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Posterior Reversible Encephalopathy Syndrome: Not Always Posterior, Not always Reversible

Vishal Gupta

R e v e r s i b l e  P o s t e r i o r  L e u k o e n c e p h a l o p a t h y  S y n d r o m e (RPLS)\(^1\) is classically characterised by rapid onset of neurological symptoms like headache, altered sensorium, convulsions and visual disturbances coupled with neuro-imaging findings of symmetrical parieto-occipital oedema. Described by Hinchey et al in 1996, (though case reports with features of RPLS were already published), it has been also referred by various other terminologies as Posterior Reversible Encephalopathy Syndrome (PRES), Brain capillary leak syndrome, APPLE (Acute Predominantly Posterior Leukoencephalopathy syndrome), although none of the above names are completely satisfactory. Some cases are not confined to posterior region or white matter of brain, neither it is always reversible.

RPLS is seen in various etiologies like chronic hypertension, chronic and acute renal failure, eclampsia, pre-eclampsia, immunosuppressive drugs use like cyclosporin and tacrolimus, Hemolytic Uremic Syndrome (HUS), Systemic Lupus Erythematosus (SLE). They present with similar clinical and radiological features. Clinical signs may include acute onset of headache, visual disturbances, seizures and altered sensorium.\(^2\) Majority of patients have high blood pressure on presentation although some may have normal or mildly elevated blood pressure.

The patho-physiology of PRES remains unproven and controversial. The most popular hypothesis remains the breakdown of auto-regulation of cerebral blood flow in the event of abrupt increase in blood pressure.\(^3\) Blood flow to brain is regulated by arteriolar constriction and dilatation over a range of blood pressure. Breakdown of auto-regulation occurs above a mean arterial blood pressure of 160 mm hg; it may break down at higher blood pressure in cases of chronic hypertension. The rate of increase in blood pressure also plays an important role. Uncontrolled hypertension leads to hyperperfusion which in turn damages blood brain barrier. It also causes extravasation of fluids and blood products into the brain parenchyma leading to vasogenic brain oedema. However, breakdown of auto-regulation theory cannot explain PRES in the absence of hypertension.

Endothelial dysfunction has also been implicated in causing PRES.\(^4\) Systemic inflammatory state as seen in sepsis, eclampsia, auto-immune diseases causes endothelial dysfunction. When blood pressure increases, it results in arteriolar constriction which increases endothelial dysfunction causing tissue hypoxia and vasogenic oedema. Specially in cases of eclampsia markers of endothelial dysfunction like lactate dehydrogenase and dysmorphic red blood cells are commonly seen. Secretions of trophoblastic cytotoxic factors from poorly perfused fetal unit may provide the initial stimulus. Markers of endothelial cell dysfunction have also been reported in patients with RPLS in other settings like SLE, chronic renal failure, HUS, etc. Both the hypotheses have their drawbacks, hence more research is warranted in understanding of patho-physiology of PRES.

The clinical signs and severity varies and may not necessarily correlate with radiological involvement. Patients may be comatose or just have mild confusion or agitation.\(^5\) Visual disturbances may range from blurred vision to cortical blindness. In seizures, mostly tonic clonic are common. Convulsive and non-convulsive status epileptics that may be refractory to multiple agents are also encountered. Headache is usually constant, non-localised, severe to moderate and un-responsive to analgesia. A wide variety of etiologies like acute hypertensive episodes, eclampsia, immune suppressive and chemotherapeutic agents, vasculitis, acute or chronic renal failure, porphyria, contrast media exposure has been implicated. Hence increased suspicion of PRES in such cases will be helpful.

Though MRI is the gold standard for diagnosis,\(^6,7\) most patients in emergency department require urgent CT scan of brain to rule out other differentials like central venous thrombosis, intra cranial bleeds and cerebrovascular accidents. Neuro-imaging in majority of cases shows vasogenic oedema in cortical or subcortical white matter of parieto occipital region. Lesions of frontal lobes are seen mostly in superior frontal gyrus along with edema in posterior circulation.

Focal or confluent areas of increased signal on T2 weighted images are most commonly observed.\(^8\) Fluid Attenuated Inversion Recovery (FLAIR) sequences can detect subtle peripheral lesion and increase sensitivity. Gadolinium contrast studies show increased gyri-form signal suggesting blood brain barrier dysfunction.

Based on FLAIR findings some researchers have classified PRES into mild, moderate and severe, depending on extent of hyper intensities and presence of mass effect.\(^9\) Mild PRES was defined as cortical or subcortical white matter edema without parenchymal haemorrhage, mass effect, herniation, or minimal involvement of only one of the group of cerebellum, brainstem, or basal ganglia. Moderate PRES was defined as confluent edema extending from the cortex to the deep white matter without extension to the ventricular margin, or mild involvement of two of the group of cerebellum, brainstem, or basal ganglia. Mild mass effect with no

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herniation or midline shift, particularly if parenchymal haemorrhage was present, was also classified as moderate. Severe PRES was defined as confluent edema extending from the cortex to the ventricle, or edema/haemorrhage causing midline shift/herniation. Alternatively, involvement of all three of the group of cerebellum, brainstem, and basal ganglia was considered severe. As brain cortex is tightly packed than white matter, it usually resists edema. Increased concentration of adrenergic nerves in anterior circulation than posterior, can explain increased finding in posterior circulation.

Follow up studies in majority of cases show partial or complete reversal within few days to weeks after treatment.

Other investigations required to rule out differential diagnosis should be considered, as clinical and radiological findings are not specific. The tests include blood counts, creatinine, electrolytes and other liver function tests. Patients may require EEG monitoring as seizures are common and persistent. Altered sensorium may be due to non-convulsive status epilepticus.

Prompt recognition of PRES with rapid management of trigger leads to hastened recovery. Increased blood pressure should be managed aggressively. In case of malignant hypertension, blood pressure should be reduced to about 100 diastolic. Care should be taken that the blood pressure should not fall by more than 25% of the current reading. Prompt delivery should be done in eclampsia. Withdrawal of offending agent should be considered. Anti epileptics, airway protection and mechanical ventilation with supportive care in intensive care may be required.

In this edition of JAPI, PK Yadav and D Sen have described clinico-pathological profile and outcome of patients with Posterior Reversible Encephalopathy Syndrome. Preponderance of females in the study may be due to high level of suspicion with consequent detection of PRES following eclampsia and pregnancy-induced hypertension. 80% normal CT scan in study also suggest that MRI should be the preferred modality of investigation if other the causes of altered sensorium -especially stroke in golden hour of thrombolysis, is not suspected. MRI changes may not be restricted to posterior area, but may be diffused. Basal ganglia are involved in good number of cases in present study. Overall mortality rate is good in PRES, with majority gaining full clinical and radiological recovery9 as seen in this study also, however in some cases mild residual features may persist. Further studies and clinical trials with larger number of patients will help us further understand the disease better and optimize treatment. Early recognition and prompt treatment is the key to a good outcome.

References

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Clinicoradiological Profile and Outcome of Patients with Posterior Reversible Encephalopathy Syndrome

Praveen Kumar Yadav¹, Dipanwita Sen²

Abstract

Background: Posterior Reversible Encephalopathy Syndrome (PRES) is a potentially reversible neurologic illness presents with abrupt onset of symptoms of headache, seizures, visual blurring and occasionally altered mentation.

Aims and Objectives: To study Demographic profile, Clinicoradiological features, Etiology and Prognosis of patients admitted with a diagnosis of PRES in the department of Neurology at a Tertiary Health care centre in Eastern India.

Materials and Methods: A retrospective-prospective, observational, Non-interventional study. 24 patients admitted in the department of Neumedicine satisfying the diagnostic criteria of PRES were included in the study during the study period July 2014-June 2017.

Results: Out of 24 patients, 19 (79.1%) were females and 5(20.8%) were male. Mean age for females was 28.5 years/S.D of ±13.5.and for males were 42.28 years/S.D± 8.5. Overall mean age was 35.26 (SD±18.34). It was more common in females (Relative risk of 3.8; Odds Ratio: 9.7, p<0.001). Most common symptom was headache in 83.3%. Vomiting (77%), seizures (75%), Cortical Blindness (45.8%) and Altered sensorium (20.8%). In patients having seizures most of them were recurrent (62.12%) and 18.9% had status epilepticus.

Most common precipitating cause was postpartum state (37.5%), Accelerated Hypertension (20.8%), chronic renal failure (16.6%), Pregnancy (12.5%) and chemotherapeutic agents (8.33%). More than 60% of postpartum and pregnant patients had normal blood pressure recordings. MRI scan showed parietocipital involvement most commonly (62.5%), followed by diffuse involvement (33%), Asymmetric brain involvement (16.6%), Basal ganglia/thalamus and cerebellar involvement in 12.5% each. Haemorrhage and infarcts were seen rarely. Most of the patients improved with no residual imaging findings or neurological deficits.

Conclusion: Early diagnosis with appropriate Imaging is very important to achieve good Neurological outcomes. Post Partum and pregnant patients with PRES may have normal blood pressure measurements.

Introduction

Posterior Reversible Encephalopathy Syndrome (PRES) or Reversible posterior leukoencephalopathy syndrome (RPLS) is a clinical radiographic syndrome of heterogeneous etiologies that are considered together because of similar findings on neuroimaging studies and identical set of clinical features.

As this entity was more studied in children, it is often—but not means always—associated with acute hypertension.

If promptly recognized and treated, the clinical syndrome usually resolves within a week, and the changes seen in magnetic resonance imaging (MRI) resolve over days to weeks.

PRES is sporadic and its incidence is unknown but it has been reported worldwide without any gender differences, both children and older people can be affected.

The pathophysiology of PRES is poorly understood. There are several theories.

Breakdown of cerebral autoregulation due to a rapid rise in blood pressure leading to disruption of the blood–brain barrier is the most popular one. A second mechanism is endothelial dysfunction due to circulating toxins which is more relevant for triggers such as immunosuppressive therapy, sepsis, autoimmune disease and pre-eclampsia, which all may affect the blood–brain barrier and lead to subsequent vasogenic edema. Inherent deficiency of adrenergic innervation which controls cerebral autoregulation in the posterior circulation is the reason behind the posterior prelication of Vasogenic edema.

PRES is a syndrome with visual loss, headache, altered mental function, seizures and nausea. The symptoms usually develop quite quickly over a few hours, reaching their worst in 12–48 h. Seizures are the most frequent, in up to 90% of cases and often preceding any of the other manifestations. Brain CT only shows lesions in PRES in about 50% of cases and brain MRI is not always performed—hence the diagnosis can easily be overlooked unless other symptoms are recognised.

There have been many publications, mostly case reports and imaging studies. Only a few publications have been concerned with the clinical features. In India there has been only one large study looking at the clinical and radiological profile of PRES patients by Patil et al. There are no studies so far from Eastern Part of
India on PRES. Hence a need for further study into the clinical and radiological picture of PRES was seen and so this study was done.

Aims and Objectives

To study demographic, etiological, and clinic-radiological profile of patients presenting with PRES and their outcome at a tertiary care hospital in Eastern India.

Material and Methods

A retrospective observational and non-interventional study was conducted at a tertiary care Hospital in Durgapur, West Bengal. Patients with diagnosis of PRES admitted in the department of Neurology during the year July 2014 to June 2017 were included in this study. Patient’s data were collected from medical records which included patient demographics, Clinical features, blood pressure values, comorbidities, drug history, laboratory investigations and neuroimaging details.

Diagnostic Criteria

The presence of all 3 of the following criteria were mandatory for inclusion: (1) clinical history of acute neurologic change including headache, encephalopathy, seizure, visual disturbance, or focal deficit; (2) brain imaging findings of focal vasogenic edema; and (3) clinical or radiologic proof of reversibility. Hypertension was defined as a systolic blood pressure of 140 mm Hg or greater or a diastolic blood pressure of 90 mm Hg or greater.

The case records were carefully studied and the clinical features at presentation, comorbidities, demographics, neuroimaging findings and other laboratory parameters were collected. The etiology of the PRES was taken as diagnosed by Neurologist.

Exclusion Criteria

Cases lacking both clinical and imaging findings favouring PRES with an alternative diagnosis were excluded from the study.

M R I B r a i n i m a g i n g

Standard sequences was unenhanced FLAIR and T1- and T2-weighted images in all patients, with diffusion-weighted imaging in all patients. Contrast Imaging was done in which pathologies like acute disseminated encephalomyelitis or meningitis were suspected.

Magnetic Resonance Venography was done in suspected patients to rule out our cortical or deep venous thrombosis.

Few of patients had a CT Brain done in emergency department or from outside Referring hospitals.

The patient’s improvement of symptoms and signs were obtained from case records. Repeat MRI was done in most of the patients to assess the reversibility of lesions. In patients with financial issues in repeating the study total clinical resolution was taken as a marker of reversibility. However patients who had persistent neurodeficits with no follow up imaging were excluded from the study.

Statistical analysis was done by computer software SPSS-11, trial version. Categorical data were analyzed by mean, standard deviation (S.D.), percentage and Chi-square test. The level of significance was set at ‘*p* < 0.05, and 95% confidence interval (CI) was used throughout.

Results

Demographic

Out of 24 patients studied 19(79.1%) were females and 5(20.8%) were male. In the female population mean age was 28.5 years and S.D of ± 13.5. In the male population the mean age was 42.28 years and S.D ± 8.5. Overall mean age was 35.26 (SD ± 18.34). It was more common in the female population (Relative risk of 3.8: Odds Ratio: 9.7, p<0.001)

Most common age group involved was 20-30 years (58.3%).

Clinical Features

Most common symptom was headache in 83.3%. Vomiting (77%), seizures (75%), Cortical Blindness (45.8%), altered sensorium (20.88%) and papilledema in (5.5%).

Seizures were generalised tonic clonic seizures in all patients. Most patients having seizures most of them were recurrent (62.12%) and 18.9% had status epilepticus.

Precipitating Cause

Most common precipitating cause was post partum state (37.5%). Out of which 81.81% was after 1 week of delivery. Accelerated Hypertension (20.8%), Chronic renal failure with hypertension (16.6%), Pregnancy (12.5%), Immunosuppressive agents (8.33%) and acute renal failure (4%). In the pregnancy group all the cases...
were in the 2nd trimester. In the Post partum and pregnancy group blood pressure was normal in 63.6%. The Immunosuppressive agent implicated was Tacrolimus in one patient with history of renal transplant one year back. Other patient was on Mycophenolate for idiopathic thrombocytopenic purpura.

**Symptoms & Signs**

**Neuroimaging**

CT Scan was done in 62.5% of the patients, out of which 80% had normal CT scan which on MRI Imaging showed features of PRES. MRI showed Parieto-occipital involvement in 62.5%, 33% had diffuse involvement, Asymmetric involvement of brain was seen in 16.6%, basal ganglia and cerebellum involvement was seen in 12.5% each. Hemorrhage was seen in 8.33%. One patient had subarachnoid bleed and one was small frontal parenchymal bleed. Infarct was seen in one patient (4.16%). The infarct was internal posterior watershed infarcts.

**Prognosis on follow up and outcome**

Overall outcome was good. Headache resolved in 3-4 days. Vision improved in 95% of the patients in 1 week. Patients with bleed and infarct had residual neurological deficits.

Follow up MRI Could be done in 10 patients after 6 weeks and in 80% the findings had resolved after 6 weeks. 1 patients had persistent occipital edema with visual field defect. The patient with infarct had residual spasticity and brisk reflexes with mild cognitive impairment at 6 week follow up.

There was no mortality in our study group. One patient with chronic kidney disease and accelerated hypertension had Recurrence of PRES after one year and presented with seizures and fresh parietocippital edema.

**Discussion**

After Hinchey et al’s initial description in 1996, both its clinical spectrum and underlying pathophysiology remain poorly defined. A clinical diagnosis of PRES includes the presence of headache, seizures, encephalopathy, and visual disturbances, as well as radiologic findings of focal reversible vasogenic edema, best seen on magnetic resonance imaging (MRI) of the brain.

PRES is characterized by headache, seizures, confusion, and visual disturbance. Other focal neurologic deficits are uncommon. Seizures, which might begin focally, are usually generalized tonic-clonic and often multiple. It may be associated with visual loss and hallucinations to suggest occipital lobe onset. Visual abnormalities include cortical blindness field defects like hemianopia, visual neglect, and blurred vision.

The name of PRES may be considered as a misnomer as radiographic lesions in PRES are rarely isolated to the “posterior” parieto-occipital white matter and usually can the cortex, frontal lobes, basal ganglia, and brainstem. No clear cut evidence is there showing a clear relationship between clinical patterns and specific imaging findings of extent or location of edema however some studies have suggested roles of vasogenic edema in patients with normal blood pressure and more cerebellar and basal ganglia involvement in Pregnancy related cases having high blood pressure.

Abrupt hypertension is seen to be a major mechanism of PRES in substantial number of cases, and hyper perfusion is further validated with the fact that with the adequate control of blood pressure, the clinical signs and symptoms and radiological findings reverse. However, this theory is not fully comprehensive because PRES may affect normotensive patients and does not occur uniformly and predictively in patients with hypertensive surges above the normal upper limits of cerebral auto regulation.

The differential diagnosis to be considered are posterior circulation stroke, encephalitis, reversible cerebral vasocnstriction syndrome (RCVS), cerebral venous thrombosis, arterial dissection and primary CNS vasculitis.

MR Venography and MR Angiography should be done to rule out venous thrombosis and RCVS or Arterial dissection.

In posterior circulation stroke altered sensorium, focal deficits, visual loss and high blood pressure may be seen. However seizures would be rare and Diffusion restriction in MRI scans would be seen in posterior circulation stroke. The calcareous and paramedian occipital lobe structures are usually spared in posterior leukoencephalopathy syndrome, the differentiation is crucial as aggressive blood pressure control is desirable in PRES, in contrast to the management recommendations for acute stroke, which permit mild to moderate hypertension.

More than 70% of patients with PRES are hypertensive, though a significant proportion has normal or only mildly raised blood pressure.

Our study was planned mainly to study the Clinico-radiological profile of patients with PRES and the outcome of these patients. The clinical spectrum of findings and the etiological causes were similar to most of the studies conducted in India and worldwide.

The important differences were Pregnancy and postpartum states were the most important etiological factor (37.5%). In this group of patients one noteworthy point was that more than 60% of the patients had normal or minimally raised blood pressure values. Most of the studies showed blood pressure to be elevated in this group of patients (50-60%).

PRES was most common in postpartum period after 1 week in our series. It is in contrast to other Indian study which showed it to be common in the antenatal period. Mean age of pregnant and postpartum females were 28.5 yrs and 90% of them were primigravida.

Our study as in contrast to few large studies did not show high prevalence of autoimmune disorders in patients with PRES.

Radiological findings when compared to other studies, all
showed a similar pattern of involvement. However the important difference was lack of brain stem involvement in our study and comparatively less cerebellar involvement. The lack of autoimmune disorders in our study population could be one reason for this finding as it is more seen with such disorders. CT scan was normal in 80% of the cases in the initial presentation thus pointing that PRES cases would be missed if we rely on Normal CT scans in ruling out a diagnosis of PRES.

Outcome of patients with PRES was excellent. There was no mortality in our series.

The Limitation of our study was follow up imaging could not be performed in all the patients due to financial constraints. Seriously ill patients with underlying Sepsis, multiorgan dysfunction and autoimmune disorders were not there in the study group. Treatment of PRES, the types of antiepileptic drugs used and its duration have not been studied.

Conclusion

This study highlights that PRES is reversible mostly, if diagnosed early with high clinical suspicion and appropriate investigations. Atypical imaging patterns are quite common and should be kept in mind before excluding PRES. Usually there are no residual neurological deficits. PRES should be always considered in pregnant and postpartum patients even with normal blood pressure.

References

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Occupational Exposure to Blood and Body Fluids among Post-graduate Students in Tamilnadu: A Cross-sectional Study

Praveen Kumar P1*, Shadiya C1, Sivakumar K2, Shenbagasree3, Raveendran M2

Abstract

Objectives: Post Graduate students are exposed to blood and body fluids due to occupational accidents because of the environment in which they work. This study is to calculate the incidence of such events among the junior residents of medical colleges in Tamilnadu, various factors responsible, the circumstances under which they occur and the response of the junior residents after such injury.

Methods: A cross sectional study was conducted among 6 medical colleges in Tamilnadu in July 2016. A pretested questionnaire was used to collect data from 752 junior residents after informed consent. Data was analyzed using SPSS v20.0 p value <0.05.

Results: The response rate was 88.5% with mean age of the doctors being 28.4(SD 2.94). Most of them were from medical specialty 64%. The prevalence of exposure in the preceding 1 year was calculated to be 68.33% with significant male preponderance 75.31%. The average incidence was 1.85/year/PG. Only 81% of residents were fully immunized against HBV. Most common source of exposure was mucocutaneous splash 50.4% followed by needle prick injury 31.3%. Emergency room and IMCU had the highest source of exposure (two-thirds). Admission day 24 hours duty was the most common cause of exposure 69.65% and the reasons given were fatigue, work overload, insufficient paramedic employment and lack of basic materials like gloves in the emergency department. High risk exposures were seen in 16% with only 51% of reported cases taking PEP. The reporting rate was only 30.5%. After an interval only 36.6% of the residents had their blood screened.

Conclusion: There is a high prevalence of exposure among junior residents. Efforts should be made to decrease the incidence of occupational exposure, increase the working standards, increase the reporting of such events and to ensure appropriate PEP is taken post exposure.

Introduction

Post Graduate students are exposed to blood and body fluids due to occupational accidents because of the environment in which they work. These include needle prick or other sharp injury, mucocutaneous splash of blood and other body fluids (in eyes, nose or mouth) or blood contact with damaged skin. These percutaneous injuries expose the junior residents to more than 20 different blood-borne pathogens. According to WHO Report 2002, 40% of HBV and HCV cases and 2.5% of HIV cases among health care workers worldwide are the result of occupational exposure. These result in 500 cases of HIV infection, 15000 HCV infections and 70000 HBV infections annually. The risk of infection for health care workers from occupational exposure depends on the nature and frequency of exposure and the prevalence of pathogens in the community.

These occupational exposures are often under reported. So, the injuries reported through standard reporting systems are often the tip of the iceberg. The occupational exposure among post graduates is not well documented. Therefore the aim of this study is to examine the epidemiology of occupational exposures in the main medical colleges in Tamilnadu, circumstances leading to such accidents and the response of the Doctors to such exposures.

Material and Methods

A cross sectional study was conducted among the junior residents working in the clinical departments from six medical colleges in Tamilnadu (Coimbatore, Chennai, Salem). A convenient sampling technique was used. Ethical Committee clearance was obtained from Coimbatore Medical College Hospital. Participation of the junior residents was voluntary and anonymous after informed consent. Based on the previous published studies and WHO guidelines a self-administered questionnaire was developed. It was first pretested among 10 post graduates as a pilot study to determine if the questions were clear, the comfort level to answer them, the choices given were compatible with the experience and necessary changes were made to it. The result of the pilot study was not included in the study proper.

The prevalence of occupational exposure among post graduates in the last one year was calculated. Data was coded and entered into the database and analysis was done using IBM SPSS v.20.0 software. Significance level was taken as p<0.05.

Results

Out of 850 Postgraduate students 752 responded, thereby the response rate was 88.5%. Mean age of the post graduates was 28.4 (SD 2.94). The sex ratio was almost equal (M-380, F-372)
with most of them being unmarried 61.2%. The post graduates working in medical specialties were 64% and surgical specialties were 36%. The overall full course HBV vaccination was also calculated to be low 81% (609/752). The demographic characters of the residents are shown in Table 1.

Among the 752 respondents, 514 PGs had at least one exposure in the last 12 months, thus the prevalence rate was 68.35%. There was a significant sex ratio difference with male preponderance(M = 302,75.31%, F = 212,24.69% ). Odds ratio was 1.24 with CI 0.99 to 1.56 (p <0.05). (Figure 1) The average incidence of occupational exposure was 1.85 per year per PG.

An overview of the nature of activity leading to occupational exposure is listed in Figure 2. Mucocutaneous splash was the most common source of exposure 50.4% p<0.05, followed by needle prick injury 31.3%. Other causes were contact with blood through damaged skin 10.5% and during needle recapping 5.7%.

The place of work in the hospital

Table 1: Socio-Demographic variables of the study population

<table>
<thead>
<tr>
<th>Socio-Demographic variables</th>
<th>Nos.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-27</td>
<td>314</td>
<td>41.76%</td>
</tr>
<tr>
<td>27-30</td>
<td>236</td>
<td>31.38%</td>
</tr>
<tr>
<td>&gt;30</td>
<td>202</td>
<td>26.86%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>380</td>
<td>50.53%</td>
</tr>
<tr>
<td>Female</td>
<td>372</td>
<td>49.47%</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>292</td>
<td>48.8%</td>
</tr>
<tr>
<td>Single</td>
<td>460</td>
<td>61.2%</td>
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<tr>
<td><strong>Department</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>481</td>
<td>46%</td>
</tr>
<tr>
<td>Surgical</td>
<td>271</td>
<td>36%</td>
</tr>
<tr>
<td><strong>Hepatitis B Vaccination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>609</td>
<td>81%</td>
</tr>
<tr>
<td>No</td>
<td>142</td>
<td>19%</td>
</tr>
</tbody>
</table>

Leading to exposure is categorized in Figure 3. Emergency room (medical casualty and trauma ward) had the highest exposure rate with 35% p<0.05 , followed by Intensive medical care unit (IMCU) 29.8% p<0.05. General ward had 15.6% incidence followed by operation theatre 13.8% and labour ward 5.8%.

Relation between the duty timings and the incidence of occupational exposure and the reason given for the occurrences was calculated Figure 4. Admission day duty (24 hour) reported the highest incidence with 69.65%, OR=3.60 p<0.0001 compared to day duty 22.18% and night duty 8.17 %. This suggests statistically much significance when residents are subjected to continuous 24 hours duty. The reasons suggested by them for such incidences was estimated with the main reason stated being fatigue and lack of concentration 63.42% followed by case overload 24.12% and patient aggression during procedures 12.45%.

Standard Precautions (SP) include a group of infection prevention practices that apply to all patients, regardless suspected or confirmed infection status, in any setting in which healthcare is delivered. SP at the time of exposure was taken only by 31.71% of the doctors. Reason cited for not practicing SP was non-availability 46.7% of (materials like gloves), followed by overloaded work and lack of time 32.5%, while 20.8% residents felt it wasn’t necessary to use SP on all patients Figure 5.

Among the exposures, 82 (16%) reported as having been from a high-risk patient which includes patients or their spouses with history of HIV, HBV, HCV, iv drug abuse or unknown no-attender patients brought to the hospital by government free ambulance service.

Out of 82 residents, only 42 (51.22%) took complete course of post exposure prophylaxis. The number of reported cases to the medical officer in-charge in the hospital was only 25 (30.48%). Only 30 residents 36.59% had their blood screened for infectious diseases 3 months later (Figure 6).

