterjee4

Abstract

**Background:** Heart failure is a major public health problem with rising prevalence and accounts for a substantial number of OPD and emergency visits. Despite advances in pharmacotherapy and various devices being added to the armamentarium in managing heart failure the mortality continue to remain high. Therefore, we seek to find an easy bedside tool for risk stratification and prognostication of patients suffering from chronic heart failure for identifying patients with high risk and tailoring appropriate therapy for better outcome.

**Methods:** Consecutive patients, clinically diagnosed as heart failure supported by objective evidence of cardiac dysfunction: either a LVEF < 45% or LA dilatation, or both was studied to find out the etiologies, symptoms and signs, derangement of laboratory parameters and echocardiographic findings including IVC diameter and was followed up for six months at monthly intervals.

**Results:** A prospective observational study was performed on 62 patients. Majority of heart failure occurred in the age group of 51 to 60 years. Acute coronary events, infections, arrhythmias were the commonest precipitating factors. An increase in LVIDD, LA diameter, LA volume index was significantly associated with increase in mortality \( (p=0.002, p=0.034, p=0.011\) respectively. An increase in IVC diameter was found to be significantly associated with increased mortality \( (P=0.001)\)

**Conclusion:** In a country with limited resources like India, inferior vena caval diameter, as a surrogate marker of congestion, may prove to be a cost effective way in predicting and prognosticating patients with heart failure.

Methods

The study was an observational, descriptive longitudinal study conducted in the Department of Cardiology, R.G. Kar Medical College and Hospital, Kolkata. All patients attending OPD and Indoor of Department of Cardiology, R.G. Kar Medical College and Hospital during the period of data collection, clinically diagnosed as Heart Failure supported by objective evidence of cardiac dysfunction: either a LVEF < 45% or LA dilatation (> 4 cm diameter in the parasternal long axis), or combination of both, and gave informed consent constituted the study population. A total of 62 patients were included in the study. Purposive sampling was done and all the 62 subjects, was prospectively recruited for the study during the stipulated time period and followed up for 6 months.

A detailed history, general survey and physical examination with especial emphasis on the cardiovascular system were performed. Routine blood examination and echocardiography was performed to note for chamber dimensions, regional wall motion abnormalities, left atrial volume index, ejection fraction, valvular regurgitations and IVC diameter and its respiratory variations. Other echocardiographic abnormalities, if any, were also noted. The mean IVC diameter was considered in the study.

The patients were followed up every month for 6 months including emergency visits and hospital readmissions. At each visit the complaints, if any, was noted, detailed general survey and physical examination was performed the medications reviewed. The routine

Introduction

Heart failure is a growing problem with over 20 million people affected worldwide with an estimated prevalence of 2 % in developed nations, rising with age and affects 6-10% of people over age 65 with males affected more than females.1

The estimated prevalence of HF in India due to coronary artery disease, hypertension, obesity, diabetes and Rheumatic Heart Disease (RHD) alone in 2000 ranged from 1.3 million to 4.6 million, with an annual incidence ranging from 491 600 to 1.8 million. Both estimates are projected to rise and does not account for other important causes of HF such as alcoholic, familial, hypertrophic and idiopathic dilated cardiomyopathies, pericardial disease and endomyocardial fibrosis.2

Previous studies found inferior vena cava ultrasound to be a rapid, reliable means for identification of CHF in the acutely dyspnoeic patient.3

The aim of our study was to assess the relation between inferior vena cava (IVC) diameter, clinical variables, and outcome regarding number of emergency visits, hospitalization and mortality in patients with chronic heart failure (CHF).

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blood parameters were repeated and echocardiography performed. The medications were optimised if necessary. Patients requiring emergency visits and hospital readmissions were followed up closely. Only those patients who could be followed up for 6 months or those who expired during the study period were included. Patients who were lost to follow-up were excluded. The data collected was summarised. The results were then analysed in Microsoft Excel (2016), R and IBM-SPSS (v20). Survival analysis including Kaplan Meier, Log Rank (Mantel Cox), log survival distribution function, Hazard Function, Receiver-operating Characteristic curves and Cox Regression models were used and the sensitivity, specificity and level of significance (p value) of the parameters studied were calculated.

**Results**

In the study population 33 patients were male and 29 were female. A total of 17 patients were in the age range of 51 to 60 years, followed by 16 patients in the age range of 41 to 50 years. Thus, in this study, the incidence of heart failure increases with advancing age, peaking in the age group of 51–60 yrs., and then decreasing over time.

Infection precipitating an acute coronary syndrome was the dominant cause of heart failure at the time of first presentation, followed by infection and acute coronary syndrome alone. The other precipitating causes included infections with arrhythmias. 34 patients were known diabetics, 31 were hypertensive and 3 had RHD (Rheumatic Heart Disease). 20 patients had past history NSTE-ACS (Non-ST Elevation – Acute Coronary Syndrome), 6 had STEMI (ST-Elevation Myocardial Infarction), 5 CSA (Chronic Stable Angina), 3 patients had undergone PTCA (Percutaneous Transluminal Coronary Angioplasty) and 1 CABG (Coronary Artery Bypass Grafting). 4 patients had hypothyroidism, 2 hyperthyroidism, 6 had COPD (Chronic Obstructive Pulmonary Disease), 2 had asthma and 2 CKD (Chronic Kidney Disease). One patient had peripartum cardiomyopathy. Majority of the male patients were smokers (n=25). The other common addictions were chewing tobacco (n=8) and alcohol (n=7). Among the patients in the study 36 patients were overweight, 24 had normal weight and 2 were obese.

The mean IVC diameter in the study population was 21.33 mm with a standard deviation of 2.22 mm at the time of presentation. Survival analysis showed that an increased IVC diameter was associated with significantly increased mortality from heart failure (p = 0.001). Patients with a IVC diameter of more than 21 mm (green line) had a significantly higher mortality than those with a IVC diameter of < 21 mm (blue line) (Figure 1).

The area under curve for Left Ventricular Internal Diameter in Diastole (LVIDD) was 0.726 (0.6 to 0.85 at 95% CI), LA diameter 0.94 (0.89 to 1.00 at 95% CI), LA volume Index 0.93 (0.87 to 1.00 at 95% CI) and that of IVC diameter was 0.992 (0.87 to 1.00 at 95% CI) (Figure 2).

The area under curve for Left Ventricular Ejection Fraction (LVEF) was 0.909 (0.83 to 0.98 at 95% CI) whereas that of TAPSE was 0.901 (0.82 to 0.99 at 95% CI) (Figure 3).

By 5 months 23 patients died of which 5 patients died at 1 month, 5 at 2 months, 3 at 3 months, 3 at 4 months, 7 at 5 months and 4 patients after 6 months.

Cox regression analysis of patients suffering from heart failure who had to make an unscheduled OPD visit or required readmission for ACS, infections and arrhythmias had an increased IVC diameter had a significantly increased event rate (p = 0.019 for ACS, p = 0.004 for infections and p = 0.047 for arrhythmias) than those with a lesser IVC diameter.

Log rank survival analysis showed that a deceased haemoglobin and albumin level was associated with significantly increased mortality in patients with heart failure (p= 0.007 and 0.028 respectively). Log rank survival analysis showed that increased serum creatinine, bilirubin, cholesterol was associated with a significantly increased risk of events (p= 0.004 for bilirubin, p = 0.028 for bilirubin, p = 0.043).

**Discussion**

The study demonstrates a male preponderance in patients with heart failure. The incidence of heart failure peaked in the age range of 51–60 years, and then gradually decreasing with passing years due to increased death rate. Acute coronary events, infections, arrhythmias were the commonest precipitating factors for the first visit with heart failure. A vast majority of the patients were smokers or addicted to tobacco. 61.3% of the study population was either overweight or obese.

The higher risk for AMI in South Asians in their younger age is largely determined by the higher levels of risk.
Factors and the nine conventional risk factors (abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits and vegetables, alcohol and regular physical activity) collectively explain 86 per cent of the AMI risk in south Asians. Regular alcohol consumption is not protective for AMI in south Asians.4

The Kaplan Meier survival function at 1 year show significant divergence in the plot between those having a IVC diameter of <21mm and those having a IVC diameter of >21 mm respectively. The ROC curve of the echocardiographic parameters show that IVC diameter is exquisitely sensitive in predicting future cardiac events (AUC 0.992).

Pellicori et al (2013) found a strong relation between IVC diameter and plasma NT-proBNP levels and that, IVC diameter was a strong predictor of prognosis, providing information similar to NT-proBNP (widely considered to be one of the most robust prognostic markers in patients with HF). The IVC diameter was found to be related to many features of congestion, including clinical signs, decreasing albumin, and renal and hepatic dysfunction.5

Infections, acute coronary events, arrhythmias and angina were the most frequent causes of hospital readmissions or emergency visits. Cox regression analysis showed that IVC diameter can predict and prognosticate patients with heart failure suffering from common precipitating factors necessitating rehospitalisation / emergency hospital visits like acute coronary events, infections, angina or arrhythmias.

Worsening HF as the sole reason for readmission was reported most often.6 Hospitalization for HF (HHF) patients have a very high post-discharge mortality and rehospitalisation rate that has not improved in the last 2 decades despite all the available therapies. In-hospital mortality for HHF is 2% to 7%, but as high as 20% in patients with severe renal impairment and/or low systolic blood pressure (representing 2% to 5% of all HHF patients).7 Precipitants for HHF include cardiac factors such as myocardial ischemia, atrial fibrillation, and uncontrolled hypertension; non-cardiac factors, such as exacerbation of COPD and infections, patient-related factors, such as medication nonadherence etc.7

LVIDD and Left ventricular end diastolic volume, increased in 52% and 87% of patients respectively. The left atrial diameter and left atrial volume index was increased in 18% and 29% of the patients respectively. TAPSE was found to be impaired in 72.6% of patients. An increase in LVIDD, LA diameter, LA volume index (LAVi) was significantly associated with increase in mortality (p=0.002, p=0.034, p=0.011 respectively). A decline in LVEF or TAPSE was found to be associated with significantly increased mortality (p=0.01 and P=0.039 respectively).

In our study, progressive decline in renal function as evidenced by rising serum creatinine levels portends a bad outcome (p=0.004). Development of hypoalbuminemia and anaemia during the follow-up period carried a significantly high mortality risk (p = 0.007 and 0.005 respectively). Analysis of the ROC curves showed anaemia and hypoalbuminemia had a fairly high sensitivity for predicting future cardiac events. Development or progression of hyperbilirubinemia during the follow-up period carried a significantly high mortality risk (p=0.028). High Cholesterol levels were associated with only a modest increase in risk of mortality. Analysis of the ROC curves showed serum creatinine and bilirubin levels had a high sensitivity for predicting future cardiac events.

Thus IVC diameter could predict survival in patients with heart failure suffering from common precipitating factors necessitating rehospitalisation / emergency hospital visits like acute coronary events, infections, angina or arrhythmias.

Conclusions

The peak incidence of heart failure occurs at an earlier age in our study population. Majority of patients with heart failure suffer from diabetes, hypertension or ischemic heart disease. Inferior vena caval diameter measured by echocardiography can be considered as a surrogate marker for congestion and an increase IVC diameter is associated with significantly high mortality. The ROC curve show that IVC diameter measured by echocardiography is exquisitely sensitive in predicting future cardiac events in patients with heart failure.

Among the other echocardiographic parameters changes in LVIDD, LA diameter, left atrial volume index, TAPSE and ejection fraction are also useful in predicting future cardiac events in patients with heart failure. Progressive decline in renal or liver function portend to a worse prognosis. Amongst the blood parameters, a rise in serum creatinine or total bilirubin levels was significantly associated with increased mortality as was the decline in albumin and haemoglobin levels. The common causes of hospital readmissions or emergency visits include infections, acute coronary events, arrhythmias or angina. IVC diameter can predict and prognosticate patients with chronic heart failure suffering from these common precipitating factors. Thus in a country with limited resources like India, inferior vena caval diameter, as a surrogate marker of congestion, may prove to be a cost effective way in predicting and prognosticating patients with chronic heart failure.

References

Prevalence of Hyperuricemia in Indian Subjects attending Hyperuricemia Screening Programs-A Retrospective Study

Gauri Billa¹, Ramesh Dargad², Ashwani Mehta³

Abstract

Objectives: To determine the prevalence of hyperuricemia (HU) in patients with hypertension (HTN) and type 2 diabetes mellitus (T2DM) in the Indian setting.

Methods: A retrospective analysis of patients undergoing screening for HU in health clinics across India between April to May 2017 was carried out. Data regarding demographics, history of T2DM and HTN and uric acid levels (easy touch uric acid monitoring system) were recorded during the program.

Results: Data from 3044 screening programs was analysed. The mean age of the study population was 47.9 years; about two-thirds of the subjects were males. Of the 29391 subjects screened, 25.8% were found to have HU. The proportion of diabetics, hypertensives and diabetic hypertensives who had HU was 33.6%, 35.1%, and 34.4% respectively. A trend towards increased prevalence of HU was seen with increasing age and increased duration of diseases like HTN and diabetes.

Conclusion: High prevalence of HU was observed in T2DM and HTN and in patients with both co-morbidities. Age-wise analysis revealed an increasing trend of HU with age. Further, the prevalence of HU also increased with increasing duration of T2DM and HTN.

Introduction

Hyperuricemia (HU) is characterized by elevated levels of serum uric acid (SUA); the levels are increased due to either overproduction or under-excretion of uric acid (UA) (a final oxidation product of purine metabolism in humans). On the physiochemical basis, HU is defined as SUA levels > 7 mg/dL.¹ HU can be classified as primary or secondary depending upon its occurrence as a consequence of another coexisting disease or drug.² The dietary intake of purine-rich foods (red meat, seafood, beans) or high fat dairy product/alcohol/sweetened soft drink or under-excretion of UA due to renal dysfunction and use of thiazide and loop diuretics or extreme levels of physical activity are the main causes for increased production of SUA.³

The level of SUA depends upon the balance between its hepatic production and renal excretion. The high levels may trigger oxidative stress, production of urate (due to xanthine oxidoreductase) and plasma triglycerides, endothelial dysfunction, thereby leading to an impact on smooth muscle proliferation, oxidative metabolism and platelet aggregation. High levels of SUA have been evident throughout all regions of the world, including Philippines and Seychelles: 25%, USA: 21-22%, Japan: 20-26%, Indonesia: 18%, Russia and Nigeria: 17%, Brazil: 13%, Turkey: 12%, Taiwan: 10-52%, Thailand: 9-11%, Mexico: 11%, Sweden: 10-16%, Italy 9-12%, Iran and Saudi Arabia: 8%, China: 6-25%, Spain: 5-11% and South Korea: 5%.⁴ Elevated levels of SUA have been associated with an increased risk for not only type 2 diabetes mellitus (T2DM) and hypertension (HTN) but also for dyslipidemia, metabolic syndrome, hyperinsulinemia, gout, stroke, atherosclerosis, chronic kidney disease, congestive heart failure, obesity, coronary artery disease and stroke.⁵ ⁶ ⁷ Similar results have been reported from India where patients with T2DM (25.35%), metabolic syndrome (47.1%), obesity (44.6%), and HTN (37.33%) have a higher prevalence of HU in comparison to healthy individuals.⁸-¹⁰ In a study, hypertensive patients with coexisting HU were reported to be at a greater risk of uncontrolled HTN, in spite of good compliance with their antihypertensive treatment.¹¹

Considering the growing incidence of HTN and DM in developing and developed countries and having the potential link between high SUA levels and impaired renal function and cardiovascular complications, it was important to know whether emphasis should be laid on early screening of SUA levels. This would help in early detection, prevention, and management of complications of T2DM and HTN (two major public health problems). Indicators that are easy to assess and have a high predictive value (like Easy touch uric acid monitoring system) may help in providing an accurate UA levels.¹²

There is a paucity of available information regarding the burden of HU in the Indian population and about its association with age, gender and comorbidities like T2DM and HTN. Hence, the present retrospective, cross-sectional study was planned to determine the prevalence of HU in subjects attending multiple HU screening programs across India.

Methods

Study design

Abbott Healthcare Private Limited has been conducting HU screening programs across India since 2017. In these HU screening programs, subjects identified as having risk factors for HU are referred for UA test. UA levels are

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Table 1: Proportion of subjects with hyperuricemia by underlying conditions, age categories and gender

<table>
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<th>Parameters</th>
<th>Total Number of subjects</th>
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<th>P-value</th>
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<td>Hypertension</td>
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<td>By age</td>
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<td>3581</td>
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<tr>
<td></td>
<td>31-50 years</td>
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<td>&gt;50</td>
<td>12070</td>
<td>3900 (32.3)</td>
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<tr>
<td></td>
<td>Males</td>
<td>19761</td>
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Table 1 provides the proportion of HU subjects in diabetic, hypertensive and diabetic + HTN conditions.

Gender-wise, a slightly higher proportion of males experienced HU than females (27.5% versus 22.3%).

Age-wise, a higher proportion of subjects with age > 50 years were found to have increased UA levels as compared to subjects with age ≤ 30 years (32.3% versus 17.1%) and 31-50 years (32.3% versus 22.3%).

Relationship between Hyperuricemia and Age, Gender, and Duration of Disease in subjects with type 2 diabetes and hypertension

Age

With progression in age, elevated UA levels were reported in higher proportion of diabetics aged > 50 years than diabetics aged 31-50 years and ≤ 30 years (37.7% vs 29.4% vs 22.3%, respectively). Similarly, a higher proportion (29.4%) of diabetics with age 31-50 years reported HU than the diabetics with age ≤ 30 years (22.3%).

Gender

The proportion of males and females having HU was comparable in subjects with T2DM or hypertension (Table 3).

Duration of Disease

With an increase in the duration of disease (from the period of < 2 years to > 5 years), the proportion of HU subjects steadily increased from 34% to 38.4% in subjects with T2DM and from 36.7% to 42.2% in hypertensive subjects (Table 4).

Relationship between Hyperuricemia and Age and Gender in Subjects with T2DM and Hypertension

The elevated UA levels were reported...
in a higher proportion of subjects with age >50 years (38.4%) against patients of other age categories (≤ 30 years [30.3%] and 31-50 years [17.3%]). Similar results were observed when subjects with age 31-50 years were compared against ≤ 30 years (30.3% vs 17.3%). Comparing by gender, high UA levels were reported in a higher proportion of females than males (38.4% vs 33.3%) (Table 5).

There was a statistically significant association between gender (male vs. female; p = 0.02) and different age categories (≤ 30 years vs. 31-50 years; p = 0.0075, 31-50 years vs. > 50 years; p < 0.0001, ≤ 30 years and > 50 years; p < 0.0001) with respect to prevalence of HU in subjects with both T2DM and HTN (Table 5).

Discussion

Diabetes and HTN have emerged as a major public health issue worldwide and have been important risk factors for coronary artery disease, heart failure and cerebrovascular disease, resulting in increased morbidity and mortality, decreased quality of life and high economic loss. It is estimated that by 2025, the number of diabetic and hypertensive adults would rise up to 300 million and 1.56 billion worldwide, respectively. Subjects with both DM and HTN are at increased risk of developing atherosclerosis, retinopathy, renal failure, and nontraumatic amputation and CVD. Since, both diabetes and HTN impose a huge burden in India, there should be strategies for early diagnosis of these disorders by improving monitoring and management of risk factors.

Various studies have reported HU to be an independent risk factor for T2DM and HTN and by lowering the SUA levels, the risk of these disease may be lowered. Elevated SUA levels induce endothelial dysfunction, which lead to reduced insulin-stimulated nitric oxide-induced vasodilatation in skeletal muscle, resulting in reduced glucose uptake in skeletal muscles. Hence, screening of SUA levels at regular periods may serve as a good, fast, reliable, cheap and a minimally invasive procedure to circumvent the onset or progression of diabetes and HTN. In 2005, Dai et al evaluated the accuracy of Easy Touch UA monitoring system by evaluating 177 Easy Touch readings and reported this monitoring system to be an acceptable diagnostic device in terms of providing accurate UA measurements. In the present study as well, Easy touch UA monitoring system was used to assess SUA levels.

Cardiovascular risk factors like HTN, obesity, dyslipidaemia have found to be more prevalent in T2DM than in subjects without T2DM and HTN. DM and HTN are known to coexist together in ~40-60% of T2DM patients. In our study as well, approximately half of the subjects with T2DM were associated with HTN.

We report the overall prevalence rate of HU as 25.8%, with higher proportion of males having elevated SUA compared to females. Similar prevalence of HU was documented in previous studies from different population. Additionally, we found that >30% of the subjects with T2DM with or without HTN had HU. The proportion of diabetic subjects with HU (~33.6%) was much higher in our study as compared to previous published literature where around 25% of T2DM patients were reported to have elevated SUA levels. This may be due to variation in genetic and geographical factors since our’s was a PAN-INDIA study.

Furthermore, around 35.1% of hypertensive subjects had HU. Our results were in accordance to the earlier study where HU was reported in 26–33% of patients with essential HTN. In 2016, Shrivastav et al in a cross-sectional, case control study, conducted among 125 subjects (with age of 20-50 years), reported 37.3% of the subjects with essential HTN to have HU. In addition, significant higher mean SUA levels were reported in newly diagnosed cases of essential HTN than healthy normotensive subjects (6.56 ± 0.76 mg/dl versus 4.91 ± 0.97 mg/dl, p < 0.001).

The prevalence of HU varies with age and gender. In the previous literature, SUA levels were reported to increase with advancing age. In the US study conducted from 1959 to 1960, the SUA values in males rose rapidly to a peak level at 20–24 years followed by a slight decline and a rise at 55 to 59 years. In females, the SUA levels rose to a minor peak at 15-19 years followed by a decline and levelling at approximately 40 years and reached peak levels at
50-54 years and 60-64 years, due to a decline in the production of estrogen due to menopausal conditions. In our study as well, the proportion of HU subjects increased with progression in age; maximum subjects were evident in the age category of > 50 years followed by 31-50 years and ≤ 30 years. Similar results were reported in T2DM subjects with and without HTN. In hypertensive subjects, there was a slight increase in proportion of HU subjects as the age progressed from ≤ 30 years to 31-50 years (29.1% to 31%). Our findings were contrary to the earlier reported results where the highest prevalence of HU was reported in 20-39 years of age category, with a subsequent decline in the proportion of HU subjects with age in cases of essential HTN.

Various studies have reported higher SUA levels in males than females. This may be due to the presence of estrogen in premenopausal females, which enhances renal urate clearance or excretion by inhibition of renal urate reabsorption via organic ion transporter, resulting in low SUA levels. The results of our study were in concordance with the earlier published data. We also observed a higher proportion of males to have HU than females (27.5% versus 22.3%). However, when the data was split by T2DM and HTN alone, a higher proportion of females had HU than males (38.4% versus 33.3%), this may be due to more severe condition of the patient or low estrogen production, leading to a decrease in tubular excretion of UA.

Duration of disease plays an important role in increasing the SUA levels. In our study as well, a trend in increase in the proportion of HU subjects was reported with an increase in the duration of T2DM and HTN.

Our study has few limitations. First, it was not a prospective study, but a retrospective analysis of data collected from ongoing healthcare clinics. Hence, the scope of finding the association between the SUA levels and different patient characteristics, including weight or BMI, antihypertensive or antidiabetic or other medications, systolic and diastolic BP, diet, smoking status, alcohol consumption, different stages of HTN, other comorbidities etc was limited. Second, there was no healthy control group, which limited the ability to compare the SUA levels between patients of different comorbidities and healthy individuals.

In conclusion, the overall prevalence of HU in patients attending the screening programs was 25.8%. More than 30% of patients with T2DM, HTN and both comorbidities had elevated SUA levels. There was an increasing trend in the prevalence of HU with age and progressing years of duration of T2DM and HTN. Thus, there is a need to do prospective case control studies in Indian population to corroborate the results of the current study and to determine if early screening of SUA levels may help to reduce the risk of comorbidities and its further complications.

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Conflict of Interest
This work was supported by Abbott Healthcare Private Limited. Dr. Gauri Billa authored this article in the capacity of an employee of Abbott Healthcare Pvt Limited. All other authors have declared and confirmed that there is no conflict of interest with respect to the authored article.

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References
Methanol Poisoning

DB Kadam¹, Sonali Salvi², Ajay Chandanwale³

Abstract

Mortality associated with methanol has been of great concern time and again. The concurrence of cases from a particular area raises doubts about methanol as the culprit. Knowledge of the patho-physiological changes that occur in the body after methanol consumption is essential for all practicing doctors. This article elucidates the clinical presentation and emergency management of these cases under the framework of basic physiological and biochemical phenomena after methanol exposure.

Conversion of methanol to formaldehyde by hepatic enzyme alcohol dehydrogenase triggers the cascade of metabolic events. The manifestations begin as early as 30 minutes and progress to decompensated metabolic acidosis in about 12 hours, if left untreated. Seizures, hypoglycemia and blindness frequently complicate the picture. Acute kidney injury warrants urgent haemodialysis. Fundoscopic examination and arterial blood gas analysis are the key diagnostic elements. The management comprises of intravenous sodium bicarbonate, correction of dyselectrolytemia, ethanol, folic acid and haemodialysis, if necessary. The basic steps in approach must be carried out in the emergency department and followed-up with meticulous monitoring in the intensive care unit for salvage as well as prevention of long term sequelae.

Methanol poisoning in Malwani near Malad, Mumbai claimed large number of deaths due to delay suspecting and diagnosis led to delay in management.¹ Hence following principles of management are designed to tackle this type of disaster in future.

There are in several guidelines for the management of methanol intoxication in literature. However, in resource limited settings and primary health care level, all the investigative and treatment modalities are not readily available. This article aims at diagnosis and optimum management of methanol poisoning at incipient level so that large scale morbidity and mortality is prevented.

The most common cause of methanol poisoning in India is adulteration of alcoholic drinks. These alcoholic drinks are illicit liquor produced by unauthorized persons. Methanol claims to give early kick when mixed with alcohol. Hence, adulteration is done. Secondly, it is cheaper than ethanol, which makes it suitable for mixing.

The other subset of patients with methanol poisoning presents as suicidal or accidental ingestion. Methanol is used as a solvent in printing and copy solutions, adhesives, paints, polishers and stabilizers. It is also used for window cleaners, antifreeze, as a fuel in alcohol lamp and as an additive in gasoline. Methanol is known as an industrial alcohol and is mixed up with ethanol that is used for medical purposes to prevent ingestion of the same. This is colored, usually blue, to identify medical alcohol called as denatured spirit. Consumption of this for the purpose of suicidal attempt is another way of presentation.

Absorption, Distribution and Metabolism

Methanol as an alcohol is rapidly absorbed through gastro-intestinal tract, so the average absorption half-life is 5 minutes and reaches maximum serum concentration within 30 – 60 minutes and well dissolves in body water. Methanol is not toxic by itself, but its metabolites are toxic. The absorption of methanol can be delayed in the presence of ethanol or food.

Methanol is metabolized in different phases mainly in the liver. The initial enzyme in its metabolism is alcohol dehydrogenase (Figure 1)

Clinical Manifestations

Clinical manifestations of poisoning with methanol alone initiate within 0.5 – 4 hours of ingestion and include nausea, vomiting, abdominal pain, confusion, drowsiness and central nervous system suppression. Patients usually do not seek help at this stage. Associated ethanol consumption will delay manifestations of methanol poisoning. When adulterated alcohol is the cause, manifestations are seen after 12 – 24 hours. In this group, many patients will arrive together with the same symptoms and from same residential area. Left untreated, methanol poisoning can lead to significant mortality and morbidity.²

After a latent period of 12– 24 hours, decompensated metabolic acidosis occurs; which presents as acute

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Fig. 1: Metabolism of methanol. ADH: Alcohol Dehydrogenase; FDH: Formaldehyde dehydrogenase; F-THF-S: 10-Formyl Tetrahydrofolate Synthetase; All the toxic effects of methanol are due to formaldehyde and formic acid
dyspnea and dizziness. The period of latency depends on the dose absorbed and ethanol consumed. Interference with neural axoplasmatic transport by formaldehyde and/or formate probably accounts for the ocular manifestations. Formaldehyde is toxic to visual fibres leads to blurred vision, photophobia, changes in visual field, accommodation disorder, diplopia, blindness and less commonly nystagmus. Blurred vision with unaltered consciousness is a strong suspicion for methanol poisoning.

Severe metabolic acidosis with anion gap and increased osmolality are highly suggestive of methanol and/or ethylene glycol poisoning. Figure 2 describes the triage in casualty.

**Important Differential Diagnoses**

An important point in management of toxic alcohols, particularly methanol poisoning, is proper and early diagnosis. Since emergency estimation of serum methanol concentration is not available in most parts of the country, clinical differential diagnosis is very important.

Convulsions and central nervous symptoms: Central nervous symptoms, particularly convulsions are the signs of severity of toxic alcohol intoxication and hypoglycemia.

Tachypnea and acidemia: Acidemia is a noteworthy laboratory finding in the differential diagnosis of toxic alcohol and the non-toxic alcohol. The body response to acidemia is tachypnea and hyperventilation (Kussmaul’s breathing). This is diagnosed by the normal cardiovascular and respiratory findings in presence of acute dyspnea. However, ethanol poisoning leads to alcoholic ketoacidosis resulting in mild acidemia.

Ethylene glycol is metabolized by the enzyme alcohol dehydrogenase to glycolic acid (GA), which is then transformed into glyoxylic acid. Glyoxylic acid is further converted to highly toxic oxalate. Calcium oxalate crystals may form and accumulate in blood and other tissues. The precipitation of calcium oxalate in the renal cortex results in decreased glomerular filtration and renal insufficiency.

**Investigations**

Investigations are done to support the clinical diagnosis. They are not a must for starting treatment. Treatment should be started immediately on clinical suspicion alone (Figure 3).

**For Detection of Methanol and its Products**

Serum methanol level: Estimation of serum alcohol level is probably important in early hours of intoxication. This is unavailable in most of the centres. Serum methanol level > 20 mg/dl indicates severe poisoning.

Serum formaldehyde or formic acid level: Presence of these indicates definite methanol poisoning. These tests are not available in most centres.

Urinary formic acid level: Formic acid in urine is estimated by a gas chromatographic method. Evidence of formic acid in urine is confirmative of methanol poisoning. However, this facility may not be available at all the centres.

Detection of toxic alcohols in blood and/or body fluid: WHO has recommended the following methods for detection of toxic alcohols in blood or body fluid like saliva. These are qualitative and based on colorimetry. Two of these are enzyme-based methods (alcohol oxidase and alcohol dehydrogenase) and other two utilize oxidizing agents (sodium periodate and potassium permanganate). A combination of these methods allows us to detect all three important alcohol intoxications: methanol, ethylene glycol, and diethylene glycol. These methods utilize easily obtainable and relatively inexpensive reagents and no sophisticated equipment. All the studies can be completed within 40 minutes and thus can be performed either in a clinical facility or even outside the facility as the patient is being transported. 3

**For detection of complications due to methanol products:**

Fundoscopy: Presence of papillitis
indicated by hyperemic red optic disc indicates formaldehyde toxicity when ophthalmic symptoms are present (Figure 4).

Arterial blood gases: Blood gas analysis in severe toxicity reveals severe metabolic acidosis with pH < 7.3 and HCO3 < 20 mEq/L. PaCO2 is reduced and PaO2 is raised. Most patients with severe poisoning will present with pH < 7.0 and HCO3 < 5, which is a life threatening situation.

Serum lactic acid: Lactic acid level is raised secondary to formaldehyde induced mitochondrial toxicity. Tissue hypoxia leads to CIRCULUS HYPOXICUS as shown in figure 5.

Other investigations for end organ toxicity: Blood sugar level, liver function tests, electrolytes, ECG. X-ray chest is required in critical patients.

Electrolytes should be done in all cases to calculate the anion gap.

Anion gap is calculated as (Na) – (Cl + HCO3)

It is normally 8 – 12.

In methanol poisoning, it is increased to more than 20.

Serum osmolality – this is calculated as

\[ 2 \times \text{Na} + \frac{\text{Blood Glucose}}{1.8} + \frac{\text{Blood Urea Nitrogen}}{2.8} \]

It is measured directly by freezing point technique. A Gap of more than 25 between calculated and measured one indicates presence of abnormal alcohol. Vapor pressure method should not be utilized. Vapor pressure depression osmometers cannot detect the presence of volatiles (alcohols) in solution, whereas freezing point instruments can, because volatile solute increases the total vapor pressure of solutions.

**Treatment**

Sodium Bicarbonate: Life threatening complication of methanol intoxication is severe metabolic acidosis. Hence correction of acidosis is of prime importance. Sodium bicarbonate deficit is calculated as 0.5 x body weight in kg x (18 – observed bicarbonate). This calculated deficit is injected to patient in ml as half dose bolus and half dose over next 30 minutes. Repeat arterial blood gas analysis is done every two hourly and correction as above is given till pH normalizes. If pH is less than 7 and/or S. Bicarbonate is less than 5, full correction is warranted.

Correction of electrolyte imbalance: especially hyperkalemia and hypokalemia should be detected promptly and corrected.

Serum Sodium level can be low due to the presence of methanol and should be monitored and corrected.

Ethanol administration – oral administration of ethanol as 1 ml/kg of absolute alcohol diluted in 4 volumes of water is given as loading dose and followed by 0.5 ml/kg alcohol every 2 hourly. In practice one can use foreign liquors on sale like whisky, rum, brandy, gin as 60 ml stat and 30 ml every 2 hourly till acidosis persists or for 12-24 hours. If the patient is unconscious then same can be given through Ryle’s tube. Intravenous alcohol drip can be given if absolute alcohol is available as 30 ml in one pint of 5% dextrose every 4 – 6 hourly depending on patients condition. Close watch should be kept on hypoglycemia and electrolyte imbalance, especially hypokalemia, in patients on ethanol therapy. Oral alcohol group should receive additional histamine H2 receptor blocker and proton pump inhibitor to prevent vomiting and aspiration pneumonia.

Fomepizole – 15 mg/kg as bolus followed by 10 mg/kg every 12 hourly for 24 hours. However availability is an issue for this drug.

Hemodialysis: Patients with severe metabolic acidosis (pH < 7.1 and HCO3 < 10) will require hemodialysis for rapid correction of acidosis and elimination of methanol. Hemodialysis should be done with femoral vein as vascular access with 250 -300 ml/min as blood pump speed, - 50 as transmembrane pressure and for 4 – 6 hours duration. Hemodialysis leads to rapid clearance of methanol.

**Fig. 5:** Following is the algorithm suggested for management of methanol poisoning

**Fig. 6:** Diagrammatic representation of circulus hypoxicus
of methanol and its toxic products. Patient should be hemodynamically stable with resuscitation methods prior to hemodialysis.6

Folinic acid/folic acid: this degrades formic acid into carbon dioxide and (CO₂ + H₂O). Hence folic acid or folic acid should be administered. Folic Acid or Folinic Acid 1 mg/kg (usually 50 mg) every 4-6 hours, IV in 5% Dextrose over 30-60 minutes.7

**Approach to Methanol Poisoning Epidemics**

By definition, occurrence of more than three cases of methanol poisoning in one area within 24 hours is suggestive of methanol poisoning epidemic. When this is noted, should be communicated to public health authorities and police administration. Public announcement system should be put to use in this locality and persons drinking alcohol from the same source should be advised to report to medical centre even if they are asymptomatic. This plays an important role in prevention of methanol poisoning morbidities and mortalities. Immediately on suspicion of methanol poisoning epidemic, all neighboring medical institutes should be alerted for having sufficient stock of sodium bicarbonate and hemodialysis facilities should be kept ready. In Maharashtra such epidemics are seen predominantly around the following festivals/days – 2nd day of Holi, Gatar Amavasya (the day prior to Shravan month), Bhau beej (4th day of diwali)

**When to Suspect?**

Any person coming with vague generalized symptoms and
Severe acute dyspnea
Visual symptoms
History of alcoholic drink in past 24 – 48 hours
Urine examination shows severe acidic pH
Papillitis on fundoscopic examination
ABGs showing severe metabolic acidosis (pH < 7.3) with no overt cause

on history and clinical examination.

In centres where there are no facilities available for ABG
As soon as methanol poisoning is suspected and patient has acidic breathing with urine pH strong acidic, sodium bicarbonate 100 ml should be given stat and 100 ml in drip of normal saline should be started and the patient should be referred at higher centre after giving loading dose of 60 ml ethanol.

In centres where ABG is available but dialysis facility is not available, patients can be managed with acidosis correction by sodium bicarbonate, competitive inhibition by ethanol and addition of folic/folinic acid. Fomepizole if available can be given. Most of the patients can successfully be managed without mortality and morbidity at such centers. Only patients with pH < 7.1 and bicarbonate < 10 meq/L, despite correction done by intravenous sodium bicarbonate, should be considered for hemodialysis due to constraints of available facility.

In centers where hemodialysis facility is available:
In addition to sodium bicarbonate, ethanol, folic acid therapy, hemodialysis should be considered early in all patients with severe acidosis and symptoms of decreased visual acuity or ‘fogging of vision’ (also called as the “snowstorm effect”).

In methanol epidemic, one doctor/paramedic should be assigned for each patient for close follow up and monitoring. repeated ABGs, electrolytes, blood sugar levels and vital parameters measurements are required for these patients.

**Long Term Sequelae**

Visual deficits and neurological impairment are the residual defects seen. These have been described as long as after six years in a study.

Optic nerve atrophy, temporal pallor of the optic nerve head, visual field defects, and loss of visual acuity (severe to deep blindness) are the vision related abnormalities. Polyneuropathy and encephalopathy manifesting as ataxic gait and sensory impairment on the distal part of the legs are the usual neurological incapacities that can be observed in surviving cases.8

**Our Experience of Methanol poisoning**

In the year 2005, we had 21 patients of methyl alcohol consumption. Patients were triaged on the basis of arterial blood gas analysis report (pH< 7.2, serum bicarbonate less than 10 Meq/L) and fundoscopic findings of acute papillitis. On fundoscopy, retinal changes were observed in eight patients. Out of these, three patients had severe papillitis. Acidosia was present in six patients. All the cases were treated with oral alcohol by nasogastric tube. Injection sodium bicarbonate was administered to all six patients with acidosis. In four patients, we had to resort to hemodialysis. Mechanical ventilator support was required in three hypoxic patients and these were those who had severe changes on fundoscopy. Mortality occurred in two cases and one patient on ventilator recovered. Of the three patients with papillitis, two expired. Hence, severe fundoscopic features can be used to predict poor outcome in methanol poisoning if there is no access to blood methanol levels.

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Obstructive Sleep Apnea and Ophthalmic Disorders—Clinical Implications

S Ramnathan Iyer¹, Revati R Iyer², Vatsal Parikh³, S Ramchandani⁴

Abstract
Sleep is essential for physical, mental and emotional well being. Body systems require sleep of good quality and quantity for their proper functioning. There are several sleep disorders. Obstructive sleep apnea hypopnea syndrome (OSAHS) is one of the most important disorders identified in the last 50 years. The disorder has systemic ill effects by virtue of cyclical hypoxia and sympathetic stimulation. It is a risk factor for the development of hypertension, ischemic heart disease, type 2 diabetes mellitus, stroke and dementia. Retina being the highest oxygen consuming part of the body, is particularly vulnerable to the effects of hypoxia. Several eye disorders have been identified to be associated with OSAHS. In clinical practice identifying and treating sleep disorders have been rewarding.


Introduction
Sleep is a basic biologic function and is essential for life. It is an active state that is critical for our physical, mental and emotional well being. The normal duration of adult sleep varies between 5-9 hours with an average of 7 hours. Sleep is not a protected state. Sleep disorders have the capacity induce stress in body systems and repeated nocturnal insults can generate disorders eg. cardiometabolic disorders. There are nearly 88 disorders of sleep. Sleep disordered breathing (SDB) is one of the most common disorders of sleep. It encompasses a spectrum of disorders viz snoring, upper airway resistance syndrome, obstructive sleep apnea-hypopnea syndrome (OSAHS). OSAHS is one of the most important disorder identified in the last 50 years and has a high prevalence. It has deleterious systemic consequences like hypertension, diabetes, ischemic heart disease, stroke and dementia. Repetitive pharyngeal collapse and cyclical nocturnal hypoxemia are the hallmarks of OSAHS. Retina is the highest oxygen consuming part of the body and is therefore liable to get affected adversely by nocturnal events in patients with OSAHS. Also patients of non-arteritic anterior ischemic optic neuropathy and retinal detachment often report visual loss on awakening from sleep.

Sleep Disordered Breathing (SDB)
SDB basically means disordered breathing in sleep. SDB can be observed in any age and its prevalence increases with age.¹,² In elderly subjects polysomnography shows predominance of obstructive events over central or mixed events. Therefore several elderly subjects suffer from OSAHS. It must also be remembered that there is also increased prevalence of hypertension, diabetes, several retinal diseases with advancing age. In India Udawadia etal³ reported habitual snoring in 26 % of the study population (middle aged urban Indian men) and the estimated prevalence of SDB was 19.5% and that of OSAHS (SDB with daytime hypsomolence) was 7.5%. In our study snoring in elderly was found to be 69.5%.⁴ With advancing age there is reduction of lean tissue and increase in fat content. Central obesity is a common feature of ageing process. The fat of this central obesity is also metabolically active. It is also observed that blood glucose increases as age advances.⁵ People over the age of 65 years constitute more than 40% of cases of diagnosed diabetes.⁶

Obstructive Sleep Apnea Hypopnea Syndrome and its Consequences

In OSAHS there is repetitive pharyngeal collapse in sleep resulting in cyclical hypoxemia, cyclical hypertension and release of stress hormones and catecholamines. Habitual snoring and excessive daytime sleepiness are two prominent symptoms of OSAHS. Snoring in society is a common occurrence and is generally perceived as a sign of sound sleep. Snoring is usually evident when a group of subjects sleep together as in sleeper coaches of railway trains.