Discussion

The prevalence rate of occupational exposure among post graduates was 68.35%. This is much high compared to the previous studies conducted in other parts of the country.4,5 There was a significant male preponderance with male being at more risk than female. (OR = 1.24) The average incidence of occupational exposure was 1.85 per annum per PG. This is in accordance with the WHO Report which showed an average of 0.2 to 4.5%.1 In contrast to the previous studies, needle stick injury was not the leading cause of occupational exposure.2,4 Mucocutaneous splash was the most common source 50.4% followed by needle prick injury 31.3%. Most common mechanism of injury was during needle re-capping after usage. According to OSHA guidelines (Occupational Safety and Health Administration) needle recapping practice should not be done in hospitals.
Reasons cited being non availability of the materials, overloaded work and lack of time. The difference between knowledge, attitude and practice (KAP gap) was significantly high among the junior residents. It was seen that in spite of high risk exposure, only 51% of the residents took a complete course of post exposure prophylaxis, but this was found to be high compared to other studies conducted. 4, 5 PEP can prevent the risk of HIV infection by 90%. The use of more intense educational programmes by the hospital administration in sensitizing the residents and easy approach to the reporting authority for starting PEP can reduce the risk of infection.

In our study too there was a gross under reporting of high risk exposures incidents to the official medical authority (30%). 1,4, 5 The screening of their blood after 3 months was done only by 36.6% which is a worrisome attitude. The most likely reasons given were incidents being forgotten, under estimation of the risk, a wide KAP gap, and fear of a positive serological test, overloaded work and restricted time.

The overall full course HBV vaccination rate among the post graduates was also found to be low (81%). The risk of HBV transmission is 95% preventable by immunizing. The administration authorities in the medical colleges should make sure that the junior residents are fully immunized.

**Conclusion**

College administration should emphasize and make adequate measures to safeguard the junior residents from such occupational hazards. Hence there is an urgent need for establishing a state wise surveillance system for monitoring of occupational exposure to achieve infection control among the health care workers. These exposures can result in risk of infection and can cause serious mental ill-health.

**References**

Etiology of Classic Fever of Unknown Origin (FUO) among Immunocompetent Indian Adults

Priscilla Rupali*, Divyani Garg2, Surekha Viggweswarupu3, Thambu David Sudarsanam3, Visalakshi Jeyaseelan4, Ooriapadickal Cherian Abraham3

Abstract

Background: Fever of unknown origin (FUO) has been a vexing problem for physicians for decades. The advent of imaging, functional scans, guided procedures and advanced molecular techniques has made many of the hitherto undiagnosed diseases easily diagnosable. FUO epidemiology can be geographically unique varying from country to region. Studies done in India are scarce, with variable definitions.

Methods: This prospective observational cohort study recruited 300 consecutive patients presenting with classic FUO as defined by Durack and Street. Potential diagnostic clues (PDCs) were identified and workup proceeded towards establishing a confirmatory diagnosis.

Results: Among the 300 classic FUO in our series, infections, neoplasms and NIIDs contributed to 48%, 21.6% and 20.6% of the cases. Tuberculosis and Melioidosis were the most important infections. Hematological malignancies like Non Hodgkins' lymphoma, Hodgkins' lymphoma and Leukemia contributed to 78% of neoplasms causing FUO whereas solid organ malignancies contributed to 18% of the cases. Among the NIIDs, Systemic lupus erythematous, Granulomatous diseases and Vasculitis contributed to 26%, 18% and 14.5% respectively. Diagnostic tests of utility included image guided biopsies (100%); CT scan of abdomen and or thorax (92.4%) and Lymph node biopsies at 72%. Mortality was 5%. A boot strapping analysis was done on PDCs contributing to each specific diagnostic category and algorithms were developed.

Conclusions: This is the largest series of FUO from South India. Systematic sequence of investigations without start of empirical therapy led to a diagnosis in 99.4% which is the highest in described literature.

Introduction

Fever of unknown origin (FUO) has perplexed physicians for generations. The causes of FUO are more than 200 and detailed knowledge of various medical conditions is required to reliably make a diagnosis. Petersdorf and Beeson in 1961 in their original paper defined FUO as fever more than 38.3°C (101°F) on several occasions with a duration of greater than 3 weeks and uncertain diagnosis after 1 week of inpatient hospital investigations. With the advent of HIV infection, organ transplantation and improvement of intensive care facilities this was subsequently revised by Durack and Street et al into 4 categories: Classic FUO, Neutropenic FUO, Nosocomial FUO and HIV associated FUO. However despite the advances in diagnostic techniques and facilities the proportion of undiagnosed entities has continued to be substantial in the case of classic FUO. The diagnosis and spectrum of FUO has been elucidated from the developed countries, but data from India and other developing countries is limited. The main causes of classic FUO include infections, neoplasms and Non infectious Inflammatory Diseases (NIID).

However in developing countries, infections are a prominent cause of FUO unlike in developed countries, where all three play an important role. Therefore diagnostic approach in India to FUO has to be distinctly different from that in the developed countries considering the different spectrum and costs. FUO series from India have included data from East (Kolkata), West (Mumbai), Central (Wardha) and North India (Delhi) with no data from South India, hence this study was designed to prospectively evaluate classic FUO in a tertiary care hospital with a view to elucidating various causes of FUO, identifying potential diagnostic clues (PDC) and using these to develop an algorithmic approach applicable in a resource limited setting.

Material and Methods

This was a prospective observational cohort study performed over a 20 month period from December 2010 to July 2012, at Christian Medical College (CMC) Vellore, Tamil Nadu, India. CMC Vellore is a tertiary care hospital with patients across the country accessing care.

We enrolled patients (age > 15 years) who fulfilled the following criterion for classical PUO as defined by Durack and Street et al. Temperature of >38.3 degree C (101 degree F) on several occasions as documented by a health care practitioner for > 3 weeks duration and in whom there was a failure to establish a diagnosis with appropriate investigations after 3 outpatient visits or 3 days as an inpatient.

We excluded patients with HIV associated FUO, Neutropenic (< 500
cells/mm³) FUO and nosocomial FUO and those on steroids (> 10 mg/day) or other immunosuppressants for at least 2 weeks or those on chemotherapy for a malignancy. Moribund patients with FUO who were unlikely to survive the duration of diagnostic investigations were also excluded. Preliminary tests were done to exclude an acute febrile illness and then were recruited into the study.

Based on localizing clinical features, patients were then subjected to second rung of tests usually an imaging - Ultrasound Abdomen, CT Abdomen and Thorax (contrast-enhanced), CT or MRI brain/spine. Analysis, aspiration, cultures and biopsies of fluid, collections and tissue were done if clinically indicated. Endoscopies with biopsies and cultures and PET scanning were also considered if required. All demographic and clinical variables were collected in a structured data form by the principal investigator. Repeated and detailed physical examinations were done every two days. We provided assistance to the investigation of FUO but no rigid protocol/algorithm was followed. The final diagnosis established at discharge or during follow-up comprised the main outcome of the study. Only diagnoses confirmed by a diagnostic test or sufficiently validated by a therapeutic trial with reasonable certainty were accepted. The laboratory test or diagnostic method that diagnosed the cause of fever first was also recorded. Tests were halted as soon as the diagnosis was established, and appropriate treatment initiated. Patients with empirical therapy were strictly monitored and followed up to ensure a sustained clinical response. If no diagnosis was obtained despite detailed and invasive evaluation on first admission and patients were clinically stable, they were counselled against empirical therapy and advised to come back for a re-evaluation after 6 weeks if symptoms persisted with the intention that the disease would have progressed enough for us to make a diagnosis.

**Definition for disease states**

Tuberculosis (TB) was diagnosed when M. tuberculosis grew in culture on tissue/tissue fluid or granulomas were seen on histopathology with a compatible clinical picture and a clinical response to antituberculosis therapy (ATT).

Occult tuberculosis was diagnosed when we were unable to obtain a tissue or culture diagnosis during that admission but was proven later by positive cultures for M. tuberculosis or a dramatic response to empirical ATT with clinical and radiological resolution.

Infective endocarditis was diagnosed when Modified Duke’s Criteria were fulfilled.

Melioidosis was diagnosed based on growth of Burkholderia pseudomallei on culture from appropriate sample (pus, blood, urine).

Enteric fever was diagnosed when blood/bone marrow culture grew Salmonella typhi/paratyphi or WIDAL positivity with rising titres in a compatible clinical setting with response to treatment for enteric fever.

Rheumatoid arthritis diagnosis was made based on the 2010 American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revision of the 1987 ACR classification criteria for RA.

Various rheumatological diseases were diagnosed based on their established criteria.

Lymphomas or haematological malignancies were diagnosed based on histopathology and Immunophenotyping from appropriate tissue.

Diseases as defined above with relevant clinical and laboratory features were noted and grouped into the three major etiological groups i.e., infections, neoplasms and non-infectious inflammatory diseases (NIIDs).

Sample size was calculated to be 96 based on the prevalence of tuberculosis of 40% (25-50%) among FUO studies in India

Sample size = (1.96² * p * (1 - p))/D²

P= prevalence of the disease (%), D= confidence interval (taken as 10%). Summary statistics and tests of significance (Chi square test for categorical variables and student t-test for continuous variables) were done using statistical software package SPSS version 16.

**Institutional review board approval and funding**

IRB approval was obtained prior to starting the study and funding was provided through an internal fluid research grant, to a post graduate student in Department of General Medicine and was subsequently submitted to the Tamilnadu Dr MGR Medical University as a PG dissertation.

**Results**

A total of 300 consecutive patients were recruited into the study. Almost 65% were male with an average age of 40 years (median 40; range 15-76 years). Two-thirds of our patients were from Tamil Nadu (31%) and West Bengal (32%) with the rest from South and North Indian states. The mean duration of fever prior to presentation was 148 days (median: 90; range 21 to 1460).

Overall the striking clinical features included anorexia (58%) and weight loss (61%) in two-thirds, followed closely by pallor (41%) hepatitisplenomegaly (33%) and lymphadenopathy (30%). A third (32%) of them had symptoms localizing to the respiratory tract i.e., cough and dyspnea and 12% localizing to the CNS - headache, seizures or focal deficits with the rest to the musculoskeletal system. Important localizing lab tests included elevated alkaline phosphatase (56.5%), and an abnormal chest X-ray (25%). Median Hb was 12.45. (Range: 3.6 -15.3), median ESR and CRP were 46 (range: 7-140) and 7 (range: 2-218), respectively.

In our cohort, infection was the most common cause of classic FUO accounting for 48% of all cases, followed by neoplasms in 21.6% cases and non-infectious inflammatory diseases in 20.6% of the cases. Miscellaneous and undiagnosed cases accounted for the remaining 8.6% and 1.6% of the cases.

Among the infections, tuberculosis in varied forms was the leading cause of infectious FUO accounting for 61% of the cases, followed by Melioidosis (10%), subacute bacterial endocarditis (4%) and visceral abscesses (4.8%), invasive fungal infections (3.4%), disseminated histoplasmosis (2.7%) and fungal endocarditis in 0.7%. Other causes accounted for 10% and included varied causes like delayed diagnosis of Enteric fever, Visceral leishmaniasis, Type II Lepra reaction, Brucellosis etc.

Among the tuberculosis patients, disseminated (45%), extra-pulmonary (33%) and pulmonary in 14% were the commonest clinical presentations with occult tuberculosis in 8% of the cases. Among the extra-pulmonary
The diagnosis was made from blood infections and 5% of overall cases of a PUO accounting for 10% of all causes of infection contributing to emerged as the second most important. Among invasive fungal infections, disseminated histoplasmosis and fungal (Candida) endocarditis contributed to 1.6% of the causes of PUO.

Neoplasms caused FUO in 22% (n=64) of cases. Haematological malignancies were the commonest neoplasms accounting for 78% with lymphoma accounting for 60%, leukemias 9% and multiple myeloma 9%. Solid organ malignancies like colon, lung, prostate accounted for 18% (n=12) of FUO. Less common causes were hepatocellular and poorly differentiated carcinoma.

Non-infectious inflammatory diseases (NIID) caused classic FUO in 21% of the cases and among these, systemic lupus erythematosus (SLE) was the most common (26%) followed by vasculitis (14.5%), Mixed Connective Tissue Disease and Adult onset Still’s disease at (8%). Other infrequent causes included Rheumatoid Arthritis, Kikuchi-Fujimoto disease, Seronegative spondyloarthropathy, Inflammatory bowel disease and Sarcoidosis.

Rarer causes of PUO, like hyperthyroidism, accounted for 2% of all cases. Among those fevers in which no cause could be found, 8.6% were self-limited and truly undiagnosed cases were seen in only 1.6% of the cases. Other rare causes included Non-infectious inflammatory diseases (NIID), Malignant lymphoma, solid organ tumours, Lepra reaction, Spondyloarthropathy, Inflammatory bowel disease and Sarcoidosis.
Infections were the most common cause of FUO across all age groups. In patients < 50 years, NIIDs were second most common (occurring in the third decade, between 20 to 29 years of age) but in patients > 50 years neoplasms were second (occurring in the 5th decade, between 40 -60 years). Infections were uncommon in the very young (< 20 years) (Table 1).

Invasive procedures were needed to make a diagnosis in 69% of the cases and image guided biopsies had the highest diagnostic yield 100% followed by lymph node and bone marrow biopsies with cultures at 63% and 19%. Non-invasive tests including CT scans, revealed a diagnosis in 72.4%. Diagnosis was made based on clinical picture alone in 3% of the cases.

We noted every symptom, sign or abnormal laboratory test that contributed to a specific diagnostic category and the final diagnosis. The variables which were seen in maximum proportion in a particular diagnostic category i.e., infections, neoplasms and NIIDs were then subjected to univariate analysis and the significant variables were noted. Potential diagnostic clues (PDCs) both clinical and laboratory in each specific diagnostic category (Table 4) were used to construct an algorithm for evaluation of classic FUO (Figure 1).

The mortality in this FUO series was 5% (n=15) and the commonest diagnosis among patients who expired was lymphoma or disseminated tuberculosis. Two patients died without a diagnosis ever being made.

**Discussion**

This is the largest prospective observational cohort study of classic FUO from South India. Most studies from developing countries show that infections are the most common cause of FUO, and they accounted for 48% of cases in our series. Classic FUO in India is often also due to delayed diagnosis of acute febrile illnesses with lack of confirmation either through culture or molecular techniques and further compounded by lack of specificity of serology in an endemic setting. The previous studies elucidating the causes of classic FUO have used inconsistent and different definitions of disease processes thus questioning their validity and reliability. In addition there can be varying causes of FUO depending on the geographical location and prevalence of local diseases and hence causes of fever are often different in East, West, North and South India. We used very strict definitions of disease in our study validated in a previous published FUO study. Infections as the major category...
of FUO has predominated over the decades and this has remained consistent. In our study, Tuberculosis comprised 1/3 (29%) of all cases and 2/3 (61%) of the infections similar to previous Indian studies. In the latest case series described from Kolkata, 28% of the patients had tuberculosis with 72% having extrapulmonary tuberculosis. In the series by Kejarival et al., tuberculosis was again the commonest diagnosis but pulmonary tuberculosis was not seen presenting as FUO unlike our series, where pulmonary tuberculosis was seen in 14% of the cases. In our studies, diagnosis was most often established from specimens other than sputum AFB smear or culture e.g., bronchoalveolar lavage, pleural fluid or molecular techniques.

Melioidosis was the second most common infection contributing to a classic FUO and this has not been described before as an important cause in previous studies. We feel that this is because though abscesses have been described in previous studies as a common cause of FUO in previous studies, the etiological agent of Melioidosis i.e., Burkholderia Pseudomallei was probably not identified in these patients. Limited experience, lack of validated diagnostic strategies and dependence on automated blood systems often leads to misdiagnosis of this organism. The Microbiology laboratory in our hospital has a standard protocol for identification based on typical morphology (closed safety pin appearance), appearance of culture plate (metallic sheen), oxidase negativity, testing with polyclonal antiserum (in house preparation of antiserum in rabbits) and resistance to Gentamicin and Polymyxin B on antimicrobial susceptibility. This organism is often dismissed as a contaminant as it is a non fermenting gram negative bacillus and on isolation from specimens from non sterile sites it may be overgrown by commensal organisms. There has been a decrease in prevalence of endocarditis as a cause of FUO, probable to due to earlier recognition of the same due to better culture techniques and availability of Transoesophageal Echocardiography (TOE).

Among the neoplastic causes of FUO apart from haematological causes of malignancies, solid organ cancers also caused FUO. This is unlike what has been described from other case series. In fact, in the series by Bandyopadhyay et al., solid organ cancers did not present as FUO.

Infections were the commonest cause across all age groups. There seemed to be a clear distinction between <50 years and >50 years for the second most common cause. NIID were common in the <50 years age group vs. neoplasms in >50 years age group. This seems to be different compared to what is seen in Western Literature where NIIDs were the commonest cause of FUO as compared to infections and neoplasms. The number of undiagnosed cases in our series is in one of the lowest in published literature and we attribute this to the fact that we are a tertiary care centre with all the facilities available on site and inclusion of only established and health care documented cases strictly documenting temperatures rather than just based on patient history, thus fulfilling the criteria of classic FUO. This low percentage of undiagnosed cases (1.6%) is in sharp contrast to all other case series so far, which have described undiagnosed cases between 7 to 51%. Every attempt was made to obtain unequivocal confirmation of diagnosis by invasive or non-invasive means for e.g., diagnosis of an infection was based only on cultures in the background of a compatible clinical picture; diagnosis of a neoplasm was based on confirmatory histopathological and/or immuno-histochemical evidence. A diagnosis based on clinical judgement without conclusive microbiological or histopathological evidence was made in only 3.7% of the cases and empirical therapy was instituted in these patients with close follow up to ensure that the initial diagnosis was correct. Only patients who had complete clinical and radiological resolution to empirical therapy consistent with the original clinical diagnosis were deemed to have that disease process. This was mostly limited to occult tuberculosis and undifferentiated collagen vascular disease.

On evaluation of various diagnostic tests, the following were found to have a diagnostic yield of >50% - diagnostic splenectomy (100%); CT thorax and Abdomen (83%), lymph node biopsy (70%), Ultrasound abdomen and PET scan (67% each) (Table 3). We found that imaging with guided biopsies were the mainstay of diagnosis. Our study suggested lymph node biopsies should be done early if lymphadenopathy is detected, with repeated screening for the same as these have a high diagnostic yield. Bone marrow biopsies though often done were found to have a fairly low diagnostic yield of 19%, similar to other series of FUO up to 25% suggesting that they should only be a third rung of investigations. We found rare causes of PUO in our case series, likely due to the large sample size and diagnostic abilities.

Limitations include a possible referral bias; patients referred to us were usually evaluated elsewhere and referred after non-response to a therapeutic trial, leading us to suspect an alternate diagnosis. We were unable to conclusively establish a causal spectrum of FUO from South India alone, as our centre sees a large number of cases from Eastern India.

In conclusion, infections are most important cause of classical FUO with extrapulmonary tuberculosis being the most frequent, in India. Melioidosis is an emergent cause of FUO seen often in diabetics. Lymphoma is the commonest neoplasm FUO and SLE was the most common non-infectious inflammatory disease causing FUO. Invasive tests especially lymph node biopsy have a high diagnostic yield in FUO and hence patients should be referred to centres where these can be done in case of diagnostic dilemmas. The number of cases in our series who remained undiagnosed was extremely small as compared to previous studies, probably due to a strict documentation of fever in hospital, an aggressive diagnostic approach to FUOs and avoidance of empirical therapy as much as possible.

Acknowledgements

We gratefully acknowledge, the Departments of Medicine, Infectious Diseases, Biostatistics and our patients who have helped us with this study.
A Study of Relation of CPK-MB Levels with ECG Parameters in Organophosphorous Poisoning Cases

Rishab Sharma1, Ravindra K Tiwari2, Muralidhar3, Sanjiv Maheshwari4, Rajesh Jain4, Archana Gokhroo4

Abstract
Organophosphorous compounds are one of the most commonly used compounds used for suicidal intentions in the developing world. CPK-MB levels are frequently raised among the OPC poisoning patients and ECG changes are also frequently observed among the OPC poisoning patients. Here we have studied association between CPK-MB levels and ECG changes to predict prognosis in OPC poisoning patients presenting in the emergency department.

Methodology: A prospective cross-sectional study was conducted among 60 patients with a history of exposure to OPC poisoning admitted in casualty department of tertiary care hospital. Age, sex, occupation, intention of ingestion, compounds involved, route of ingestion, occupation, ECG manifestations and CPK-MB levels at time of admission were recorded.

Patients with organophosphorous compounds mixed with any other poison or patients who were chronic smokers or suffering from chronic heart diseases, myopathy or had history suggestive intake of drugs like statins, fibrates, dexamethasone were excluded from the study.

Results: Average CPK-MB levels were relatively high in OPC poisoning patients. CPK-MB levels in patients with abnormal ECG and normal ECG had significant difference. In patients with VT and VF, the CPK-MB levels were significantly high. The CPK-MB levels in dead patients were significantly high in comparison to discharged patients. In the present study within each ECG parameter there was significant difference in CPK-MB levels of dead and survived patients.

Conclusion: CPK-MB levels were frequently high among the OPC poisoning patients. On admission CPK-MB levels were significantly higher in patients with normal ECG as compared to abnormal ECG. Mortality was observed in patients with QTc prolongation, VT and VF. Within each ECG parameter significant difference was observed in CPK-MB levels among survived and expired patients.

irreversible cholinesterase inhibitors with potential human toxicity. OPC poisoning is an important preventable public health problem in developing countries. Though accidental poisoning can occur following exposure or inhalation, serious poisoning often follows suicidal ingestion. A high incidence of mortality has been reported in past, and is attributed to delay in diagnosis and improper treatment.

Organophosphate compounds are irreversible inhibitors of the enzyme acetyl cholinesterase, binding to the esteric site of the enzyme. They inhibit both cholinesterase and pseudo-cholinesterase activity. This inhibition causes accumulation of acetylcholine at synapses with resultant overstimulation of neurotransmission. The clinical features are due to excess acetylcholine at the muscarinic and nicotinic receptors which leads to initial stimulation and eventual exhaustion of cholinergic synapses. Respiratory paralysis and cardiac arrest are considered as the most common causes of death in these patients.

Since agriculture is the main occupation in Rajasthan, OPCs are widely and easily available

Introduction
Organophosphorus compounds are possibly the most widely-used insecticides worldwide. They are
in ordinary shops. They are often stored in an improper manner due to lack of awareness of their hazards. Organophosphorus insecticides can be involved in more than 75% of all cases of acute poisoning in hospital practice.\(^6\)

Cardiac complications that often accompany poisoning with these compounds may be serious and are often fatal. These complications are potentially preventable, if they are recognized early and treated adequately. Some specific ECG changes like: Prolonged QT interval/QTc, Extrasystoles, T inversion, ST elevation, ST depression, Conduction Block, Polymorphic ventricular tachycardia, Ventricular fibrillation have been frequently associated with acute OPC poisoning patients.\(^7\)

Raised CPK-MB levels have been associated with acute OPC poisoning patients mainly due to skeletal muscle and respiratory muscle involvement. High levels of CPK-MB have been associated with mortality in acute OPC poisoning patients.\(^8\) The extent, frequency, and pathogenesis of the cardiac toxicity from these compounds have not been clearly defined. However, according to a recent report, the mortality rate has declined considerably following intensive management.\(^9\) The current body of knowledge largely consists of limited studies and case reports. Therefore, many physicians may not be fully aware of the cardiac complications of OPC poisoning.

This study aims at studying the relation between ECG parameters and CPK MB levels in acute OPC poisoning patients which will help in predicting mortality and managing the cardiac complications in the patients.

**Material and Methods**

The Prospective hospital-based cross-sectional study was conducted for a period of one and half year from March 2013 to December 2014. 60 patients with a history of exposure to OPC poisoning and who hadn’t received treatment, admitted in casualty department were used as the study subjects. Relatives of patient were asked to produce the suspected compound. Qualifying patients had undergone detailed history, clinical examination, biochemical examinations. CPK-MB levels and ECG was recorded at the time of admission in casualty.

Patients with OPC poisoning and mixed with any other poison or patients who were chronic smokers or suffering from chronic heart diseases, myopathy or had history suggestive intake of drugs like statins, fibrates, dexamethasone were excluded from the study.

The age, sex, occupation, intention of ingestion, compounds involved, route of ingestion, occupation, ECG manifestations at time of admission, CPK MB levels at time of admission were recorded.

ECG was assessed for rate, rhythm, PR interval, P wave size, QRS width, QTc interval, QRS voltage, abnormal Q wave, ST segment, T wave, U wave. The Q-T interval was corrected (QTc) according to the formula of Bazett.

Ethical clearance was obtained by the institution’s ethical clearance board. Procedure required venepuncture which is minimally invasive procedure and is routinely performed in most of the outpatients. Venepuncture was done using strict aseptic precautions. Informed consent was taken before levelling the CPK-MB.

The quantitative data was expressed as mean ± standard deviation. For qualitative data chi-square test\(^10\) was applied. For quantitative data the unpaired student t-test was applied to find the significance of difference between two means.

The statistical software namely SPSS 11.0, Stata 8.0, Systat 11.0 and Medcalc 9.0.1 were used for analysis of data.

Microsoft word and Excel have been used to generate graphs, tables etc.

**Results**

In our study, we found that the maximum number of cases (38%) were from the 20-29 years age group. It was surprising to note that 18% patients were in <19 years age group (Figure 1).

In our study we found that 55% of patients were male and 45% were female. Phorate was the most common OPC compound, used by 30% of the patients. Followed by chlorpyriphos, monocrotophos, methylparathion, quinalphos, malathion, dichlorvos, dimethioate (Figure 2).

Most common intention of poisoning was suicidal (70%) followed by accidental (30%). No case of homicidal poisoning was recorded. In our study Oral route (78%) was observed as the most common route of poisoning followed by inhalational ± Dermal route (22%).

Prevalence of OPC poisoning was observed more in rural population, with 44 patients belonging to rural
areas and 16 from urban area. In the study, 33% (20) of the case seen were farmer by occupation. Followed by housewife (17), student (15), employee (6).

The CPK-MB levels in dead patients were significantly high in comparison to discharged patients (Table 1). P value was <0.05.

Average CPK-MB levels were relatively high in OPC poisoning patients and in patients with VT and VF, the CPK-MB levels were significantly high (Table 2). In the present study we observed that within each ECG parameter there was significant difference in CPK-MB levels of dead and survived patients (Table 3). We also compared the CPK-MB in patients with abnormal ECG and normal ECG (Table 4). Result was significant and P-value was observed <0.05.

### Discussion

Organophosphorus (OP) pesticide poisoning is a major clinical and public health problem across the world including much of rural Asia. It accounts for as much as 80% of pesticide-related hospital admissions. Hospitals in rural areas mainly handle the impact of this problem with a case fatality of 15–30%.

The possible mechanisms of cardiac toxicity are related to sympathetic and parasympathetic over-activity, hypoxemia, acidosis, electrolyte derangements and a direct toxic effect of the compounds on myocardium. On the other hand, the use of atropine as the antidote for OP poisoning itself may induce lethal arrhythmias. The lack of timely identification of the poisoning or its clinical toxidrome and failure to proper cardiac monitoring for potential life threatening complications may endanger the lives of the patients.