The other nocturnal symptoms include witnessed apneas, choking, dyspnea, restlessness, diaphoresis, acid reflux, drooling, somniloquy, frequent changes of posture in sleep, unable to sleep supine and bruxism. The daytime symptoms apart from sleepiness include fatigue, morning headache, poor concentration, decrease libido or impotence, decreased attention, depression, decreased dexterity and personality changes-mood swings and angry behavior. In OSAHS there is intermittent hypoxia, recurrent arousals from sleep and sleep fragmentation causing sympathetic stimulation. Sympathetic stimulation results in the release of stress hormones and catecholamines. Both these effects are known to decrease insulin sensitivity.

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and worsen glucose tolerance. OSAHS conduces to myocardial ischemia and arrhythmias, hypertension, myocardial infarction, increased severity of congestive heart failure and cardiac death. Habitual snoring predicts the onset of diabetes. It must be appreciated that OSAHS is a risk factor for the development of diabetes and this has been reviewed recently. OSAHS is a hypercoagulable state and can induce thrombosis in various sites of the vascular system. OSAHS is also a risk factor for stroke. This association has been recently reviewed (Figure 1). Sleep disordered breathing in pregnancy may have adverse effects on the mother and fetus (pregnancy induced hypertension and small for gestational age birth). Approximately 28% of children born in India are of low birth weight and low birth weight is associated with elevated levels of glucocorticoids in later life (a story from womb to the tomb).

OSAHS can affect all age groups. Subjects with obesity, short neck, retruded chin, neck circumference ≥43 cms, macroglossia (both relative and absolute), narrow mandible, narrow maxilla are prone to develop OSAHS. Owing to anatomical reasons OSAHS can be seen in non-obese subjects also. Males are usually more affected than females but there is increased prevalence in post menopausal women. Polysonography is essential to diagnose OSAHS.

Management of OSAHS chiefly rests on achieving optimal body weight and usage of Continuous Positive Airway Pressure (CPAP). CPAP is an established mode of treatment for OSAHS. This device has several systemic benefits. Several studies have documented improvement of insulin sensitivity also. This has important clinical implications. Insulin resistance is the core issue in type 2 diabetes mellitus.

**Retina, Oxygen and Sleep**

Oxygen is essential for retinal function. It is known that retina has 2 domains - avascular retina and inner vascular retina. The retina is the most metabolically active tissues consuming oxygen more rapidly than many other tissues including brain. The difficulty of measuring oxygen intraretinally in humans or animal models of human diseases has prevented a more complete understanding of the role of oxygen in retinal diseases. It is known that inner and outer halves of retina are different domains in terms of oxygen and this has important therapeutic implications. Inner retinal PO2 averages about 20 mm Hg and this dependent on an effective autoregulation of the retinal circulation. This mechanism protects it from effects of systemic hypoxia, hyperoxia and increased intraocular pressure in healthy animals. Failure of retinal circulation results in tissue hypoxia. This hypoxia underlies the vasoproliferation in diabetic retinopathy and retinopathy of prematurity. On the other hand, choroidal blood flow is not regulated metabolically so systemic hypoxia and elevated intraocular pressure lead to decreases in choroidal pO2 and photoreceptor oxygen consumption. However this lack of regulation allows choroidal pO2 to increase dramatically during hyperoxia. This phenomenon offers a chance to use oxygen therapeutically in retinal vascular diseases and retinal detachment.

**Linkages of SDB-OSAHS with Retina and Diabetic Retinopathy**

The first author had proposed for the first time in 2003 that cyclical hypoxia of OSAHS can have deleterious effects on the retina. Diabetic retinopathy is a known complication of diabetes mellitus. Cyclical hypoxia of OSAHS can stimulate angiogenesis in retina leading to progressive diabetic retinopathy. Recently McNabb has reported association of obstructive sleep apnea with several eye disorders, viz. floppy eyelid syndrome, anterior ischemic optic neuropathy, optic neuropathy,
Diabetic retinopathy is a disease predominantly of retinal vasculature. Initially there is capillary occlusion and then to vascular proliferation. Animal experiments have demonstrated that retina is hypoxic early in the disease. For many years tissue hypoxia has been suggested to be involved in the progression of diabetic retinopathy and retinal neovascularization in general. In fact there is a difference in the intensity of insult to body tissues due to continuous low grade hypoxia and cyclical hypoxia. Sympathetic stimulation due to cyclical hypoxia is core feature of OSAHS, resulting in fluctuating blood pressure, insulin resistance and cardiovascular effects. Therefore retina suffers in cyclical hypoxia by dual mechanism-direct and via sympathetic system activation. Further sleep complaints are common in diabetic subjects. Gislason et al reported that diabetes was associated with near frequent complaints of difficulty in initiating sleep (21.1%), difficulty in maintaining sleep (21.9%) and excessive daytime sleepiness (12.2%). The relation of type 2 diabetes mellitus and sleep has been reviewed recently. Also there are several similarities between type 2 diabetes mellitus and obstructive sleep apnea.

It is difficult to explain why the retina microvasculature is affected more than the brain in patients of diabetes. Arden et al suggested that dark adaption aggravates hypoxia by depriving the inner retina of the small amount of oxygen that diffuses from the choroid during light adaption. Avoiding a long period of dark adaptation eg. sleeping during night could be a alternative therapy of diabetic retinopathy. However this is not practically useful. It must be remembered that is the quality of sleep which is more important than quantity in terms of reference of hypoxia to retina. Hypoxia may induce the synthesis of Vascular Endothelial Growth Factor (VEGF). Also the concentration of VEGF is higher in proliferative diabetic retinopathy. It is known that no treatment stops retinopathy apart from panretinal photocoagulation. If early circulatory retinal changes preceding VEGF up regulation could be detected clinically, then interfering with leucocyte adhesion or using other pharmacological techniques to increase retinal blood flow might be effective. It must be remembered that treatment of SDB-OSAHS is highly rewarding. Correction of hypoxia in sleep is expected to give favourable results in patients with diabetic retinopathy.

Merritt et al conducted a limited channel sleep study on 44 adults with type 2 diabetes mellitus suffering from diabetic retinopathy. They stated that, the extra burden of hypoxia to an already ischemic retina along with recurrent activation of sympathetic nervous system and fluctuating blood pressure could play as contributory factors. They concluded that SDB may play an aetiological role in the development and/or progression of diabetic retinopathy. Shiba T et al in a study concluded that diabetic retinopathy patients with nocturnal desaturation, reoxygenation caused by SDB may relate to the development of progressive diabetic retinopathy. Mason RH et al observed that individuals with clinically significant macular edema have high prevalence of SDB. Further, Mason RH et al assessed whether treatment of obstructive sleep apnea (OSA) with CPAP will improve visual acuity in patients clinically significant macular oedema (CSMO). They concluded that usage of CPAP ≥ 2.5hr/night over six months in individuals with CSMO and OSA may be associated with improvement in visual acuity.

Based on these observations it therefore becomes imperative to screen patients of diabetes for SDB.

**Retinal Detachment**

Retinal and vitreous degeneration are precursors to retinal detachment. OSAHS can be present since childhood due to anatomical factors like macroglossia, retracted chin etc. Snoring may not severe since subjects often sleep prone to enlarge the airway. Daytime sleepiness may be replaced by hyperactivity in children. OSAHS by virtue of effects viz hypoxia and oxidative stress can cause degenerations in retina paving the path for retinal holes and retinal detachment in adult life. The oxidative stress aggravates aging process. It is a matter of coincidence that patients of retinal detachment who are injected with silicone oil in the posterior chamber are advised to sleep prone to produce desired results. Recently Linsemeier et al have suggested that hyperoxia may be useful in preventing photoreceptor damage in patients with retinal detachment.

**Glaucoma**

Glaucoma is a slowly progressive, insidious optic neuropathy. It is usually associated with chronic elevation of intraocular pressure. The mechanism by which raised intraocular pressure injures the optic nerve is not known. Recent evidence indicates reduced ocular blood flow and by implication reduced oxygen is contributing factor.
in retinal damage. Studies have shown that retinal oxygenation can be partially or completely restored during arterial occlusion by making animals hypoxic. OSAHS has been found to be associated with glaucoma. Margherita et al have reported that the prevalence of normal tension glaucoma (NTG) in OSAHS patients is higher than expected in a white population of the same age and that OSAHS may be an important risk factor of NTG. Mojon et al have reported high prevalence of glaucoma in patients with sleep apnea syndrome. As discussed above, these observations should compel the ophthalmologist to rule out OSAHS in patients with glaucoma. CPAP usage must be done under ophthalmological monitoring since CPAP can raise intraocular pressure.

**Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)**

Non-Arteritic Anterior Ischemic Optic Neuropathy is a disease characterized by sudden painless mostly irreversible and generally non-progressive visual loss accompanied by nerve fibre bundle field defects, a relative afferent papillary defect and optic disc oedema. NAION by definition involves a mm segment of optic nerve head and results in visible disc swelling. The pathophysiological aspects of NAION remain unclear. Vast majority of the cases of NAION are idiopathic but some specific etiologies have been reported. The risk factors include i) aging ii) small optic nerve head iii) neurovascular changes associated with hypertension and diabetes. Many patients notice the symptoms of NAION early morning. Hayreh et al observed in a prospective study that in at least 399 (73.3%) of 544 episodes of NAION patients discovered visual loss upon first awakening or at first opportunity to use vision critically after sleeping suggesting that nocturnal arterial hypertension may play an important role. Mojon et al state that it is unclear as to how sleep apnea syndrome can cause NAION. However it is hypothesized that apneic spells of OSAHS might result in acute increases in blood pressure, intracranial pressure or nocturnal hypoxemia which could cause optic nerve oedema and ischemia. It must also be noted that systemic hypertension, arteriosclerosis, vasospasm or medications may reduce the autoregulatory capacity of the optic disc. Exaggerated decreases in nocturnal blood pressure eg. by aggressive antihypertensives therapy especially if drugs are taken late at night might also contribute to the development of NAION. It must be remembered that OSAHS is a risk factor for both Type 2 diabetes and hypertension and OSAHS itself has been associated with NAION. There have been case series that have demonstrated a possible association between sleep apnea syndrome and NAION.

**Floppy Eyelid Syndrome (FES)**

Floppy eyelid syndrome is characterized by the presence of an easily everted upper eyelid associated with keratoconjunctivitis. Patients of FES are usually overweight and has been associated with obstructive sleep apnea. Patients usually have loose rubbery tarsus, spontaneous eyelid eversion, loss of lid to globe contact at night, chronic papillary conjunctivitis, meibomian gland dysfunction and loose and easily everted upper lids. Patients of OSAHS may also visit the ophthalmologist with complaints of unrefreshed feeling with heaviness and burning in eyes. Woog JJ reported 3 cases of obstructive sleep apnea with FES. Recognition of OSAHS in patients with FES is important since management of OSAHS is highly rewarding not only for ophthalmic complaints but also for systemic well being.

**Papilledema**

Association of sleep apnea syndrome and papilledema has been recognized. Purvin et al have reported 4 cases of disc edema and sleep apnea syndrome. Owing to episodic nocturnal hypoxia and hypercarbia in OSA there is increased intracranial pressure secondary to cerebral vasodilation. Sustained raised intracranial pressure (ICP) causes papilledema due to obstruction of retrograde axonal transport at the level of optic disc. Continuous intracranial pressure monitoring has shown that although the daytime measurements of CSF pressure are within normal range, marked episodic nocturnal increases of ICP occur in patients with sleep apnea syndrome. The rise in pressures range between 50-750 mm of H2O. This can lead to persistent disc edema. Also these patients are at risk for visual loss secondary to papilledema (PE). Visual field defects can also occur. The diagnosis of OSAHS in PE may not be appreciated because daytime cerebrospinal pressure measurements are normal. Also patients tend to present with visual loss rather than with symptoms of increased intracranial pressure. Pseudotumor cerebri (PTC) is a syndrome of elevated ICP with a variety of causes including chronic obstructive pulmonary disease (COPD). Patients with underlying cause of COPD have persistently raised ICP as compared to patients with OSAHS. Also COPD can coexist with OSAHS (overlap syndrome). Therefore patients of PTC should be screened for OSAHS.

**Suggested Hypothesis**

Based on the various facts stated above it is compelling to suggest that OSAHS should also be suspected in patients with age related macular degeneration, macular edema and vascular disorders of retina like branch retinal vein occlusion and retinal vein thrombosis.

**Conclusions**

Sleep disorders have the potential to disturb body systems. OSAHS is a systemic disease. There is a close association of OSAHS with various retinal and visual tract diseases. Suspecting and treating OSAHS in a given patient is expected to give favourable results.

**Acknowledgements**

Thanks to Dr. J.C. Suri and Dr. Zahir Udwadia for their guidance. Also thanks Dr. K. Iyer, Shri S.V. Iyer, Smt. Vijaylakshmi Iyer, Mr. K. Sriram, R. Venkatraman, Smt. Minakshi K, and Dr. Bhagyalakshmi Venkatraman for their help and support.

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Cutaneous Lymphangiectasia of Genitalia: A Rare Occurrence

Savita Arya¹, Asha Nyati², Moti Lal Bunkar³

Case History

A 70 years old male presented with complaints of multiple raised lesions over scrotum and penis since five years. On local genital examination, there were single and grouped, non-tender, non-pruritic, translucent and papulovesicular lesions involving scrotum, supra pubic region and thigh. Penile lesion was tender, ulcerated and nodular, more over prepuce and glans penis with no regional lymphadenopathy (Figure 1). The routine blood investigations, ultrasonography of the abdomen and pelvic organs revealed no abnormality. Screening tests for human immunodeficiency virus, VDRL, hepatitis B virus, chlamydia and filariasis serology were also non-reactive. Biopsy revealed thin-walled and ectatic lymphatic channels in the superficial dermis. The dermal papillae and the dermis showed proliferating, congested capillary sized blood vessels, melanophages and diffuse as well as perivascular mild inflammatory infiltrate suggestive of lymphangiectasia (Figure 2b, H and E, 40 X). Patient advised for ablative treatment like but he refused due to social reason and later lost to follow up.

Discussion

Cutaneous lymphangiectasias (CL) or acquired lymphangioma is a lymphatic malformation, mostly congenital, whereas the acquired CL occurs due to obstruction of deeper lymphatic vessels secondary to other etiology.¹ It involves dermal and subcutaneous lymphatic channels and characterized by presence of a circumscribed eruption of thin- walled, translucent vesicles and ranges from clear, fluid filled blisters to smooth, flesh-coloured nodules, sometime coexisting lymph oedema. The lymphatic vessels of the superficial dermal plexus drain a fixed area of skin through the vertical collecting lymphatics to the deep plexus. The damage to deep lymphatic vessels leads to back-pressure and dermal backflow, with subsequent dilatation of the upper dermal lymphatics.² It has to be differentiated from herpes genitalis, genital warts or molluscum contagiosum. Mostly CL is asymptomatic but pruritus, burning or painful lesion and sometime foul smelling viscous discharge may also occur. The diagnosis is mainly clinical, aided by histopathological finding of dilated lymphatics in the dermis. Treatment should be directed towards the etiology and aimed at reduction of underlying lymph edema and control of infection.

References


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Received: 05.12.2016; Accepted: 12.06.2017
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White Powder Over Palm: An Unusual Presentation of Hyperuricemia in Polyarticular Gout

Renu Saigal¹, Laxmi Kant Goyal², Dev Kumar Jain³

A 70 years old male presented with polyarthritis (both small & large joints) and multiple subcutaneous swellings since 25 years (Figure 1 A, B, C). There was white powder present over palm which oozed out from the body and reappear after wiping (Figure 1D). Patient was on corticosteroids for years together and he did not give history of acute flare of arthritis.

Laboratory investigations revealed Hb -11.0 g% TLC -12000 cells/ Cumm, ESR 85 mm l¹ hour. Serum Creatinine was 1.8 mg%, S. uric acid was 12.0 mg%. On aspiration of subcutaneous swellings, joint fluid and on examination of white powder needle shaped crystals were seen under light microscope (Figure 1E). X-ray of foot showed erosions with overhanging edge (Martel’s sign) (Figure 2). Final diagnosis was polyarticular gout with multiple tophi and chronic kidney disease. In patients with repeated attacks of acute gout, tissue deposits of monosodium urate crystals surrounded by granulomatous inflammation known as tophi are found in numerous tissues including joint and skin.¹ Tophi are associated with destruction of surrounding cartilage and bone. Bone erosion with overhanging edge (Martel’s sign) is characteristic of gouty arthritis.

Monosodium urate (MSU) crystals identification in synovial fluid/tophi is considered the gold standard for diagnosis.² The MSU crystals are needle shaped negatively birefringent crystals, easily detected by polarizing microscope. Under light microscopy also MSU crystals may be seen as needle shaped crystals.

Though uric acid is secreted in sweat² but excretion of uric acid in sweat as white powder is rare. Literature showed uremic frost in chronic renal failure patients composed of urea³ but we did not find frost composed of uric acid. The finding of uric acid as white powder on palm highlights the rarity in this report.

References


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Erythema Nodosum Leprosum as a Rare and Challenging Cause of Pyrexia of Unknown Origin

Himanshu Narang\(^1\), Prayas Sethi\(^2\), Neha Rastogi\(^1\), Sudheer Arava\(^4\), Arvind Kumar\(^2\), Neeraj Nischal\(^2\), Naveet Wig\(^3\)

**Abstract**

A 30-year old male presented with fever for last 1 year. There were associated multiple painful skin eruptions with hyperpigmentation and scaling over whole body which had been progressively increasing. He also had anasarca along with generalized weakness. He presented to us in shock after an acute episode of gastroenteritis. After stabilization, he was evaluated for cause of fever. Routine fever workup (for typhoid, syphilis, malaria, filariasis, HIV, scrub typhus, leishmaniasis) was negative. CECT chest and abdomen revealed hepatosplenomegaly. There was no response to intravenous (IV) antibiotics and anti-fungal medications. Slit skin smears revealed 3+ acid fast bacilli (AFB). Skin biopsy revealed fragmented acid-fast bacilli with dense collection of neutrophils and foamy histiocytes in upper and middle dermis suggestive of Erythema Nodosum Leprosum (ENL). A diagnosis of ENL with lepromatous leprosy was made and patient started on steroids and thalidomide and subsequently on multidrug therapy (MDT). On therapy, patient’s symptoms improved, and skin lesions resolved. Though Leprosy itself is a well-known common cause of PUO in India, its first presentation as ENL is rare and needs good index of suspicion and timely management.

**Case Report**

A 30-year old male, resident of western UP, shopkeeper by profession, presented with complaints of fever for more than a year. Fever was intermittent, high grade (up to 103-degree F) that lasted for 2-3 days, then resolved spontaneously only to recur after 7-8 days. It was associated with multiple painful skin eruptions over whole body (Figures 1-4). These lesions used to resolve with some unknown medication. This continued for 6 months, when patient started developing non-pitting edema of bilateral lower limbs. Around a month before presentation, patient developed hyperpigmentation of face (Figure 1), abdomen (Figure 2) and extremities along with swelling of bilateral upper limbs. He also developed severe generalized weakness so much so that he could not walk out of house without support. Patient presented to us with acute gastroenteritis and shock.

On presentation, patient was in shock with a blood pressure (BP) of 65/36 milli-meter of mercury (mm Hg), with a heart rate of 140/min and a respiratory rate of 20/min. His shock responded to IV fluids and BP improved to 90/50 mm Hg and heart rate was 110/min after fluid resuscitation. General physical examination revealed anasarca, with multiple erythematous to hyperpigmented skin eruptions involving trunk and extremities. Some lesions were thin and atrophic with presence of scaling. Induration was present in forehead and bilateral ear lobes. Left ulnar nerve was thickened, non-tender. Bilateral common peroneal nerves were tender. Mild focal hyperalgesia was present over trunk and extremities. However, there were no motor deficits. Nails in bilateral hands and feet had features suggestive of onychomycosis. Conjunctival congestion was present. There was no pallor, icterus or any lymphadenopathy.
Fig. 3: Lower limbs had non-pitting edema with extensive scaling [black arrow] and patchy hyperpigmentation [white arrow].

Fig. 4: Gross swelling of upper extremity with scaling and induration of skin [black arrow]. Features suggestive of severe onychomycosis involving all nails were also present [white arrow].

Fig. 5: Erythema nodosum leprosum reaction: (A) Upper dermal mixed inflammatory infiltrate with dermal edema. (B) The inflammation is extending in to the subcutaneous fat. (C) Prominent peri-neural and peri-adnexal inflammation rich in neutrophils.  (D) Inflammation is involving the erector pili muscle [Arrow]. (E) Acid fast stain reveals few fragmented bacilli within the macrophages [Arrow].

Table 1: Investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>At admission</th>
<th>At follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (gm/dl)</td>
<td>8.8 (Normocytic normochromic)</td>
<td>12.1</td>
</tr>
<tr>
<td>Platelet count</td>
<td>3,23,000</td>
<td>2,88,000</td>
</tr>
<tr>
<td>TLC (per ml)</td>
<td>18,000</td>
<td>6,700</td>
</tr>
<tr>
<td>ESR (mm/1st hr)</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>4.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.6</td>
<td>9</td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>4.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>8.1</td>
<td>7.3</td>
</tr>
<tr>
<td>Na’ (meq/dl)</td>
<td>139</td>
<td>144</td>
</tr>
<tr>
<td>K’ (meq/dl)</td>
<td>3.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Total Bilirubin (mg/dl)</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>AST (IU/mL)</td>
<td>19</td>
<td>30</td>
</tr>
<tr>
<td>ALT (IU/mL)</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>ALP (IU/mL)</td>
<td>255</td>
<td>128</td>
</tr>
<tr>
<td>Total protein (g/dl) -</td>
<td>4.5</td>
<td>6</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.2</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Abbreviations: *cells/ml-cells per millimeter cube (millilitre); *mg/dL- milligram per deciliter; *g/dL- gram per deciliter; *meq/dL- millequivalents per deciliter; *IU/mL- international units per millilitre, TLC-Total Leucocyte Count, AST – Aspartate transaminase, ALT – Alanine transaminase

Abdominal examination revealed mild splenomegaly. Rest of the systemic examination was unremarkable.

Abdominal examination revealed mild splenomegaly. Rest of the systemic examination was unremarkable.

Lab findings revealed microcytic hypochromic anemia with a haemoglobin of 8.8 g/dl, along with leukocytosis with TLC of 18000/cu mm with presence of toxic granules (Table 1). Erythrocyte Sedimentation Rate (ESR) was raised. Patient had acute kidney injury (AKI) on presentation with a serum creatinine of 4.0 mg/dl which came back to normal in 3 days. However, patient had persistent hyponatremia along with borderline hypokalaemia. Hypoalbuminemia (2.2 gm/dl) was also present. Blood and urine cultures were sterile. Serum procalcitonin was raised to 41ng/mL. Chest X-ray was normal. Contrast Enhanced Computed Tomography (CECT) chest and abdomen revealed hepatosplenomegaly but no other abnormality (Table 2).

Routine fever workup (for typhoid, syphilis, chronic malaria, filariasis, HIV, scrub typhus, leishmaniasis) was negative. Patient was empirically started on broad spectrum antibiotics with a possibility of gastrointestinal sepsis. Even after resolution of gastroenteritis, fever persisted with no improvement in skin lesions. Blood for fungal cultures was sterile. Serology for aspergillus and histoplasma were also negative. Serum galactomannan was positive (1.36). Despite rK39 antigen being negative, in view of long duration of fever associated with hyperpigmentation and hepatosplenomegaly, kala azar was kept a strong possibility. In view of this, patient was started empirically on injection liposomal amphotericin B, but there was neither any symptomatic improvement, nor resolution of skin lesions.

Fundus examination revealed bilateral steroid induced posterior subcapsular cataract, further strengthening our suspicion of chronic steroid use. Due to the presence
of hyperpigmentation along with hyponatremia in a chronic diseased state, with presentation in shock, adrenal insufficiency was suspected; however, serum cortisol and ACTH levels came out to be normal. Anemia workup was suggestive of anemia of chronic disease.

Slit skin smears were prepared from ear lobules, forehead and back, which revealed 3+ acid fast bacilli. Skin biopsy (Figure 5) revealed fragmented AFB with dense collection of neutrophils and foamy histiocytes in upper and middle dermis suggestive of Erythema Nodosum Leprosum (ENL).

A final diagnosis of ENL with lepromatous leprosy was made and patient was started on steroids and thalidomide followed by multidrug therapy (MDT) for leprosy comprising rifampicin, clofazimine and dapsone, on which his skin lesions improved. His fever completely resolved, and anasarca markedly decreased, along with an improvement in general well-being within a week of onset of therapy. Hyponatremia and hypokalaemia also improved with treatment. At 2-month follow-up, skin lesions had resolved completely (Figures 6, 7, 8).

Discussion

Since pyrexia of unknown origin (PUO) was first defined by Petersdorf and Beeson more than 5 decades ago, the definition has subsequently evolved with advancement in medicine as well as greater availability of resources. PUO was initially defined as an illness of more than 3-week duration with fever > 38.3-degree C (101°F) documented on at least 2 occasions, whose diagnosis could not be determined despite 1 week of extensive in-patient evaluation. However, the current definition of PUO further includes ruling out immunocompromised state and performing general microbiological and imaging investigations before classifying any fever as PUO.

Erythema nodosum leprosum is a Type 2 lepra reaction, seen in patients with lepromatous end of spectrum of leprosy. It is characterised by crops of painful erythematous nodules on limbs but may involve whole body. Other features include neuritis, anemia, fever, lymphadenopathy, orchitis, uveitis and glomerulonephritis.

As per official estimates, prevalence of leprosy in India is 0.66/10,000 population, with an Annual New Case Detection Rate (ANCDR) of 9.71 per 100,000 population. ENL is known to occur in 5% of BL cases and 26% of LL cases.

Leprosy (Hansen’s disease) is a chronic infectious disease caused by the AFB, Mycobacterium leprae. It mainly affects skin and peripheral nerves, however, can also involve eyes, bones, testes and internal organs. The disease manifestation has a broad spectrum depending on host’s immune status, varying from tuberculoid at one end to lepromatous at the other end of the spectrum.

Erythema nodosum leprosum, aka Type 2 lepra reaction, is an immune complex reaction usually seen in patients with lepromatous end of the spectrum. It is characterized by crops of multiple painful erythematous lesions that may last for a few days, but frequently recur. Systemic manifestations include fever, malaise, neuritis, arthritis, orchitis and lymphadenitis. Hepatosplenomegaly may be present. Skin biopsy reveals an infiltrate of polymorphonuclear leukocytes over a background of chronic inflammation and dense collection of acid fast bacilli (M. leprae).

In our patient, clinical presentation was different from classic ENL presentation in that fever and skin lesions were of very long duration. Also, skin lesions were not similar to those seen in classical ENL. There was patchy hyperpigmentation along with scaling over whole body. This could be attributable to chronic topical steroid use. Possibility of chronic fungal skin infection was also there which was supported by the presence of hyperpigmentation and severe onychomycosis in nails of both hands and feet. Nail changes are frequently encountered in patients with leprosy. Kaur et al and others have observed that onychomycosis is associated in 5 percent of these patients. The fungal infection of nails might be due to spread of superficial dermatophytic infection, or caused by another fungus, like *Candida albicans*. Serum precipitins for aspergillus was negative on initial evaluation. However, serum galactomannan had come back positive. This might be due to false positivity of serum galactomannan assay. With regards to the long duration of fever, it is highly likely that this patient would have received antibiotics like amoxicillin-clavulanate which can explain the positive galactomannan assay. Also, systemic fungal infection would have responded to amphotericin B that the patient had initially received. Patient’s anemia was attributable to the presence of chronic diseased state. The generalized weakness is explained by anemia, and the fact that malaise is a known feature of ENL. His acute worsening in weakness might be attributable to borderline hypokalemia, which also got corrected with therapy.

Vooren et al have shown that ENL most commonly occurs during first year of MDT. However, Kumar et al have analysed Indian data and found that here ENL has maximum incidence during second year of MDT. ENL is rarely the presenting feature of leprosy. ENL presenting as PUO is an even rarer
entity. ENL is known to present in myriad atypical clinical manifestations. These include necrotic, hemorrhagic, pustular and bullous lesions. Histopathological examination and detection of acid fast bacilli in skin lesions leads to definitive diagnosis and rules out other clinical mimics. These findings also highlight the need to have strong clinical suspicion for this disease, failing which a delay in diagnosis is likely, as was the case with our patient.

Table 2: Fever Work-up

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Patient Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray Chest</td>
<td>Normal</td>
</tr>
<tr>
<td>Ultrasound abdomen</td>
<td>Mild heptosplenomegaly</td>
</tr>
<tr>
<td>HIV 4th Generation assay</td>
<td>Non-reactive</td>
</tr>
<tr>
<td>rK39</td>
<td>Negative</td>
</tr>
<tr>
<td>Blood Cultures</td>
<td>Negative</td>
</tr>
<tr>
<td>CECT Chest and abdomen</td>
<td>Mild heptosplenomegaly</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Conclusion

This case was a diagnostic challenge because of rarity of erythema nodosum leprosum presenting as PUO. On searching “Erythema nodosum leprosum” and “pyrexia of unknown origin” in PubMed database, only 2 case reports were found. Definite cause is found in only 50% of PUO cases. Rest remain undiagnosed with only symptomatic treatment being prescribed. Routine fever or fever with heptosplenomegaly workup usually does not include leprosy/lepra reaction because of its low prevalence as well as classical clinical features of skin and nerve involvement. This case reinforces the need to consider leprosy and its reactions in cases of PUO with skin lesions that may not be like those as mentioned in classical teachings.

References

Guillain–Barre Syndrome as Presenting Feature in a Patient with Systemic Lupus Erythematosus

Amey Beedkar¹, Archana Sonawale², Juhi Kawale³

Abstract
Guillain–Barré syndrome. GBS as initial manifestation of lupus is exceedingly rare and has been reported in a few cases in the literature. We report here a 35 year old woman who presented with 10 day history of progressive muscle weakness and paraesthesias in all four limbs. She was diagnosed as SLE with renal involvement and was treated with steroids and cyclophosphamide.

Introduction
Various neurological features have been reported in association with systemic lupus erythematosus (SLE). However, Guillain–Barré syndrome (GBS) as a presenting feature of SLE appears is rare.¹ We report a patient presenting with GBS, in whom lupus nephritis also diagnosed. The GBS failed to respond to intravenous immunoglobulin treatment, but both GBS and lupus nephritis responded very favourably to intravenous pulses of cyclophosphamide and methyl prednisolone. GBS as initial manifestation of lupus is exceedingly rare and has been reported in a few cases in the literature.²³ GBS in lupus is a complex and poorly understood phenomenon.

Case
A 35-year-old woman was referred to our hospital because of a 10-day history of progressive muscle weakness of arms and legs and paraesthesias in both hands and feet. Her medical history was unremarkable. Physical examination on admission revealed a blood pressure of 130/90 mmHg. Neurological examination showed absent deep tendon reflexes, and severe symmetrical proximal muscle weakness. Laboratory examination revealed haemoglobin 6.5 gram%, an erythrocyte sedimentation rate of 84 mm/h; C-reactive protein 71 mg/l; urea 12.3 mmol/l; creatinine 150 μmol/l; serum albumin 3 gram/dL; LDH 434 U/l; Coombs-positive haemolytic anaemia; but normal thrombocyte and leucocyte counts. Qualitative urine analysis revealed the presence of protein (3 plus). Later, also active urinary sediment was found (10–25 leukocytes, hyaline and coarse granular casts). The cerebrospinal fluid revealed a normal cell count and total protein. Oligoclonal immunoglobulin bands were absent.

The nerve conduction study (day 1) showed loss of F responses, and decreased amplitudes of sensory nerve action potentials and compound muscle action potentials in arms and legs. Because of the clinical picture of rapid progression of symmetric proximal limb weakness to total paralysis in 2 weeks, associated with areflexia, the diagnosis GBS, was made according to the Asbury criteria.⁴ Retrospectively the patient also fulfilled the American College of Rheumatology (ACR) case definitions for GBS published in 1999.

On day 1 treatment was started with intravenous immunoglobulin G (2 g/kg bodyweight per day, for 5 days. Muscle weakness rapidly progressed to a quadripareisis.

Because of proteinuria with active urinary sediment, additional investigations were performed, including autoimmune serology. This revealed a 3+ positive antinuclear antibody (ANA) test, anti-dsDNA positive, but no antineutrophil cytoplasmic antibodies (ANCA), or anticardiolipin autoantibodies, and decreased C3 and C4 values. Based on the presence of proteinuria with cellular casts, autoimmune haemolytic anaemia, a positive ANA and the presence of anti-DNA auto-antibodies the diagnosis SLE with renal involvement was made, according to the ACR criteria.

USG guided renal biopsy was done, which showed glomeruli with mesangial and endocapillary proliferation. Focally, glomeruli showed crescent formation and splitting of the glomerular basement membrane. The biopsy findings were classified as a mesangiocapillary lupus nephritis with a membranous component (WHO class IV.C) with a NIH activity index of 10 and a chronicity index of 7.

Because of this severe form of lupus nephritis the patient was treated with intravenous pulses of cyclophosphamide (750 mg/m2) and high oral doses of prednisone (1 mg/kg body weight).⁵ In the first 6 months the patient was treated with monthly pulses of cyclophosphamide 750 mg/m2, together with intravenous hydration and MESNA (2-mercapto-ethane-sulphonate) to reduce the urothelial toxicity of cyclophosphamide. In addition, prednisone 60 mg/day was given for 4 weeks and thereafter monthly tapered to a maintenance dose of 10 mg. Intra- venous immunoglobulin was not given.

This treatment regimen was tolerated well. Muscle strength improved, first proximally, then distally. By that time the proteinuria had decreased to 3.7 g/24 h and renal function had become normal. Six months after the onset of the GBS the patient was in an excellent condition, muscle strength and tendon reflexes were normal without any physical restraints.

Twenty-four-hour protein excretion was 150 mg and the complement C3 and C4 values were 70 and 35 mg/ml, respectively.
A Rare Survival in Celphos Poisoning

Praveen Kumar P1, Babu M1, Poornima Nair1, Rajeswari1, Sreejith V Ravi1, Sivakumar K2, Sanbakasree2, Raveendran M3

Abstract
Aluminium phosphide poisoning releases phosphine gas which causes inhibition of cytochrome oxidasation, inhibition of electron transport chain and thereby myocardial suppression. It is known to cause various electric abnormalities in the heart from ST-T depression to fatal tachyarrhythmias. Here we present a case of celphos poisoning presenting with both supraventricular tachycardia and ventricular tachycardia.

Introduction
Celphos (Aluminium Phosphide) is one of the most common suicidal poisoning agent in southern India. It can easily be bought over the counter and has no effective antidote. Its toxicity results from the release of phosphine gas when the tablet gets into contact with moisture. Phosphine gas primarily affects heart, lungs, gastrointestinal tract and the kidneys. Here we present a case of Celphos poisoning with varying electric abnormalities in the heart.

Case Report
55 year old male was referred from a private hospital with alleged history of consumption of 2 celphos tablets (kurunai marundhu). He was given stomach wash (contraindicated) and of the neuropathy is insufficient in about 50% of the cases.2 The efficacy of intravenous immunoglobulin for GBS in lupus nephritis is controversial.2 Plasma-exchange may have a beneficial effect on the neuropathy4 but does not convert an additional effect for lupus nephritis.4

In this patient suggest that GBS developed as a feature of lupus. Therefore, the association of GBS with lupus seems to have implications for both treatment and prognosis. Prednisone and cyclophosphamide should be considered in patients with GBS as a feature of lupus.

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Aluminium Phosphide Poisoning, a solid fumigant pesticide (for stored cereal grains), widely used in India (Quickphos, Celphos, Rice tablet). Most commonly used for suicidal deaths, in North India. Each Tablet weighs 3gm and liberates 1gm of phosphine (PH₃) gas which has high dissolution and diffusion capacities. For the silver nitrate test on gastric aspirate, diluted gastric content is heated in a flask up to 50°C for 15-20 mins, keeping silver nitrate paper on the mouth of the flask. If phosphine is present then the paper will turn black due to silver phosphate. The aim of therapy is to sustain life till phosphine gets excreted from the body. Antacids 60ml per hour may reduce PH₃ absorption. There is no antidote to phosphine. Magnesium Sulphate has membrane stabilizing properties. Dose 1gm iv stat then 1gm iv hourly for three hours, 1gm continuous infusion daily for 4 to 7 days. It does not have mortality reduction benefits. Mortality is still high from 30 to 100% depending upon whether the tablets are fresh ones opened from new packs or old exposed tablets. The management of Celphos poisoning is still supportive therapy. After ingestion, removal of unabsorbed poison from the gut (“gut decontamination”), especially if administered within 1–2 hours, can be effective. Potassium permanganate (1:10,000) gastric lavage can decompose the toxin. The rationale behind the use of a mixture of soda bicarbonate and coconut oil in our patients is guided by the chemical reaction of AlP with moisture and HCl, liberating phosphine gas which rapidly gets absorbed through gastric mucosa. As the poison itself causes a lot of gastric mucosal damage, it exposes a lot of raw area for phosphine absorption. The mechanism by which coconut oil reduces the toxicity of phosphides is unknown but most probably it forms a protective layer around the gastric mucosa, thereby preventing the absorption of phosphine gas. Secondly, it helps in diluting the HCl and again inhibiting the breakdown of phosphide from the pellet.

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Discussion
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Fig. 1: Supraventricular tachycardia

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Conclusion
Since death is rapid and survival after significant poisoning is difficult, prevention is the logical option. The most effective way for prevention is to either ban or impose strict regulation on the sale of aluminium phosphide tablets. Shielding of tablets in smaller plastic with holes and spikes so that they can’t be swallowed as such, is likely to reduce the incidence of Aluminium phosphide poisoning.

References

Hamman’s Syndrome - in Young Asthmatic Female

Radhika Nair K1, Kishore Kumar U2, Bhuvan Shetty3, Sanjana Joseph4, Shabnam Jameela4

Abstract
Spontaneous pneumomediastinum (SPM) is a rare condition where there is presence of air in the mediastinum without any precipitating trauma, surgery or other conditions. It usually develops after alveolar rupture and air penetration into the pulmonary interstitium, the hilum and the mediastinum. It is commonly seen in young males, asthmatics on inhalational drugs, or following severe vomiting, parturition, weight lifting. A young female, known case of bronchial asthma presented to us with history of breathlessness and cough of 3 days and mild swelling of the face and neck of 2 days duration. On examination, she was dyspneic, had subcutaneous swelling of the face, neck and chest bilaterally with palpable crepitations. CT thorax showed pneumomediastinum, pneumoperitoneum, pneumothorax and pneumorrhachis. A diagnosis of Hamman’s syndrome was made and patient was treated symptomatically and recovered.

Case Presentation
A 18-year-old female, known asthmatic since the age of 10 years presented to the Emergency in the evening hours with history of breathlessness and cough of 3 days duration. She was initially admitted in primary care facility and was started on antibiotics and nebulized bronchodilators. Her symptoms improved with treatment, but noticed painful swelling of face and neck after a day of starting treatment. There was no history of trauma, history of pleural fluid aspiration, history of recent surgery or similar history in the past.

On clinical examination her vitals were stable with 98% SPo2 in room air, B.P 110/70 mmHg, Pulse rate 80 beats/min and was afebrile. There was swelling of cheeks, neck and chest (Figure 1) with palpable crepitations over these areas. Normal vesicular breath sounds with equal intensity and diffuse polyphonic rhonchi were heard all over the lung fields bilaterally.

Blood hematology and biochemistry were within normal limits. Chest X-ray (Figure 2) showed subcutaneous emphysema. Subsequent CT thorax showed (Figures 3, 4 and 5) pneumomediastinum, pneumoperitoneum, minimal pneumothorax and pneumorrhachis and ruled out causes like perforation of esophagus. A diagnosis of spontaneous pneumomediastinum (SPM) or Hamman’s syndrome was made.

Patient was managed with nebulised salbutamol, oxygen, rest and symptomatic measures. Her symptoms improved and subcutaneous emphysema resolved over a week’s period. She was discharged and was advised out-patient follow-up.

Discussion
Pneumomediastinum or mediastinal emphysema refers to the presence of air in the mediastinum.1 SPM, which was initially described by Laennec in 1819, was further characterized in case series by Hamman in 1939.2,3 It is a rare condition defined by the presence of air in the mediastinum with no apparent causes like trauma or surgery, which may precipitate pneumomediastinum. Pneumomediastinum may also occur following barotrauma, tracheobronchial injury, procedures like bronchoscopy and cardiothoracic surgeries, frequent retching and vomiting, weight-lifting, parturition, and straining against a closed glottis.3,4 A history of bronchial asthma and associated coughing bouts has been reported as a possible factor in the development of SPM in up to 25% of cases.5 In patients with bronchial asthma pneumomediastinum may occur secondary to air trapping due to airway narrowing or mucous plugging, especially after bouts of cough. This sudden increase in intra-alveolar pressure causes rupture of alveoli with escape of air into the pulmonary interstitial spaces. Air then extends along the perivascular sheaths, eventually dissecting into the mediastinum producing mediastinal emphysema-the Macklin effect.5 There may be associated pneumothorax in sporadic cases. Dissection along the carotid perivascular sheaths produces subcutaneous emphysema in the soft tissues of the head and neck.

Fig. 1: Fullness of the upper anterior chest and neck

Fig. 2: Chest X-ray showing subcutaneous emphysema

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Diagnosis can be made from X-rays of chest and cervical region - if no trauma or perforation suspected - which will reveal air in the mediastinum in the form of transparent bands around the heart, and subcutaneous neck emphysema and occasional pneumothorax. Chest CT may be required if minimal pneumomediastinum is present (which may not be visualized in X-ray) and it also helps anatomically to locate air in the mediastinum. Bronchoscopy and esophagoscopy may be indicated if tracheobronchial or esophageal perforation (Boerhaave syndrome) is suspected.