The CPK-MB levels in dead patients was observed <0.05. In the present study it was observed that oral route (78%) was the most common route of poisoning followed by inhalational route (22%). Inhalational route with or without dermal route was observed in accidental poisoning cases where the patient was exposed while spraying the poison in the fields. Similarly in other studies, oral route was the most common route followed by inhalational route.

In the present study 44 patients (73.33%) were from rural background as OPC compound is mostly used in rural areas. 16 patients (26.67%) were from urban background. Similarly in studies conducted by Shankar Laudari et al. and P Karki et al OPC poisoning incidence was higher among rural populations.

It was striking to note that 15 (25%) cases were students. Although most common cases according to occupation were farmers followed by housewife, students, employee. Similarly in other studies farmers were the most common occupational group as the poisoning is more prevalent in rural communities.

In the present study, the most common ECG abnormality on admission was QTc prolongation (18.3%) followed by ventricular fibrillation, ST depression, ventricular tachycardia, conduction block, extrasystoles. Although ST elevation and T inversion are reported abnormalities in certain studies but it was not observed in any patient in our study. Similarly in study conducted by Shankar Laudari et al. and P Karki et al in several other series the frequency of QTc prolongation was shown to be 20 to 80% depending on the severity of the poisoning and the type of the toxic agent. With respect to ECG parameters, no significant difference in distribution was observed between male and female patients.

The most commonly involved organophosphorus compound in our study was parathion, which was implicated in 18 (30%) patients. Other compounds used were chlorpyrifos (23%), monocrotophos (15%), methyl parathion (11%), quinalphos (7%), malathion (7%), dichlorovos (5%) and dimethiato (2%).

The cause of poisoning was suicidal intentions in 42 (70%) patients. In 18 (30%) patients it was accidental in nature. No case with homicidal intent was registered. Similarly, in other studies the most common intention of poisoning was suicidal followed by accidental.
ventricular tachycardia and ventricular fibrillation survived despite aggressive resuscitative measures.

In the present study it was observed that the abnormal ECG parameters were associated with significantly high CPK-MB levels, which were mainly due to skeletal muscle and respiratory muscle involvement. With normal ECG the levels of CPK-MB were observed as 29.25±47.44 ng/dl. Prolonged QTc interval was the most commonly observed ECG abnormality and the levels of CPK-MB observed were 33.72±44.83 ng/dl.

In study conducted by Shou-Hsuan Liu et al, the CPK-MB levels with normal ECG were 11.37±6.75 ng/dl and with prolonged QTc interval the CPK-MB levels were 28.89±60.65 ng/dl.

**Conclusion**

This study was done to predict increased mortality rate in OPC poisoning patients based on specific ECG parameter and CPK MB levels.

In our study mortality was observed only in patients whose on admission ECG had QTc prolongation, VT and VF. We observed that the CPK-MB levels recorded were frequently high among the OPC poisoning patients. There was significant difference among on admission CPK-MB levels in expired patients and survived patients. On admission CPK-MB levels were significantly higher in patients with normal ECG as compared to abnormal ECG. Within each ECG parameter significant difference was observed in CPK-MB levels among survived and expired patient.

**References**

Serum Zinc Level in Decompensated Liver Disease and its Correlation with Stage of Hepatic Encephalopathy

Rajesh Kumar Meena¹, Sundarmurthy G², Pushpa Saravanan¹, Karthik P¹, Karthika Ramadoss¹, Vivekanandan A¹

Abstract

Background and Study Aims: This cross-sectional study was done to assess the serum Zinc levels in decompensate chronic liver disease (DCLD) patients with various stage of hepatic encephalopathy (HE) and determine the role of Zinc deficiency in precipitation of hepatic encephalopathy.

Patients and Methods: This prospective cross-sectional study was conducted at Rajiv Gandhi Government General Hospital and Madras Medical College Chennai. We enrolled 75 adult diagnosed cases of DCLD. All cases were further evaluated for serum Zinc levels and all divided according to class of liver cirrhosis and stage of hepatic encephalopathy. The data was analyzed with SPSS soft ware version 22.

Results: Ninety six percent patients of liver cirrhosis were male (72/75) while 4% were female (3/75), 30-50 year of age group (63%) was predominantly affected. All DCLD patients (75/75) with HE had low serum zinc level. There was statistically significant association between low serum zinc level and grade of HE (p-value 0.001) or class of liver cirrhosis (p-value 0.001). Our study also showed statistically significant association between low serum zinc level and hypoalbumenia (p-value 0.029).

Conclusion: All patients in DCLD particularly with hypoalbumenia and in hepatic encephalopathy should be evaluated for hypozincemia. As our study has concluded, hypozincemia in associated with cirrhosis and higher incidence of encephalopathy. Further study is indicated to establish role of correcting hypozincemia to prevent worsening of cirrhosis and development of encephalopathy.

Introduction

Chronic disease like liver cirrhosis and its complications are a major health problem particularly in developing countries like India, where large population are living with poverty, poor hygienic environment. Burden of cirrhotic patients is ever increasing and most of the patients are admitted to hospital with complication of cirrhosis.

Cirrhosis is defined anatomically as a diffuse process with fibrosis and nodule formation. It is the end result of the fibro genesis that occurs with chronic liver injury.¹

Diffuse fibrosis cause distortion of architecture with regenerative nodule formation, which results in decreased liver cell mass and reduced blood flow to the liver.¹²

In India most common cause of cirrhosis is alcohol abuse and viral hepatitis. Reversible fibrosis with ongoing injury in course of time lead to decompensate condition, which is associated one or more complication like ascites, jaundice, Hepatic encephalopathy and upper gastrointestinal (UGI) bleed.

Hepatic encephalopathy (HE) is life threatening complication that can be occur in acute or chronic liver failure. About 30% patients of cirrhosis die due to hepatic coma.³ HE in patient with liver failure is associated with poor prognosis and higher mortality. In cirrhotic patient HE develops due to one or more precipitating factors or due to fulminate liver failure or it could be a result of prolonged portocaval shunting.

Hepatic encephalopathy is probably precipitated by gut derived neurotoxin such as ammonia. Other key factors are astrocytes dysfunction, disturbed neurotransmitter regulation and oxidative stress in astrocytes.

Zinc (Zn) is second most abundant trace element in the body. Zn is associated with more than 300 enzymatic functions.⁴ It is an important co-factor in urea cycle, has a great role in conversation of ammonia to urea. Zn is an important part of natural defence mechanism involving of reactive oxygen species, it also act as an antioxidant, anti apoptotic agent, and anti-inflammatory agent. So hypozincemia seems to accelerate the manifestations of cirrhosis of liver, considering which we have done this study to establish correlation between hypozincemia and hepatic encephalopathy. Aim of this study to assess the serum Zinc levels in decompensate chronic liver disease (DCLD) patients with various stage of hepatic encephalopathy (HE) and determine the role of Zinc deficiency in precipitation of hepatic encephalopathy.

Material and Methods

This prospective observational study was conducted during April 2014 to September 2014 in Institute of Internal Medicine at Madras Medical College, Chennai (India). After obtaining a fully informed written consent, the 75 patients were enrolled into...
A thorough physical examination was done for signs of liver failure like icterus, pallor, spider nevi, palmar erythema, and clubbing, ascetic and pitting oedema. Hepatic encephalopathy patients were clinically graded according to West Han's classification (WHC). All patients also classified by Modified Child's classification and severity of liver cirrhosis were assessed by Child–Pugh score. The informed consent was taken from every patient or from their attendant after detail explanation of procedure regarding the study, and all such manoeuvres was performed under medical ethics and through the cooperation of whole research team. They were subjected to appropriate laboratory investigations including complete blood count and liver function tests, renal function test, coagulation profile (PT/INR). All patients were then advised for fasting serum zinc level whereas the cirrhotic patients who were not vitally stable were admitted and then their serum zinc level was assessed by taking 2cc venous blood sample on coming morning. The normal range of serum zinc level is 11-19 mmol/ L and the value ≤11 mmol/L was considered as low (6). The serum zinc status was reviewed and labelled as “low” when the serum level was below the normal range (6). The data was analyzed by SPSS software version -22. P-value ≤0.05 was considered significant.

### Discussion

Hepatic encephalopathy is one of the most serious complications in DCLD. In industrialised countries most common aetiology in cirrhosis is viral hepatitis followed by alcohol. In our study most common aetiology was alcohol abuse (90% cases) followed by viral hepatitis. Like other previous studies in our study also Male population were predominantly affected. In our study 63% cases were middle age between 30 to 50 year age group. Majority of DCLD patients presenting with HE have clear precipitating factors. Most common factors were constipation, infection and UGI bleeding. UGI bleeding is most common factor according to Sheila Sherlock. Serum zinc level was significantly low in DCLD in our study. Kar K et al. and Marcus R et al. also had similar result. In our study all DCLD patients admitted with HE. More ever patients with higher grade of HE had low serum zinc level. Zinc is important co-factor for many enzymes. Zn has key role in physiological detoxification of ammonia via urea cycle in liver and as a co-factor in ornithine Transcarbamylase (OTC) so low zinc level associated with decreased OTC activity and higher

### Results

Ninety six percent patients of liver cirrhosis were male (72/75) while 4% were female (3/75). In our study were common causes of cirrhosis is Alcohol (91%) followed by viral (8%), Wilson (1%) shown in (Table 1). 87% patients consumed alcohol for more than 10 year duration in Alcohol related DCLD. In our study most common presenting complaint was abdominal distension, pedal oedema. Other Common symptoms have been depicted in (Table 2). It was found that hepatic encephalopathy was more common in middle age group between 30-50 year age (63%). There was 5% mortality in hepatic encephalopathy during the course of treatment. In our study common precipitating factors of HE were constipation and upper gastrointestinal bleeding (Table 3). In our study maximum patients were in grade-I and grade-II HE (38% and 32%) as (Table 4). All DCLD patients had Zn deficiency and low serum zinc level was significantly associated with higher grade of HE. In our study there was statistically significantly association between low serum zinc level and grades of hepatic encephalopathy (p-value 0.001) (Table 5 Figure 1). This study showed low serum Zn level has statistically significant association with higher modified child-Pugh class (p-value 0.001) (Table 6 Figure 2). In our study we found there was statistically significant association between hypoalbuminemia and low level of serum Zn (p-value 0.029) (Table 7 Figure 3).

### Aetiology of cirrhosis

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>68</td>
<td>90.7</td>
</tr>
<tr>
<td>HBV</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Alcohol and HBV</td>
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<td>4</td>
</tr>
<tr>
<td>Wilson</td>
<td>1</td>
<td>1.3</td>
</tr>
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</table>

### Common presenting complaints in DCLD patients with HE

<table>
<thead>
<tr>
<th>Presenting feature</th>
<th>Patients</th>
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</thead>
<tbody>
<tr>
<td>Fever</td>
<td>28</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>42</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7</td>
</tr>
<tr>
<td>Constipation</td>
<td>41</td>
</tr>
<tr>
<td>Ascites</td>
<td>61</td>
</tr>
<tr>
<td>Bleeding</td>
<td>34</td>
</tr>
<tr>
<td>Pedal oedema</td>
<td>49</td>
</tr>
<tr>
<td>Disorientation</td>
<td>41</td>
</tr>
<tr>
<td>Confusion</td>
<td>14</td>
</tr>
<tr>
<td>Coma</td>
<td>4</td>
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### Precipitating factors in hepatic encephalopathy

<table>
<thead>
<tr>
<th>Precipitating factor</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
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<tr>
<td>UGI Bleeding</td>
<td>34</td>
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<tr>
<td>Constipation</td>
<td>41</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7</td>
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<tr>
<td>Hyponatremia</td>
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<td>Hypokalemia</td>
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<tr>
<td>Hyperkalemia</td>
<td>9</td>
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<tr>
<td>Diuretics</td>
<td>21</td>
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### Patient according WHC grading

<table>
<thead>
<tr>
<th>HE grade</th>
<th>Frequency</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHE</td>
<td>10</td>
<td>13.3</td>
</tr>
<tr>
<td>Grade I</td>
<td>26</td>
<td>34.7</td>
</tr>
<tr>
<td>Grade II</td>
<td>24</td>
<td>32.0</td>
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<tr>
<td>Grade III</td>
<td>11</td>
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</tr>
<tr>
<td>Grade IV</td>
<td>4</td>
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### Serum zinc level in various WHC grade

<table>
<thead>
<tr>
<th>HE Grade</th>
<th>Patients</th>
<th>Serum Zinc Level (mcg/dl)</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>60-69</td>
<td>50-59</td>
</tr>
<tr>
<td>MHE</td>
<td>Count</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Grade I</td>
<td>Count</td>
<td>1 (3.8)</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>Grade II</td>
<td>Count</td>
<td>0</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Grade III</td>
<td>Count</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Count</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>8 (10.7)</td>
<td>12 (16)</td>
</tr>
</tbody>
</table>
plasma concentration of ammonia. Low plasma zinc impairs nitrogen cycle in muscle and increase glutamine in blood. As result in advanced grade in HE significantly more drop in plasma Zinc. Short term oral Zinc supplement is very useful as an adjunct treatment in DCLD patient with hepatic encephalopathy.14 Study done in Egypt by Mohsen Maher et al.15 had similar results. In our study serum Zinc level was significantly low in higher class of cirrhosis and the correlation was statistically significant, similar conclusion was made by Soomro AA, et al. In DCLD patients other factors like malnutrition, poor oral intake and diuretic use is also related to low Zn level.

Serum Zinc is bound loosely with albumin in plasma and availability of serum albumin decides the amount of zinc transported in blood similar results seen Kar K et al16 study also. In our study low serum albumin level was associated more lower serum Zn level. Hence this study also indicates that low serum Zn level may be contributed by significant hypoalbuminemia. As conclusion we found that all patients in DCLD particularly with hypoalbuminemia and in hepatic encephalopathy (HE) should be evaluated for hypozincemia. As our study has concluded, hypozincemia in associated with cirrhosis and higher incidence of encephalopathy. Further study is indicated to establish role of correcting hypozincemia to prevent worsening of cirrhosis and development of encephalopathy.

Table 6: Comparison of serum zinc level with child pugh class

<table>
<thead>
<tr>
<th>CP Class</th>
<th>Patients</th>
<th>Serum Zinc Level (mcg/dl)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>60-69</td>
<td>50-59</td>
</tr>
<tr>
<td>Class A</td>
<td>Count</td>
<td>6 (66.7)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Class B</td>
<td>Count</td>
<td>2 (8.3)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Class C</td>
<td>Count</td>
<td>0</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>8 (10.7)</td>
<td>12 (16)</td>
</tr>
</tbody>
</table>

Table 7: Comparison between serum Zn level and serum albumin level

<table>
<thead>
<tr>
<th>Serum albumin (gm/l)</th>
<th>Patients</th>
<th>Serum zinc level (mg/dl)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>60-69</td>
<td>50-59</td>
</tr>
<tr>
<td>3.5–5</td>
<td>Count</td>
<td>4 (40)</td>
<td>2 (20)</td>
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<td>Count</td>
<td>4 (7.4)</td>
<td>9 (16.7)</td>
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<tr>
<td>≤2.5</td>
<td>Count</td>
<td>0</td>
<td>1 (9.1)</td>
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<tr>
<td>Total</td>
<td>Count</td>
<td>8 (10.7)</td>
<td>12 (16)</td>
</tr>
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Fig. 1: Distribution of HE grade according serum Zn level. In our study statistically significantly association low zinc values and higher grades of hepatic encephalopathy (p-value 0.001)

Fig. 2: Comparison of serum Zn level and Child Pugh score. In our study low serum Zn level have statistically significant association with higher child-Pugh score (p-value 0.001)

Fig. 3: Comparison between serum zinc and serum albumin level. In our study patients with low serum albumin statistically association with low level of serum Zn (p-value 0.029)

References

2. Bruce R, Bacon Cirrhosis and its complication Harrison’s principles of internal Medicine 18th edition page 2592-2605
4. Adrienne cheung and Andrew cheung MD The Child-Pugh score: Prognosis in chronic liver disease and cirrhosis (classic series) July16 2013
Allergic Rhinitis often precedes Asthma

Effective treatment of Allergic Rhinitis may reduce Asthma progression

For effective treatment in Allergic Rhinitis and Allergic Rhinitis with Asthma

Ref:
1. Respir Rev. 2005 Dec;8:153
Co-relation of Cerebral Venous Sinus Thrombosis with Vitamin B12 and Homocysteine Levels in a Tertiary Care Centre

Manasi Harale1*, Anand Alurkar2, Anita Basavaraj2, DB Kadam3, A Chandanwale5

Abstract

Background: The syndrome of intracranial venous and sinus thrombosis is a distinctive cause of cerebrovascular disease in the young. The important prothrombotic states which predispose to the development of Cerebral Venous Sinus Thrombosis (CVST) include hyperhomocysteinemias. Homocysteine metabolism requires vitamin B12 as a cofactor. This study is in order to study the clinical profile of patients with CVST and to evaluate the presence of homocysteinemia and its co-relation with B12 levels.

Materials and Methods: 50 patients of CVST diagnosed by imaging of brain above 18 years and their 50 age matched controls were included in study. In all the patients, homocysteine levels and vitamin B12 levels were done.

Results: Of the 50 patients, 35 were found to have elevated homocysteine levels, resulting in an incidence of 70%. Relationship between homocysteine level of Control group and that of Patient group with P value < 0.05 makes significant difference. Thus, homocysteine levels of patient group are higher than that of control group. Hyperhomocysteinemia is seen in majority of males of 30-40 year groups and majority of females 50-60 year group. Almost same number of patients have vitamin B12 value <200 (46%) and ≥200 (54%). As P = 0.05, there is significant difference between B12 levels of control group and patient group. Thus, B12 levels of patient group are lower than that of control group. While comparing, B12 and homocysteine values, it is found that as p < 0.05; so, there is significant difference between homocysteine and B12. Thus, if B12 value is low, homocysteine value tends to be high. However, when homocysteine is high, B12 need not be low.

Conclusions: B12 levels in CVST patients are lower. If B12 levels are low, homocysteine levels are high. Hyperhomocysteinemia may not be always associated with low B12 level. Hyperhomocysteinemia is associated with CVST.

Introduction

The syndrome of intracranial venous and sinus thrombosis termed as cerebral venous sinus thrombosis (CVST) is a distinctive cause of cerebrovascular disease in the young. Magnetic resonance imaging and magnetic resonance angiography are the best diagnostic methods for diagnosis of CVST and heparin is the first-line treatment.

It is one of the commonest causes of stroke in India. CVST usually occurs in the setting of pregnancy and puerperium. CVST in the nonpuerperal setting is less common. The pathological hallmark of CVST is hemorrhagic infarction. CVST is primarily a disease of the young and can present in protean ways with a wide spectrum of clinical manifestations. These include headache, altered sensorium, seizures, focal neurological deficits, papilloedema and cranial nerve palsies. Headache is the most frequent and often the earliest manifestation.1

The diagnosis of cerebral venous sinus thrombosis requires high index of suspicion. CT brain may show direct or indirect signs of cerebral venous thrombosis. It may be normal in 10% of patients. In such cases advanced neurological diagnostic like Magnetic Resonance Imaging with venography is necessary to confirm cerebral venous thrombosis. It has been found that early diagnosis of cerebral venous thrombosis is essential because early treatment may prevent morbidity and may even be life saving.

The important prothrombotic states which predispose to the development of CVT include Factor V Leiden mutation, antiphospholipid antibody syndrome, Protein C deficiency, Protein S deficiency, antithrombin III deficiency, fibrinogen deficiency, polycythemia rubra vera, paroxysmal nocturnal hemoglobinuria, sickle cell disease, haemytic anaemia, thrombocytthemias and hyperhomocysteinimias. Recently, Factor VIII elevation has also been identified as a thrombophilic factor which can cause CVST. Among the thrombophilic states, Factor V Leiden mutation has been identified as the commonest hereditary prothrombotic state while APLA syndrome is the commonest acquired prothrombotic state.

Persons homozygous for homocysteinuria are at high risk for premature arteriosclerotic vascular disease and venous thrombosis, as homocysteine is toxic to vascular endothelium, can potentiate the oxidation of low density lipoprotein cholesterol and promote thrombosis2

Homocysteine (Hcy) is a sulphhydryl amino acid compound that is generated from protein breakdown and the essential amino acid methionine as it is metabolized to cysteine. Hcy can be metabolized by two major pathways (Figure 1). When methionine is in excess, Hcy is directed to the transulphuration

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pathway, where it is irreversibly sulfonconjegated to cysteine by cystathionine B-synthase with vitamin B₆ as a cofactor. Hcy is also remethylated in a methionine-conserving pathway. This process requires methionine synthase, vitamin B₁₂ as a cofactor, and methyltetrahydrofolate as a cosubstrate. The methionine-conserving pathway requires folic acid and methyltetrahydrofolate reductase (MTHFR). There is a strong inverse correlation of plasma Hcy with plasma folate concentration. In contrast to folate, serum vitamin B₁₂ or vitamin B₆ levels show only a weak correlation with plasma Hcy. Deficiencies in any of these above enzymes, folic acid, or the cofactors may lead to some degree of hyperhomocysteinemia.

This study is in order to study the clinical profile of patients with CVST and to evaluate the presence of homocysteinaemia and its co relation with B12 levels.

**Methods**

This study includes 50 patients of CVST admitted/outpatient department in Sassoon General Hospital, Pune and KEM hospital, Pune.

The data was managed in Microsoft excel spreadsheet. This graphical representation is done with the help of Main effect plot, Interval Plot, and individual value plot. Correlations among different measurements were assessed using Pearson’s correlation coefficients. A p value <0.05 was considered statistically significant. Demographics and General information like count, average and percentage for various parameters with all permutations and combinations were calculated in Microsoft excel. One way analysis of variance (ANOVA) is used to investigate relationship of control group with observed patients. All specific graphs like interval plot, individual value plot and box plot are drawn and all statistical analysis was done using Minitab16.

**Results**

The mean age of presentation was 35.4 years and median was 35 years. The maximum incidence of CVT was in age group 31 to 40 years. The youngest subject included in the study was 18 years old and oldest subject was 64 years old. The study population comprised of 23 women (46%) and 27 men (54%). The sex ratio (M: F) was 1:0.85. In our study, there was an almost equal gender distribution. The maximum clustering of cases is in the age group 31-40 years for either gender. The mean age of presentation for men is 37.85 years while for women, it is 33.93 years.

Those who presented within 48 hours were considered to have acute onset, with onset longer than 48 hours but less than 1 month were considered sub acute, and with onset more than 1 month as chronic (Bousser et al., 1985). In the present study, 27 cases (54%) of CVST had sub acute presentation, followed by 19 cases (38%) with acute presentation. The commonest clinical presentation was headache (88%) followed in decreasing order of frequency by altered sensorium (56%), seizures (56%), and papilledema (54%). Motor neurological deficits occurred in 30% patients while cranial nerve palsies were observed in 10% of cases. Visual disturbances were observed in 20% of our study cohort. In the present study, 22 cases were conscious contributing 44% of the cases and 16
Fig. 2: ANOVA method- control group clusters at a value of homocysteine below 16 while that of the patient group has majority of the patients with value above 16

Table 1: As p < 0.05, there is significant difference between HCy and B12 at 95 % confidence level

<table>
<thead>
<tr>
<th>Homocysteine less than or equal to 16ul/L</th>
<th>Homocysteine level &gt;16 ul/L</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>vit. B12 &lt;200</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>vit. B12 equal to or more than 200</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>

cases were drowsy i.e. 32% incidence. Total number of patients with altered sensorium was 28 (56%).

Majority of the patients (86%) had involvement of more than 1 cortical venous sinus.

The commonest sinus involved was transverse sinus (76%) followed by superior sagittal sinus (60%). Cortical veins were involved in 60% of our study population.

The mean haemoglobin was 9.9 gram% with a standard deviation of 2.5, median was 9.5 gram %. The lowest haemoglobin was 4.8 with the highest being 16. In majority of patients ESR was in the range of 1-10, Mean ESR was 14.6. The median was 10.minimun was 8 and maximum was 42. 84% of study patients had PT< 15 while 8 patients had PT between 16-18. Thus, majority of our study patients had baseline PT within normal range. 15 patients were subjected to CSF analysis whenever there was suspicion of meningitis of which 12 were normal and abnormality seen in rest 3 patients with pleocytosis being the maximum.

Of the 50 patients, 35 patients were found to have elevated homocysteine levels. The homocysteine values ranged between 11.2 to 65. The mean was 25.69. The median was 23.615.

To find relationship between Hcy and homocysteine values, it is found that as p < 0.05, there is significant difference between HCY at 95% confidence level. Thus, homocysteine levels of patient group are higher than that of control group.

In the present study, to find relationship between homocysteine level of Control group and homocysteine level of Patient group, one way ANOVA method was used. P value < 0.05 makes significant difference in HCY at 95% confidence level. Thus, homocysteine levels of patient group are higher than that of control group.

Vitamin B12

Almost same number of patients have vitamin B12 value <200 and ≥200. 23 patients (46%) have low vitamin B12 level and 27 patients (54%) have normal vitamin B12 level. As P > 0.05, there is no significant difference between vitamin B12 levels of control group and patient group. These findings are in concordance with findings of Misra et al. While comparing, vitamin B12 and homocysteine values, it is found that as p < 0.05, there is significant difference between HCy and B12 at 95 % Confidence level. Thus, if vitamin B12 value is low, homocysteine value tends to be high. However, when homocysteine is high, vitamin B12 need not be low.

To conclude, there is no correlation between vitamin B12 levels in CVST patients. If vitamin B12 levels are low, homocysteine levels tend to be high Hyperhomocysteinemia may not be always associated with low vitamin B12 level. Hyperhomocysteinemia is associated with CVT.
Impact of Nocturnal Continuous Positive Airway Pressure on Clinical and Spirometric Lung Functions in Obstructive Sleep Apnoea

Mahendra Nilkanth Borse1*, Jairaj P Nair2, NT Awad3, Sameer Vaidya1, Karthikeyan G1

Abstract
Introduction: Nocturnal CPAP therapy is advised as standard treatment for OSA patients. However, in literature there exists a mixed opinion regarding its effectiveness. So to study its effectiveness objectively in Indian population, study was undertaken.

Aims and Objective: To assess compliance to nocturnal CPAP treatment; to assess changes in lung functions in terms of FEV1, and to assess symptomatic changes in term of STOP BANG score, after 1 year of nocturnal CPAP use.

Study Design: Retrospective and Prospective, Observational

Materials and Methods: A prospective study was carried out in Dept. of pulmonary medicine of Lokamanya Tilak municipal medical college and hospital, Mumbai. 25 patients of OSA (13 Patients of OSA and 12 patients of overlap syndrome) who were previously diagnosed on level 2 polysomnography were included .Their baseline characteristics including symptoms of OSA were obtained from patients record and interview. Lung functions before the start of CPAP therapy were obtained from the records and were followed from January 2015 to November 2016. Lung functions repeated at the end on the study period at the same centre and clinical improvement was assessed through interviewing individual patient and scaling symptoms in terms of STOP BANG score.

Results: Among them, 20 were males with mean age of 55.58 years (±10.5) and 5 were females with mean age of 55.26 years (±9.7). The mean AHI was 25.7 (±12.3). Among 25 patients, 19 were using regular overnight CPAP termed as compliant and 6 were not using CPAP termed as non-compliant. Repeated lung function at the end of 1 year showed statistically significant improvement (p value=0.012) in FVC among 15 compliant patients who were using overnight CPAP whereas only 1 non-compliant patient showed improvement in FVC. Similarly repeated FEV1 at the end of 1 year also showed statistically significant improvement (p value=0.006) among compliant patients of OSA and overlap syndrome. The mean improvement in FEV1, was 0.146(±0.23) among compliant patients whereas, there was mean decline of 0.246(±0.21) among patient non-compliant to CPAP treatment. All the compliant patients taking overnight CPAP showed improvement in STOP BANG score.

Conclusion: There was significant clinical and lung functions improvement in OSA and Overlap syndrome patients treated with CPAP over a period of 1 year. However present study has a limitation of sample size and short duration. Further study may be necessary in this context with larger sample size and for larger duration.

Introduction
Obstructive sleep apnoea (OSA) is mainly characterised by the narrowing or collapse of nasopharyngeal airway during sleep. It is defined as more than 5 respiratory disturbances (either hypopnoea or apnoea) of sleep combined with symptoms of daytime sleepiness. Since the study by sullivian et al2 concluded that continuous positive airway pressure (CPAP) is effective treatment of OSA syndrome, there has been constant debate on usefulness and effectiveness of CPAP in treatment of patients with OSA. The effectiveness of CPAP in OSA is mainly based on its effect as a pneumatic splint. Currently CPAP is widely accepted therapy for OSA and for patients with OSA and COPD (overlap syndrome). Study by O’Brien A1 and Whitman K showed greater decline in lung function among compliant overlap syndrome patient. Whereas, study by di Miguel J et al showed statistically significant improvement in lung function after 6 months of CPAP use in patients of overlap syndrome.

So, to study the effectiveness of nocturnal CPAP in patients of OSA and overlap syndrome among Indian

References
6. Harrison’s Textbook of internal Medicine 19e.
population the study was undertaken.

Type of Study
Retrospective and prospective; observational study.

Material and Methods

25 patients of obstructive sleep apnoea (13 patients of OSA and 12 patients of overlap syndrome) who were presented to department of pulmonary medicine of Lokmanya Tilak Municipal medical college and hospital, Sion, Mumbai were included in this study. The study was carried out from January 2015 to November 2016. Written and informed consent was taken from each patient and relative. The diagnosis of OSA was obtained from previous records and were based on level 2 polysomnography (emblerta®). The spirometric lung functions, performed in the same institute (By using Ultima™ pulmonary function with RTD) at the time of diagnosis were obtained from the records. According to titration study, CPAP machine and pressure were prescribed to the patients. Those who were using overnight CPAP were termed as compliant and non-users of CPAP were termed as non-compliant. Patients were interviewed regarding symptoms of OSA at the time of presentation in terms of STOP BANG score in terms of snoring; tiredness during daytime; observed apnoeas; blood pressure; BMI> 35 Kg/m2; Age > 50 yrs; Neck circumference >40 cm and gender. STOP BANG score was recorded prior to the beginning of treatment with CPAP. The diagnosis of overlap syndrome was made in patients with FEV1/FVC ratio less than 0.7 along with symptoms of obstructive sleep apnoea. Data were obtained in terms of smoking index; co-morbidities like diabetes mellitus; hypertension; thyroid status and alcohol consumption status.

Patients were prospectively followed for the period of 1 year from the starting of use of nocturnal CPAP and at the end of study period of 1 year patients were re-evaluated in terms of daily hours of CPAP use and STOP BANG score. Spirometric lung functions were repeated again in accordance with ATS/ERS guideline. Statistical analysis was done with IBM® SPSS® Statistics version 20 software.

Results

Total 25 patients were included in the study. Among them, 20 were males with mean age of 55.58 years (±10.5) and 5 were females with mean age of 55.26 years (±9.7). The mean AHI was 25.7(±12.3) and advised overnight CPAP therapy.

Among 25 patients, 13 were of obstructive sleep apnoea and 12 patients had an underlying COPD (Overlap syndrome). Baseline characteristics of study population are mentioned in table-1. Among 25 patients, 19 were using regular overnight CPAP termed as compliant and 6 were not using CPAP termed as non-compliant. Repeated lung function at the end of 1 year showed statistically significant improvement (p value=0.012) in FVC among 15 compliant patients who were using overnight CPAP whereas only 1 non-compliant patient showed improvement in FVC.

Among 19 compliant patients, 15 patients showed mean improvement of 0.257 (±0.14) Litre whereas, 4 patients showed mean decline of 0.187 (±0.27) Litre in FVC. Among 6 non-compliant patients, 1 patient showed improvement of 360 ml whereas 5 patients showed mean decline of 0.32 (±0.1) Litre.

Similarly change in FEV1 also showed statistically significant improvement (p value=0.006) among compliant patients of OSA and overlap syndrome. The mean change in FEV1 was 0.146 (±0.23) among compliant patients whereas, there was mean decline of 0.246 (±0.21) among patient non-compliant to CPAP treatment.

Though the association was not statistically significant, there was

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<th>Table 1: Baseline characteristics of population</th>
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<tr>
<td>Sex (No.)</td>
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<tr>
<td>Weight at the time of diagnosis (Kg)</td>
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<tr>
<td>BMI at the time of diagnosis (Kg/m²)</td>
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<td>Neck circumference (Centimetre)</td>
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</tr>
<tr>
<td>Compliant patients</td>
</tr>
<tr>
<td>No of patients</td>
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<tr>
<td>Mean FVC</td>
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<tr>
<td>Non-compliant patients</td>
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</tr>
<tr>
<td>Compliant patients</td>
</tr>
<tr>
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<td>Mean FEV1</td>
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<tr>
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<td>Improvement</td>
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<td>Obstructive sleep apnoea</td>
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<th>Table 5: STOP BANG Score among compliant and non-compliant patients</th>
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<tr>
<td>Patients</td>
</tr>
<tr>
<td>Compliant patients</td>
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<tr>
<td>Non-compliant patients</td>
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<td>Total</td>
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improvement of FVC among 9 patients of overlap syndrome whereas 3 patients showed decline in FVC at the end of 1 year of CPAP treatment. Among 13 patients of OSA, 7 patients showed improvement in FVC whereas 6 patients showed decline in FVC.

There is statistically significant improvement was seen in terms of FEV₁ among OSA patients (p value =0.035) showed improvement among 8 patients and decline among 5 patients.

All the compliant patients taking overnight CPAP showed mean improvement in STOP BANG score. The mean improvement in compliant OSA patient is by 3 and among compliant overlap syndrome patients by 5. All non-compliant patients reported worsening in terms of STOP BANG score.

**Discussion**

The present retrospective and prospective observational study on 12 patients of overlap syndrome and 13 patients of OSA showed statistically significant improvement among compliant patient over the period of 1 year. Overall among 19 compliant patients who were using daily nocturnal CPAP for the duration of at least 1 year showed improvement of 163 ml in FVC. In literature there exists a mixed opinion regarding the impact of nocturnal CPAP on lung function. In Mansfield and Naughton’s study on effect of CPAP on COPD with sleep disordered breathing patients the observed statistically significant improvement of 50 ml in FEV₁ among compliant patients. They also showed similar improvement of 140 ml in FVC. Whereas, in the study conducted by Sforza et al. showed decline of FEV₁ by 84 ml over the period of 1 year among OSA patients. In the present study the improvement of 163 ml in FVC and 146 ml in FEV₁ over the period of 1 year can be explained by the fact that 9 patients of 19 had underlying COPD (overlap syndrome) and were also compliant to their COPD treatment by means of bronchodilators so both CPAP as well as adequate optimisation of underlying COPD might had contributed to so much improvement in lung function moreover nocturnal CPAP also improves lung function by means of increasing lung volumes and decreasing the resistance in upper airway and intrathoracic airways.

The similar improvement was observed among compliant patients in terms of STOP BANG score. In present study all compliant patients showed improvement in score whereas, none of non-compliant showed improvement. The STOP BANG score improved by 5 among patients with overlap syndrome whereas, by 3 among OSA patients. This is in accordance with the literature mentioning CPAP eliminates snoring and apnoea experienced by the patient as well as also improves daytime somnolence by improving quality of nocturnal sleep.

**References**

Clinical Characteristics and Outcomes of Percutaneous Coronary Intervention in Patients with STEMI: A Single-Center Experience

Rishi Kumar Gupta1*, Simmi Manocha2, Subrat Akhoury3, Umesh Kohli4

Abstract

Objective: Percutaneous coronary intervention (PCI) is the best-known intervention for reperfusion in patients experiencing ST-elevation myocardial infarction (STEMI). Early intervention improves short- and long-term outcomes of PCI, while a delay may reduce the benefits. This retrospective study was conducted to assess the clinical profile and outcomes in patients presenting with STEMI and undergoing primary PCI at a cardiac care center in Haryana (India).

Methods: In this retrospective study, the demographic characteristics, disease presentation, procedural details, and outcomes of 310 consecutive patients with STEMI who underwent PCI between 2010 and 2015 at a cardiac care center in North India, were analyzed. All patients were treated with standard primary PCI protocol.

Results: The mean age of the patients was 57.2±12.6 years. The average duration of chest pain was 230.3±186.2 minutes. Risk factors included previous history of coronary artery disease (CAD; 9.7%), diabetes mellitus (25.5%), hypertension (24.8%), smoking (24.5%) and family history of CAD (4.8%). About half of the patients had anterior wall myocardial infarction (AWMI). The median door to ballooning (DTB) time was 47 minutes. Overall, 29 out of 310 patients developed complications. In total, eleven patients of 310 had died (3.5%).

Conclusion: Primary PCI is effective in the management of STEMI in the Indian scenario. Despite the delayed presentation of STEMI patients to a cardiac intervention center, recommended DTB can still be achieved, which is important for better intervention outcomes. The study also confirms the younger age of STEMI patients in India, compared with Western population.

Introduction

Coronary artery disease is one of the most common causes of death in the Indian population, with acute STEMI being its most dramatic manifestation, resulting in high morbidity and mortality. Primary PCI is the standard of care for patients with STEMI. With advancements in procedural techniques, medications, and early intervention, the short- and long-term clinical outcomes of PCI have significantly improved. However, in India multiple logistic problems limit the availability of primary PCI to the vast population. Nonetheless, the number of patients undergoing primary PCI is increasing owing to the growing economy. According to the American College of Cardiology and American Heart Association (ACC/AHA) 2013 guidelines, primary PCI is the preferred mode of reperfusion in patients with STEMI with symptom onset within 12 hours. It is also recommended in patients who have STEMI with cardiogenic shock or acute severe heart failure, irrespective of the time from onset of myocardial infarction (MI). Primary PCI offers the greatest survival benefits in high-risk patients. A delay in intervention has been shown to reduce the benefits. Evidence on early primary PCI is available from all over the world; however, there is limited data available in the Indian scenario.

This retrospective study was conducted to evaluate the primary PCI results in a suburban private multispecialty hospital in India.

Methodology

In this retrospective study, we screened our hospital database of consecutive STEMI patients who underwent primary PCI between March 2010 and July 2015. Patients with incomplete data and rescue percutaneous transluminal coronary angioplasty (PTCA) (n=42) were excluded from the study. The study cohort included a total of 310 patients with STEMI. The primary PCI procedure was performed using the standard protocol by three interventional cardiologists who lived within 5-6 km of the hospital. The services of the cardiologists were called once the patient arrived, the diagnosis was confirmed and a patient consent was obtained for primary PCI. By the time the cardiologist arrived, the patients were shifted to the cardiac care unit and prepared for primary PCI and the catheterization laboratory team was activated.

In our hospital, it is not mandatory to pay advance deposits, as this precondition will result in a significant delay in initiating the primary PCI. A consent to pay is sufficient to start the procedure. This facility helps to expedite the process.

Primary PCI was done for culprit artery; a soft wire was crossed across...
25.5% of the patients, while 24.8% had diabetes mellitus. A history of CAD was present in 9.7% of the patients. The average duration of chest pain was 230.3±186.2 minutes. A previous door to ballooning time was 57.2±12.6 years (median: 57 years; range: 23–90 years). Among these, 85.5% of the patients were male.

### Results

Demographics and Clinical Profile and Findings

In this study, the mean age of the patients was 57.2±12.6 years (median: 57 years; range: 23–90 years). Among these, 85.5% of the patients were male. The average duration of chest pain was 230.3±186.2 minutes. A previous history of CAD was present in 9.7% of the patients. Comorbidities, such as diabetes mellitus, were present in 25.5% of the patients, while 24.8% of the patients had hypertension. Approximately one-fourth (24.5%) of the patients were smokers. A family history of CAD was reported in 4.8% of the patients.

Clinical findings, including blood pressure, lipid profile, and cardiac enzymes, are summarized in Table 1. The left ventricular ejection fraction at admission was 41.52±8.72%.

#### Diagnosis

About half of the patients (50.31%) had single-vessel disease (SVD), while 29.36% of patients had double-vessel disease (DVD), and 19.99% of patients had triple-vessel disease (TVD). About half of the patients (49.35%) had AMI and 36.77% of the patients had inferior wall MI. Inferior posterior wall MI was noted in 13.87% of patients.

#### Procedural details

The median door to ballooning (DTB) time was 47 minutes (Figure 1). All patients underwent PTCA as follows. Three patients required only thrombectomy and angioplasty without stent implantation. The details of the procedure conducted are presented in Table 2. Two patients required staged CABG for severe disease after culprit vessel angioplasty. Staged PTCA for other nonculprit vessel was performed in 38 (12.9%) patients before discharge.

In the majority of the patients (94.5%), the route of access was the right femoral artery, while the radial artery was the route of access in 5.5% of the patients. Predilatation was performed in 49.51% of the patients. Thrombus aspiration was done in 68.28% of the patients. Post-dilatation was required in 57.61% of the patients. Overall, drug-eluting stents were used in 84.84% of the patients, while bare-metal stents were used in 16.77% of the patients. Glycoprotein IIb/IIIa inhibitors were used in 63.87% of them. The use of antiplatelet agents, statins, and antihypertensive drugs is shown in Table 2.

#### Procedural Outcomes/Complications

The majority of the patients (90.61%) did not develop any complication. Only 29 (9.4%) patients developed complications, the most common being hypotension/bradycardia (2.9%, n=9) and complete heart block (2.3%, n=7). Only two patients developed severe bleeding requiring blood transfusion. Twenty patients developed left ventricular failure, while 16 patients developed cardiogenic shock. One patient developed stent thrombosis, which was managed with thrombectomy and balloon angioplasty. Staged PTCA was required in 38 (12.9%) patients (Table 3). Nine (2.9%) patients had complete heart block requiring TPI, and 7 (2.3%) patients had ventricular tachycardia within 1 week of PCI. Of the 310 patients, 11 (3.5%) patients died: 8 patients had cardiogenic shock (2 patients were diabetic and had severe TVD and poor LV function and TIMI flow I or II post procedure), 2 patients (aged 79 and 82 years, respectively) had multivessel disease; 2 patients had cardiac rupture on 2nd and 3rd day of PCI to RCA; and one patient developed pancreatitis, pneumonitis, acute renal failure, and died due to multiorgan failure.

#### Discussion

In this retrospective study conducted at a single cardiac care center, data from 310 patients with STEMI who underwent primary PCI were analyzed. The mean patient age in this cohort was 57.22 years, which was comparable to that reported (52 years) in a study conducted by Subban et al. This is considerably younger than patients presenting with STEMI in Western
countries and similar to the STEMI subset of the CREATE registry.\(^2\) Age group distribution also showed higher percentage of younger patient’s, 17.2% less than 45 years and 59.7% between 45-65 years, almost 27% patients were aged less than 65 years of age. This indicates that the STEMI population undergoing primary PCI is younger in India than in Western countries and that males may require more intensive management of cardiovascular (CV) risk factors than females.

Diabetes, hypertension, and smoking were identified to be the major CV risk factors among STEMI patients undergoing primary PCI, in this study. The prevalence of these risk factors was comparatively lower than that reported in another Indian single-center study.\(^2\)

Majority of procedures (94.5%) were performed through femoral route, but lately radial route was also being used more frequently (5.5%). Default strategy of primary PCI was thrombectomy followed by stenting. Later, direct stenting without thrombectomy was also frequently used. Still predilatation was required in 49.5% cases. In primary PCI, postdilatation was reserved only for patients with less than acceptable result after stenting because of fear of slow flow/no reflow. Post dilatation was required in 57.6% of the patients.

In the present study, drug-eluting stents were used in the majority of the patients (84.84%), while bare-metal stents were used in 16.77% of the patients. A study reported that in patients with STEMI and cardiogenic shock, stents were used in about 90% of patients. More than 60% of used stents were bare-metal stents, while drug-eluting stents were used in about 40% of patients.\(^8\)

It has been noted that during primary PCI in STEMI, microvascular obstruction persists despite the restoration of epicardial flow, due to atheromatous and thrombotic embolization as well as vasospasm. Glycoprotein IIb/IIIa inhibitors were used in a significant proportion of patients (63.9%). As a standard strategy, all these patients received intracoronary bolus, prolonged infusion for 12-24 hours was used if there was slow flow/no reflow. In such cases, the local administration of pharmacotherapy offers several hundred-fold higher concentrations of drugs in the epicardial artery and microcirculation as compared with systemic administration. This may probably increase the dose-dependent antiplatelet and antithrombotic effects focusing on the culprit lesion. The intracoronary administration of glycoprotein IIb/IIIa inhibitors ensures rapid action, greater effectiveness, and higher safety.\(^7\) In this study, intracoronary glycoprotein IIb/IIIa inhibitors were used in 63.87% of the patients.

In this study, in-hospital mortality was 2.3% compared with 4.2% reported by Subban et al. More than 90% of the patients did not develop any complications. Hypotension/bradycardia and complete heart block were the most common complications.

The average duration of chest pain at the time of arrival was 230.34±186.21 minutes in this study. Early PCI has been associated with reduced complications of STEMI resulting from longer ischemic times or unsuccessful fibrinolytic therapy; it also allows earlier hospital discharge and resumption of daily activities. There is generally a delay in the onset of symptoms of STEMI and the patient reaching hospital for medical care, both of which may be attributed to symptoms other than chest pain, assumption that symptoms are self-limited and not serious, fear of embarrassment in case of false alarm, symptoms assumed to be related to other preexisting conditions, and lack of knowledge of need of rapid action.\(^5\)

A standard measure for assessing a hospital’s capability for managing STEMI with mechanical perfusion is DTB time.\(^7\) The importance of shorter DTB time in the management of STEMI has been well recognized. Both ACC and ESC have suggested a DTB time of 90 minutes or a PCI-related delay of 60 minutes as standard. Generally, it includes the time from arrival at the hospital to ECG, the decision of PCI, patient’s consent, STEMI team activation, financial process, and sheath to balloon time.\(^10\) In this study, the median DTB was 47 minutes. In the Indian scenario, a delay on the part of the patient in giving consent and a delay in financial processes contribute significantly to delay in DTB.\(^11\)

The major logistic problems that hinder the timely availability of primary PCI to patients in India include: mode of transportation to the cardiac care centre, availability of interventional cardiologists, financial constraints. In India, most of the patients reach the hospital through their own means of transport, and this delay can have a significant impact on treatment outcomes. The availability of ambulance services to all patients needs to be tackled appropriately. The second logistic problem is the availability of interventional cardiologists. Majority of the hospitals in India do not have on-site interventional cardiologists. However, in our centre, the services of interventional cardiologists are called for as soon as the patient arrives, the diagnosis is confirmed and a patient consent is obtained for primary PCI. The third logistic problem is the financial constraint. Majority of the patients in India are self-paying and are not covered under medical insurance by the government. Finances are important factors that determine the treatment outcomes of acute myocardial infarction. However, in our center, payment of advance deposits is not mandatory; a consent to pay is sufficient to begin the procedure. Taken together, the immediate availability of an interventional cardiologist and a facility to begin the procedure without paying advance deposits may have largely contributed to the improved treatment outcomes in our study.

Limitations

The main limitations of this study are the relatively smaller sample size and lack of follow-up. Further, these observations are reported from a single center and may not be generalized. However, this study highlights the benefits of early primary PCI in patients with STEMI.

Conclusion

This study has shown that primary PCI is effective in the management of STEMI in the Indian scenario. Despite logistic problems contributing to late presentation of patients with STEMI in India, it was possible to achieve recommended door to balloon time in our study, since we had an on-site interventional cardiologist available immediately and our center does not mandatorily require payment of advance deposits to begin the procedure. Thus, primary PTCA protocol could be activated in the casualty itself. The study also confirms the younger age of STEMI patients in India, compared with
Western population. The risk profile of very young STEMI patients in India is similar to that reported in the Western populations.

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Microbial Pattern in Acute Exacerbation of COPD and its Relevance to COPD Severity

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Abstract

Background: COPD is a major cause of morbidity and mortality throughout the world. Many people suffer from this disease for years, and die prematurely from it or its complications. Exacerbations and hospitalizations in particular constitute the most important direct health related costs associated with COPD. Infections, both viral and bacterial cause exacerbations. During exacerbations there is either increase in bacterial load or acquisition of new strains. The present study was planned to analyze the microbial pattern among COPD patients during exacerbations and their relation to COPD severity.

Objectives

1. To determine the sputum microbial pattern in patients with acute exacerbation of COPD.
2. To compare the grouping of COPD patients by Combined COPD risk assessment method using CAT score and mMRC, severity grades vs Past year exacerbations each separately.

Methods: This is a cross sectional study done at Department of Pulmonary Medicine, Government Medical College, Trivandrum from November 2015- November 2016 among patients admitted with acute exacerbation of COPD. 89 patients were included in this study. Sputum was sent for culture and sensitivity. History of past year exacerbations and spirometry values were noted and COPD was grouped using Combined COPD assessment method using mMRC, CAT score, severity grades and past year exacerbations separately. Data was analysed using SPSS v16.

Results: Of the 89 subjects, microbial isolates were seen in 34.7% cases. Pseudomonas aeruginosa was the predominant isolate in 10.1% of the cases. Tuberculosis was diagnosed in 6.7% cases who presented with acute exacerbation. Using CAT score, 92.6% were categorised into risk groups B and D with a high impact of symptoms than using mMRC(74.7%). Based on severity grades, 72% patients had a high exacerbation risk compared to the use of past-year exacerbations (30.4%).

Conclusions: Pseudomonas aeruginosa was predominantly isolated from COPD exacerbation patients. Classifying COPD patients into risk groups A-D, using either CAT/ mMRC and severity grades, past-year exacerbations do not provide comparable results as using them individually.

Introduction

Chronic Obstructive Pulmonary Disease (COPD), the third leading cause of death in the world, represents an important public health challenge that is both preventable and treatable. WHO predicts that COPD will become the fourth leading cause of death worldwide by 2030. COPD is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years, and die prematurely from it or its complications.

Exacerbations and hospitalizations, in particular, constitute the most important direct health related costs associated with COPD. Often, the prevalence of COPD is directly related to the prevalence of tobacco smoking, although in many countries, outdoor occupational and indoor air pollution – the latter resulting from the burning of wood and other biomass fuels – are major COPD risk factors.

There is gathering evidence that exacerbations accelerate the progressive decline in lung function in COPD patients, making their prevention even more important. In general, exacerbation frequency increases with disease severity, as represented by airflow obstruction.

Infections, both viral and bacterial cause exacerbations. Bronchoscopic studies have shown colonization of lower airways in 20% of stable COPD patients. During exacerbations there is either increase in bacterial load or acquisition of new strains. Hence the present study was planned to study the microbial pattern among the COPD patients during exacerbations and their relation to COPD severity.

Objectives

1. To determine the microbial pattern in patients with acute exacerbation of COPD.
2. To compare the grouping of COPD patients by Combined COPD risk assessment method using CAT score and mMRC, severity grades/Past year exacerbations, each separately.

*COPD assessment test (CAT) / Modified Medical Research Council (mMRC) and
*Severity grades/Past year exacerbations, each separately.

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Material and Methods

This is a cross sectional study done at Department of Pulmonary Medicine, Government Medical College, Trivandrum from November 2015- November 2016 among patients admitted with acute exacerbation of COPD in the Department of Pulmonary Medicine, Government Medical College, Trivandrum.

89 patients admitted with acute exacerbation during that period were taken for study. Sputum was sent for culture and sensitivity. History of past year exacerbations and spirometry values were noted and COPD was grouped using Combined COPD Risk Assessment method using mMRC, CAT score, severity grades and past year exacerbation separately. Data was analysed using SPSS v16.

Results

The age in the cases varied from 45-80 years (66.5±/- 8.5). 61.8% of patients were above 60yrs. Out of 89 patients, 73(79.8%) were males and 16(20.2%) were females. 79.8% were smokers out of which 27% were current smokers and 52.8% were ex-smokers. All females in our study were non smokers. Mean smoking index was 871.8±544.8. Passive smoking was seen in all the females and biomass fuel exposure (firewood smoke exposure) was present in 25.8% cases. Occupational exposure (tea shop workers exposed to fire wood smoke) was seen in 10.1% cases.73% of the patients had grade 2/3 mMRC dyspnoea and all the patients had worsening of dyspnoea at the time of admission. Mean FEV1 was 1.03± 0.41. 68.5 % patients belonged to GOLD 3 or 4 severity of grading.

Of the 89 subjects, microbial isolates were seen in 34.7% cases. Pseudomonas was the predominant isolate in 10.1% of the total cases. Tuberculosis was diagnosed in 6.7% cases who presented with acute exacerbation (Figure 1).

In the second part of our study, comparison between grouping of COPD patients based on Combined COPD Risk Assessment method using COPD assessment test (CAT) / Modified Medical Research Council (mMRC) and Severity grades / Past-year exacerbations were done separately and compared.

Using CAT, more patients (92.6%) were categorised into risk groups B and D with a high impact of symptoms than using mMRC(74.7%). Based on severity grades, 72% patients had a high exacerbation risk compared to the use of past-year exacerbations (30.4%).

To test the inter rater agreement between the four combinations of grouping of COPD patients, Cohen’s Kappa was calculated.

Inter rater agreement was tested and the results were, Between CAT and mMRC (κ = 0.554) moderate Between severity grades and past-year exacerbations (κ = 0.21) fair.

Discussion

The use of antibiotics in COPD exacerbations is controversial (6). There is evidence supporting the use of antibiotics in exacerbations of COPD in patients having clinical suspicion of infection such as sputum purulence.7 Antibiotics should be given for patients with three cardinal symptoms i.e., increase in breathlessness, increase in sputum volume, sputum purulence or any of the symptoms were sputum purulence is one of the symptoms and those going for mechanical ventilation. The recommended duration of antibiotics is 5-10 days. In patients with frequent exacerbations or severe airflow limitation, sputum culture should be sent as gram negative organisms like pseudomonas aeruginosa is common and higher antibiotics are indicated. In our study, we observed predominantly isolates of Pseudomonas. 10.1% of patients in our cohort showed positive culture to pseudomonas. Similar study done by Chawla et al also showed Pseudomonas in 25.95% cases.