SPM often follows a benign course and is often under diagnosed due to a clinical presentation similar to many respiratory pathologies. The diagnosis of pneumomediastinum should be suspected when an asthma patient experiences substernal chest pain during an acute asthmatic attack. The presence of subcutaneous emphysema in the neck and a “crunching” sound heard over the heart during systole should raise the suspicion of the diagnosis even further. Though an infrequent entity it should be also considered in the differential diagnosis of acute chest pain especially among young people without risk factors for ischaemic heart disease. It is however important to differentiate it from far more serious differentials such as Boerhaave syndrome. Occasional complications include tension pneumomediastinum, unilateral or bilateral pneumothorax, tension pneumopericardium and cardiac tamponade.

Treatment is mainly conservative and most of the pneumomediastinum resolves spontaneously. Observation of the patient for development of any complication, rest and cardio-pulmonary monitoring is the mainstay of management. Pure oxygen treatment increases the diffusion pressure of nitrogen in the interstitium and promotes rapid absorption of the free air. Mediastinoscopy may be rarely required for cases of life threatening tension pneumomediastinum. Thoracotomy and drainage may be needed in cases of pneumothorax.

Pneumorrhachis (epidural emphysema or epidural pneumatosis), which was first described in 1977, denotes air in the spinal epidural space and is mostly traumatic or iatrogenic origin. Spontaneous combination of pneumomediastinum with epidural pneumorrhachis without thoracic trauma is very rare. Pneumorrhachis in bronchial asthma is extremely rare; only 14 cases were reported till 2009, and we could find another 2 thereafter. Mechanism of pneumorrhachis in bronchial asthma is thought to be due
to rupture of alveoli due to the acute increase in the intra-alveolar pressure and escape of air sequentially into the perivascular space, facial planes of the neck, into the posterior mediastinum and finally to the epidural space.\textsuperscript{11}

**Conclusion**

It is important to keep a diagnosis of SPM in mind in cases of undiagnosed chest pain, and in cases of surgical emphysema. Once diagnosed, it may reassure the caregiver and temper the management plan to follow a path of expectant observation and watch for any sinister signs requiring surgical interventions.

### References


### Concurrent Intramedullary and Intracranial Tuberculomas

**Shailendra Ratre\(^1\), Sushma Choudhary\(^2\), Yadram Yadav\(^3\), Vijay Parihar\(^1\), Jitin Bajaj\(^4\), Anurag Pateriya\(^4\)**

**Abstract**

Tubercular involvement of the central nervous system (CNS) is well known. CNS involvement can occur in the form of tuberculosis meningitis (TBM), tuberculous vasculitis, tuberculoma and rarely brain abscess. Tubercular granulomas generally solitary and occur in the brain but they may be multiple and involve other areas such as spinal cord, epidural space and subdural space also. Tuberculoma in the spinal cord is rare. Co-occurrence of intracerebral and intramedullary spinal tuberculoma is extremely rare in children with only few cases reported till date. We are reporting one such case in children and review of literature.

**Introduction**

Tubercular involvement of the central nervous system (CNS) is seen in approximately 0.5-2% of all patients with systemic tuberculosis.\(^1\) The most frequent manifestations of CNS tuberculosis are tuberculous meningitis and intra-cranial tuberculomas. Tuberculomas are tumour like masses resulting from enlargement or coalescence of caseated tubercles. CNS tuberculomas most commonly affect the intracranial compartment; spinal intramedullary tuberculomas (SITs) are very rare and constitute only 0.2 to 5% of all CNS tuberculomas.\(^2\) Co-occurrence of intracerebral and intramedullary tuberculoma is exceedingly rare with only few paediatric case reports.\(^3-6\) We are reporting one such case in children with review of literature.

**Case Report**

A 14-year-old boy presented with increasing asymmetric spastic quadriaparesis for 15 days. He had past history of TBM with obstructive hydrocephalus (Figure 1a) for which right sided ventriculoperitoneal shunting was done 4 months back. He was on Anti Tubercular Therapy (ATT) (isoniazid, rifampicin, pyrazinamide, and ethambutol). On examination, he was conscious and oriented. He was quadriplegic for 15 days. He had increasing asymmetric spastic quadriaparesis and finally to the epidural space.\(^11\)

**References**

lower limb. Repeat MRI cervical spine and brain revealed resolution of cranial and spinal tuberculoma (Figure 3A, 3B).

Discussion

Tuberculosis can involve almost any organ of the body. CNS tuberculosis is a serious form of extra-pulmonary tuberculosis and is associated with significant mortality and morbidity. TBM is the most frequent form of CNS tuberculosis and constitutes approximately 1% of all forms of tuberculosis. Intracranial tuberculoma can occur at any age.

Spinal intramedullary tuberculomas are rare and constitute only 0.2 to 5% of all CNS tuberculomas. The most common site of IT is the thoracic spinal cord. IT occurs by haematogenous spread from a pulmonary focus, although occasionally an extra pulmonary focus may be found. The clinical symptoms may be variable with subacute spinal cord compression, focal neurological deficits or totally asymptomatic.

Co-occurrence of intracranial and intramedullary spinal tuberculoma is very rare in paediatric population with only four cases reported till date. Thacker and Puri reported a 6-year-old girl who presented with progressive paraparesis in whom imaging revealed intramedullary tuberculoma with incidentally discovered multiple intracranial tuberculoma. Chitre et al reported a case of concurrent intracranial and lumbar intramedullary tuberculomas in a 6-year-old girl who developed the intracranial and intramedullary tuberculomas while on antituberculous therapy for previously diagnosed tuberculous meningitis. Kulkarni et al reported a 4-year-old boy who presented with fever, headache
Fig. 3: MRI images showing resolution of cranial (a) and cervical (b) intramedullary tuberculomas after 1 year of chemotherapy

and vomiting in whom imaging revealed multiple intracranial and cervical intramedullary tuberculomas. Recently Goel et al. reported concurrent intracranial and conus intramedullary tuberculoma in a 18 months old female child.

The MRI is the diagnostic tool of choice in the evaluation of intramedullary tuberculosis. The tuberculous lesion appears isointense on T1-weighted MRI images (T1WI) with slight or no expansion of the cord. On T2-weighted MRI images (T2WI) it appears isointense to hyperintense, sometimes with central high signals. The MRI picture varies with the stage of the tuberculoma formation.

The ideal treatment of intramedullary tuberculoma remains controversial. Both surgery and chemotherapy had shown good results in different series. Many authors have recommended medical treatment of intramedullary tuberculomas with good results rather than surgical treatment. Surgery is generally indicated when a) there is no response to chemotherapy, b) the diagnosis is in doubt, and c) there are large lesions with rapid deterioration in neurological function.

Conclusion

Concomitant cranial and spinal intramedullary tuberculoma is a very rare occurrence in children. Clinicians and neurosurgeons should keep index of suspicion while treating cranial or spinal tuberculomas. MRI is the modality of choice in diagnosis as well as in evaluating the response of treatment modality. Medical therapy is primarily used. Early surgery has definite role in patients of intramedullary spinal tuberculomas with profound neurological deficit.

References

Multisystem Involvement of Langerhans Cell Histiocytosis

Abhijit Ahuja¹, Abhay Uppe², Girija Nair

Abstract
Langerhans cell histiocytosis presents with involvement of skin, bone and lungs. We discuss this case of breast LCH who developed pulmonary cystic lesions leading to bilateral pneumothoraces. PET scan showed involvement of thyroid and marrow involvement. A new nodule developed at ICD site after 9 months and was diagnosed as LCH nodule. This could be because of seeding of LCH cells at ICD site. We review LCH with involvement of multiple systems.

Introduction
Langerhan’s histiocytosis was formerly known as histiocytosis X and refers to a group of conditions characterized by the uncontrolled stimulation and proliferation of a normal antigen-processing cell, the Langerhan’s cell.

LCH is a disease of abnormal clonal proliferation of a unique type of cell in the monocyte-macrophage cell line known as the Langerhans cell. LCH is known to involve skin (39%), bone (77%), lymph node (19%), bone marrow, liver, spleen, lung, endocrine and CNS.¹ Cytokines, soluble secondary products of lymphocytes and monocytes regulate cell growth and differentiation of hemopoietic stem cells by binding to specific receptors to target cells. Langerhans cells are subject to be regulated by cytokines. The morphology of LCH cells and the clinical signs and symptoms suggests that cytokines maybe important in the pathogenesis of this disorder. Most of the cytokines were of T cell origin and they directly contributed to pathologic sequelae of LCH including fibrosis, bone resorption and necrosis. The term histiocyte refers to large white blood cells resident in tissues, including Langerhans cells, monocytes/macrophages and dermal/interstitial dendritic cells.² The WHO classification of haematopoietic and lymphoid tumours divides disorders of these cells into the following three categories:³

1. Dendritic cell disorders – includes Langerhans cell histiocytosis, secondary dendritic cell processes, juvenile xanthogranuloma, solitary histiocytomas with a dendritic phenotype and Erdheim-Chester Disease.

2. Macrophage related disorders – includes primary and secondary hemophagocytic syndromes, sinus histiocytosis with massive lymphadenopathy and solitary histiocytoma.

3. Malignant histiocytic disorders – includes monocyte related leukemias, extramedullary monocyte tumor and dendritic cell

Case report
A 35 year old lady, non smoker, diabetic on insulin since 3 years, came to us with complaints of breathlessness, mMRC grade 4 since 4 days which was of sudden onset and right sided chest pain since 4 days.

She had history of left breast mass in 2008, cut section was creamish white firm consistency with multiple tiny cystic spaces and on microscopy proliferating ductotubular units embedded in stroma suggestive of benign fibrocystic mastopathy. Her chest radiograph showed bilateral small thin walled cavities. It was diagnosed clinically as left TB mastitis by surgeon, for which he patient was treated with anti tuberculous chemotherapy for 18 months.

In 2010 she underwent an excision biopsy of the persistent breast mass and the biopsy report showed the fibro-fatty and fibro-muscular stroma showing scattered nodules with sheets of round to oval cells with abundant eosinophilic cytoplasm and vesicular folded and grooved nucleus, morphology suggestive of Langerhan’s cell histiocytosis of breast. CD1a of the sample was positive. However patient gave no history of any treatment at that time.

The patient underwent a bronchoscopy with TransBronchial Lung Biopsy, in 2012 due to symptoms of breathlessness for 1 month. The histopathology of the lung biopsy sample was features suggestive of pulmonary Langerhan’s cell histiocytosis. The IHC report showed the sample cores containing an almost exclusive population of mononuclear cells with an abundant eosinophilic cytoplasm. The mononuclear cells display an immunopositivity for CD1/S100 protein and focal immunoreactivity for CD68.

The patient was lost to follow up and came back in 2014 with acute onset breathlessness.

On examination, the breath sounds were decreased on the right side.

Chest radiograph revealed right sided pneumothorax, with multiple bilateral thin walled large bullae. Right sided ICD insertion was done. Column movement and Bronchopleural

Fig. 1: Chest X-ray showing right sided pneumothorax with bilateral large thin walled cystic lesions

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A PET scan was advised by the oncologist which showed active uptake of FDG in pre and parasternal soft tissue, cervical and mediastinal nodes. There were pulmonary lesions, infiltrative lesions in thyroid and marrow which were suggestive of histiocytosis involvement. No active disease in the left breast or elsewhere in the body (Figure 2).

The patient was started on chemotherapy with vinblastin + oral steroids as per oncologist opinion. During the course of hospitalization serial chest radiographs revealed a loculated pneumothorax on the left side for which a USG guided Pig-tail catheter was inserted. The patient was discharged with both catheters in-situ (Figure 3).

The ICDs were removed after a month and the patient still comes for regular follow-up after 6 months. She received 5 courses of vinblastine.

After 6 months she presented with a small nodule at the site of right ICD scar. FNAC and excision biopsy of the right nodule suggested histiocytosis subcutaneous nodule (Figure 4).

Repeat CT scan showed expanded right lung with few bullae and few cysts in the left lung.

**Discussion**

Our patient has a history of a left breast mass diagnosed as LCH of the breast on excision biopsy 4 years back. She presented with bilateral pneumothoraces and underlying multiple large lung cysts. Bilateral ICDs were inserted and patient was sent home with bilateral ICDs as bilateral BPF was present. She was prescribed chemotherapy with vinblastin by the oncologist and she completed 5 cycles out of the 6 cycles advised. Her general condition improved as well as closure of the BPF within a month, so ICDs were removed. On presentation after nearly 1 year, the lung cysts had reduced considerably in size and bilateral atelectactic lower lobes had re expanded. Incidentally noted the patient had a subcutaneous nodule at the scar site. On biopsy this nodule showed cellular features of LCH.

The subcutaneous nodule of histiocytosis developed at right ICD scar, perhaps as a result of seeding of the LCH cells. It has not been previously reported of LCH cells seeding unlike other malignant cells.

Our patient initially had breast involvement later on lung was involved. Lung involvement is seen in approximately 10% of cases. It is less frequent in children than in adults, in whom smoking is a key etiologic factor. Although the lung has been considered a “risk organ”, more recent studies have suggested that it has less of an effect on prognosis. In adults, pulmonary involvement with Langerhans’ cell histiocytosis usually occurs as a single-system disease and is characterised by focal Langerhans’ cell granulomas infiltrating and destroying distal bronchioles. High-resolution computed tomography (HRCT) of the chest is essential to the diagnosis, typically showing a combination of nodules, cavitated nodules, and thick- and thin-walled cysts. A high macrophage count in bronchoalveolar lavage (BAL) fluid is a common but nonspecific finding that merely reflects exposure to tobacco smoke. BAL is useful for eliminating infections and the other infiltrating lung disorders that can be seen in young adults. Langerhans’ cells can be identified in BAL fluid, but, in contrast to what was initially hoped, this test shows a very low sensitivity and is rarely useful in the diagnosis of the disease.

The definite diagnosis of pulmonary Langerhans’ cell histiocytosis requires identification of Langerhans’ cell granulomas, which is usually achieved by surgical lung biopsy at a site selected by chest HRCT. In practice, however, lung biopsy is performed on a case-by-case basis.

Breast involvement with LCH has not been described in literature. Our patient first presented with a breast mass which was diagnosed with a LCH mass, later after 2 years came with lung lesions which were diagnosed as pulmonary LCH. She does not have any bone or skin lesions which are commonly associated with LCH. The left breast excision scar is healthy. But the right ICD scar developed a nodule which on biopsy came out to be CD1a positive suggestive of LCH nodule.

In view of a new nodule at ICD site, it is concluded that this is due to seeding of LCH cells at the ICD site. There have been no descriptions of seeding of LCH cells as also breast LCH. Hence this is a rare presentation indeed of LCH.

**References**

Central Neurocytoma- A Rare Brain Tumor

Hozefa Runderawala1, Ajay Kantharia2, Pradyumna Oak3, Amit Mahore4

Abstract
Central neurocytoma are rare, slow growing, intraventricular tumors of neuronal origin, typically located in the lateral ventricles, near the Foramen of Monroe with characteristic imaging features. They generally occur in young age with favorable prognosis. With clinical, histological and immunohistochemical background, we report a case of central neurocytoma.

Introduction
Central neurocytoma is a slow growing, benign neoplasm with a favorable prognosis and affects mainly young adults.1–3 These low grade and slowly growing primary brain tumor were firstly described by Hassoun et al in 1982.4 They comprise 0.25% to 0.5% of all primary brain tumors.5 There is no reported gender predilection.6 Central neurocytoma is typically located in the lateral ventricles, near the Foramen of Monroe. We report a case of central neurocytoma histologically and immunohistochemically proved in 33-year-old female.

Case Report
33-year-old female, no major comorbidities, presented with chief complaints of headache since 15 days which got worsened a day back was associated with non-bilious vomiting and diplopia. Headache was diffuse in nature and present throughout the day. She had no history of fever or loss of consciousness.

On examination, she was well nourished and adequately built. She was afebrile, pulse was 80 beats/min, regular, blood pressure in right brachial artery 120/80mm of Hg. Neurological examination did not reveal any focal deficit or any cranial nerve involvement. Laboratory parameters were within normal limits. Within few hours, she became unconscious with decorticate rigidity, pulse rate dropped to 40 beats/min, pupils were semi dilated bilaterally with sluggish reaction to light. She was shifted to Intensive Care Unit (ICU), was intubated and mechanical ventilatory support given due to irregular breathing, features suggestive of acute decompensated hydrocephalus. Her MRI brain could not be done due to acute deterioration of neurological condition and hence CT brain was done and patient was taken for surgery without waiting for MRI brain.

Computed Tomography of Brain revealed hyper dense lesion in mid line in the region of Foramen of Monroe measuring approximately 2.1 X 1.6cm, causing third verteicle obstruction leading to bilateral lateral ventricles hydrocephalus and peri verteicular oozing with diffuse cerebral edema (Figure 1).

Right Parasagittal craniotomy was done, decompression of tumor was done and biopsy taken and was sent for histopathological examination. Macroscopically it was multiple small gray white pieces of tissue. Microscopically, the tumor composed of monotonous round cells with perinuclear halos, nuclei contain fine chromatin granules. On immunohistochemistry, tumor cells were positive for Synaptophysin, Neuron specific Enolase and GFAP (Glial fibrillary acidic protein), negative for Chromogranin A (Figure 2) and Ki-67 less than 5% in maximum proliferating area. Histological and immunohistochemical profile compatible with diagnosis of central neurocytoma.

Discussion
Central neurocytoma is a rare WHO grade II neuroepithelial intraventricular tumors, constituting only 0.25%-0.50% of all intracranial tumors.7 Initially described in 1982 by Hassoun et al, central neurocytoma is a rare tumor of neuroglial origin.4 The initial description classified them as WHO grade I lesions, however this was upgraded in 1993 to WHO grade II as it was recognized that at least some of these tumors exhibited more aggressive behavior.8 These tumors typically affect young adults around third decade. They are characteristically located in the supratentorial ventricular system. Half of the cases involve the lateral

Fig. 1: Computed tomography showing hyper dense lesion in mid line in the region of Foramen of Monroe causing dilatation of bilateral lateral ventricles

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ventricles near the Foramen of Monroe, whereas 15% are located in both the lateral and third ventricles. About 13% of central neurocytoma are bilateral and only 3% occur in third ventricle as an isolated location.\(^7\)

The typical clinical presentation is with signs and symptoms of increased intracranial pressure induced by obstructive hydrocephalus. Patients may present with acute symptoms related to sudden development of ventricular obstruction and elevated intracranial pressures, generally there is insidious onset of symptoms. Schild et al analyzed 27 patients with central neurocytomas regarding their presenting symptoms, and 93% of patients complained of headaches, 37% had visual changes, and 30% experienced nausea and vomiting at presentation.\(^3\) In another study by Wang et al, out of 27 patients, 21 presented with headache and 6 with vomiting.\(^9\)

The imaging method such as CT and MRI are used to evaluate location and assist on the diagnosis of the tumor, but the definite diagnosis is established by pathology analysis (electron microscopy and immunohistochemical studies).\(^10\) Based on location and histomorphology, the differential diagnosis of masses located in ventricular system, are oligodendroglioma, ependymoma and neuroblastoma.\(^11\) In light of the cellular monotony, peri nuclear halos and frequent calcification, oligodendroglioma becomes the principal entity in the differential diagnosis. In most of the cases, these two are virtually indistinguishable at H and E stain. Immunostaining for Synaptophysin is the simplest way to distinguish neurocytoma from oligodendroglioma since the latter is nonreactive.\(^11\)

Central neurocytomas carries good prognosis. The best treatment for central neurocytoma appears to be complete surgical resection. Patient with incomplete excision may benefit from radiotherapy.\(^12\) Well differentiated neurocytomas are associated with good 5-year survival rate.

**Conclusion**

Central neurocytomas are slow growing, rare, benign intraventricular tumors of neuronal origin. The diagnosis is established by typical location of tumor, histology and immunohistochemistry. The treatment of choice is complete surgical removal of tumor, radiotherapy in incomplete excision. In our case of typical neurocytoma, confirmed with microscopic examination and immunohistochemistry, treated with surgical decompression of tumor.

**References**

Protean Neurological Manifestations in Chikungunya

Ajay Chauhan1, Varun Rehani2, Prabhat Kumar2, Gargi Sasmal3, Parul Goyal4

Abstract
Unplanned urbanization and secondary migration has caused increased spurt in arboviral diseases especially Dengue and Chikungunya. With this exponential rise in these illness, now we are beginning to notice uncommon presentations of these common illnesses. Here we present two interesting cases: one of paraparesis and another of quadriparesis with respiratory involvement secondary to Chikungunya, although the mechanism in one is hypokalemia and the other is GBS secondary to Chikungunya. Just the magnitude of cases presenting in metros and major cities of our country warrant sensitizing the physicians about these uncommon manifestations.

Introduction
Chikungunya, an arboviral disease transmitted by Aedes mosquitoes is gaining significant public health proportions due to rapid migration, unplanned urban settlements and poor sanitation. Usually the disease passes off harmlessly in 5 to 7 days; with few patients suffering from fatigue and post fever arthralgia. Delhi this year experienced an exponential rise in the number of Chikungunya cases with some patients presenting with unusual clinical manifestations. Neurological syndromes are rarely known to occur with chikungunya barring few reported cases of encephalitis, encephalopathy or myeloneuropathy. We present two cases who presented with sudden onset limb weakness. The attributable aetiology for both was chikungunya, but the underlying causative mechanisms were eclectic.

Case 1
A 40-year-old male with no previous co morbidities presented with complaints of fever since three days, which was continuous and high grade with associated chills. Fever was accompanied by multiple joint pains. This was followed two days later by bilateral lower limb weakness with subsequent involvement of both upper limbs. He, however did not give any history of loose stools, vomiting, altered sensorium, rash, breathlessness, hoarseness of voice, dysphagia, difficulty in closing his eyes or band like sensation around his waist. Also, patient did not give any history of loose stools, dysphaiga, difficulty in closing his eyes or band like sensation around his waist. Also, patient did not give any similar complaints in past. Patient had been living in a slum for past 03 years which had ubiquitous mosquito breeding sites.

At presentation, his vitals were stable. Power in bilateral lower limb and upper limb were 2/5 and 3/5 respectively. Deep tendon reflexes were absent in both upper and lower limbs and bilateral plantars were flexor. No sensory deficit was noted. All other systemic examination was normal. Lab investigations revealed a Hemoglobin of 12.0gm%, TLC: 8000/mm3, PLATELET: 1.8L/mm3, PCV: 33.6%. Kidney and liver function tests were normal. Hyperkalemia with a Potassium of 2.3meq/L was documented. His ECG also showed prominent U waves in precordial leads NCCT head and CSF evaluation was normal. Patient was started on oral and parenteral potassium supplements. Recovery of power was seen in all the 4 limbs within two days of initiating treatment.

Further, investigations were done to find the underlying association for Hypokalemia. S. magnesium levels were normal. ABG was normal with a pH of 7.41. 24-hour urinary potassium was 15mmol/L. Thyroid function with a TSH of 1.553micro IU/L, FT3 of 2.74pg/mL ad FT4 of 1.21ng/dL was also normal. CPK and CK-MB were also in normal range. In view of acute febrile illness with polyarthralgia, malarial, dengue and chikungunya serologies (IgM) were sent. In addition, a malaria antigen kit was also done, the result of which was negative. Later on, chikungunya serology came out to be positive. NCV and EMG were planned but couldn’t be undertaken as power along with reflexes had recovered in the affected limbs.

Patient was managed conservatively with antipyretics and continued potassium supplementation. At the time of discharge (post admission: day 4), power in all four limbs was 5/5 and serum potassium was 4.9 meq/L.

Case 2
A 45 years old male presented with a history of progressive ascending quadriparesis involving both lower limbs simultaneously followed by upper limb involvement in a span of 2 days. There was an associated history of hoarseness of voice which was not associated with visual changes, facial deviation, slurring of speech or nasal regurgitation.

Bowel and bladder were not involved and no seizure, headache or vomiting was present and there were no sensory complaints. No back pain or band like sensation or pain during flexion of neck was present. Patient however had a history of fever for 3 days associated with multiple joint pains from 10 days with no associated GI or respiratory symptoms.

On examination, patient was conscious oriented having BP of 130/80 mmHg, pulse 100/min with respiratory rate of 20/min and single breath count of 20. On neurological examination there was no facial deviation or loss of wrinkling of forehead and bilateral uvula moved normally with vocalization however gag reflex was absent. Tone was flaccid in all four limbs and power in lower limb and upper limbs were 2/5 and 3/5
A manifestation of chikungunya fever is an arboviral disease that usually manifests as a self-limiting disease with high fever, severe arthralgia, myalgia, and maculopapular rashes. Rare but severe complications may occur, such as myocarditis, hepatitis, and neurological manifestations. Unlike our patients, most of these complications are seen in elderly patients or those with underlying medical illnesses.

NCV was done which showed acute motor axonal and demyelinating neuropathy. Blood studies showed Hb 12 g/dl with 8000/cumm of TLC and 1.5 lac/cumm of platelet count with other biochemical test within normal range including serum potassium of 4.1 meq/L.

Work up for fever showed negative results for dengue and malaria but chikungunya IgM serology in blood was positive. CSF examination done showed albumin-cytological dissociation with sugar of 40 mg/dl and protein being 2 g/L with absence of cells. Chikungunya serology in CSF was negative. ANA and anti-ganglioside antibodies were negative.

Based on all the above findings a diagnosis of post-chikungunya Guillain Barre Syndrome was made and patient was started on intravenous immunoglobulins in standard dose for 5 days however the illness progressed with absent movement of all four limbs and respiratory involvement. Thus, patient was intubated on 3rd day of admission and put on ventilator. Currently the patient is tracheostomized and on SIMV mode of ventilation with no progression since past week.

**Discussion**

Chikungunya fever is an arboviral disease that usually manifests as a self-limiting disease with high fever, severe arthralgia, myalgia, and maculopapular rashes. Rare but severe complications may occur, such as myocarditis, hepatitis, and neurological manifestations. Unlike our patients, most of these complications are seen in elderly patients or those with underlying medical illnesses.

Various neurological sequelae have been known to occur with chikungunya fever, with peripheral neuropathy having predominant sensory component being the most common. Neurological tropism of chikungunya virus seems to be lower than other arboviruses such as Dengue, West Nile or Yellow fever viruses, yet several studies have described, (especially during epidemics) neurological manifestations. Just the magnitude of cases presenting in metros and major cities of our country warrants sensitizing the physicians about these uncommon manifestations.

Most common diagnostic dilemma remains whether neurological symptoms are due to persistence of the virus or an inappropriate immune response. In some cases, IgM antibodies against chikungunya virus have been found in CSF of patients with meningitis, supporting the theory of neuroinvasion. However, in our view a negative CSF serology and albumin-cytological dissociation we made a diagnosis of post-chikungunya Guillain Barre Syndrome and treated accordingly.

Hypokalemic paralysis is known to be precipitated by infections. Other precipitating causes include high carbohydrate diet, exposure to cold and strenuous exercise. Viral fever, particularly dengue infection has been extensively found to be associated with hypokalemic paralysis. Considering the existing similarities between dengue and chikungunya, the latter may also be an important cause for hypokalemic paralysis. The exact mechanism however is not known. Possible mechanism could be viral infection causing catecholamine release which causes redistribution of potassium within the cells. Another possible mechanism can be inadequate potassium intake precipitated by fever and dehydration.

There is no recommendation of supplementing potassium (post correction) on a long term basis after having ruled out other causes of hypokalemia.

In both the cases no sensory involvement was noted. It is to be noted that though the patients were middle aged and no associated comorbidities were present; still they presented with atypical complications. Association between hypokalemic paralysis and chikungunya is not commonly seen as in the presentation of GBS with bulbar involvement secondary to chikungunya. Thus, we present these cases of Chikungunya with rare neurological manifestations.

**References**

A Patient of Tumour Induced Osteomalacia Undiagnosed for 11 years

Nikhil Gokhale¹, Yojana Gokhale², Pravin Mahajan³

Abstract

We report a 45 years old woman, bedridden due to severe bone pain, back pain, multiple spontaneous fractures over 10 years. She had low serum Phosphates. We detected a swelling in her right groin and suspected tumour induced osteomalacia. Resection of the tumour led to reversal of metabolic bone disease. Patient became ambulatory within 6 weeks of tumour resection.

Introduction

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome in which patients present with bone pain, fractures, and muscle weakness.¹ TIO also known as oncogenic osteomalacia results from abnormal phosphate metabolism caused by small endocrine tumours that secrete the phosphaturic hormone, fibroblast growth factor 23 (FGF23).² FGF23 later inhibits resorption of phosphates from proximal renal tubules, leading to renal phosphate loss and hypophosphatemia,³ resulting in defective bone mineralization. These are generally mesenchymal tumors of extremities, sinuses, mandible, maxilla and thorax.⁴ They are benign, slow growing, and predominantly of phosphaturic mesenchymal tumor of mixed connective tissue (PMTMCT).² The biochemical markers of oncogenic osteomalacia include hypophosphatemia, hyperphosphaturia, decreased tubular phosphate reabsorption, increased serum alkaline phosphatase in the presence of normal calcium, 25(OH) vitamin D, and normal or slightly elevated serum PTH.⁵ Due to lack of knowledge of the existence of the disease, the length of time from onset of symptoms until diagnosis is often long.¹ As a result, patients frequently present with multiple fractures, height loss, and generalized debilitated status. But when the tumour is resected, there is dramatic resolution. FGF23 has a half life of approximately 45 min and disappears rapidly from the circulation⁶. A TIO-like syndrome can also be seen in association with other diseases such as prostate cancer, oat cell cancer, hematologic malignancies, neurofibromatosis, epidermal nevus syndrome, and polyostotic fibrous dysplasia of bone.⁷

Case

A 45 year old female presented with history of progressive back pain, generalized body pain for 11 years and inability to walk due to which she was bedridden for 3 years. Her back pain started in 2005. She presented to us in March 2016, but had destroyed all medical records out of frustration. She underwent spinal instrumentation in 2007 for spontaneous vertebral fracture without any relief. In 2010 the implants were removed. She developed progressive painful difficulty in walking and three years prior to her present visit she was bedridden. She had to be physically lifted for bathing, toilet etc. On examination, patient was in severe distress, had scoliosis, surgical scar in the lumbar region, deformed proximal forearms, all bones were tender, she could actively raise her leg to only 5 degree and did not allow passive SLR or hip rotations due to pain. Power at shoulder was 4/5 and at hips 3/5, Deep tendon reflexes were 2+, plantars flexors and sensations preserved. On systemic examination there was 5x5 cm swelling in right groin (Figure 1) extending up to labia majora, it was soft to firm, nontender, without impulse on coughing. On inquiry she said it started as a pea size swelling in right labia majora in 2004 and progressed to its present size. Fine needle aspiration cytology of the swelling was performed and she was told it was benign, report was missing. Investigations (Table 1) revealed low serum phosphates, normal Calcium, 25-OH-D and intact PTH, raised Alkaline phosphatase. The blood pH was normal (no acidosis) and Serum Creatinine 0.5mg/dl. Twenty four hour urinary P was 102.5mg (33.107 mmol/L) and Creatinine was 297 mg (26.254 mmol/L). Calculated Fractional Tubular resorption of phosphate (TRP) 0.89 and The ratio of the renal tubular maximum resorption rate of phosphate to the glomerular filtration rate (TmP/GFR) 0.49 mmol/L.

Her skeletal survey revealed severe osteopenia with multiple stress fractures (Figure 2 A, B, C) viz. bilateral femur neck, Bilateral

Fig. 1: Swelling in right inguinal region
lymphadenopathy.

The tumour was resected with in 2 weeks, measured 5x4x3cm. On microscopy, it was composed of spindle and short oval cells in oedematous stroma in which foci of osteoclastic giant cells are scattered. The cellular portions of the tumour line pseudocystic tumour. The less cellular areas show large vascular spaces, reported as ‘Phosphoturic mesenchymal tumour’ (Figure 3). Six weeks post operatively she was without pain, could walk with support, actively raise legs to 90 degree. Serum Calcium 9 mg/dl, P 4mg/dl and at 12 weeks postoperatively, she could walk without support, Serum Ca 8.6mg/dl, P 4.3 mg/dl

**Table 1: Baseline investigations**

<table>
<thead>
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<th>Patient’s values</th>
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<td>Hemoglobin</td>
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<td>WBC</td>
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<td>ESR</td>
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<tr>
<td>S creatinine</td>
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<td>S Ca</td>
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<tr>
<td>S P</td>
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<tr>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>25-OH-D</td>
</tr>
<tr>
<td>PTH intact</td>
</tr>
<tr>
<td>Blood pH</td>
</tr>
<tr>
<td>Na</td>
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<tr>
<td>K</td>
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<tr>
<td>Cl</td>
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<tr>
<td>HCO3</td>
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<tr>
<td>24 hour urinary P</td>
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<tr>
<td>24 hour urinary creatinine</td>
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<tr>
<td>Creatinine phosphokinase</td>
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<tr>
<td>Thyroid function test</td>
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<tr>
<td>RA test &amp; anti-CCP</td>
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<tr>
<td>SGPT</td>
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<tr>
<td>TRP</td>
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<td>TmP/GFR</td>
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</table>

**Discussion**

TIO should be suspected in patients who present with consistent symptoms (bone pains, stress fractures and muscle weakness) and with hypophosphatemia, and approach should be as follows:

1. If hypophosphatemia is present, the presence of renal phosphate wasting should be confirmed by calculating percent tubular reabsorption of phosphate (%TRP) and tubular maximum for phosphate corrected for glomerular filtration rate (TmP/GFR).

2. Hypophosphatemia may be due to genetic or acquired cause. In a child genetic/familial conditions like X-linked hypophosphatemic rickets (XHL) or autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessive hypophosphatemic rickets (ARHR) and hereditary hypophosphatemic rickets with hypercalciuria (HHRH), Fanconi syndrome are more likely, though there are reports of TIO in paediatric age group too. Where as in adults with symptomatic hypophosphetemia, acquired causes like TIO are more likely and a thorough search for the tumour, clinical and by PET-CT or Octreoscan should be performed. Other causes of acquired hypophospatemic osteomalacia may be renal tubulopathy due to drugs, heavy metals, paraproteinaemias. Serum FGF23 is high in TIO and low in renal tubulopathies. In patients presenting in childhood or adolescence short stature, history of bow legs in relatives, urinary loss of Ca, amino acids should be looked for, followed by genetic studies. The diagnostic approach for suspected TIO should be as depicted in Figure 4.

**Calculation of Renal phosphate wasting**:

\[
\% \text{TRP} = 100 \times \left[ 1 - \left( \frac{U_p}{P_p} \times \frac{P_{cr}}{U_{cr}} \right) \right]
\]

[Concentrations of urine and plasma phosphate (Up and Pp), Concentrations of urine and plasma creatinine (Ucr and Pcr)]

When phosphates are normal tubular resorption is 85-95%.

TmP/GFR can be determined using a nomogram or calculated as follows:

The formula used to calculate TmP/GFR is dependent on the value of TRP ($\leq 0.86$)

If TRP is $\leq 0.86$ (86%); then

\[
\text{TmP/GFR} = 0.49 \text{ mmol/L}
\]
TmP/GFR = TRP x plasma phosphate (Pp)
If TRP is >0.86 (86%); then
TmP/GFR = 0.3 x TRP/(1-0.8xTRP) x (Pp)

One should use correct units for serum and urinary phosphat and creatinine. If there is no urinary phosphate wasting in a patient with hypophosphatemia, the values for TRP and TmP/GFR will be high. In TIO and other causes of renal phosphate wasting, these values are abnormally low.7 Table 2 depicts normal range of TmP/GFR for various age and gender. In our patient TmP/GFR was 0.49 mmol/l, i.e. very low. After confirming renal phosphate wasting as the etiology for hypophosphatemia, additional lab tests that can be helpful in making the diagnosis of TIO are 1,25-vitamin D level (low or abnormally normal), calcium and PTH (usually normal). One can estimate serum FGF23 level in adult patients, (not performed in our patient, due to non-availability), for confirming FGF23 dependent phosphate wasting. Genetic testing (PHEX, FGF23, DMP-1, ENPP1) is important in paediatric and adolescent patients. In adults, after narrowing the diagnosis to TIO, ask the patient if she/he has noticed any new ‘lumps’, a careful physical examination including oral cavity should be performed, as the tumors that cause TIO can sometimes be found in the subcutaneous tissue or jaw.

Localizing studies: (Functional imaging followed by anatomical imaging)7

As tumors can arise in bone or soft tissue, occur from head to toe, and are typically very small in size, locating these tumors is often quite challenging. A step-wise approach is advocated. Functional imaging with FDG-PET/CT is very sensitive to localize, tumours of TIO, however, it is non-specific and may detect metabolic activity in a healing fracture. Another important functional imaging modality is 111Indiumoctreotide scintigraphy, ideally combined with single photon emission CT and CT. In either case emphasis should be placed on making sure these imaging tests cover the entire body, from head to toe, including the hands and feet.

Once suspicious lesions have been identified with functional imaging, one should proceed to anatomical imaging to confirm the location of the tumor, with X-rays, CT, and/or MRI. Usually functional and anatomical scan is successful in locating tumour in TIO, but in case where there is doubt, selective venous sampling or aspiration, from suspicious lesion with estimation of FGF23 can be used for confirmation, prior to surgical excision. Despite functional imaging, total body MRI, tumor localization may not be successful. If this is the case, imaging studies should be repeated, every 1-2 years, in hopes that a tumor may be more evident with time.

Treatment

Surgical excision with a wide margin is the treatment of choice after localizing the tumour.1 Serum P normalizes within 3-5 days, confirming the diagnosis of TIO. Clinical improvement depends on initial condition of the patient, but generally occurs over weeks to months, as in our patient. Recurrence of tumour is seen in <5% patients.

Medical treatment7

When the tumor cannot be localized or is not surgically resectable, medical therapy with phosphate supplementation (15-60mg/kg, i.e 1-3gm/d, in 4-6 divided doses) and calcitriol (15-60ng/kg, i.e 1.5microg/d, starting dose) is indicated. Goal of therapy is to achieve at least ‘low-end of normal for age-appropriate normal range of phosphorus’. Phosphate supplements cause GI upset, to minimize them, give small frequent doses along with meals. A baseline ultrasound examination of kidneys and three monthly monitoring of Serum P, Ca, urinary Ca/Creatinine, Urine for occult blood (if U Ca/Cr ration >0.2), and dose adjustment of Calcitriol to avoid hypercalciuria and nephrocalcinosis is important. If Serum P is low increase Phosphate supplement, if serum Ca is low give Ca supplement, if PTH is high increase Calcitriol. The dose at which Serum P and PTH are in target and Urine Ca/creatinine is <0.2 should be maintained. Other drugs used in medical treatment of TIO are Cinacalcet7 (an agonist of Calcium sensing receptor) and Octerotide (somatostatin analog).

Robert McCance (1947) is often credited13 with the first reported case of TIO. The first person to clearly recognize that the disease was the result of a ‘rachitogenic’ substance was Andrea Prader14. In 1959, he described an 11 1⁄2-year-old girl who developed severe rickets over the course of a year. Her investigations revealed decreased tubular phosphate reabsorption but otherwise normal kidney function. A tumor, classified as a giant cell granuloma, was identified in a rib and resected with resultant healing of her rickets. Prader highlighted the association between the resection of the tumor and the cure of the rickets and posited that the granuloma was secreting a ‘rachitogenic’ substance. The first identification of FGF23 as the putative phosphatonin was when mutations in FGF23 were identified by Econs11 in the autosomal-dominant hypophosphatemic rickets (ADHR) consortium as the cause of ADHR. Once identified as the cause of ADHR, elevations in serum FGF23 were soon found in TIO by White16 in 2001. The discovery of FGF23 has paved the way toward a better understanding of the pathophysiology and treatment of TIO and has also provided a window

Table 2: Normal ranges for tubular maximum for phosphate corrected for GFR

<table>
<thead>
<tr>
<th>Age</th>
<th>Male mg/dl (mmol/l)</th>
<th>Female mg/dl (mmol/l)</th>
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<tbody>
<tr>
<td>Newborn</td>
<td>5.7-8.1 (1.27-2.59)</td>
<td>5.7-8.1 (1.27-2.59)</td>
</tr>
<tr>
<td>1 month-2 years</td>
<td>3.6-5.4 (1.15-1.73)</td>
<td>3.6-5.4 (1.15-1.73)</td>
</tr>
<tr>
<td>2-12 years</td>
<td>3.5-5.0 (1.22-1.60)</td>
<td>3.5-5.0 (1.22-1.60)</td>
</tr>
<tr>
<td>12-16 years</td>
<td>3.4-4.6 (1.09-1.47)</td>
<td>3.4-4.6 (1.09-1.47)</td>
</tr>
<tr>
<td>16-25 years</td>
<td>3.3-5.9 (1.07-1.89)</td>
<td>3.18-4.61 (1.02-2.05)</td>
</tr>
<tr>
<td>25-45 years</td>
<td>3.09-4.18 (0.99-1.34)</td>
<td>2.97-4.45 (0.951-1.42)</td>
</tr>
<tr>
<td>45-65 years</td>
<td>2.78-4.18 (0.89-1.34)</td>
<td>2.72-4.39 (0.87-1.40)</td>
</tr>
<tr>
<td>65-75 years</td>
<td>2.47-4.18 (0.79-1.34)</td>
<td>2.47-4.18 (0.79-1.34)</td>
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Fig 3: Microphotograph of the tumour: spindle and short oval cells, foci of osteoclastic giant cells (black arrow)
into areas of mineral metabolism physiology that for years had been unexplained. Tumors associated with TIO have included a wide range of histopathological diagnoses. The prototypical phosphaturic mesenchymal tumor (mixed connective tissue variant) (PMTMCT) contains neoplastic cells that are spindled to stellate in shape, with low nuclear or mitotic activity (i.e. normochromatic with small nuclei and indistinct nucleoli). Numerous osteoclast-like giant cells are a frequent finding. Weidner in 1991 proposed a classification system based on the histological findings of TIO, and designated the tumors as phosphaturic mesenchymal tumors. These were then subdivided into four categories; mixed connective tissue variant (PMTMCT), osteoblastoma-like variant, non ossifying fibroma-like variant, and ossifying fibroma-like variant. The first group, PMTMCT, occurred in soft tissue, and was predominantly, benign in nature. The remaining three groups tended to occur in bone and were benign in nature. On immunohistochemistry staining, 70% tumours are FGF23 positive. Metastasis is rare, though reported. While metastases are rare, infiltration of surrounding connective tissue is typically present, which has significant implications for surgical management and emphasizes the importance for wide surgical margins to avoid persistence or recurrence.