In an Indian study done by Anand K Patel et al in Gujarat in 2011-2012, Streptococcus pneumonia was found to be the commonest pathogen.8 But still Pseudomonas was isolated from 14.7% cases which was comparable to our study results. Pseudomonas was predominantly found among those patients with severe and very severe obstruction.

Klebsiella pneumonia was found as the predominant isolate in study by Madhvi et al.9 Few authors have found higher incidence of Pseudomonas and Enterobactericeae. Groenwegan et al, in his study on more severe COPD patients, found H. influenza as the most common pathogen.10 However data on relationship between organisms and COPD severity (lung function) is scarce.

In our study, using CAT, more patients (92.6%) were categorised into risk groups B and D with a high impact of symptoms than using mMRC (74.7%). Since CAT and mMRC do not provide the same COPD risk group classifications, it may be preferable to restrict to one symptom assessment tool. While CAT assesses the general health status of COPD, mMRC was developed to measure dyspnea. A CAT score ≥10 has been shown to have a significant impact on daily life in patients with COPD. Furthermore, patients with a CAT score ≥10 are likely to have breathlessness on most days and get exhausted easily. Due to its comprehensiveness, CAT scoring may be preferred for classifying patients into COPD risk groups A-D.
Based on severity grades, 72% patients had a high exacerbation risk compared to the use of past-year exacerbations (30.4%), when classifying patients into COPD risk groups A-D. Despite the clear definition of an exacerbation, it is still difficult to ensure a correct recording of the exacerbation history. On the contrary, spirometry-based severity grades are objective and reliable. The direct comparison of these two risk assessments might be difficult and could explain the discrepancy between them. Due to a higher validity and reliability, spirometry-based severity grades may be preferred for COPD classification into risk groups A-D.

The new GOLD guidelines propose specific therapy according to risk group classifications. Misclassification due to the use of different tools could lead to inconsistent management and treatment of the affected severe COPD patients. Therefore, it might be advantageous to use only one tool to assess symptoms and exacerbation risk.

Conclusion
Psedomonas aeruginosa was predominantly isolated from groups C and D, emphasizing the need for higher antibiotics in COPD exacerbations in these groups. Tuberculosis was diagnosed in 6.7% cases who presented with acute exacerbation emphasizing pulmonary tuberculosis be ruled out in all cases of COPD exacerbations. Also, classifying COPD patients into risk groups A-D, using either CAT/ mMRC and severity grades, past-year exacerbations do not provide comparable results as using them individually. This may warrant variations in therapy within each group.

References

Study on Assessment of Thyroid Status among Critically Ill Patients Admitted in a Tertiary Care Hospital

Inturi Bhavana1, Reshma Kommineni1, G Kusuma Gayatri2

Abstract
Introduction: Any acute severe illness can cause abnormalities of circulating TSH or thyroid hormone levels in the absence of underlying thyroid disease.

Aim: To assess thyroid status among critically ill patients admitted in a tertiary care hospital.

Material & Methods: A hospital based cross sectional study was done among 100 critically ill patients admitted to Katuri Medical College and Hospital, Chinarakondrpadu, Guntur. All critically ill patients aged above 18 years admitted to Intensive Care Unit, Emergency ward and patients suffering from Acute renal failure, Acute Respiratory failure, Congestive cardiac failure, Diabetic ketoacidosis, Septicemia and Advanced HIV infection were included. 3ml of early morning sample containing plain clotted blood were collected and sent for T3, T4, TSH estimation. The hormone estimation was done by chemiluminescence assay.

Results: In the study, of 100 critically ill patients out of which 16 patients had acute renal failure, 18 patients had acute respiratory failure, 18 patients had congestive cardiac failure, 16 patients had Diabetic ketoacidosis, 18 patients had Sepsis and 14 patients had Advanced HIV. Among 100 patients, 60% had low T3, 26% had low T4, 10% had high T4 and 4% had low TSH.

Conclusions: Abnormalities in thyroid function were more common in critically ill non thyroidal illness patients.

introduction
Any acute severe illness can cause abnormalities of circulating TSH or thyroid hormone levels in the absence of underlying thyroid disease. The most striking abnormality detected in critically ill euthyroid patients is a highly significant reduction in the mean total serum triiodothyronine (T3) level. Critical illness is often associated with alterations in thyroid hormone concentrations in patients with no previous intrinsic thyroid disease. Changes in parameters of

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thyroid function are very common but any acute severe illness can cause abnormalities of circulating TSH or thyroid hormone levels in the absence of underlying thyroid disease.²³

Assessment of thyroid function in ICU:

The nonthyroidal illness syndrome, also known as the low T3 syndrome or euthyroid sick syndrome, describes a condition characterized by abnormal thyroid function tests encountered in patients with acute or chronic systemic illnesses. The laboratory parameters of this syndrome include low serum levels of triiodothyronine (T3) and high levels of reverse T3, with normal or low levels of thyroxine (T4) and normal or low levels of thyroid-stimulating hormone (TSH).⁴

This condition may affect 60 to 70% of critically ill patients. The changes in serum thyroid hormone levels in the critically ill patient seem to result from alterations in the peripheral metabolism of the thyroid hormones, in TSH regulation, in the binding of thyroid hormone to transport-protein and in receptor binding and intracellular uptake. Medications also have a very important role in these alterations.⁴

The decreased 5'-monodeiodinase activity is often not recognized because measurement of serum T3 is rarely utilized as a screening test for thyroid function (nor should it be). The serum T3 value should be high (or high-normal) in hyperthyroidism but low (or low-normal) in non thyroidal illness. Rarely, a very sick patient with hyperthyroidism will have a low serum T3 concentration.⁵

The severity of illness correlates well with the reduction in total serum T3 level. The major cause of these hormonal changes is the release of cytokines such as IL-6. The most common hormone pattern in sick euthyroid syndrome (SES) is a decrease in total and unbound T3 levels (low T3 syndrome) with normal levels of T4 and TSH. Low T3 is an important marker of mortality in critically ill patients. T4 and TSH did not vary between survivors and non survivors.⁶

The enhanced sensitivity and specificity of TSH assays have greatly improved laboratory assessment of thyroid function. The use of immune chemiluminesmetric assays (ICMAs) for TSH is sensitive enough to discriminate between the lower limit of the reference range and the suppressed values that occur with thyrotoxicosis. The finding of an abnormal TSH level must be followed by measurements of circulating thyroid hormone levels to confirm the diagnosis of hyperthyroidism (suppressed TSH) or hypothyroidism (elevated TSH). Radioimmunoassays are widely available for serum total T4 and total T3.

Aim

To assess thyroid status among critically ill patients admitted in a tertiary care hospital.

Material and Methods

A hospital based cross sectional study was done among 100 critically ill patients admitted to Katuri Medical College and Hospital, Chinakondrupadu, Guntur.

Inclusion Criteria

All critically ill patients aged above 18 years admitted to Intensive Care Unit, Emergency ward and patients suffering from Acute renal failure, Acute Respiratory failure, Congestive cardiac failure, Diabetic ketoacidosis, Septicemia and Advanced HIV infection were included.

Exclusion Criteria

History s/o thyroid illness, clinically evident thyroid enlargement, or signs of thyroid disease

Patients receiving massive blood transfusion or having steroid or dopamine therapy and drugs known to interfere with thyroid hormone metabolism.

Methodology

Informed written consent was taken from the study participants prior to the start of the study. Demographic data, History, Clinical examination and details of investigations were done and recorded in the study proforma.

3ml of early morning sample containing plain clotted blood were collected and sent for T3, T4, TSH estimation. The hormone estimation was done by chemiluminescence assay.

Statistical Methods: Data entry was done using Microsoft excel 2010 version and analysis using EPI INFO version 7. Data was presented in percentages and proportions. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%).

Results

The mean age of the study population was 45.74±16.65 years with majority (26%) from 31-40 years age group. Male & female sex ratio was 1.6.

Out of 100 patients 48 (48%) were found to have fever, 18 (18%) breathlessness, 16 (16%) had vomiting, 6(6%) had cough.

With regards to co morbid conditions, 28 (28%) were found to be hypertensive and 72 (72%) had diabetes mellitus. 14 patients (14%) were HIV Reactive.

The mean systolic and diastolic blood pressure was 120.29±25.86 and 76.32±14.25 mm Hg respectively. The mean pulse rate was 101.38±14.09, mean respiratory rate 24.30±6.21 and mean temperature 37.67±0.54. APACHE score found that 40 Patients (40%) had APACHE Score >15, 38 Patients (38%) had 11-15 and 22 Patients (22%) had 6-10.

On investigations, the mean haemoglobin (%) was 11.04±3.10, mean platelets were 2.10±1.01 lakh and the mean random sugar level was 190.40±131.79. 16 cases had ketone bodies in urine.

Out of 100 critically ill patients, 54% had abnormal serum sodium, 44% had abnormal serum potassium and 8% had abnormal serum chloride.

With regards to renal parameters, serum urea was >40 mg/dl in almost half the cases (48%). Among 100

### Table 1: Thyroid abnormalities in different clinical conditions

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Thyroid abnormality</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Renal Failure (n=16)</td>
<td>Low T3 -- 06 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Acute Respiratory Failure (n=18)</td>
<td>Low T4 -- 04 (25%)</td>
<td></td>
</tr>
<tr>
<td>Congestive Cardiac Failure (n=18)</td>
<td>Low T4 -- 08 (44.4%)</td>
<td></td>
</tr>
<tr>
<td>Diabetic Ketoacidosis (n=16)</td>
<td>Low T4 -- 06 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Septicemia (n=18)</td>
<td>Low T4 -- 10 (62.5%)</td>
<td></td>
</tr>
<tr>
<td>Advanced HIV (n=14)</td>
<td>Low T4 -- 08 (57.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Chinakondrupadu, Guntur. Medical College and Hospital, study was done among 100 critically ill patients admitted in a tertiary care hospital.
critically ill Patients, 16 patients (16%) expired.

Thyroid function tests

Among 100 patients, 60% had low T3, 26% had low T4, 10% had high T4 and 4% had low TSH.

The mean T3 was 0.63 ± 0.42, T4 5.38 ± 2.01 and TSH was 3.25±2.10.

Thyroid function tests in different clinical conditions among the critically ill patients (Table 1).

Out of 16 Patients of Acute Renal failure, 37.5% had low T3, 25% had low T4 and 100% had normal TSH. Out of 18 Patients of Acute Respiratory failure, 55.6% had low T3, 44.4% had low T4 and 100% had normal TSH. Among the 18 patients with congestive cardiac failure, 55.56% had low T3, 22.2% had low T4 and 11.12% had high TSH.

Out of 16 patients with diabetic ketoacidosis, 62.5% had low T3, 37.5% had low T4, 12.5% had high TSH. Among the 18 patients with septicemia, 88.89% had low T3, 66.66% had low T4 and 11.1% had low TSH.

14 patients with advanced HIV, 57.14% had low T3, 28.5% had low T4, 57.14% had high T3 and 100% had normal TSH.

Discussion

Critical illness is often associated with alterations in thyroid hormone concentrations in patients with no previous intrinsic thyroid disease. The metabolic support of the critically ill patient is a relatively new target of active research and little is as yet known about the effects of critical illness on metabolism.

In our study, of 100 critically ill patients out of which 16 patients had acute renal failure, 18 patients had acute respiratory failure, 18 patients had congestive Cardiac failure, 16 patients had Diabetic ketoacidosis, 18 patients had Sepsis and 14 patients had Advanced HIV. T3 ,T4 and TSH analysis were done, 60 Patients (60%) had low T3 level, 40 (40%) patients had normal T3, 36 patients(36%) had low T4, 64 patients(64%) had normal T4 level and TSH was low in 4 patients(4%), 76 patients (76%) had normal TSH and 20 patients (20%)slightly high Mean ± SD 3.25 ± 2.10.

Study by Kiran Bhat et al (2016) observed that (59.1%) of the patients showed abnormality in one or more than one parameter of thyroid function tests. And low fT3 (50%) was the commonest abnormality followed by high TSH (12.4%), low TSH (8.8%) and low fT4 (4.7%) concentration.

In present study of 18 patients of sepsis, 16patients (88.89%) had low serum T3 level, low T4 level with high APACHE score with death of 6 patients. And TSH is normal in 10(55.55%) patients. All sepsis patients had low Hb% with total count more than 13670 cells/cumm. It indicates that among sepsis, with low T3 and T4, high APACHE score favor more death rate.

Joseph et al. reported that, 21/110 (19.0%) patients had abnormal thyroid function at diagnosis of TIDM. Of these, 16 had normal thyroid function on reassessment after 45 (3–540) days. Abnormalities of thyroid function occurred were more common in children with diabetic ketoacidosis (DKA) than those who did not have DKA (9/29, 31.0% vs 12/81, 14.8%, p<0.025). At the end of the observation period, five (4.5%) patients had minor abnormalities of thyroid function not requiring treatment and three (2.7%) were treated.

In our study of 14 advanced HIV patients, 8 patients (57.14%) had low T3, 4 patients (28.58%) had low T4 level, total 8 deaths including 6 HIV with tuberculosis, 2 with HIV with acute GE. In 2 patients both Hb%& TC were low, in 4 patients low Hb% and high TC level, in 2 patients normal Hb% and high TC with APACHE score.

Palanisamy P et al (2010)_R did a study on 150 HIV positive subjects divided into groups based on CDC criteria to investigate level of serum lipids and thyroid hormones. They reported that thyroid dysfunction is frequent in HIV infection and that with progression of disease there is a primary hypothyroid like stage that occurs in patients.

Desai Vidya Sripad et al (2015)_R study found that FT3 and FT4 as the most powerful and independent factor of ICU mortality among the complete thyroid panel of indicators. The cumulative death rate was significantly higher in patients with low T3 syndrome as compared to those without (18%).A significant association was found between patients death rate, Low T3 syndrome and APACHE II and other inflammation indices.

Though many similar kind of studies were done in different places, the findings of the present study are pertinent to the study area.

Conclusions

Present study has found that abnormalities in thyroid function were more common in critically ill non thyroidal illness patients. T3 level was low in 60% patients of critically ill non thyroidal illness patients with normal or low-normal T4 TSH levels.

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In Obese Type 2 Diabetes with HbA1c > 9%

In Type 2 Diabetes with High PPHG

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Infections and HLH - Experience from a Tertiary Care Centre

Ujjwayini Ray¹*, Soma Dutta², Syamasis Bandyopadhyay³, Susovan Mondal⁴

Abstract

Introduction: HLH is a rare but potentially fatal condition that may be triggered by connective tissue disorders, malignancies and in a significant number of cases by infections. HLH is often difficult to diagnose because of its similarity with a host of other infective and inflammatory conditions. Prompt identification of the underlying cause is important as it guides treatment decisions. Early initiation of appropriate therapy reduces morbidity and mortality.

Aims: To study patients with infection associated secondary HLH in a tertiary care facility.

Settings and Design: We conducted a prospective study to identify patients with secondary HLH triggered by infections (IA-HLH), the type of infections triggering HLH and the course and outcome of the patients. Patients' data were collected from September 2015 to October 2016.

Methods and Material: Between September 2015 and October 2016, consecutive patients meeting the diagnostic criteria for IA-HLH, based on the HLH2004 protocol of the Histiocyte Society, were included in the study.

Results: In the course of over a year we diagnosed 20 patients with infection associated secondary HLH. Twelve cases were secondary to dengue, four were triggered by typhoid fever and two cases each were precipitated by tuberculosis and Epstein Barr virus infection. Of the 20 patients, three patients with dengue induced HLH died of hemorrhagic complications. Rest recovered without any sequel.

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is characterized by dysregulated activation of CD 8+ T lymphocytes and macrophages that engulf erythrocytes, leucocytes, platelets and their precursor cells. HLH is a distinct clinical entity characterized by fever, pancytopenia, splenomegaly, and haemophagocytosis in bone marrow, liver or lymph nodes and is associated with considerable mortality and morbidity. Haemophagocytic lymphohistiocytosis (HLH) is a devastating and rare disorder with an estimated incidence of around 1.2 cases per million patients per year and a high mortality rate of around 47%.1 HLH may be familial or secondary to a variety of infections, collagen vascular diseases or malignancies. Infections, particularly infections with intracellular microbes constitute about 40% of all secondary or reactive HLH. Unlike other forms of HLH, infection associated HLH carries a relatively better prognosis provided the inciting infection is diagnosed early and treated promptly.

Subjects and Methods

From September 2015 to October 2016 patients diagnosed with infection associated HLH (IA-HLH) were included in the study.

The diagnosis of HLH was based upon the criteria, which were used in the HLH-2004 trial.2 Five of the 8 criteria are required to be fulfilled for diagnosis of HLH to be made.

The last two tests soluble CD25 level and NK cell activity are not done in our hospital and patients who satisfied at least 5 out of the remaining six criteria were included in the study.

H score of the patients were also calculated. The “H score” is a scoring system that has been developed to generate a diagnostic score that estimates the probability of HLH; this combines scores for immunosuppression; fever; organomegaly; levels of triglycerides, ferritin, alanine aminotransferase, and fibrinogen; degree of cytopenias; and presence of hemophagocytosis in the bone marrow aspirate.3 An Hscore of ≥250 confers a 99 percent probability of HLH, whereas a score of ≤90 confers a <1 percent probability of HLH.

Results

Between September 2015 and October 2016, 20 patients with infection associated secondary HLH were diagnosed. The patients fulfilled at least five criteria required to establish HLH as per the HLH diagnostic criteria, 2004. The mean age at diagnosis was 28.4 years [median 23 (range 4-67)]. All patients had fever at presentation and at least a bi or trilineage cytopenia, elevated liver enzymes and hyperferritinemia. The mean ferritin level was 30893.545 ng/ml (Reference range: paediatric: 7-140 ng/ml; adult: 10-250 ng/ml). The average platelet count was 54000 mm⁻²; (reference value [RV]: 4000 - 10000 mm⁻²). Twelve cases were secondary to dengue virus infection, four were triggered by typhoid fever and two cases each were precipitated by tuberculosis and Epstein Barr virus infection. Out of the 12 patients in whom bone marrow study was undertaken, nine of them had evidence of haemophagocytosis in bone marrow biopsy (Figure 1). The H scores of all the patients were calculated. Three patients had H score less than 190. In these patients the probability of HLH varied from 8.8% to 70.9%. The remaining patients had H score over

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All four patients were treated with prompted investigations for HLH despite appropriate antibiotics. Progressive bicytopenia isolation of enteric fever was established following with high fever. The diagnosis of induced HLH initially presented and retroperitoneal lymphadenopathy. Patients had periportal, peripancreatic ascites and in addition one of the hepatosplenomegaly with minimal in both patients. The patients also had bilateral pulmonary miliary nodules. Radiological investigations were suggestive of tuberculosis along with evidence of haemophagocytosis. Table 1: Depicting the clinical and laboratory features of the 20 patients with IA-HLH Y: Yes; N: No; TG: Triglyceride; ND : Not done

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All patient had fever & Pan/Bicytopenia. Except Patient No.3 all had Splenomegaly.

Dengue associated HLH

Out of the 20 cases of IAHLH diagnosed over a period of one year, 12 cases were triggered by dengue. In 2016, there was a major outbreak of dengue and consequently the increased number of dengue related HLH cases.

A mild disease in majority of cases, less than 2% of dengue patients present with severe manifestations, dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), both conditions resulting in considerable mortality and morbidity. A total of 74 dengue-associated pediatric and adult HLH cases have been described in the published literature since 1966, with a cumulative case-fatality rate (CFR) of 9.5%. It is possible that the diagnosis of dengue induced HLH is missed as clinicians tend to focus on the underlying infection rather than the overwhelming cytokine production. HLH is a potentially life threatening disorder and several cases reported in the literature show dengue induced HLH can be fatal. The pathophysiology of severe dengue (DHF, DSS) is not always well understood and it is now being increasingly believed that macrophage activation may play a role in some cases of severe dengue. It is fairly well established that cross protection among the four dengue serotypes is limited and secondary infection by a different serotype may predispose to DHF and DSS. Many studies found that primary dengue infections could be associated with severe DHF and dengue-associated hemophagocytic inflammation.
syndrome. The increasing reports of haemophagocytosis associated with dengue infection in both endemic and non-endemic areas have raised concern of the potential threat of this emerging syndrome in causing severe and fatal complications. So it is important to look for associated HLH in cases of severe dengue. Amongst our patients, three patients with dengue induced HLH succumbed to hemorrhagic complications. Two of them had H score of 216 and one patient had score of 172. The patient with the H score 172 had the stormier onset and succumbed a day after admission in our hospital. The fibrinogen and triglyceride levels were normal in the patient probably as a result of therapeutic interventions in an outside facility and hence the low H score.

**TB associated HLH**

TB-HLH was first published in the 1980s and there has been increasing number of reports of TB HLH in the recent years. Padhi et al., reviewed a total of 55 articles describing nearly 70 cases of TB-HLH published in the world literature till March 2014. Since then around 16 more cases have been reported in the literature including a series of 8 cases by Zhang Yun et al. One aspect that is almost certain from these case reports and reviews that that HLH associated with TB carries a high mortality (of approximately 50%) for patients not receiving appropriate treatment or due to a delay in commencing treatment. Treatment with anti-TB drugs and chemo-immunotherapy improves outcome.

Both the patients of disseminated tuberculosis improved after institution of anti-tubercular therapy and dexamethasone. TB HLH patients generally present with PUO and establishing the etiological diagnosis without much delay can be challenging. In our patients, radiological findings along with histopathological evidence in the bone marrow helped in the diagnosis of tuberculosis. The bone marrow study proved to be particularly helpful as it provided evidence of tuberculosis infection and suggestion of haemophagocytosis.

**Typhoid induced HLH**

Enteric fever, transmitted via the faeco-oral route, is endemic in the developing countries of Asia, Africa, Latin America, the Carribean, and Ocenia with an estimated 13.5 million episodes in 2010. There are few cases of enteric fever induced HLH reported in the literature and it is possible that secondary HLH due to typhoid fever go unrecognized possibly due to lack of awareness about this entity. As early as the mid-1800s, haemophagocytic macrophages, which are macrophages that have consumed red and white blood cells, were observed in the tissues and blood of recently deceased typhoid fever patients.

Leucopenia and splenomegaly, two of the diagnostic criteria of HLH are also pathognomonic features of typhoid fever and as a result secondary HLH triggered by enteric fever may be difficult to identify. In enteric fever patients with progressive bicytopenia despite appropriate antibiotics, the diagnosis of HLH should be taken into consideration and investigated accordingly.

**EBV induced HLH**

EBV-HLH is a major subtype of secondary HLH that is induced by a primary EBV infection. Epstein–Barr virus-associated haemophagocytic lymphohistiocytosis (EBV-HLH) is the most frequent subtype of secondary HLH triggered by infections. EBV-HLH is a clinicopathological syndrome comprising of a dysregulated immune response and cytokine storm, manifested clinically by fever, splenomegaly, and cytopenia. Without early and effective therapy, EBV-HLH has a high mortality rate, frequently due to multiorgan failure. Recently established diagnostic and therapeutic guidelines, particularly the introduction of the chemotherapeutic drug etoposide have contributed to improvements in survival rates. Etoposide appears to interfere with EBV – induced lymphocyte transformation and suppresses formation of EBV nuclear antigen. The incidence of EBV-HLH is relatively high in Asian countries, indicating the underlying genetic background in the pathogenesis of EBV-HLH. In Japan EBV associated HLH is seen in around 40% of all secondary HLH patients.

In children and adolescents EBV HLH has been observed in primary EBV infections whereas in adults it may be possible that acquired immune dysfunction is required to trigger the onset of EBV-HLH in EBV-immune adults. Among our cases, patient 1 (4 years old male boy) had no history to suggest immune dysfunction and the second patient (31 years adult male) subsequently received a diagnosis of pre B cell ALL. The first patient recovered spontaneously but in the second case IV Ig followed by etoposide was administered for resolution of the HLH.

**Diagnostic challenges**

The main challenge in recognizing IA-HLH is due to its wide spectrum of manifestations but lack of specificity in the clinical findings. Persistent cytopenias, rising liver enzymes, unresponsiveness to appropriate antibiotics in the setting of an infectious disease are some of the diagnostic pointers for this disease. In case of infections, a simple blood investigation that shows elevated levels of serum ferritin should raise the suspicion of a coexisting HLH. A single value of ferritin more than 10,000 ng/ml in the absence of iron overload conditions like hemochromatosis and thalassemia syndromes can act as a surrogate marker for HLH with a sensitivity of 90% and specificity of 96%. Fever, hepatosplenomegaly, cytopenias, hepatitis, hypofibrinogenemia, hyperferritinaemia, hypertriglycerideremia, hyponatremia with evidence of haemophagocytosis in the bone marrow are amongst the clinical features that support the diagnosis of HLH. All our patients except three had ferritin levels over 10000ng/ml. In our study the mean ferritin level was found to be as high as 30893.545ng/ml. Although haemophagocytosis is the hallmark of the disease, it is seldom found at presentation in case of secondary HLH and may not be evident until late in the course of disease progression. Bone marrow biopsies performed in the initial stage of disease may be normal or demonstrate very non-specific changes.

Tests for molecular markers such as the soluble CD 25, natural killer cell activity, are not regularly performed in most hospitals and if available the reports are obtained after some time and therefore may not be a timely preference for diagnosing HLH. Consequently, IA-HLH may be under diagnosed with the HLH 2004 or proposed HLH 2009 Diagnostic Criteria as these protocols include molecular biomarkers. So a modification of the diagnostic criteria has been proposed. In this approach, diagnosis requires three of four clinical findings (fever,
spleenomegaly, cytopenias, hepatitis) plus one of four immune markers (hemophagocytosis, increased ferritin, hypofibrinogenemia, absent or very decreased NK cell function).

Along with these criteria the H Score may be a useful tool which can complement these diagnostic criteria and help in establishing IA-HLH.

The H Score was recently designed and validated to assess individual risks of HLH. Fardet al in their study reported that a cut off H score of 169 ensured rather high degrees of sensitivity, specificity, and classification accuracy. The H Score is now preferred by many to the previous HLH-2004 criteria because the latter were suffering from substantial limitations. First, these criteria were established in a pediatric population to diagnose the hereditary primary form of HLH and suffer from substantial limitations in diagnosing the adult or the reactive form of the disease. Second, the weight of each criterion was unknown and the cut-off values were merely empirical. Third, some of the investigations (eg, NK cell activity, soluble interleukin-2 receptor level) are high end tests performed by reference laboratories and are not available in many of the centers.

This present study also corroborated the usefulness of the H score for establishing the diagnosis of HLH. All our patients expect one had H Score more than 169. In fact 17 out of the 20 patients included in the study had H score over 200 with a probability of more than 90% of developing HLH.