So, to sum up, patients with TIO / Phosphaturic mesenchymal tumours often present with many years of symptoms (bone pain, stress fractures and muscle weakness), or growth retardation and rickets in paediatric age, before they are diagnosed. Hypophosphatemia caused by impaired renal phosphate reabsorption is the biochemical hallmark of the disease. A systematic diagnostic approach for renal phosphate wasting and a thorough search for tumour is important in clinching the diagnosis.

**Conclusion**

TIO is a rare debilitating but curable condition and physicians should consider it while evaluating patients with osteomalacia and low serum phosphates. Thorough search for tumour, clinical as well as with functional and anatomical imaging is indicated considering severe disability caused by the condition and its potential reversibility.

**References**

Dabigatran – the First Approved DTI for SPAF

Abhijit Trailokya¹, JS Hiremath²

Abstract
Atrial fibrillation (AF) is commonly occurring arrhythmia in clinical practice. AF is easy to recognize but difficult to treat. Stroke is the most devastating complication of AF and is associated with a huge disease burden on the society. Effective stroke prevention is a priority for patients with AF. Two-thirds of strokes due to AF are preventable with suitable anticoagulant therapy. VKA like warfarin, acenocoumarol remains the gold standard for stroke prevention in AF (SPAF). However, it is associated with numerous limitations such as a high risk of drug-drug, drug-food interactions and need for frequent PT/INR monitoring. Dabigatran etexilate is a selective, specific, reversible direct thrombin inhibitor that has been approved in United States, European countries and in India for SPAF and primary venous thromboembolism prevention and treatment. The efficacy and safety of dabigatran in AF has been established the “Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY)”, a randomized clinical trial. As per RE-LY trial 150-mg dose of dabigatran was superior to warfarin with respect to stroke or systemic embolism, and the 110-mg dose was superior to warfarin with respect to major bleeding. The adverse event profile of dabigatran etexilate was generally similar to that of warfarin in the RE-LY study, except for the incidence of dyspepsia. Dabigatran has edge over VKAs like warfarin and acenocoumarol including predictable pharmacokinetic and pharmacodynamic profile, minimal drug-drug and no drug-food interactions while no monitoring is needed. Dosing schedule is dabigatran 150mg BID patients with normal renal function. 110 mg BID is specifically for elderly patients above 80 years and over, as well as for patients at an increased risk of bleeding and in renal impairment CrCL 15-30 mL/min dosing is 75mg twice daily. Dabigatran is only NOAC with approved specific reversal agent.

Introduction
Atrial fibrillation (AF) is commonly occurring arrhythmia in clinical practice accounts 1/3 of hospital admissions for cardiac rhythm disturbances. AF is easy to recognize but difficult to treat. The consequences of AF have been clearly established in multiple large observational cohort studies and include increased stroke and systemic embolism rates if no oral anticoagulation is prescribed, with increased morbidity and mortality. The estimated number of individuals with AF globally in 2010, was 33.5 million (20.9 million men and 12.6 million women) with significant regional variations and heterogeneity. Mortality associated with AF was increased by 2-fold in both genders from 1990 to 2010.¹ AF does occur in isolation, but also commonly seen in association with cardiovascular disease like hypertension, sleep apnoea, diabetes and obesity. Stroke is a very common and serious complication of atrial fibrillation (AF), which is the utmost prevalent clinically significant cardiac arrhythmia.² Effective stroke prevention can be done by means of anticoagulation therapy is very important.

AF-related Stroke Is Preventable
AF is the most common cardiac arrhythmia and is associated with increased risk of stroke, heart failure, hospitalization and death. AF is the main contributor for stroke in elderly. Therefore it is important to actively screen patients for AF.³ Effective stroke prevention is a priority for patients with AF.¹ Two-thirds of strokes due to AF are preventable with suitable anticoagulant therapy. A meta-analysis of 29 trials in 28,044 patients showed that the vitamin K antagonist (VKA) warfarin reduces the risk of stroke and all-cause mortality. 64% reduction in stroke and 24% reduction in all-cause mortality compared with placebo. Aspirin also reduced the risk of stroke, but less effectively than warfarin (19% reduction compared with placebo).⁵ But Warfarin is used in only 55% of the Eligible Patients with AF. Underuse of warfarin is greatest in elderly patients who are at the highest risk of stroke. About 60% of patients never get VKA, around half of patients who do get it stop taking it especially in the developing world, and of those who still take it only half are in therapeutic range. So, only a small minority are well treated.⁶

The GARFIELD registry, a study of 19 countries in 2009–2011, discovered that 38.0% of patients with high risk of stroke had not received anticoagulant therapy, whereas 42.5% of those at low risk (score 0) did.⁷ The PINNACLE Study in the United States found that less than half of high-risk patients were receiving OACs therapy.

Vitamin K Antagonist Usage in India
India the two most common VKAs are warfarin and acenocoumarol. Successful anticoagulation with VKAs requires to maintained PT/ INR within recommended range and required regular INR monitoring with dosage adjustment. Nevertheless, several

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places in India lack laboratories with standardized measurement of prothrombin time (PT)/INR. One of the retrospective study conducted in India, Out of a total of 1631 PT ratios and INRs recorded, only 17.8% were in the therapeutic range. In India there are different dietary habits are more prone for VKAs (warfarin and acenocoumarol) food interactions. Green leafy vegetables, cauliflower, cabbage and other foods rich with vitamin K in the Indian diet cause lability in INR values and extremely challenging in maintaining PT/INR in required range. Over the counter medications may also alter INR values and result in under or over anticoagulation. NOACs like dabigatran may overcome the challenges associated with VKAs and improve patient’s outcome provided if it is available in economical coast.

**Challenges Associated with VKAs**

Complications, Compliance, convenience, confidence, convenience and cost are the five Cs of anticoagulation, plays an important role in the anticoagulation management. Vitamin K antagonists are widely used oral anticoagulants worldwide. Oral vitamin K antagonists (VKAs) such as acenocoumarol and warfarin have long been the mainstay of stroke prevention in patients with atrial fibrillation (AF). Nevertheless, the use of warfarin and acenocoumarol in clinical practice is challenging due to problems such as drug-drug and drug-food interactions, a narrow therapeutic index and unpredictable anticoagulant effects, all of which result in the need for regular laboratory monitoring. So there is need to develop an effective oral anticoagulant with reliable pharmacokinetic profile so can be taken as fixed daily dosage, regardless of patient’s weight, age, ethnicity or gender. It would be in preventing thromboembolism episodes with good safety profile. It should have no or less interactions with commonly taken medicines and food. An anticoagulant with above mention properties would be easy for patients to on long term basis with no need for dosage titration with regular monitoring. These are the objectives behind developing NOACs. NOACs available in India till date are Dabigatran, Rivaroxaban and apixaban. Assessment of CHA2 DS2 VAS and HAS-BLED scores for stroke and bleeding risk is indicated in patient and guides anticoagulation therapy.

**Dabigatran Eteixilate**

Dabigatran etexilate is indicated for the prevention of stroke and systemic embolism in patients with non-valvular AF (NVAF) and one or more risk factors. It is also indicated for treatment of VTE and prevention of recurrent VTE as well as for the primary prevention of venous thromboembolism (VTE) after total hip or knee replacement.

Dabigatran etexilate is a small molecule prodrug of dabigatran. Dabigatran is a potent, reversible and competitive direct inhibitor of thrombin, responsible for converting fibrinogen to fibrin in the coagulation cascade. Dabigatran inhibits both free and fibrin-bound thrombin, thereby preventing thrombus formation.

**Dabigatran Approval Status**

On the basis of RE-LY trial dabigatran etexilate has been approved by USFDA and EMA as well as in many other countries worldwide, for Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension. EMA has approved 150mg twice daily and 110mg twice daily doses. On other hand USFDA has approved 150 mg twice daily dose and the 75mg twice daily dose in patients with severe renal impairment (creatinine clearance 15-30 ml/ min). In India dabigatran got approval for prevention of stroke, systemic embolism and reduction of vascular mortality in adult patients with atrial fibrillation on Dec 2011 for all the three strengths i.e. 75mg, 110mg and 150 mg by DCGI.

Dabigatran Dosing schedule

Prevention of stroke and SEE in adult patients with NVAF with one or more risk factors (SPAF). The recommended daily dose of Dabigatran is 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term.

For the following groups the recommended daily dose of Dabigatran is 220 mg taken as one 110 mg capsule twice daily: Patients aged 80 years or above and Patients who receive concomitant verapamil.

For the following groups the daily dose of Dabigatran of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding: Patients between 75-80 years, Patients with moderate renal impairment, Patients with gastritis, esophagitis or gastroesophageal reflux, other patients at increased risk of bleeding.

Premature discontinuation of oral anticoagulant, like Dabigatran, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events.

Missed dose of Dabigatran If patient miss a dose of dabigatran, he can take it as soon as he remember. If patient’s next dose is less than 6 hours away, skip the missed dose. Do not take two doses of dabigatran at the same time.

**Pharmacokinetic profile of dabigatran**

A. Absorption: Rapid
B. Bioavailability: 3-7% (approx. 6.5 %) and remains relatively static under fast or fed conditions.
C. Predictable pharmacokinetic profile with low-inter and intra-individual variability
D. Plasma concentration of dabigatran peaks within 1h (delayed 2hrs by food).
E. Half-life elimination: 12-17 hours
F. T max: 2 hrs. (in healthy subjects)
G. Metabolized by microsomal carboxylesterases to active drug dabigatran in the liver. Does not affect CYP activity

**Dabigatran in Renal Impairment**

As per USFDA labelling the dosage of Dabigatran 150 mg twice daily for patients with CrCL >30 ml/min and for patients with CrCL 15-30 ml/min it is 75 mg orally, twice daily. For CrCL <15 ml/min, no recommendations can be made. As per European regulation dabigatran is contraindicated in Patients with severe renal impairment (CrCl < 30 ml/min).

Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with dabigatran to exclude patients with severe renal impairment (i.e. CrCl < 30 ml/min). Renal function should
be assessed during treatment with dabigatran at least once a year or more frequently as needed.\textsuperscript{11}

\textbf{Hepatic impairment: The pharmacokinetics and pharmacodynamics of dabigatran were not affected by moderate (Child-Pugh class B) hepatic impairment following a single oral dose of dabigatran etexilate 150 mg. Dabigatran is contraindicated in hepatic impairment or liver disease expected to have any impact on survival.}\textsuperscript{11}

\textbf{Contraindication}\textsuperscript{11}

Dabigatran is contraindicated in patients with active pathological bleeding. History of a serious hypersensitivity reaction to Dabigatran and Mechanical prosthetic heart valve.

\textbf{Recommendations for discontinuation of dabigatran etexilate before elective invasive or surgical procedures}\textsuperscript{11}

<table>
<thead>
<tr>
<th>Renal function (CrCl in mL/min)</th>
<th>half-life (hours)</th>
<th>Dabigatran should be stopped prior to elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>~ 13</td>
<td>2 days before</td>
</tr>
<tr>
<td>≥ 50 &lt; 80</td>
<td>~ 15</td>
<td>2-3 days before</td>
</tr>
<tr>
<td>≥ 30 &lt; 50</td>
<td>~ 18</td>
<td>4 days before</td>
</tr>
</tbody>
</table>

Types of surgery associated with a high risk of bleeding (or major surgery where complete haemostasis may be required), including, but not limited to, cardiac surgery, neurosurgery, abdominal surgery or surgeries involving a major organ. Other procedures such as spinal anaesthesia may also require complete haemostatic function.

\textbf{Recommendations for Converting to or from other Oral or Parenteral Anticoagulants}\textsuperscript{11}

Converting from or to Warfarin

When converting patients from warfarin therapy to Dabigatran, discontinue warfarin and start Dabigatran when the INR is below 2.0.

For CrCl <50 mL/min, start warfarin 2 days before discontinuing Dabigatran

For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing Dabigatran

For CrCl <15 mL/min, no recommendations can be made.

Converting from oral to Parenteral Anticoagulants\textsuperscript{11}

For patients currently receiving a parenteral anticoagulant, start Dabigatran 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

For patients currently taking Dabigatran, wait 12 hours (CrCL ≥30 mL/min) or 24 hours (CrCL <30 mL/min) after the last dose of Dabigatran before initiating treatment with a parenteral anticoagulant.

Patients can stay on Dabigatran while being cardioverted.

\textbf{Drug Interactions}\textsuperscript{11}

Dabigatran etexilate is a substrate for P-glycoprotein (P-gp), there is potential for interaction when it is co-administered with P-gp inhibitors or inducers. Concomitant use of Ketoconazole, Dronedarone, Itraconazole, cyclosporine with dabigatran are contraindicated. Concomitant use of Tacrolimus with dabigatran is not recommended. Cautions to be exercised in case concomitant use with Verapamil, Amiodarone, Quinidine, Clarithromycin, Ticagrelor and Posaconazole.

Co-administration of dabigatran etexilate with P-gp inducers [e.g. phenytoin, rifampicin, carbamazepine, hypericum (St John’s wort)] should be avoided. There is no change in dabigatran exposure when dabigatran is co-administered with the P-gp substrate digoxin.

The concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate by approximately 2.5-fold, mainly related to situations when switching from one anticoagulant to another. Furthermore, concomitant use of anti-platelets, ASA or clopidogrel approximately doubled major bleeding rates with both dabigatran etexilate. UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter.

When dabigatran was co-administered with pantoprazole, a decrease in the dabigatran AUC of approximately 30% was observed. Proton-pump inhibitors (PPI) like pantoprazole were co-administered with dabigatran in clinical trials, and concomitant PPI treatment did not appear to reduce the efficacy of dabigatran. Ranitidine administration together with dabigatran had no clinically relevant effect on the extent of absorption of dabigatran.

Pregnancy: Dabigatran category C. Breast-feeding should be discontinued during treatment with dabigatran. No human data available on fertility.

Common adverse events with dabigatran: Increased Risk of Thrombotic Events after Premature Discontinuation, Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves and Dyspepsia.

Dabigatran prolongs the thrombin time (TT), ECT, and aPTT.

\textbf{Antidote for Dabigatran}

A specific reversal agent (idarucizumab) is available when reversal of the anticoagulant effect of dabigatran is needed: For emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding. On October 2015, the U.S. FDA approved idarucizumab (Praxbind), a monoclonal antibody fragment that binds tightly to dabigatran and nullifies its anticoagulant activity.

\textbf{Clinical Development of Dabigatran}

PETRO Study: Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with non-valvular atrial fibrillation.

This was the first evaluation of dabigatran, in patients with atrial fibrillation (AF). Patients (n = 502) were randomized to receive blinded doses of 50-, 150-, or 300-mg dabigatran twice daily alone or combined with 81- or 325-mg aspirin or open-label warfarin administered to achieve an international normalized ratio of 2 to 3 for 12 weeks.

Long-Term Open Label Extension of the Prevention of Embolic and Thrombotic Events on Dabigatran in Atrial Fibrillation (PETRO-Ex study):\textsuperscript{14}

The results of Prevention of Embolic
Thrombotic events in patients with persistent atrial fibrillation—Extension (PETRO-Ex) trial, an extension of the 3-month PETRO study, also showed that 50 mg twice-daily and 150-mg daily doses of dabigatran etexilate were not effective and that the 300-mg twice daily dose resulted in high major bleed rate. No serious liver toxicity was observed. PETRO-Ex study, suggests that 150 mg twice daily is an appropriate dose for further study in the prevention of stroke in high-risk patients with atrial fibrillation because Thromboembolic event rates were lowest in the dabigatran 150 and 300 mg BID groups. Major bleeding was most frequent in the 300 mg BID group. No significant liver function abnormalities were noted in any of the dabigatran groups.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)16

RE-LY trial is the randomized, double-blind phase III trial evaluated the efficacy and safety profile of dabigatran (110 or 150 mg twice a day) on 18113 patients, compared to warfarin. The median length of the follow-up period was 2 years. The primary efficacy outcome was stroke or systemic embolism. The primary safety outcome was a major haemorrhage. Stroke or systemic embolism had a rate of 1.53% per year in the group of dabigatran 110 mg twice a day, and 1.11% per year in the group of dabigatran 150 mg twice a day (Figure 1). Both doses of dabigatran were non-inferior to warfarin (p < 0.001). For the prevention of thrombotic events, the dose of 150 mg was superior to warfarin (relative risk 0.91; 95% CI 0.74–1.11). Rates of other ischaemic and thrombotic outcomes, including net clinical benefit, were also not significantly different between the two dabigatran groups.17

Guidelines Recommendations18

Current ESC 2016 guidelines on AF says when oral anticoagulation is initiated in patients with AF who is eligible for NOAC (Dabigatran, apixaban, rivaroxaban), a NOAC is recommended in preference to VKAs (warfarin, acenocoumarol) – it has class I level A evidence.

Dabigatran Vs acenocoumarol19

Observational study done by Jennie Korenstra et al. In total, 920 consecutive AF patients were enrolled (478 acenocoumarol, 442 dabigatran), of which 2 x 383 were available for analysis after propensity score matching. Mean follow-up duration was 1.5+0.56 year. The mean calculated stroke risk according to the CHA2DS2-VASc score was 3.5%/year in dabigatran vs. 3.7%/year acenocoumarol-treated patients. The actual incidence rate of stroke or systemic embolism was 0.8%/year [95% confidence interval (CI): 0.2–2.1] vs. 1.0%/year (95% CI: 0.4–2.1), respectively. Multivariable analysis confirmed this lower but non-significant risk in dabigatran vs. acenocoumarol after adjustment for
the CHA2DS2-VASc score [hazard ratio (HR) dabigatran \(\frac{3}{4}\) 0.72, 95% CI: 0.20–2.63, P = 0.61]. According to the HAS-BLED score, the mean calculated bleeding risk was 1.7%/year in both groups. Actual incidence rate of major bleeding was 2.1%/year (95% CI: 1.0–3.8) in the dabigatran vs. 4.3%/year (95% CI: 2.9–6.2) in acenocoumarol. This over 50% reduction remained significant after adjustment for the HAS-BLED score (HR dabigatran \(\frac{3}{4}\) 0.45, 95% CI: 0.22–0.93, P = 0.031). Authors concluded that in ‘real-world’ patients with AF, dabigatran appears to be as effective, but significantly safer than acenocoumarol.

A retrospective observational study of patients prescribed dabigatran between 2010 and 2013 conducted by Yap LB et al. Data was available for 510 patients: median age 68 years (range 20–91). This showed that patients frequently preferred the dabigatran due to convenience when given a choice to switch from warfarin. Reassuringly, they found that there were no adverse events related to dabigatran.

The major advantages of dabigatran over vitamin K antagonists (VKA) like acenocoumarol and warfarin are: the absence of periodic laboratory analysis i.e. PT/INR monitoring, the low extent of dietary and drug interactions and the favourable efficacy and safety profile, which may decrease the rate of clinical complications because of vitamin K inhibitors in selected patients.21

**Comparison with other NOACs**

Large scale head to head randomized comparative studies among available NOACs are not available till date. In all the trials NOACs had been compared with warfarin (Table 1). In ROCKET AF trial Rivaroxaban did not demonstrate superiority of rivaroxaban compared with warfarin for the prevention of stroke and systemic embolism, with a similar rate of major bleeding and a substantial reduction in intracranial haemorrhage.22 In ARISTOTLE, apixaban reduced the risk of stroke or systemic embolism by 21% compared with warfarin (1.27% vs 1.60% per year; hazard ratio, 0.79; 95% confidence interval, 0.66–0.95). The reduction was significant and demonstrated the superiority of apixaban over warfarin for the primary outcome of preventing stroke or systemic embolism (P = 0.01 for superiority). Apixaban also reduced all-cause mortality by 11% (P = 0.047) and major bleeding by 31% (P < 0.001) compared with warfarin.23 In the RE-LY trial, dabigatran was shown to have superior safety with equivalent efficacy (when it was administered at a dose of 110 mg twice daily) or superior efficacy with similar safety (when it was administered at a dose of 150 mg twice daily) for stroke and systemic embolism.24 Stroke or systemic embolism had a rate of 1.53% per year in the group of dabigatran 110 mg twice a day, and 1.11% per year in the group of dabigatran 150 mg twice a day. Dabigatran etexilate 150 mg twice daily was significantly (p < 0.001) more effective at preventing stroke and systemic embolism than warfarin (relative risk reduction of 35%). dabigatran etexilate 150 mg twice daily was significantly (p = 0.004) more effective than dabigatran 110 mg twice daily at preventing stroke and systemic embolism (relative risk reduction of 28%). It is more expensive than warfarin, but is more cost effective.