The majority of the laboratory work-up necessary to establish the diagnosis of HLH include tests done routinely with a fast turn-around time (eg, CBC, triglycerides, fibrinogen, and ferritin). These findings, combined with a good clinical examination should be enough to raise suspicion of HLH in an appropriate clinical setting, prompting exhaustive investigations to establish HLH and detect the underlying pathology that triggered the cytokine storm.

Treatment

The mortality of HLH is very high without HLH directed therapy. Early recognition and initiation of therapy is therefore of utmost importance. Regarding EBV-associated HLH, early immunotherapy with etoposide results in high cure rates. For infection associated HLH, the treatment of the underlying infection and supportive care is sufficient in 60-70% of cases. Patients with reactive HLH associated with an infectious organism except leishmaniasis, may need specific HLH therapy since pathogen specific therapy cannot stabilize the disease activity by itself in around 30-40 % of cases. In this study, patients diagnosed with tuberculosis and typhoid fever received specific antibiotics for the underlying infections and the rest were managed symptomatically. Nine of the patients were administered HLH specific therapy in the form of dexamethasone, IV Ig or etoposide. Of the three patients who died, two of them received HLH specific therapy.

Conclusion

Hemophagocytic lymphohistiocytosis (HLH), a life-threatening clinicopathological condition caused by excessive immune activation is being increasingly recognized in clinical practice. The high mortality rate associated with HLH is due at least in part to delays in diagnosis that result from the similarity between the initial clinical features and a wide range of infective and inflammatory conditions. Acquired HLH is often caused by infections, malignancies or collagen vascular diseases. Infections are responsible for precipitating HLH in around 40% of cases. Infection associated HLH carry a slightly better prognosis if diagnosed and treated sufficiently early. Dengue induced HLH seems to be the cause of hemorrhagic complications in certain patients. The recently developed H Score is a useful tool and can be used to estimate an individual’s risk of having reactive hemophagocytic syndrome.

References

Pulmonary Involvement in Peoples Living with HIV (PLHIV)

Shubhangi V Dhadke¹, Vithal Dhadke²*, Reshma Kshirsagar³, Manish Dhadke⁴

Abstract

Background: Pulmonary system is most commonly involved system in PLHIV as lungs are continuously exposed to the infection as they are rich in macrophages, dendritic cells, lymphocytes etc. In PLHIV immunity is suppressed, hence lung are prone for infection and non infectious pulmonary diseases. It is most common complication in HIV patient. Pneumonia is most common pulmonary manifestation followed by tuberculosis and pneumocystis jirovecii pneumonia. Other infection like mycobacterium avium complex (MAC), fungal infection, non specific interstitial pneumonitis, kaposis sarcoma (KS), and lymphoma causes pulmonary involvement. Incidence of bacterial pneumonia is 0.8-2 per 100 person year. Encapsulated organism like streptococci, H. influenzae are responsible for most cases of pneumonia. Incidence of pneumonia increase by 6 times in untreated HIV patient. Pneumocystis jirovecii pneumonia is hallmark of AIDS. Incidence range from 2-3 cases per 100 person- years. Pneumocystis jiroveci pneumonia is most commonly seen in patient having CD4 count <200/micro litre.

About 1/3 of deaths all AIDS related death are associated with tuberculosis. Tuberculosis is the primary cause of death in10-12% of HIV infected patients.¹ About 60-80 % HIV infected patient With Tuberculosis have pulmonary disease,

Mycobacterium avium complex infection is late complication of HIV infection mostly seen in patient With CD4 count <50.

Aims and Objectives

1. To study pulmonary involvement in people living with HIV diagnosed by ELISA method.
2. To study radiological findings in lungs of PLHIV with pulmonary disease by chest X-ray, High resonance computed tomography, ultrasonography of thorax etc.
3. To study co-relationship between CD4 count and pulmonary disease in PLHIV.

Methods: This is descriptive clinical study with cross sectional design with 100 HIV positive patients to study pulmonary involvement. The study was conducted in Dr. V.M. Government Medical college, Solapur Present study was carried out on PLHIV with pulmonary involvement. The period was from dec 2012 to Nov. 2014. Present study was conducted after NACO (National AIDS Control Organization) permission.

After pre-test counselling, blood sample were tested for anti -HIV antibodies ELISA method. A detail clinical history and examination was done and information related to each patient was filled in proforma.

After taking written informed consent was taken from patient eligible for this study.

Chi-square/z test has been used to find the significance of study

Results

1. Pulmonary disease maximum in age group of 31-50 yrs of age.
2. In present study male patient to female patient ration was 1.7.
3. In present study prevalence of tuberculosis was maximum in patient followed by bacterial pneumonia and pneumocystis jiroveci pneumonia respectively.
4. Most of the bacterial pneumonia patients had consolidation on chest x-ray PA view.

Conclusion

1. In present study prevalence of bacterial pneumonia was maximum in patient having cd4 count >200cells/micro lit, prevalence of tuberculosis was maximum in patient having cd4 count between 150-500/micro lit, prevalence of Pneumocystis Jiroveci pneumonia maximum in patient having cd4 count <50/micro lit.
2. In pulmonary tuberculosis patient consolidation, pleural effusion, fibro nodular infiltrate, cavity, Pneumothorax, bilateral extensive tuberculosis were common findings on chest X-ray.
3. In pulmonary tuberculosis patient most common radiological findings are consolidation, mediastinal lymphadenopathy, fibro nodular infiltrate, cavity, Pneumothorax on HRCT thorax.

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Introduction

Pulmonary system is most commonly involved system in PLHIV. In PLHIV immunity is suppressed, hence lungs are prone for infectious and non infectious pulmonary disease. Pneumonia is most common pulmonary manifestation followed by tuberculosis and pneumocystis jiroveci pneumonia.

Pneumocystis jiroveci pneumonia is hallmark of AIDS. Incidence ranges from 2-3 cases per 100 person-years. Pneumocystis jiroveci pneumonia most commonly seen in patient having CD4 count <200/micro litre.

About 1/3 of death all AIDS related death associated with tuberculosis. Tuberculosis is the primary cause of death in 10-12% HIV infection. About 60-80% HIV infected patient With Tuberculosis have pulmonary disease, 30-40% have extra pulmonary involvement.

Aims and Objectives

1. To study pulmonary involvement in peoples living with HIV diagnosed by ELISA method.
2. To study radiological findings in lungs of PLHIV with pulmonary disease by chest x ray. High resonance computed tomography, ultrasonography of thorax etc.
3. To study co-relationship between CD4 count and pulmonary disease in PLHIV.

Material and Methods

Methodology

This is descriptive clinical study with cross sectional design with 100 HIV positive patients to study pulmonary involvement in peoples with HIV (PLHIV) patient.

Source of Data

The study was conducted in Dr. V.M. Government Medical college, Solapur, Maharashtra, India. Present study was carried out on PLHIV with pulmonary involvement. The period is from Dec. 2012 to Nov. 2014. Present study was conducted after NACO (National AIDS Control Organization) permission

Inclusion Criteria

1. Age>13 yrs
2. HIV positive patient diagnosed by ELISA method
3. Patient having pulmonary symptoms

Exclusion Criteria

1. Age <13
2. HIV negative patient
3. PLHIV with only upper respiratory tract infection
4. PLHIV not willing to give consent

After pre-test counselling, blood sample were tested for anti–HIV antibodies ELISA method.

A detail clinical history and examination was done and information related to each patient was filled in proforma.

After taking written informed consent from patient eligible for this study

Following investigations were done.

1. Chest x ray PA view of all patients
2. Sputum for AFB -1 sample on admission, 2 sample on early morning
3. Sputum for gram staining
5. Sputum for culture and sensitivity
6. PAS Stain for mycobacterium avium complex
7. Pleural fluid study i.e. cyto, biochem or in suspected cases pleural fluid ADA
8. Ultrasonography of thorax in case of pleural effusion to rule out pulmonary involvement.
9. HRCT thorax in suspected patient in whom chest X-ray PA view is normal.
10. Fine needle aspiration cytology (FNAC ) of lymph node in patient present with lymphadenopathy.
11. Blood culture, LFT, RFT, CBC, CD4 count in All patient.
12. ESR

Statistical Methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements were presented on mean ± SD(mean –max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance.

Chi-square/z test has been used to find the significance of study parameters on categorical scale between two or more group.

Observations and Results

In this study maximum about 71% were tuberculosis patient, followed by 22% were bacterial pneumonia patient followed by 7% were pneumocystis jiroveci pneumonia this difference is statistically highly significant.

When this test was applied to show relationship between CD4 and bacterial pneumonia patient X2=41.06, DF=5, P<0.01 Which is highly significant.

In this study maximum 95.5 % pneumocystis jiroveci patient showed ground glass haziness on chest x ray out of which 33.33% patient had 1 zone involvement and 66.66% patient had >1 zone involve. 83.33% patient had lower zone involvement followed by upper zone 16.66%. Para hilar opacity present in 71.42% patient. Statistically it is not

4. In pneumocystis jiroveci pneumonia maximum patient had ground glass haziness and parahilar opacity. On chest X ray, Prevalence of lower zone involvement was maximum followed by upper zone.

5. In pneumocystis jiroveci pneumonia prevalence of ground glass haziness and cystic lesion was maximum on HRCT thorax.
significant.

In this study HRCT thorax was done in suspected cases whose chest X-ray was normal, to rule out pleural effusion, pulmonary involvement, suspected pneumocystis jirovecii pneumonia patient. In this study HRCT was done for 56 patients. Consolidation seen in 46.42% patient. Out of 7 patients of pneumocystis jirovecii pneumonia, HRCT thorax showed ground glass haziness in 100% patient who was suspected for pneumocystis jirovecii pneumonia.

HRCT thorax showed mediastinal lymphadenopathy (46.42%), fibronodular infiltrate (41.07%), consolidation (46.4%), cavitatory lesion (8.9%), Pneumothorax (8.9%). Statistically this is highly significant (p<0.01)

These findings are similar to the study conducted by Asmita A. Mehata et al.1 In which 72% patient had tuberculosis, 22% patient had bacterial pneumonia. 6% patient had pneumocystis jirovecii pneumonia, 2% patient had cryptogenic meningitis with pulmonary infiltrates.

Table 1: Disease wise distribution of study population

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of patient</th>
<th>percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>pneumonia</td>
<td>22</td>
<td>22%</td>
</tr>
<tr>
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</tr>
<tr>
<td>malignancy</td>
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<td>0%</td>
</tr>
</tbody>
</table>

(x²=67.22, DF=9, p<0.01)

In present study incidence of tuberculosis were maximum 71%, followed by bacterial pneumonia 22%, followed by pneumocystis jirovecii pneumonia 7%. Mycobacterial avium complex infection is rare now days because of use of HAART. Statistically this is highly significant (p<0.01)

These findings similar to the study conducted by Pu-xuan Lu et al.5 in this study 80% patient had CD4 count >150 cells/micro lit, 14% patient had CD4 count 101-150 cell/micro lit, 14% patient had CD4 count 51-100 cell/micro lit, 71.8% patient had CD4 count <50 cell/micro lit.

As immunity decreases incidence of tuberculosis also increases. CD4 T lymphocyte counts an explicit biomarker that provides assessment immune system status of HIV infected patient while pneumocystis jirovecii pneumonia is most common complications of AIDS.

In present study prevalence of pneumocystis jirovecii pneumonia 0% patient had CD4 count >150 cells /micro lit, 14% patient had CD4 count 101-150 cell/ micro lit, 14% patient had CD4 count 51-100 cell /micro lit, 71.8% patient had CD4 count <50 cell/micro lit.

Similar findings similar to the study conducted by A. Ahidjo et al.2 In which consolidation in 25% patient, pleural effusion in 16.7% patient, 20% patients had miliary tuberculosis. Upper zone

Discussion

Pulmonary system is most common system involved in PLHIV. In HIV patient decrease immunity make patient prone for infection. Low CD4 count as responsible for opportunistic infection in PLHIV.

Present study was conducted in Dr. V.M. Government Medical College, Solapur, Maharashtra, India .In this study 100 HIV positive Patient who diagnosed by ELISA method who had respiratory complains were involved. All relevant laboratory investigation including chest x-ray, HRCT, ultrasonography (thorax), pleural fluid study, sputum for AFB, sputum for gram staining (Figure 1). Sputum for GMC stain for pneumocystis jirovecii infection, sputum for PAS, sputum for culture sensitivity, FNAC of lymph node, complete blood count, liver function test, renal function test, erythrocyte sedimentation rate were performed.

In present study HRCT was done only in patient who was suspected for pneumocystis jirovecii pneumonia, cases of pleural effusion and patient who was clinically suspected to have pulmonary involvement but chest x-ray was normal.

Table 1 disease wise distribution of patient (Table 1).

In present study in tuberculosis 1.4% patient had CD4 count >500 micro lit, 36.61% patient had CD4 count 201-500 cells/micro lit, 19.71% patient had CD4 count 151-200 cells /micro lit, 14.08% patient had CD4 count 101-150 cells/ micro lit, 16.09% patient had CD4 count 51-100 cells/micro lit, 11.26% patient had CD4 count <50. chi square test applied. p<0.01. indicates it is highly significant.

This findings similar to the study conducted by Halgarkar et al.4 except instead of getting maximum number of tuberculosis seen in patient having CD4 count 201-500 cell/micro lit they get in patient having CD4 count 151-199 cells/micro lit. In this study 19.35% patient had CD4 count 201-500 cell/micro lit, 48.38% patient had cd4 count 151-200 cell/micro lit, 17.74% patient had CD4 count 101-150 cell/micro lit, 11.29% patient had cd4 cont 51-100 cell/ micro lit, 3.22% patient had cd4 count <50 cells/micro lit.

In present study HRCT thorax showed ground glass haziness in 100% patient who was suspected for pneumocystis jirovecii pneumonia.

HRCT thorax showed mediastinal lymphadenopathy (46.42%), fibronodular infiltrate (41.07%), consolidation (46.4%), cavitatory lesion (8.9%), Pneumothorax (8.9%). Statistically this is highly significant (p<0.01)

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This findings similar to the study conducted by A. Ahidjo et al.2 In which consolidation in 25% patient, pleural effusion in 16.7% patient, 20% patients had miliary tuberculosis. Upper zone

Table 3 co-relation between chest X-ray finding and pulmonary tuberculosis.

In present study prevalence of consolidations is maximum (33.80%) followed by pleural effusion (23.94%), cavitatory lesion (16.90%), fibronodular infiltrate (16.90%), miliary tuberculosis (14.08%) less frequently. Pneumothorax (8%), chi square test applied p=0.02. indicate this finding is highly specific.

Similar findings seen in study conducted by A. Ahidjo et al.2 In which consolidation in 25% patient, pleural effusion in 16.7% patient, 20% patients had miliary tuberculosis. Upper zone

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<tr>
<td>malignancy</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

(x²=67.22, DF=9, p<0.01)

In present study in tuberculosis 1.4% patient had CD4 count >500 micro lit, 36.61% patient had CD4 count 201-500 cells/micro lit, 19.71% patient had CD4 count 151-200 cells /micro lit, 14.08% patient had CD4 count 101-150 cells/ micro lit, 16.09% patient had CD4 count 51-100 cells/micro lit, 11.26% patient had CD4 count <50. chi square test applied. p<0.01. indicates it is highly significant.
Table 2: Co-relation between CD4 count and pulmonary disease

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>No. of bacterial pneumonia patient</th>
<th>No. of tuberculosi patient</th>
<th>No. of PJP patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>201-500</td>
<td>9</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>151-200</td>
<td>3</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>101-150</td>
<td>1</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>50-100</td>
<td>0</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>&lt;50</td>
<td>4</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 3: Chest X-ray findings in pulmonary tuberculosis patient

<table>
<thead>
<tr>
<th>CXR finding</th>
<th>No. of tubercular patient (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>consolidation</td>
<td>24 (33.8)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>17 (24)</td>
</tr>
<tr>
<td>pneumothorax</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Bilateral extensive</td>
<td>10 (14.1)</td>
</tr>
<tr>
<td>tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Fibro nodular infiltrate</td>
<td>12 (16.9)</td>
</tr>
<tr>
<td>MilIary tuberculosis</td>
<td>10 (14.1)</td>
</tr>
<tr>
<td>Cavitary lesions</td>
<td>12 (16.9)</td>
</tr>
</tbody>
</table>

Table 4: Chest X-ray findings in Pneumocystis jiroveci pneumonia

<table>
<thead>
<tr>
<th>CXR finding</th>
<th>No. of pts. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground glass haziness</td>
<td>6 (95.5)</td>
</tr>
<tr>
<td>1 Zone</td>
<td>2 (33.4)</td>
</tr>
<tr>
<td>1 Zone</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>Upper zone</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Lower zone</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Middle zone</td>
<td>0</td>
</tr>
<tr>
<td>B/L lower zone</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>B/L parahilar opacity</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Ground glass haziness + B/L parahilar opacity</td>
<td>5 (71.4)</td>
</tr>
</tbody>
</table>

Table 5: HRCT thorax findings in study population

<table>
<thead>
<tr>
<th>HRCT findings</th>
<th>No. of patient (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of pleural effusion, had normal CXR, pneumothorax</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Consolidation</td>
<td>26 (46.4)</td>
</tr>
<tr>
<td>Meditational lymphadenopathy</td>
<td>26 (46.4)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Fibro nodular infiltrate</td>
<td>23 (41.1)</td>
</tr>
<tr>
<td>Cavitatory lesion</td>
<td>5 (8.9)</td>
</tr>
<tr>
<td>Pneumocystis jiroveci pneumonia</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Cystic lesion</td>
<td>5 (7.14)</td>
</tr>
<tr>
<td>Ground glass haziness</td>
<td>7 (100)</td>
</tr>
</tbody>
</table>

In present study about 95.5% patient has ground glass haziness on chest x ray. out of which 66.66% patient has more than 1 zone involvement and 33.33% patient has 1 zone involvement. In present study prevalence of upper zone, middle zone, lower zone are 16.66%, 0%, 83.33% respectively. Bilateral parahilar opacity seen in 71.42% patient. Ground glass haziness indicates early stage of pulmonary alveolar infiltration of pneumocystis jirovecii. This one of the marker of AIDS. Chi square test applied. p>0.01.

This finding similar to study conducted by A.Ahidjo et al. In which consolidation in 25% patient, pleural effusion in 16.7% patient, 20% patient had milliary tuberculosis. Upper zone involvement in 15% patient, lower or middle zone involvement in 11.7% patient, lymphadenopathy in 8.3% patient, nodular infiltrates in 3.3%. These findings are highly significant. (p<0.01).

Similar findings present in study conducted by Ying Xuan et al. In which pneumocystis jiroveci pneumonia maximum patient had ground glass haziness and parahilar opacity. On chest X-ray, Prevalence of lower zone involvement was maximum followed by upper zone.

Summary and Conclusion

Present study is descriptive, clinical study with cross sectional design with 100 HIV positive patient admitted in hospital ward during period of 2012-2014. This is done to study pulmonary involvement in PLHIV.

Following observation were noted and conclusions were drown.

1. In present study prevalence of tuberculosis was maximum in patient followed by bacterial pneumonia and pneumocystis jiroveci pneumonia respectively.
2. In present study prevalence of bacterial pneumonia was maximum in patient having CD4 count >200cells/µl lit. prevalence of tuberculosis is maximum in patient having CD4 count between 150-500/µl lit.
3. In pulmonary tuberculosis patient consolidation, pleural effusion, fibro nodular infiltrate, cavity, Pneumothorax, bilateral extensive tuberculosis were common findings on chest x-ray.
4. In pulmonary tuberculosis patient most common radiological findings were consolidation, mediastinal lymphadenopathy, fibro nodular infiltrate, cavity, Pneumothorax on HRCT.
5. In pneumocystis jiroveci pneumonia maximum patient had ground glass haziness and parahilar opacity. On chest X-ray, Prevalence of lower zone involvement was maximum followed by upper zone.
6. In pneumocystis jiroveci pneumonia prevalence of ground glass haziness and cystic lesion was maximum on HRCT thorax.

References

Darbepoetin Alfa Versus Erythropoietin Alfa for Treatment of Renal Anemia in Patients with Chronic Kidney Disease at the Pre-Dialysis Stage: A Randomized Non-inferiority Trial

Mehta KS¹, Sinha SD², Bandi Vamsi³, Bala Reddy⁴, Naidu NR⁵, Thakur PA⁶, Chary Sreenivasa⁷, Reddy VPR⁸, Pandey R⁶, Durugkar S⁷

Abstract

Background: Darbepoetin alfa (DA-α) is a long-acting erythropoiesis-stimulating glycoprotein with a three-fold longer half-life than Erythropoietin alfa (EPO). The objective of this study was to determine whether DA-α is as effective and well tolerated as EPO for treating renal anemia among Indian pre-dialysis patients with chronic kidney disease (CKD).

Patients and Methods: In this phase III, randomized, active-controlled, non-inferiority study, the pre-dialysis patients with CKD who had hemoglobin (Hb) levels <10 gm/dL received either EPO (50 IU/kg, thrice weekly) or DA-α (0.45 µg/kg, once weekly) subcutaneously (1:1) for 12-24 weeks (correction phase). The patients with Hb levels ≥10 gm/dL were switched directly to DA-α or EPO for 12 weeks maintenance phase. The primary efficacy endpoint was to compare the mean change in Hb level from baseline to end of correction phase (EOC) between DA-α and EPO. Safety was also evaluated.

Results: In ITT population (n=63), the mean change in Hb from baseline to EOC was similar in the DA-α (11.28 g/dL) and EPO (11.02 g/dL) groups. The difference in the mean change in Hb between these two groups was 0.23 g/dL (95% CI -0.46, 0.86). After adjusting for covariates (using analysis of covariance model), the difference in the mean change in Hb between these two groups was 0.03 g/dL (95% CI -0.20, 0.30). In PP population (n=46), the mean change in Hb from baseline to EOC was similar in the DA-α (11.28 g/dL) and EPO (11.02 g/dL) groups. The difference in the mean change in Hb between these two groups was 0.06 g/dL (95% CI -0.20, 0.32). Safety profile of DA-α and EPO was similar.

Conclusion: Our study results demonstrate that DA-α given at a reduced dose frequency is as effective and well tolerated as EPO for treating renal anemia in pre-dialysis patients with CKD.

Introduction

Anaemia is considered to be a common complication associated with chronic kidney disease (CKD), occurs due to decreased production of endogenous glycoprotein hormone erythropoietin by the damaged kidneys. Several lines of clinical evidences have confirmed the direct relationship between the severity of the anaemia and the deterioration in kidney function. Anaemia manifestation occurs early in pre-dialysis due course of CKD and is associated with development of cardiovascular disease and increased mortality in patients with pre-dialysis CKD. Improvements of quality of life and cardiovascular complications have been seen by correcting the anaemia with the help of ESAs.

Recombinant human Erythropoietin (r-HuEPO) is a glycoprotein that is similar to endogenous human erythropoietin (HuEPO) in terms of biological activity and physical characteristics. Recombinant human Erythropoietin is a short acting erythropoiesis-stimulating agent (ESA) has been available for almost two decades as gold standard therapy for the treatment of anaemia in patients with CKD. Although treatment with rHuEPO in dialysis patients has been shown to have been shown to eliminate the need for red cell transfusions, improve survival, reduce cardiovascular morbidity and enhance quality of life. However, the benefits of rHuEPO use in pre-dialysis patients are still a matter of debate. A recent Cochrane review suggested that the treatment with rHuEPO in pre-dialysis patients corrects anaemia, avoids the requirement for blood transfusions and also improves quality of life and exercise capacity. Recombinant human Erythropoietin has been approved for the correction of anaemia in chronic renal failure patients, and it is required to be administered two or three times weekly in the majority of patients due to its short half-life. The need for frequent dosing of rHuEPO is a considerable burden on both patients and health care staff, so long-acting ESAs have some advantages over short-acting ESA. Kawahara et al. 2015 have suggested that long-acting ESAs may be more useful for pre-dialysis patients with CKD since these patients do not attend hospital frequently, unlike dialysis patients.

Darbepoetin alfa (DA-α) is an erythropoiesis-stimulating glycoprotein has 3-fold longer half-life and decreased
Clinical studies have shown that DA-α administered once every other week was superior to weekly r-HuEPO for treatment of anemia in pre-dialysis CKD patients, and also offered enhanced convenience. The longer half-life enables DA-α to effectively maintain target Hb levels with less frequent administration than the epoetins/epoetin biosimilars. Darbepoetin alfa has similar dose requirements for both the subcutaneous and intravenous routes which offers greater simplicity of anaemia management for physicians compared to the epoetins.

Clinical studies have shown that DA-α administered once every other week was superior to weekly r-HuEPO for treatment of anemia in predialysis CKD patients, and also offered enhanced convenience. In India, the efficacy and safety of DA-α in the treatment of renal anemia in pre-dialysis CKD patients is not yet investigated. Therefore, this study was designed to determine whether DA-α is as effective and well tolerated as Erythropoietin alfa (EPO) when administered at a reduced dose frequency for the treatment of renal anemia in Indian pre-dialysis CKD patients.

Materials and Methods

Ethics

The study was conducted in accordance with ethical guidelines outlined in Helsinki Declaration of 1964, as revised in 2013 and Indian regulatory laws governing biomedical research in human patients. Institutional ethics committee approval was obtained from each participating study centre before initiating study. Prior to any study-related screening procedures, written informed consent was obtained from each patient before enrolling in the study. The study was registered with clinical trial registry (CTRI: CTRI/2012/07/002835) before enrolment of first patient in the study.

Study Design and participants

This prospective phase III, randomized, open label, two-arm, parallel group, multi-center, active-controlled, non-inferiority clinical study was conducted at 14 centres across India from Sept 2012 to May 2014. In this study, clinically stable patients of either gender (aged 18-65 years) with glomerular filtration rate (GFR) between 15-59 mL/min/1.73 m2 and had baseline Hb levels 7-10 gm/dL were enrolled. All the enrolled patients were either EPO - naive or on EPO (not within one week prior to screening), and had adequate transferrin saturation (≥20%) and serum ferritin (≥100 ng/mL). The patients undergoing peritoneal dialysis or have received dialysis or expected to receive dialysis in next 6 months were excluded. Pregnant women, lactating mothers, history of uncontrolled hypertension/ diabetes, congestive heart failure, systemic haematological diseases, severe hyperparathyroidism, infections, liver disease, hypersensitive to any of the active study drug substances were excluded from this study. Study treatment period involved two phases: Correction phase (12 to 24 weeks) and maintenance phase (up to 12 weeks: 24 to 36 weeks) (Figure 1). At baseline phase, the patients who had Hb levels <10 gm/d after receiving EPO were switched to subcutaneous injection of DA-α 0.45μg/kg (X Brand name X, manufactured by Hetero Drugs Ltd, India) once weekly or EPO 50 IU/kg (Eprex®, manufactured by Cilag AG, Switzerland) thrice weekly for 12-24 weeks (correction phase) in allocation ratio of 1:1. The patients who had Hb level <10 gm/dL at the end of correction phase were considered as treatment failure and discontinued from the study. The patients with Hb levels ≥10 gm/dL at the end of correction phase were switched directly to DA-α for 12 weeks maintenance phase. The dialysis patients who had Hb level ≥ 10 gm/dL at baseline phase were directly entered into maintenance phase, and were randomized (1:1) to receive DA-α (0.45 μg/kg) once weekly or EPO (50 IU/kg) thrice weekly for 12 weeks. In each treatment group, the dose of study drug was adjusted to maintain individual patients’ Hb within a target range of ≥1 gm/dL from baseline Hb and between 10-12 gm/dL throughout the 36-week study period. In correction phase, if a patient’s previous Hb fell below 7 gm/dL after receiving first dose, dose was increased by 50% of the previous dose. Also if patient’s previous Hb fell below 11 gm/dL after achieving the target range, the dose of study drug was increased by 25%. In maintenance phase, if a patient’s Hb increased above the target range (≥11.5 gm/dL) on two consecutive weekly assessments, the dose of study drug was decreased by 25%. If a patient’s previous Hb fell below 10 gm/dL after achieving the...
target range (10-12 gm/dL), the dose of study drug was increased by 25%. To ensure adequate support of the erythropoietic response to study drug, IV iron therapy was required to be administered to patients with serum ferritin values <100 μg/L. The IV iron dosing regimen used for patients with low serum ferritin values (<100 μg/L) was determined by the individual center’s treatment protocol.

Efficacy and safety assessment

Hemoglobin level was measured throughout the study period (correction and maintenance phase). The primary efficacy endpoint was to compare the mean change in Hb level from baseline to first evaluation visit (EOC) between EPO and DA-α. Secondary efficacy endpoints that included mean change in Hb level from baseline to Week 4 and end of second evaluation period (end of maintenance phase), Hb variability (in correction phase), mean DA-α dose, proportion of patients achieving the Hb target (defined as Hb increase of ≥1 gm/dL from baseline and Hb concentration of 10-12 gm/dL) at the end of first evaluation period and time to initial achievement of Hb target. Complete blood count, serum chemistry, and urinalysis were measured at baseline and after treatment to assess safety of EPO or DA-α. Adverse events were recorded at each study visit. Safety endpoints included the incidence of treatment-emergent adverse events (TEAEs) and immunogenicity assessment after treatment with EPO or DA-α. For immunogenicity assessment, all patients were tested for anti-drug antibody titres. DA-α/EPO antibodies sampling were performed before initial dose (Day 1 of week 1) of study medications and on Day 1 of weeks 5, 13, 25 and end of maintenance within 1 hour of dosing. Since there were various time points at which the screening, evaluation periods were ending in various subgroup of patients, the time points for immunogenicity varied accordingly in such patients. The samples were measured for relevant antibodies by ELISA method.

Statistical Analyses

Considering an estimated difference in mean change of Hb levels equal to 0.03 gm/dL for Darbepoetin versus EPO, and non-inferiority margin fixed at -0.5 gm/dL, 88 evaluable patients in the ratio of 1:1 to either DA-α or EPO treatment groups (44 patients in each treatment group) were required to assure at least 80% power for the non-inferiority test. Taking 20% of dropout rate, a total 110 patients (55 patients in each treatment group) was required to draw conclusion of this study. Efficacy analysis was performed on intent to treat (ITT) and per protocol (PP) population. ITT population includes the patients who were randomized, and received at least one dose of study drug, had baseline and at least one efficacy assessment at the evaluation period. PP population includes the patients who had completed all the study visits as per protocol without major protocol deviations. Safety analysis was performed on safety population, which included the patients who were randomized, and received at least one dose of study drug. The mean change in Hb level from baseline to first evaluation period (EOC) between EPO and DA-α was analyzed using analysis of covariance (ANCOVA) method with treatment as main effect and baseline Hb value as covariate. Within the framework of ANCOVA, the 95% CI for difference in mean Hb of treatments was calculated to assess the non-inferiority. The non-inferiority was accepted if the lower limit of two-sided 95% CI was above the non-inferiority margin -0.5 gm/dL. Change in Hb level from baseline to Week 4 in two treatment arms was analyzed using two sample t-tests at 5% level of significance. The p-value of ≤0.05 was considered as statistically significant. Proportion of patients achieving the Hb target (≥1 gm/dL from baseline and Hb concentration of 10-12 gm/dL) at the end of first evaluation visit (EOC) was analyzed by logistic regression. The time to initial achievement of Hb target was analyzed using Kaplan-Meier. All statistical analysis was performed using SAS® Version 9.4 (SAS Institute Inc., NC, USA).

Results

Patient disposition and characteristic

A total of 139 patients not requiring dialysis were screened for anaemia (Figure 2). Of these, a total of 63 patients (31 patients DA-α and 32 patients EPO) who met eligibility criteria were enrolled and randomized (ITT population). The PP population consisted of 46 patients (23 patients in each group). The demographics characteristic of safety population is presented in Table 1. Majority of patients were female in both the treatment groups, with the mean (SD) age of all enrolled patient was 50.3 (11.69). The mean (SD) dose of DA-α at week 1 and 12 was 25.70 (6.08 μg) and

![Fig. 2: Patients subjected in the analysis. *includes the patients who were randomized, and received at least one dose of study drug, had baseline and at least one efficacy assessment at the evaluation period. **Includes the patients who had completed all the study visits as per protocol without major protocol deviations.](image-url)
The difference in the mean change in Hb between these two groups was 0.02 g/dL (95% CI = -0.55, -0.59, p=0.94). This difference was not statistically significant despite the reduced frequency of DA-α administration. Similar trend of early increase in Hb levels from baseline was observed in PP population (difference in the mean change: -0.00, p=0.99). At the end of second evaluation visit, difference in the mean change in Hb levels between both the treatment was not statistically significant in ITT (p=0.5555) and PP population (p=0.8267).

In ITT population, the proportion of patients who achieved the target Hb level by the end of the first evaluation visit (EOC) was similar in both the treatment groups (DA-α vs EPO: 41.94% vs 56.25% respectively; OR [95% CI] = 0.57 [0.21 - 1.54], p=0.2654). Similar trend was observed in PP analysis (DA-α vs EPO: 39.13% vs 86.95% respectively; OR [95% CI] = 0.57 [0.21 - 1.54], p=0.2654). In ITT, the KM estimated median time to achieve the target Hb after DA-α and Erythropoietin alfa treatment was 6 weeks and 4.5 weeks. Similar trend was observed in PP population (DA-α: 6 weeks and Erythropoietin alfa: 4 weeks). The proportion of patients who maintained their Hb levels within the target Hb range (10-12 g/dL) by the end of maintenance phase was statistically similar in both the treatment groups (DA-α vs EPO: 54.84% vs 65.63% respectively; OR [95% CI] = 0.61 [0.22-1.70], p=0.3420) in ITT.
analysis. Similar trend was observed in PP population (DA-α vs EPO: 71.43% vs 95.00%, respectively; OR [95% CI] = 0.131 [0.01-1.21], p=0.0735). These results demonstrate that DA-α does not increase Hb variability compared with EPO, despite the reduced frequency of dosing. Furthermore, a smaller number of dose adjustments were noted in DA-α-treated patients compared to EPO-treated patients.

**Safety evaluation**

Eight (25.80%) patients in DA-α group and 8 (25%) patients in EPO group experienced at least one TEAE during the study period. Most of these TEAEs were either mild or moderate in severity; one patient (3.12%) in EPO group experienced severe TEAE (cardiac failure), which was considered as a serious adverse event. None of patient in DA-α group reported TEAE that was related to the study drug. In EPO group, one patient reported a TEAE that was probably related to the study drug. Four patients (13%) in DA-α group and two patients (6%) in EPO group reported Serious TEAEs. The most commonly reported events in both the treatment group were cough (DA-α vs erythropoietin: 9.67% vs 3.12%), iron binding capacity total decreased (3.22% vs 6.25%), oedema peripheral (6.45% vs 3.12%), thrombocytopenia (3.22% vs 6.25%), and serum ferritin decreased (6.45% vs 3.12%). Clinical laboratory evaluation of haematology, biochemistry and coagulation throughout the study showed no unexpected changes that could be attributable to the study drug. Vital signs were monitored throughout the study, and no changes in mean blood pressure or heart rate were observed in either treatment group. Overall, the safety profile of DA-α was similar to that of EPO, and no antibody formation to either treatment was detected.

**Discussion**

To the best of our knowledge, this is the first study designed to compare the efficacy and safety of DA-α versus EPO for treating renal anaemia among Indian pre-dialysis CKD patients. Our study achieved its primary efficacy endpoint demonstrating non-inferiority of DA-α compared to EPO, the most widely used comparator. The results of this randomized, active controlled study demonstrated that DA-α is as effective as EPO for treating renal anaemia in pre-dialysis patients, but at a reduced dose frequency. Darbepoetin alfa-treated patients successfully maintained Hb within the target and therapeutic ranges during the study, with a smaller number of dose adjustments as compared with the EPO-treated patients. Thus, the use of DA-α eliminates the need for frequent monitoring and dose adjustments. Also similar increases in Hb levels were seen in DA-α and EPO-treated pre-dialysis patients.

Evaluating iron availability for erythropoiesis is an important consideration when treating anaemia in CKD patients. Iron deficiency has the potential to inhibit the response to erythropoietin and DA-α and influence the measurements of efficacy. Hence, our study included iron supplementation in accordance with the clinical practice guidelines and recommendations for the correction of anaemia in CKD pre-dialysis patients [15, 16]. Thus, most patients in both treatment groups received iron supplementation and maintained serum ferritin concentrations above the recommended level, and there was no difference between treatment groups with respect to serum ferritin concentrations.

The safety profile of DA-α was similar to that observed in the EPO group. The majority of adverse events were related to the underlying disease and its treatment, and only one TEAE was reported as being related to EPO; none of the reported adverse events were related to DA-α. The safety data of DA-α in the present study appears to be better than the reported trials. The tolerability data are supported by previous reports suggesting that DA-α is well tolerated, with a safety profile similar to that of EPO. [17, 18]

**Conclusion**

Our study results demonstrate that DA-α given at a reduced dose frequency is as effective and well tolerated as EPO for treating renal anaemia in Indian pre-dialysis CKD patients.

**Acknowledgement**

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**References**


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Warnings and precautions: Novomix™ 30 biphasic insulin aspart is to be used by patients who have been shown to be able to effectively control their diabetes using insulin injections. The dose of insulin should be adjusted according to the patient’s clinical status. A patient who is already on an insulin regimen should not abruptly change to Novomix™ 30 biphasic insulin aspart without careful monitoring. Novomix™ 30 biphasic insulin aspart is contraindicated in patients with type 1 diabetes. Novomix™ 30 biphasic insulin aspart should not be administered intravenously. Novomix™ 30 biphasic insulin aspart should also not be administered to patients who are allergic to pork or beef proteins. Novomix™ 30 biphasic insulin aspart should be administered by subcutaneous injection. No increased risk of hypoglycaemia is associated with Novomix™ 30 biphasic insulin aspart compared to using insulin aspart alone.

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Avoiding Type 2 Diabetes Express Highway from Infancy to Old Age – Focus on Newer Risk Factors

S Ramnathan Iyer¹, Revati R Iyer², Bhagyalakshmi Venkatraman³

Abstract
The chronicity and the long term consequences of Type 2 diabetes mellitus (T2DM) demands prevention of the disease. Recognition and correction of risk factors is therefore of prime importance. T2DM being a multifactorial disease, has several risk factors. Some newer risk factors have recently been identified viz. diabetes in pregnancy, aberrations in breast feeding, sleep disorders, vitamin D deficiency and aging process. The present review gives a deeper insight into these risk factors which will help to avoid the T2DM express highway.

Introduction
Type 2 diabetes mellitus (T2DM) is a major non-communicable disease affecting millions of subjects across the globe. Its rising prevalence is a cause for concern. The disease has several adverse effects on body systems resulting in complications. T2DM results from both defects in both insulin secretion and insulin sensitivity and accounts for 90% of all diabetic cases. The World Health Organization estimated there were 135 million diabetic patients in 1995 and it is projected that this number will increase to 300 million in 2025.¹ Major contributions to the rise of diabetic patient population will be from India. This is probably a price we are paying for progress, urbanization and modern lifestyle. In India, there has been a gradual transformation of villages to towns, towns to cities and cities to metros. Society is embracing modern lifestyle. Hypertension, T2DM, sleep deprivation, sleep disorders like obstructive sleep apnea, ischemic heart disease are related to modern lifestyle. Type 2 DM is a multifactorial disorder where genetics, nutrition, life style and sleep play important roles in its genesis. The Diabetes Prevention Programme (DPP)² demonstrated that intensive changes in life style (diet and exercise for 30 minutes /day five days a week) in individuals with impaired glucose tolerance prevented or delayed the development of T2DM by 58 % as compared to placebo. This signifies that other factors are operational which need to be identified and corrected. In India, the narrow diabetic lane in 1970, over a course of years, transformed into an express highway.³ Several workers in India have documented this rise.³ Insulin resistance is the core issue in T2DM and every effort must be made to improve insulin sensitivity.

Risk Factors for T2DM– established and newer
There are several established risk factors for the development of T2DM. These include family history of diabetes, obesity, age ≥ 45 years, race/ ethnicity, previously identified impaired fasting glucose or impaired glucose tolerance, history of gestational diabetes, history of delivery of large babies, hypertension (B.P. ≥140/90mm Hg), low levels of HDLc≤ 35 mg/dl) and/ or increased triglyceride levels (≥ 250 / dl) and polycystic ovary syndrome. Stress and sleep apnea as risk factors have been mentioned.⁵


Sleep Deprivation
Sleep deprivation is sweeping the globe. Sleep has important homeostatic functions. Individuals differ in their biological sleep need, but on an average the sleep duration of adults ranges from 7-9 hours. This can be seriously compromised by competitive life style which forces subjects to push sleep to a secondary level of importance. The entertainment sector is active 24/7 adding to the woes.

Chronic Partial Sleep deprivation is the most common form of sleep deprivation. The usual causes of sleep deprivation are not allowing enough time for sleep due to work pressures, school/college/coaching classes timings, sleep disorders, excessive worry, depression, repeated awakenings from noise eg bed partner who snores loudly. Disorders like diabetes, backache, cardiac failure, asthma also cause sleep disturbances. Watching late night television/mobile phones exposes the retina to bright light which can inhibit the release of melatonin and delay the sleep onset further. We have reported rebound sleep deprivation in elderly subjects due to late arrival of their loved ones from place of work. ⁴ Also sleep deprivation can be due to destroyed sleep architecture as seen in patients with sleep disorders viz obstructive sleep apnea(unconscious sleep deprivation).

Esther Donga et al⁶ have reported that partial sleep deprivation during a single night induces insulin resistance in multiple metabolic pathways in healthy subjects. Also chronically reduced sleep times are associated with obesity.⁶ Systemic inflammation has also been described in subjects with short sleep duration.⁷ Sleep deprived subjects have tendency to overeat which promotes obesity. They can exhibit binge eating. Fast eating in
REM sleep deprived subjects has been reported by us.9 Daytime sleepiness which occurs as a consequence of sleep deprivation can be overcome by consuming drinks (tea and coffee) and food. Sleepy subjects can chew tobacco and/ or smoke cigarettes, in soporific situations. Consumption of tobacco and smoking are also risk factors for T2DM. Sleep deprivation induces or aggravates snoring by increasing muscular hypotonia and delaying contractions of the dilator muscles of the pharynx.9

Sleep Disordered Breathing- Obstructive sleep apnea (OSA)

Sleep disordered breathing (SDB) is a spectrum of disorders consisting of snoring, upper airway resistance syndrome and sleep apnea. Sleep apnea can be obstructive, central or mixed.

Obstructive sleep apnea is a common disorder which often escapes clinical recognition due to poor awareness among health professionals and also in society. In OSA there is repetitive pharyngeal collapse in sleep resulting in cyclical hypoxemia, cyclical hypertension, release of stress hormones and catecholamines. Both these effects are known to decrease insulin sensitivity and worsen glucose tolerance (Flow chart 1).

Symptoms of OSA

Habitual snoring and excessive daytime sleepiness are two prominent symptoms of obstructive sleep apnea. Snoring can decline with aging (reduction the slow wave sleep). The other nocturnal symptoms include witnessed apneas, choking, dyspnea, restlessness, diaphoresis, acid reflux, drooling, somniloquy, frequent change of posture in sleep, bruxism and unable to sleep well. Insomnia can be a presenting symptom due to repeated arousals. The daytime symptoms include sleepiness, fatigue, morning headache, poor concentration, decrease libido or impotence, decreased attention, depression, decreased dexterity and personality changes. Mood swings and angry behavior is often present which may force the subject to seek psychiatric advice. Both OSA and diabetic subjects often experience postprandial drowsiness, poor concentration, fatigue and depression.

Risk factors

The risk factors for OSA include obesity, chronic sleep deprivation, alcohol, narrow upper airway. Upper airway abnormalities have been linked to breast feeding (see later).

OSA is a risk factor for several cardiometabolic disorders viz hypertension, ischemic heart disease, diabetes and stroke. Habitual snoring predicts the onset of diabetes.10,11 Joq et al12 have reported that frequent snoring is associated with reduced glucose tolerance, as assessed by abnormal oral glucose tolerance test (OGTT) results and higher levels of HbA1c. It is known that the most important risk factor for OSA is obesity in general and central obesity in particular. Both poor sleep quality (eg OSA patients) and quantity (eg sleep deprivation) have the potential to raise blood glucose levels due metabolic aberrations. Fasting levels may be higher than post lunch levels. A 2 hrs post glucose blood glucose estimation after consumption of 82.5 gms of glucose monohydrate will be necessary for patients, who show normal fasting and postprandial blood glucose levels, to detect impaired glucose tolerance.

Epidemiological data on OSA

The Sleep Heart Health Study reported that >10% of the general population has some degree of sleep disordered breathing, with daytime somnolence correlated to the breathing disorder severity.13 The Wisconsin cohort study was a population based study in which 602 working subjects aged 30 to 60 years were enrolled and studied with an overnight polysomnogram. In this cohort 24% of men and 9% of women had abnormal apnea hypopnea index (AHI) indices (>5 events per hour).14

Results from the Sleep Heart Health Study,15 one of the largest community
Based cohort studies with overnight polysomnography, indicate that OSA is associated with impaired fasting glucose, glucose intolerance and type 2 diabetes independent of confounding factors such as age, sex, race, waist circumference and BMI. Several studies show the prevalence of sleep disordered breathing increases with age ranging from 5% to 15% in middle aged adults to approximately 24% in community dwelling adults.\(^{14,16}\)

**OSA, Lean T2DM and Obese T2DM**

Type 2 diabetes mellitus is an important constituent of metabolic syndrome both in the NCEP:ATP III and IDF criteria. However in developing countries majority of the diabetic patients are lean (60% non obese and many are lean BMI <18.5).\(^{17}\)

Although obesity is a major risk factor for OSA it can affect lean subjects due to anatomical factors on the face and upper airway viz macroglossia, retruded, small mouth. There are several similarities between Type 2 Diabetes Mellitus and OSA (Table 1).\(^{18}\)

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Type 2 diabetes mellitus</th>
<th>Obstructive sleep apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing prevalence with advancing age</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Family history</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Obesity</td>
<td>Often</td>
<td>Often</td>
</tr>
<tr>
<td>Lean subjects</td>
<td>Affected</td>
<td>Affected</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>Often insomnia, excessive daytime sleepiness, early awakenings, may have associated OSA</td>
<td>Snoring + EDS, Sleep architecture disrupted. May have associated DM (OSA risk factor for DM)</td>
</tr>
<tr>
<td>Post-prandial drowsiness</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Yes (Glycosuria)</td>
<td>Yes (Atrial natriuretic peptide release)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Part of metabolic syndrome</td>
<td>?A manifestation of metabolic syndrome. If associated with Syndrome X = Syndrome Z.</td>
</tr>
</tbody>
</table>

Fig. 1: Potential mechanisms formatting a vicious cycle where obesity may result in OSA and OSA may lead to weight gain\(^{21}\)

Obesity aggravates OSA and a vicious circle is set up. It becomes difficult to assess whether obesity is a cause or consequence of OSA.(Chicken and egg story)\(^{22}\) (Figure 1). Foster et al reported high prevalence of undiagnosed OSA (86.6%) among obese patients with type 2 diabetes.\(^{22}\) Viswanathan et al reported high prevalence of OSA in T2DM patients.\(^{23}\) Ip and associates observed an association between OSA and insulin resistance even in non obese subjects.\(^{24}\) OSA occurring in lean young subjects can lead to insulin resistance (Flow Chart 1). This Insulin resistance paves the path for T2DM /metabolic syndrome. OSA patients have shown to have increased triglycerides, total cholesterol/high density lipoprotein (HDL) ratio and low density lipoproteins and lower HDL values.\(^{25}\)

Recognition of OSA can at young age can be missed. The transitional phase from lean to obese is a very crucial. Proper sleep history from parents and relatives will often point to the presence of OSA since many years Childhood photographs would reveal a lean habitus. The clinical pointers of OSA at young age includes anatomical factors in upper airway, repeated upper respiratory infections, sleeping prone and somnambulism. Polysomnography is the gold standard for diagnosing OSA.

**Pregnancy, Sleep Disordered Breathing (SDB) and Diabetes**

Pregnancy is a diabetogenic state because the metabolic changes are accompanied by maternal insulin resistance. Pregnancy complicated by diabetes mellitus is associated with higher maternal and perinatal morbidity and mortality rates. During pregnancy majority of the women experience alterations in sleep. The physiological and biochemical changes of pregnancy places the women at risk for developing specific sleep disorders such as obstructive sleep apnea and restless leg syndrome. It must be appreciated that oxygen is also a nutrient to both mother and fetus. Pregnancy associated changes which increases the risk of sleep apnea include gestational weight gain, nasopharyngeal oedema, decreased functional reserve capacity and increased arousals from sleep. Factors which decrease the risk of sleep apnea include increased minute ventilation,
pregnancy. Pregnant women possessing craniofacial abnormalities both in bony and soft tissues are believed to be predisposed to SDB. Schutte et al. observed that 27% of a group of normal women reported third trimester snoring. Weight gain and obesity are important risk factors for the development of SDB in pregnancy. Franklin et al. observed that habitual snorers gained more weight than did the non-snorers. SDB has been proposed as a risk factor for adverse maternal-fetal outcomes including pregnancy induced hypertension and small for gestational age births. Maternal hypoxia due to SDB-OSA has adverse effects on fetus causing fetal growth retardation.

Pregnancy induced hypertension increases the risk of adverse outcomes such as prematurity delivery, fetal growth retardation and maternal morbidity and mortality. Manju Aggarwal et al. reported maternal morbidity on terms of pre-eclampsia and meconium-stained liquor was higher amongst snorers and SDB population of pregnant subjects. Also a higher chance of IUGR and intra-partum asphyxia (Apgar Score <7) was noted in babies born to mothers having snoring during pregnancy. Approximately 28% of children born in India are of Low birth weight. LBW is associated with elevated glucocorticoid levels in later life. Also LBW with stunting and muscle wasting is followed by overweight and obesity in later life. All this contributes to insulin resistance. A story from the womb to the tomb.

Genetic Basis of OSA

Although obesity is the strongest risk factor for OSA and has a clear genetic basis, causal modeling suggests that only 35% of the genetic variance in the apnea hypopnea index(AHI) is shared with pathways that determine body weight. Thus the majority of genetic variance for the AHI is likely due to influence of genes that influence other pathways including those that influence craniofacial structure, ventilatory control and possibly sleep-wake patterns.

Breast Feeding

Breast feeding is an integral part of infant growth. Craniofacial development is 90% complete by the age of 12 years. Breast feeding has nutritional, immunological and emotional benefits. Also it is important for the development of swallowing action of the tongue, proper alignment of teeth and shaping of hard palate. Breast has been designed to adapt to the shape of infant’s mouth. The tongue movement of the infant while being fed is peristaltic underneath the breast. This is critical for proper development of swallowing, alignment of teeth and shaping of hard palate. The use of bottle feeding, pacifier use and infant habits such as excessive thumb sucking etc. can cause tongue thrusts and malocclusions. This may cause OSA. Skull research has shown that before the invention of modern baby bottle about 200 years ago people had minimal malocclusion or decay. Also high palates, overjets were rare. Labbok et al. reported a direct relationship between length of breast feeding and occlusion; the longer the infant was breast fed the better was the occlusion. Further Kushida et al from Stanford described a formula for predicting OSA. It states that individuals with high palates, narrow dental arches, over jets, increased body weight and with large necks are at risk for OSA. Therefore reduced duration of breast feeding favours the development of sleep disordered breathing which may manifest in young age pining the way for development of several consequences including type 2 diabetes mellitus. In India duration of lactation is advised for 24 months. However, maternal duties may restrict breast feeding.

Vitamin D

Vitamin D deficiency and diabetes have one major trait in common: both are pandemic. The role of vitamin D in several metabolic disorders is well known. There is increasing evidence that vitamin D acts as a modulator of immune system. There is strong link between vitamin D deficiency and type 1 and type 2 diabetes mellitus. There seems to be overall trend for an inverse correlation between levels of 1,25(OH)D3 and both disorders. Vitamin D deficiency has been associated with higher risks for metabolic syndrome and T2DM. Population studies suggest that vitamin D and calcium may play a significant role in promoting beta cell function and insulin sensitivity. The National Health and Nutrition Examination Survey (NHANES), a large cross sectional study showed an inverse correlation between serum 25(OH) D and incidence of T2DM and insulin resistance. Data suggest that T2DM patients with vitamin D insufficiency have increased C-Reactive protein, fibrinogen and Hb1AC compared with healthy controls. This means that inflammation provoked by immune cells are implicated in insulin resistance and T2DM. Giulietti A et al. observed that administration of vitamin D ameliorates markers of systemic inflammation which are typically found in T2DM patients thereby possibly improving beta cell survival. Vitamin D3 supplementation of vitamin D-deficient type 2 DM patients tended to reduce insulin requirements and lower triglycerides. Evidence also indicates that vitamin D treatment improves glucose tolerance and insulin resistance.

Aging

There is a complex interaction between aging, sleep and T2DM. Somatopause occurs early in adulthood between ages 25-35 years. This age range corresponds to the human life expectancy before the development of human civilization. People over the age of 65 years constitute more than 40 percent of cases of diagnosed diabetes. It has been observed that blood glucose increases with advancing age. Modern life style has generated several disorders including sleep disorders which have an adverse effect on aging. Also, changes in sleep patterns known to occur with aging bear a close relation to the progression of aging process. Further OSA results in oxidative stress which in turn aggravates ageing. Sleep can be the hidden agenda in the aging programme.