**Summary**

Dabigatran, is a potent, competitive and reversible direct thrombin inhibitor.

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Better performers have

Volibo

for GI therapy

VoliboM

Digest
PFGE Control

Preserve
gut flora function
Eradicating Filariasis

Jayant Pai-Dhungat

W. bancrofti is widely distributed in the tropics, but largest numbers of cases of lymphatic filariasis (LF) occur in India. The current world estimate by WHO reveals that 120 million people in 83 countries of the world are infected with lymphatic filarial parasites, and that more than 1.1 billion (20% of the world population) are at risk of acquiring infection. Over 40 million people are severely disfigured and disabled by filariasis and 76 million apparently normal but having hidden internal damage to lymphatic and renal systems have microfilarimia. As for India 650 million people across at least 250 districts and 29 states in the country are at risk of filariasis.

Recently Bill Gates as guest Editor of Times of India (TOI 17/11/17) has highlighted the topic of filariasis in detail and is pretty certain, India will miss target date of stamping out elephantiasis (LF) that it was hoping to eliminate by 2020. The national health policy had aimed at eliminate filariasis by 2015. The deadline was extended to 2017 and again to 2020." He has discussed the problems and difficulties at the field level and has also suggested remedial measures to the national health policy.

The endemic areas for filariasis are places near sea coast and banks of large rivers. Man is the only definitive host. The worms are ovoviviparous whitish and translucent; female being larger than male. They may remain coiled together in abdominal and inguinal lymphatics and in testicular tissue etc.living for a long period; probably 10-15 years. Major vector in India is Culex fatigans. Gravid female releases fresh generation embryos (microfilaria) encased in its elongated sheath 250-300 microns in length. Microfilaria shows a nocturnal periodicity in circulation, correlating with the habit of vector mosquito. Once they reach mosquito stomach, they undergo infective larval development and reach proboscis during its third phase. This larva enters host through the puncture wound or penetrates the skin by themselves at the site of the bite.

Characteristic manifestations are due to obstruction of lymph vessels. Elephantiasis is a feature unique to man apparently caused by erect posture and consequent lymphatic hydrodynamic factors. Tropical eosinophilia is considered an atypical manifestation of filariasis. Diagnosis is done by direct detection of microfilaria in blood and other fluids, eosinophilia, and several serological and immune-enzyme tests which have not been very practical.

Measures in prevention and control of filariasis are eradication of vector mosquitoes, and detection & treatment of carriers. Global strategy is by mass drug administration (MDA) in endemic districts ensuring coverage of over 60% populations by administration of two drugs: Diethylcarbamazine citrate (DEC) along with Albendazole once a year for five years. A transmission assessment survey is conducted after the period to see if the district qualifies for stoppage of drug. Recently out of 256 districts many of the 96 districts failed treatment assessment.

The two drug regimen reduces the disease by 60-80% hence requires five rounds The new drug regimen is expected to clear infection faster-requiring just two rounds. It consists of three drugs: DEC+ albendazole+ Ivermectin. Ivermectin is expensive and dosage dependent which could mean adding 2-4 tablets depending upon body weight. This could also cause community non compliance.

Professor of Medicine (Retd.), TN Medical College, Hon. Physician, Bhatia Hospital, Mumbai, Maharashtra
Indian College of Physicians (ICP) Position Statement on Pharmacovigilance

Sir,

The paper ‘Indian College of Physicians (ICP) Position Statement on Pharmacovigilance’ published in JAPI is indeed an immensely useful article for current day physicians and much needed timely requirement. There is a very useful table given in the article giving some useful examples. Drugs of interest should also include the newer agents that have been introduced in the last five years i.e. anti-psychotic drugs and anti-platelet drugs etc. Authors have nicely explained the importance of pharmacovigilance and its requirement in healthcare system. However following points also need to be emphasised keeping Indian scenario in mind:

1. As cardiovascular diseases, have emerged as leading cause of mortality and morbidity and are often associated with multiple co-morbidities like diabetes, hypertension, coronary artery disease, chronic kidney disease, COPD and arthritis etc. They need to be given multiple drugs (poly-pharmacy). Poly-pharmacy not only increases the economic burden on poor socioeconomic group but also need more pharmacovigilance for their potential more chances of adverse drug reactions. There is need to generate data on cardiovascular and anti-diabetic drugs as they are given simultaneously and hardly any data available in our country. Similarly, there is need for intensive adverse drug reactions (ADR) monitoring for anti-tubercular drugs.

2. In view of increasing longevity Indians are now liable to suffer from malignant diseases as well in addition to existing cardiac conditions (Cardio-oncology). Many of the chemotherapeutic agents have potential of adverse drug reaction which need to be kept in mind. These drugs can also interact with cardiovascular drugs and vice versa thus can lead to some serious untoward reactions.

3. Our country is unique where many herbal preparations are available as over counter drugs (OTC). They may have potential adverse drug reactions. Most of the patients take indigenous drugs along with allopathic system. Currently there is no regulation on safety of such preparations. We recently had a young man who took a herbo-mineral preparation for increasing his sex potency following TV advertisement. He developed physical weakness and moderate anemia after taking this so-called sex potency drug. This was recognized and medicine stopped in time resulting in correction of anemia. Another patient who was taking isapghol regularly and had undergone kidney transplant. While taking alternative system of medicine the bio availability of cyclosporine was increased which would have resulted graft rejection. While seeing the thorough history of patients and stopping isapghol the level of cyclosporine decreased to normal level.

The above cases emphasize need for continuous phytopharmaceutical vigilance on herbal preparations similar to that of pharmacovigilance on modern drugs and it has to be clear whether ADR is due to particular drug or any other alternative drug being taken.

4. Indiscriminate use of OTC drugs is also an issue, because they are easily available without prescription so people used them for long to treat themselves without knowing the harmful effects associated with them.

Correspondence

Diagnostic Dilemma: Guillain Barre syndrome with brisk reflexes

Sagar Kawale1, Deepika Joshi2, Abhishek Pathak3

1Senior Resident, 2Professor, 3Assistant Professor, IMS, BHU, Varanasi, Uttar Pradesh

Sir,

GBS is an acute monophasic immune mediated polyradiculoneuropathy which essentially presents with progressive motor weakness and areflexia with variable sensory disturbances.2 Two distinctive pathological subtypes of GBS have been mentioned –axonal and demyelinating. In Chinese, Japanese and European population, there have many case reports mentioned of another possible subtype of GBS, i.e., GBS with preserved or exaggerated reflexes.2,3 This entity is rare in Indian subcontinent and only a few cases have been reported.2,4 Unless a high index of suspicion is maintained, such case is often missed.

A 14 year old boy with no significant past medical history presented to us with the history that 7 days back he experienced tingling sensation in both hand followed by difficulty in handling mobile phone buttons. Next day he noticed difficulty in walking followed by difficulty in climbing stairs which progressed over next 2-3 days so that he was not able to walk without support of 2 persons and also was not able to sit up from supine position. On 4th day, he noticed difficulty lifting both arms above head followed next day by mild difficulty in lifting head from pillow. However, he never experienced any difficulty in breathing, swallowing, closing eyes or any bladder symptoms.

References

There was no history any antecedent illness or recent vaccination or toxin exposure. On examination, flaccidity was noted in all group of muscles. Power in proximal and distal lower limbs was grade 2 (MRC grading) and in proximal and distal upper limbs was grad 4- and grade 3 respectively. Truncal and neck weakness was also noted. Deep tendon reflexes were brisk throughout the course of illness and superficial reflexes (plantar and abdominal) were normal. Sensory and cerebellar examination was normal. Investigations revealed normal creatine kinase and normal potassium level. MRI brain with cervical spine was normal. Nerve conduction study showed pure motor axonal polyneuropathy with absent F waves suggesting axonal variant of GBS. Albumino-cytological dissociation was noted on CSF examination (cells-3, proteins-83, normal sugar). Electromyography was done which showed decreased recruitment of motor unit potentials with normal morphology of MUAPs and without any spontaneous activity. Patients illness was static for 3 days and since the time he presented to us. He was managed conservatively and he started improving over next 3 weeks. On discharge, his power was grade 4- in lower limbs and 4+ in upper limbs and was able to walk with support on his own. Repeat nerve conduction studies after 4 weeks showed improvement in CMAP amplitudes to almost normal with impersistent F wave.

GBS with normal or brisk reflexes is uncommon in India. The variants which have described with normal or brisk reflexes are AMAN, acute motor conduction block neuropathy and acute facial diplegia with brisk reflexes. 1,5,6 A rapid recovery has been noted in patients with preserved reflexes, preceding Campylobacter jejuni or H. influenzae infection and positive anti-GM-1 ganglioside antibodies. 12 Antibody testing is not freely available in India which makes the diagnosis, analysis and further correlation more difficult.

The proposed mechanism for brisk deep tendon reflexes is dysfunction of inhibitory systems in spinal interneurons. 3 The pathophysiological mechanism is supposed to be due to distal conduction disturbances rather than axonal degeneration which produces low amplitudes of motor unit potentials on nerve conduction studies. This is termed as reversible conduction failure or acute motor conduction block neuropathy. 7 The presumed reason is conduction disturbances at node of Ranvier rather than demyelination. This motivated us to go for a needle EMG which showed decreased recruitment suggestive of early neurogenic pattern. EMG has not been done in earlier cases reported from India. 9 High cervical myelopathy and hypokalemia are the most important differential diagnoses of GBS with normal or brisk reflexes. However, a careful history, detail physical examination and thorough investigations help to avoid confounders and achieve correct diagnosis.

References

Digitised Allen’s Test

Om Prakash
Emeritus Consultant, St. Marthas Hospital, Bengaluru, Karnataka

Sir,

Allen’s test 1 has been in use to ascertain the collateral circulation of the hand through the ulnar artery. This has relevance in the context of the radial artery being harvested for CABG. The modified Allen’s test 2 consists of asking the subject to raise his hand and clench the fist.

After compressing the radial and ulnar arteries firmly, and the subject opens his palm, one notes blanching of the palmar surface. Then the pressure on the ulnar artery is released; if collateral ulnar circulation is adequate, palmar flushing occurs to some extent. When the pressure on the radial artery is released, the palm returns to the resting complexion.

In view of the subjective nature of the test and difficulty among subjects with a dark complexion, we propose using the hand held pulse oximeter which is widely used. The oximeter is placed on the index finger of the subject, and the pulse wave form and the oscillating bar are noted along with the oxyhemoglobin saturation level (SPO2). Both the radial and ulnar arteries are firmly compressed and one notes gradual reduction of the pulse wave till a horizontal line is observed; the SPO2 will also be un-recordable momentarily. Sudden release of the pressures on the ulnar artery causes the pulse wave, oscillating bar and SPO2 to return, albeit partially. Release of pressure on the radial artery will restore these parameters to the original state.

This method obviates the results and obviates ambiguous results among dark skinned subjects.

References
ELECTIONS OF API, ICP AND PRF
(Full details circular No. 1& 2/2018)
Election for Governing Body of API, Faculty Council of ICP and Board of PRF are announced for following posts

**Governing Body of API:**
- President-Elect – One; Vice President – One; General Secretary - One; Elected Members – Four posts

**Faculty Council of ICP:**
- Dean-Elect – One; Vice Dean – One; Joint Secretary – One and Elected Members – 4 posts

**Board of PRF**
- Board members – Two posts

Separate nominations must be submitted for each post.

**Rules Relating to Qualification for Election to Governing Body of API**

1. **President Elect:** To contest for the post of President Elect the candidate should be a life member of API for at least 10 years and have completed atleast two full terms of 3 years each in any elected position in the Governing Body.
2. **Vice President and Hon. General Secretary:** To contest for the post of Vice President and Hon. General Secretary the candidate should be a life member of API for at least 5 years and should have completed at least one continuous full term of 3 years in any elected position in the Governing Body.
3. **To contest for elected members and one zone member of the Governing Body, continuous membership of the Association of at least 3 years is mandatory.**

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for API posts shall be proposed by one valid member and seconded by another valid member of API and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Governing Body if elected.

**Requirements for eligibility for the contests of Dean Elect:**
- a member of API for at least 15 years and
- A Founder Fellow or a Fellow of the College of 7 year standing and
- Any person who has held the position of President/ Secretary of API or served as Vice Dean for one full term or elected member of the Faculty Council for one term.

**Vice – Dean**
- a member of API for at least 12 years and
- A Founder Fellow or a Fellow of the College of 5 year standing and
- Any person who has held the position of Secretary of API or has been a Jt Secretary from HQ for one full term or a member of the Faculty Council

**Joint Secretary & Elected Members:**
- A member of API for at least 10 years and a Founder Fellow or a Fellow of the college of 3 year standing.

**Requirements for eligibility contest of election to Board of PRF**

**Board Member**
- Member of API for at least 10 years with research experience and having 5 research publication in peer reviewed indexed journals. The members contesting for he PRF election must attach copies of the Research Papers as mentioned above (mandatory)

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for ICP posts shall be proposed by one valid member and seconded by another valid member of ICP and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Faculty Council of ICP if elected.

A member shall not contest simultaneously for more than one post (i.e President-Elect, Vice-President, Elected members, North Zone Member of the Governing Body) (Dean-Elect; Vice Dean and Elected Members of Faculty Council) and also (Director Elect, Board members of PRF) Post means not only an office-bearer but also member of the Governing Body of API or Faculty Council of ICP of Board of PRF.

Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 31st May 2018. For every post on the Governing Body / Faculty Council / Board of PRF, the nomination must be accompanied by a sum of Rs. 2,500/- (Rupees two thousand five hundred only) non refundable in the form of Demand Draft payable at Mumbai. The nomination paper NOT accompanied by the Bank Draft of Rs. 2,500/- will be deemed invalid.

**Important**

Canvassing in any form should not be done by the candidate for the election. Instead, they are requested to send a short biodata NOT MORE THAN 200 words along with the nomination paper which will be printed and circulated along with the ballot paper. Excess of bio-data beyond the first two hundred words shall be deleted. Canvassing in any form or in favour of the candidate shall not be permitted.

THE CANDIDATE WILL HAVE TO CERTIFY AND SIGN THAT THE INFORMATION PROVIDED IN HIS/HER BIODATA IS CORRECT.

The results will be declared at the end of counting of votes and announced in the subsequent issue of JAPI. The report will be placed before the Governing Body for intimation.

**DEAD LINES OF ELECTION PROCEDURE**
- Last date to receive the nomination at API Office: 31st May 2018
- Last date for withdrawal: 20th June 2018
- Last date to receive ballot papers at API Office: 31st August 2018

The full API circular No. 2/2018, ICP circular No. 1/2018 and Board of PRF 1/2018 are on API and JAPI website.

Dr. Mangesh Tiwaskar
Hon. General Secretary
Indian College of Physicians

Eligibility Criteria for the Award of Fellowship of Indian College of Physicians

5.2.1.1 Minimum experience of 10 years after Post Graduation.
5.2.1.2 Continuous membership of the Association of Physicians of India for not less than 7 yrs.
5.2.1.3 Should have made a significant contribution to research / teaching / development in the field of medicine.
5.2.1.4 Should have contributed to API by way of scientific or Organizational works.

To make the selection objective, a point system has been followed in assessing the suitability of the applications.

The Criteria used by the Credentials Committee for the award of fellowship are:

1. Qualification
2. Experience in Medical Profession
3. Publications
4. Honours / Awards
5. Research work
6. Contribution to API
7. CME & Conference (API/ICP)
8. Social welfare/ community service

The Fellowship form should be proposed and seconded by Founder Fellow / Fellow of ICP only.

- The Proposer / Seconder should not propose / second more than 3 nominees for award of ICP in a particular year.
- It is responsibility of the Nominee / applicant to get the proposal completed by the proposer and seconder along with the citation.
- API Membership No. of the proposer / seconder should be entered by the proposer / seconder themselves.
- The proposer should satisfy the requirements for proposal as under:-
  - The Nominee is a life member of API
  - The Nominee has completed 10 years after post-graduation
- The Nominee should read the Form carefully before filling the columns, to project their achievements appropriately.
- The Nominee should list their achievements in appropriate columns.
- Proof of qualifications, publications, honours, awards, must be submitted as supporting data. The supporting data should be numbered paragraph (eg 1., 2., 3., etc), For more than one supporting documents, the numbering should be in alphabets (eg 1 (a), (b), (c), etc).
- No hand written applications will be accepted.
- One original and seven Xerox copies to be submitted
- Last date for receiving application form is 31st May, 2018.

Dr. Mangesh Tiwaskar Dr. A.M. Bhagwati
Hon. General Secretary Jt. Secretary

Available on API and JAPI Websites : www.apiindia.org & www.japi.org
Format for Submission of Bio - Data of The Nominee for Consideration for Award of Fellowship of Indian College of Physicians.

1. **Name in Full (Surname First)**
   (in Block Letters)

2. **A. P. I. Membership No. and date of joining**

3. **Date of Birth**

<table>
<thead>
<tr>
<th>Address Residence</th>
<th>Address Office</th>
</tr>
</thead>
</table>

4. **Tel.:**

<table>
<thead>
<tr>
<th>Fax :</th>
<th>E-mail:</th>
</tr>
</thead>
</table>

5. **Postgraduate degree in Medicine**

<table>
<thead>
<tr>
<th>Year of passing</th>
<th>Institute</th>
<th>University</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Other Professional Qualifications</th>
<th>Year</th>
<th>Speciality / Subjects</th>
<th>University / Institute</th>
</tr>
</thead>
</table>

   a.  
   b.  
   c.  
   d.  

   Certificates Attached

6. **Experience in Medical Profession after Postgraduation in Medicine**

<table>
<thead>
<tr>
<th>Name of Hospital / Clinic / Organisation &amp; Location</th>
<th>Number of Beds (if applicable)</th>
<th>Period Served year wise (From-To)</th>
</tr>
</thead>
</table>

7. **Publications: List below.** *(If number of publications in Journals exceeds 8, publications which can qualify as research papers may be listed under Research section 9.)*

   a) **Number of Publications in Indexed National / International Journals.**

   b) **Number of Chapter in Books / monograms**

   c) **Editorship of National level or State level: Book / Monogram / Update Series**

8. **Honours And Awards** *(list below with photocopy of proof)*

   a) **Oration in National / State Association Meeting**

<table>
<thead>
<tr>
<th>Title of Oration</th>
<th>Organisation</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b) Award National / International / or State level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Title of Award</strong></td>
<td><strong>Organisation</strong></td>
<td><strong>Year</strong></td>
</tr>
</tbody>
</table>

9. **Research work** (list below)

(a) Research sanctioned & funded by Research Agency

Attach Letter of sanction.

(b) Departmental Research. (To qualify, the findings should be published in National/International Journal) Do not include papers already listed under Publications

Attach title page / Abstract

10. **Contribution to API** (list below and attach proof)

| **Post held in Organisation / Meeting** | **Name of Organisation / Meeting / CME** | **National / Zonal / Under API/ICP** | **Year** |

11. **Participation in CME or Scientific Sessions of API or ICP as Faculty**

| **Speaker / Chairperson / Other** | **Title of Talk / Session** | **Name of Meeting** | **Year** |

12. **Social welfare / Community service.** (Include under the headings given below, with documentary evidence)

(a) Emergency services during National calamities (Quakes/ Floods/Cyclones, etc)

(b) Public education Programme (Radio), TV talk/ writing in newspapers

(c) Service in Rural Areas

| **Service** | **Evidence** |

N.B : No handwritten application will be accepted. *To be typed on separate page

*One original and seven Xerox copies of sets to be submitted

Last date for receiving the application form is 31st May 2018.

Address : Turf Estate, No. 006 & 007, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai – 400 011.
Indian College of Physicians
Citation

The Fellows proposing and seconding the nomination for Fellowship of Indian College of Physicians should highlight the professional/scientific achievements of the candidate and the contribution to A. P. I. from personal knowledge in 200 words, in the format given below:

| Name ____________________________ | Name ____________________________ |
| Membership No. ___________________ | Membership No. ___________________ |
| Signature Proposer ________________ | Signature Seconder ________________ |

Note:- The Fellowship form should be proposed and seconded by Founder Fellow/Fellow of ICP only. In case there are more than 3 nominations by any proposer/seconder, the first three nominations in order of receipt in API Office and complete in all respects will be considered for award of Fellowship of ICP and the others rejected for consideration.
Olmesar
Olmesartan Medoxomil 10 / 20 / 40 mg Tablets

BP control...every hour, 24 hours

ROSUMAC GOLD
Rosuvastatin 10 / 20 mg + Aspirin 75 mg + Clopidogrel 75 mg

3D MAGIC

Nexvas
Cilnidipine 5/10/20 mg Tablets
The Nex... for Cardio Renal Protection

Etizola
Etizolam 0.25 / 0.5 / 1 mg
Shorter action... Lesser side effects
Z PROTECTION at 50% reduced price

Start 'EARLY' in Hypertension

ZILARTA 60
Antihypertensive, Anti-anginal, Anti-atherosclerotic
ZILARTA 120
Potent & Effective in Control