With advancing age there is reduction of lean tissue and increase in fat content. The prevalence of sleep disordered breathing increases with age. Central obesity is a common feature of ageing process. The potential age dependent risk factors for development of sleep apnea in the elderly are increase in body weight, decreased lung capacity, increased upper airway collapsibility, increased sleep fragmentation, decreased slow wave sleep, decreased muscular endurance, decreased ventilatory control and decreased thyroid function. The potential age dependent outcomes
can be cardiovascular, metabolic, and neurobehavioural morbidity. Therefore sleep apnea is an age dependent condition with other potential associated age dependent risk factors and outcomes.  44

Parallel between aging and T2DM

Aging can be retarded with low calorie diet. (Calorie restriction is an important tool in the management of diabetes.) Stress aggravates or can precipitate diabetes. Stress also aggravates aging. Lastly diabetes itself aggravates aging via deposition of advanced glycation end products in various tissues of the body. Type 2 diabetes mellitus is possibly a state of premature aging.  3

Continuous Positive Airway Pressure and T2DM

Treatment of obstructive sleep apnea/hypopnea syndrome (OSAHS) in patients who also have diabetes with CPAP decreases the insulin requirements.  45 In a well designed study improvement in insulin sensitivity by CPAP therapy in patients with OSA has been demonstrated by Harsch et al.  46 Forty patients of OSA were taken up in this study. Lindberg et al  47 demonstrated reductions in fasting insulin levels and insulin resistance (estimated by HOMA) after 3 weeks of CPAP treatment in 28 men with OSA compared with matched controls. We have also reported beneficial effects of CPAP in 4 patients with type 2 diabetes.  48 This has important implications since patients with impaired glucose tolerance and mild diabetes can look forward to reversal of diabetes with treatment of associated OSAHS.

Conclusions

Recognition and correction of risk factors both old and new are of paramount importance to avoid the T2DM express highway. Prevalence studies indicate that sleep deprivation and OSA are highly prevalent. Sleep consultation and management of sleep disorders is gaining ground in the prevention of T2DM. OSA treated with continuous positive airway pressure improves insulin sensitivity and therefore prevents progressive beta cell failure. Detection of OSA in pregnancy is important. Optimal breast feeding is advisable. Vitamin D status needs to be checked. Efforts to retard aging process are essential.

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References

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Comprehensive Cancer Care: The Need of the Hour

Sunitha Daniel¹, Abraham M Varghese²

Abstract
Western world has seen a tremendous improvement in the outcome of patients with malignancies over recent years, which has not reflected in developing countries like India. There are several reasons behind this, most important being the lack of resources to cater to the varying needs of cancer patients in the country, but even in resource sufficient settings the situation is not ideal. Delayed involvement of the oncologist, poor utilisation of evidence based treatment; clinicians practising on their anecdotal experience, lack of definition of cancer treatment centres and regulatory framework, poor team work are some of the reasons behind this. Apex cancer treatment centres should dedicate their time and resources in framing policies and guidelines, research activities and decentralise the direct patient care. Integration and collaboration between cancer treatment centres in private sector will help in preventing duplication and under utilisation of resources; invest in newer modalities and will avoid unhealthy competition between these centres. There should be a cultural change in the perception of disease by patients, relatives and treating physicians. Early involvement of palliative care, especially in metastatic disease, will improve the overall outcome of the patients. There is an urgent need for implementation of clinical governance and quality regulations in all aspects of oncology care delivery.

Background
Over the past 15-20 years, western world has seen tremendous improvement in the management of malignancies through systematic changes in basic and clinical research, supportive care, infrastructure development and staff training. Development of Imatinib has changed the outcome of chronic myeloid leukaemia dramatically, but improvement in survival of acute myeloid leukaemia is due to excellent supportive care. Multidisciplinary team and oncologist with special interests in subspecialties has taken the decision making away from individual physicians to the specialist team, which is proven to improve outcome and in certain countries it is established by law¹. Evidence-based-medicine and development of national and regional guidelines has clearly aided clinicians to make treatment decisions based not just on clinical outcome, but also on the availability of resources and other local priorities².

In a developing country like India, where the current mortality: incidence ratio for cancer is 68.6, as against 37.7 in very high human development index countries, the spectrum of management is completely different, largely due to a lack of well developed, unified health care system catering to the needs of the entire country³. There is no minimum standard of care or benchmark for management of most diseases, let alone malignancies. The high cost of treatment in private sector, lack of resources in public sector and scarcity of screening programmes contribute to inadequate clinical care and late diagnosis with no hope of curative potential, the details of which is beyond the scope of this article⁴,⁵. But even in relatively affluent regions of India, where people have access to modern health care, there have been frequent occasions of practices not in accordance with current evidence. This could be due to the lack of common guidelines or protocols which can be followed by all, but these practices add unnecessary financial burden to the already stretched resources of the patient and family. Nevertheless, the system has its own merits with excellent hospitals and clinicians delivering state-of-the-art service to the patients, with limited resources, both in public and private sector and hence should not be demoralised.

In the current system, where patients have the liberty to choose their own doctors, an oncologist might not get involved in the initial diagnosis and decision making process leading to fragmented management plan. The typical example is, mastectomy done by general surgeon for breast malignancy, without considering the need for neoadjuvant chemotherapy or radiotherapy.

It is surprising to notice that even experienced oncologist do lot of empirical management even when established evidence based treatment modalities are available. Sometimes chemotherapy combinations are based on the individual’s anecdotal experience than established combinations and mutations specific targeted treatments are used without checking for mutation. Other major areas of concern are knee-jerk treatment of cancers where there are no clear indication to treat by any standards and few oncologists trying to treat cancers with available modality of treatment even though there is lack of evidence for the same. For example, treating early-stage lung malignancy or impending spinal cord compression due to myeloma with chemotherapy alone without considering radiotherapy or surgery even though such facilities are available in the nearby centres.

Factors to be addressed
Indian health system is dominated by private sector and cancer treatment centres are huge revenue generators. Clinician’s income is mainly decided by the number of patients he treats, encouraging clinicians to try and treat diseases which are out of their area of expertise. There is a complete

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lack of definition of cancer treatment centres and the level of care they should provide. Similarly, there is no restriction among clinicians as to what they are expected to treat nor is there an acceptable benchmark of expertise required of them. Even in institutions where complex malignancies are managed, there is no team work, specialisation or delegation. In the private sector a doctor earns less in comparison and there are no incentives for developing the department or system, research or teaching, so clinicians end up doing unregulated private practice to top up their income. There are many instances of unethical association between doctors and other industrial allies. Because of the vast amount of generic drugs available and increasing number of private diagnostic centres, there is a huge competition in the market. The regulatory bodies are unfortunately not able to implement the laws moderating this.

**What could be done to change the system?**

There are around 25 Regional Cancer Centres (RCC) in India, operating under the joint control and funding of central and state governments, in addition to dedicated cancer hospitals owned by state governments. These bodies are mainly acting as treatment centres and the volume of patients they handle is beyond their capacity, which limits their potential in doing research, teaching or acting as apex bodies in developing policies and guidelines. These centres should integrate with each other and with other government hospitals in delegating their clinical service effectively and dedicate their time to act as policy making bodies. In this context, the concept of National Cancer Grid of India, which started in 2012 with 14 centres and later developed to 80 centres by 2016, should be highly appreciated. Unfortunately, even after 4 years of development, a single guideline has not been published online nor does it have an active website. It shows the difficulty in dedicating time for these activities beyond patient care. By decentralising the patient care using the current resources and adopting clear guidance is probably the best short term solution and in long term, formation of new centres should be considered.

For the foreseeable future, in India major public sector funding will be diverted for tackling communicable and other common non-communicable diseases and other cancer care will remain under private sector, which will be keen to develop it due to its huge income generating capacity. Private hospitals with common vision, for example mission hospitals which runs on no profit no loss basis, should try to integrate and form network cancer centres sharing the treatment burden and budget. This will improve their potential to expand and acquire newer modalities of diagnosis and treatment rather than unnecessarily duplicating similar services. It is proved that, even in India, the survival of children with cancers treated in comprehensive cancer centres, approaches that in Europe or the US. Integration will also improve their negotiating capacity with pharmaceutical and other suppliers as well as reduce unhealthy competition between hospitals and all these benefits can indirectly lead to improved patient care. If integration at financial level is not possible, hospitals with different expertise should join together for establishing multidisciplinary team or tumour board where individual cases can be discussed.

There should be a cultural change in the perception of the disease both by the clinicians and patients. Acceptance of reality is often difficult for the patients and it should be the responsibility of the clinician to communicate this to the patient and family in the best possible way taking cultural background into account rather than exploiting their reluctance to accept by giving unnecessary expensive treatment to the patient. A landmark phase III RCT showed that introduction of palliative care to metastatic non small cell lung cancer not only improved the quality of life and mood but also improved the median survival. Palliative care-when combined with standard oncology care or as the main focus of care-leads to better patient and caregiver outcomes. These include improvement in symptoms, QOL, and patient satisfaction, with reduced caregiver burden. Earlier involvement of palliative care also leads to more appropriate referral to and use of hospice, and reduced use of futile intensive care. Based on all these evidences, ASCO has given a position statement and guidelines on the early integration of Standard Oncology care and Palliative care for any patients with metastatic malignancy or those with high symptom burden. Adequate communication skills training and involvement of Specialist Palliative care physicians early in the cancer diagnosis would also aid the oncologists with patient and family communication as well as to provide holistic care. Several unnecessary interventions can be prevented by this, especially in patients with poor performance status and have survival of less than 6 months even in best centres.

There is an urgent need for implementation of various aspects of clinical governance in oncology practice. Risk management, Internal and external audits, peer review process and appraisals on the performance and practices of individual clinicians and hospitals should be done and they should be willing to change their practice based on the reports. Minimum quality maintenance should be mandatory for all hospitals, laboratories and pharmaceutical industries and should not be by choice. Professional regulatory bodies should have a strong control over clinicians and should be willing to take disciplinary action against clinicians who are violating professional conduct and having unethical relationship with industry allies.

In a country which can spend only less than 4% of its GDP for health care, with limited regulatory authorities against a strong financial drive from the corporate hospital management, pharmaceutical industry, laboratory and imaging lobbies we need to be very vigilant in optimising our resources to treat cancer patients. Policy makers should also look into these factors when implementing strategies for prevention, mortality and morbidity reduction and palliation of cancer patients in India.

**References**

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An unusual Location of Primary Extradural Meningioma

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6 year old lady was evaluated for swelling over right shoulder of 8 months duration. MRI showed a well lobulated T2W isointense mass with central hyperintensity, T1W isointense with central hypointense expansile osteolytic lesion with soft tissue component of size 6.8 x 6.3 x 5.5 cm involving spine of scapula with associated thinning of spine and focal areas of discontinuity.

Patient underwent resection of the mass. Post op HPE was consistent with meningioma, IHC- EMA, bcl2, CD56, TLE 1, synaptophysin, PG, Desmin, SMA, Caiponin, S-100 protien, CD21, MIC 2 and chromogranin A negative.

Meningiomas are divided primarily into intradural and extradural types and account for approximately 20% of all primary intracranial neoplasm. Most common locations include cerebral convexity, skull base. The reported incidence of EDM varies from 2% - 4% in various studies. They are reported to arise from various sites such as scalp, orbit, paranasal sinuses, nasopharynx, neck, skin, mediastium, lung, adrenal gland and paraspinal region. Primary extradural meningiomas are more common in females (F: M :: 2:1.2) and have a bimodal age distribution with the first peak in 2nd decade and second peak in the 5th-7th decade. Extradural meningiomas are classified into 3 types:

Type 1: extracalvarial
Type 2: purely calvarial
Type 3: calvarial with extradiscal extension.

Type 2, Type 3 is further subdivided on the basis of location: - (a) convexity (b) Skull bas

On MRI meningiomas typically appear as lobular extra axial masses with well circumscribed margins and are isointense to slightly hypointense on T1W sequence and isointense to slightly hyperintense on T2W sequence. They demonstrate avid and homogenous enhancement.

On IHC, meningioma is EMA positive in 50-100% of cases. It is also positive for ER/PR/AR.

The management of extradural meningiomas depends on the WHO grade. Grade I meningiomas are managed by surgical excision only, while grade II and grade III meningiomas require adjuvant therapy in the form of radiotherapy or stereotactic radiosurgery. This is also used for the treatment of surgically inaccessible, recurrent or anaplastic meningiomas.

References


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A 73 yr old male presented with rapidly enlarging midline neck swelling of 2 months duration. Respiratory discomfort during breathing and hoarseness of voice occurred since few days. There was no history of palpitation, tremor or sweating. A physical examination revealed signs of pallor without icterus. A large midline neck swelling was found, which moved with deglutition. The swelling was more prominent on right side and soft in consistency. All routine haematological investigations and thyroid function tests showed normal results. Clinical diagnosis was multinodular goiter. Sonography showed diffusely enlarged thyroid gland with altered echotexture. Multiple nodular echogenic lesions were noted in both the lobes. Unenhanced Computed tomography (CT) of the thorax and neck revealed a mass with no distinct margins and predominantly fatty mass (~60 HU) with no distinct margins (marked by yellow asterisk) of the thyroid gland. The mass causes enlargement of the isthmus and extends to both right and left lobes. Small portions of the right and left lobes have a soft tissue attenuation (+50 HU), consistent with normal. CT: Computed tomography; HU: Hounsfield unit

Sonography is the mainstay for imaging the thyroid gland and is usually sufficient to make a diagnosis when combined with laboratory findings and fine needle aspiration cytology. Fatty tissue infiltration or fatty masses may be iso-echoic and cannot be differentiated from normal thyroid gland on ultrasonograms. For the current patient, sonography was not diagnostic, and the diagnosis of thyrolipomatosis was based on the CT and MR imaging appearances, and exclusion of other diseases.

References

Finding the Hidden-cerebellopontine Angle Neurocysticercosis

KK Pandita¹, Sushil Razdan¹

Abstract

Neurocysticercosis (NCC) is the most common parasitic disease of the central nervous system worldwide. The lesions of NCC are considered to be readily visualized by MRI or CT scan. We present a patient, of new daily persistent headache (NDPH) with normal initial CT and MRI scan of head, who later was found to have cerebellopontine angle region NCC.

Introduction

Despite impressive gains in diagnosis and availability of antiparasitic treatments, large gaps in both basic and practical knowledge about the Cysticercus and host responses to it exist. Factors hindering further advances are the lack of clinically appropriate model infections, and inability to maintain the life cycle experimentally. Therefore, reliance on naturally infected humans is, at present, the most appropriate study of NCC.¹ We report a patient, who initially presented with new daily persistent headache of undetermined origin, and later turned out to have neurocysticercosis.

Case Report

A 30-year-old truck driver presented to us on 24th December, 2015 with complaint of headache, for the past about one month. Initially, the headache, which was frontotemporal in location, would occur daily at any time of the day and was moderate to severe in intensity, and would last few hours. For the previous 15 days he described his headache being located at frontal and occipital regions and would occur at waking hours. The headache had no relation to posture change, coughing and straining. There was no history of trauma or fall. He declined any history of substance abuse except drinking of about 120mL of alcohol every day for the past many years. Non-contrast CT scan of his head (Figure 1) done ten days prior to presentation was unremarkable. He had no history of fever, anorexia, vomiting, vision disturbance, nasal, respiratory or any other systemic symptom. There was no history of seizures. On examination, he was in good general health and he did not seem to be in distress. He was afebrile with a blood pressure of 110/70 mmHg. His general and systemic examination was normal. His neck was supple. Examination of the optic fundi didn’t reveal any abnormality. His complete blood count, erythrocytic sedimentation rate, routine blood biochemistry was within normal limits. On his insistence non-contrast MRI of brain (Figure 2) was done on 25th December, 2015 that was unremarkable. He declined consent for lumbar puncture. In view of absence of red flag symptoms and signs, we prescribed oral prochlorperazine and propranolol along with analgesics and asked him to be under close follow up. At a follow up visit on 4th January, 2016, he reported complete resolution of his headache with no new symptoms. Three days later, that is on 7th January, 2016, he reported new symptoms of sudden onset double vision and right ear fullness. His otoscopic and other ear related clinical examination was within normal limits. Neurological examination was remarkable for

Fig. 1: Serial axial images of brain, at the level of lower brainstem, of a patient with neurocysticercosis. (1) CT scan done on 14th December, 2015 showing no abnormality; (2) MRI scan done on 25th December, 2015 showing no abnormality; (3) T2 weighted MRI scan done on 7th January, 2016 showing a hyperintense lesion with perilesional oedema; (4) T2 weighted MRI done on 28th March, 2016 showing clearing of lesion; (5) MRI showing a Coalescing ring enhanced lesion in the right cerebello-pontine angle

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nystagmus in right horizontal gaze. Rest of his general and systemic examination was unremarkable. His complete blood count erythrocytic sedimentation rate, routine blood biochemistry, X-ray chest, tests for antinuclear antibody and human immunodeficiency virus were within normal limits. Fresh Contrast enhanced MRI scan of his brain revealed two coalescing ring enhancing lesions in right cerebellar pontine angle region. (Figures 3 and 5). We made presumptive diagnosis of neurocysticercosis (NCC) and administered oral deflazacort and albendazole for a period of three weeks. After ingestion of embryonated eggs of adult tapeworm from the contaminated environment, the hatched oncospheres are carried by the blood stream to various organs and lodged in the small blood vessels where they may or may not develop into viable cysts. Viable cysts form after 2-3 months. Cysticerci in the brain parenchyma initially suppress the host inflammatory response. After an incubation period, estimated to be several years, the cysticerci lose the ability to suppress the host inflammatory response, leading to parenchymal inflammation. The cysticerci induce a granulomatous response, which gradually degrades the parasites. In some cases the lesions resolve. However, in others, degradation leads to formation of calcified granulomas, which become intermittently inflamed. The lesions of NCC are considered to be readily visualised by MRI or CT scans. In addition, the process of cyst degeneration is best depicted by MRI examinations. Viable cysts appear clear to gross examination (same density as CSF), hypointense on T1 and FLAIR examinations. The first indication of degeneration is the presence of enhancement, which indicates dysfunction of the blood brain barrier, most likely due to pericyst inflammation around a still viable cyst. When the cyst becomes grossly opaque, the MRI appearance changes from no signal to a bright signal on T1 and FLAIR sequences accompanied by dense enhancement. In the case of our patient CT and MRI scan has not been able to detect the viable cyst stage and early granulomatous stage of cysticercus (Table 1). Despite their high sensitivity, conventional MR sequences can fail to detect the cysticercus cysts within the cerebrospinal fluid spaces. However, obtaining three-dimensional spoiled gradient recalled echo imaging sequences can help in improving the detection of intraventricular NCC. At the initial presentation these special sequences were not done as there was no suspicion of neurocysticercosis, clinically.

Cysticercus can produce headache by two mechanisms. One, by obstructing the flow of cerebrospinal fluid and producing hydrocephalus. Two, when pain producing structures are irritated by the inflammation that occurs when viable cyst transforms into granulomatous stage. Imaging studies did not reveal any hydrocephalus, so it must have been the early inflammation of transition phase between viable cyst and granulomatous stage irritating some pain producing structure that was responsible for the initial NDPH. So in regions of world where cysticercosis is endemic, patients presenting with NDPH of undetermined origin may be imaged by special MR sequences, like three dimensional constructive interference in steady state (3D-CISS), or followed up closely and reimaged for seeking the hidden cysticercus in the brain.

### Discussion

Review of the published literature reveals three cases of cerebellopontine angle region NCC, all having been managed with surgery. Differential diagnoses of new daily persistent headache (NDPH) include migrainous-type headache, tension-type headache, subarachnoid hemorrhage, low cerebrospinal fluid (CSF) volume headache, raised CSF pressure headache, posttraumatic headache and chronic meningitis. Our patient’s clinical profile did not suggest any of these headaches, although tension-type headache could not be ruled out. Thinking retrospectively, it is obvious that NDPH, which our patient presented with initially, must have been because of the neurocysticercosis (NCC).

After ingestion of embryonated eggs of adult tapeworm from the contaminated environment, the hatched oncospheres are carried by the blood stream to various organs and lodged in the small blood vessels where they may or may not develop into viable cysts. Viable cysts form after 2–3 months. Cysticerci in the brain parenchyma initially suppress the host inflammatory response. After an incubation period, estimated to be several years, the cysticerci lose the ability to suppress the host inflammatory response, leading to parenchymal inflammation. The cysticerci induce a granulomatous response, which gradually degrades the parasites. In some cases the lesions resolve. However, in others, degradation leads to formation of calcified granulomas, which become intermittently inflamed. The lesions of NCC are considered to be readily visualised by MRI or CT scans. In addition, the process of cyst degeneration is best depicted by MRI examinations. Viable cysts appear clear to gross examination (same density as CSF), hypointense on T1 and FLAIR examinations. The first indication of degeneration is the presence of enhancement, which indicates dysfunction of the blood brain barrier, most likely due to pericyst inflammation around a still viable cyst. When the cyst becomes grossly opaque, the MRI appearance changes from no signal to a bright signal on T1 and FLAIR sequences accompanied by dense enhancement. In the case of our patient CT and MRI scan has not been able to detect the viable cyst stage and early granulomatous stage of cysticercus (Table 1). Despite their high sensitivity, conventional MR sequences can fail to detect the cysticercus cysts within the cerebrospinal fluid spaces. However, obtaining three-dimensional spoiled gradient recalled echo imaging sequences can help in improving the detection of intraventricular NCC. At the initial presentation these special sequences were not done as there was no suspicion of neurocysticercosis, clinically.

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### References

Takayasu Arteritis with Atrial Septal Defect Presenting as Sterile Corneal Melt

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Abstract
Sterile corneal melt in a previously healthy 40 year female with features of Takayasu arteritis with incidental atrial septal defect is presented.

Introduction
Takayasu arteritis is a granulomatous vasculitis of large vessels with a predilection of aorta and its main branches and pulmonary arteries. Patients usually present with claudication, headache, syncope or constitutional symptoms like fever, malaise, night sweats. The ocular manifestations are not uncommon in Takayasu arteritis. These include ocular ischemic syndrome, hypertensive retinopathy, Takayasu retinopathy. Sterile corneal melt is a rare presentation of Takayasu arteritis.

This is a case of 40 year female who presented with decreased vision in the right eye, incidentally found to have absent pulses and low blood pressure in both upper limbs. Her CT angiogram findings were suggestive of Takayasu arteritis (Figures 1, 2). So this article implicates a rare presentation of Takayasu arteritis.

Case Profile
A 40 year female initially admitted in ophthalmology ward with history of decreased vision in the right eye for past 1 month, history of pain and redness in the right eye one month back. Ocular examination revealed a sterile corneal melt with iris prolapse in the right eye (Figure 4). She was found to have very low blood pressure and absent pulses in both upper limbs. Patient was referred for physician opinion.

The patient is totally asymptomatic other than ocular symptoms. General examination was normal. On examination of the peripheral pulses, the brachial, radial and ulnar pulses were absent on both upper limbs. She had a carotid thrill with bruit on the right side. The blood pressure in right upper limb was 80/50 mmHg, left upper limb 70/50 mmHg, right lower limb 140/80 mmHg and left lower limb was 150/70 mmHg. There was a wide and fixed second heart sound with ejection systolic murmur of grade 2/6 in pulmonary area. Her respiratory system, abdomen, central nervous system were normal. Fundus was also normal.

Her blood investigations revealed elevated ESR 100mm/hr, positive CRP, RF, HBsAg, VCTC, VDRL, Mantoux were negative. Her renal and liver function tests were normal. ECG showed features of right axis deviation with features RV overload. Chest X-Ray was normal. Echocardiography showed dilated Right atrium and ventricle with Atrial septal defect of ostium secondum type left to right shunt with moderate PAH (Figure 3).

Arterial Doppler of both upper limbs showed diffuse wall thickening of both subclavian arteries with high velocity biphasic flow and a low velocity monophasic flow in both axillary and brachial arteries. There was a venous like flow with no pulsatility in both radial and ulnar arteries. There was no evidence of thrombosis.

Carotid artery Doppler showed diffuse intimal and medial thickness of common carotid and internal carotid arteries on both sides with increased flow velocity. There was no evidence of plaque.

CT Angiogram
Ascending aorta (2.8 cm), arch of aorta (2.6 cm) and descending aorta (1.9 cm) were normal in calibre. Branches of aortic arch like brachiocephalic artery, left CCA and left subclavian artery showed severe ostial stenosis with severe narrowing right and left CCA and subclavian artery (Figures 1, 2). Both vertebral artery were smaller in calibre. These features were suggestive of Takayasu Arteritis Type 1.

She was treated with injectable steroids and tectonic keratoplasty was done in the right eye (Figure 5). The vision in the right eye was improved in the postoperative period. The inflammatory markers ESR, CRP has come down with the treatment. She was on oral prednisolone 1mg/kg/day.

Discussion
Takayasu arteritis is an uncommon disease with an incidence of 1.2-2.6 / million/year. It is more prevalent in women of child bearing age. 10-20% are clinically symptomatic. ACR 1990 classification criteria for Takayasu arteritis includes
1. Age at onset ≤ 40 years
2. Claudication of extremities
3. Decreased/ absent brachial artery pulsation
4. Blood pressure of > 10mmHg difference between the extremities
5. Bruit over subclavian arteries or carotid
6. Arteriogram abnormality

3 out 6 criteria is needed for the diagnosis. Our patient had 5 out of these 6 criteria except for the claudication.

Takayasu arteritis can be classified into 6 types based on the angiographic involvement.

Type 1: Branches of the aortic arch
Type 2A: Ascending aorta, aortic arch and its branches

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Biliary Ascariasis Mimicking as Choledocholithiasis on Endoscopic Ultrasound

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Abstract

A 47-year-old female presented with features of biliary colic with deranged liver function tests. Endoscopic ultrasound from 2nd part of duodenum revealed two round filling defects in lower end of CBD suggesting choledocholithiasis. On examining from first part of duodenum, upper and mid common bile duct showed two linear shadows with anechoic centre typical of worm in the bile duct. The diagnosis was confirmed by endoscopic removal of single Ascaris lumbricoides that was folded on itself within the common bile duct, hence being seen as two round filling defects mimicking choledocholithiasis.

Introduction

Ascaris lumbricoides is a common tropical intestinal parasite. It has potential to migrate to various areas from small bowel especially into small orifices like common bile duct and occurrence in patients with systemic diseases like Rheumatoid arthritis, SLE, Polyarteritis Nodosa and Giant cell arteritis. Takayasu arteritis presenting as sterile corneal melt has not been reported so far anywhere.4 The presence of ostium secondum ASD in our patient was possibly coincidental.

In conclusion, our report not only presents an unusual ocular presentation of Takayasu arteritis, it also reiterates the importance of systemic examination in a patient with ocular presentation.

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showed linear filling defect (Figure 2). Biliary sphincterotomy was done. On balloon sweep, two ends of Ascaris Lumbricoides came out of papilla and on further traction on balloon the entire worm was removed. The worm had folded on itself within the bile duct, hence the lower end (Figures 3, 4) of it gave two rounded echogenic shadows on endosonography. Patient was subsequently given single dose of albendazole for deworming. On follow-up after two months, she was clinically asymptomatic with normal liver function tests. In tropical countries like India, where worm infestation is common, it is not uncommon to encounter biliary ascariasis.

Discussion

Infestation with Ascaris Lumbricoides is common in the tropical countries. Increasing number of cases of hepato-biliary ascariasis are being diagnosed due to better imaging and endoscopic techniques. Majority of the infested persons are asymptomatic or have vague abdominal symptoms. Clinical spectrum of ascariasis can present with symptoms pertaining to respiratory system, gastrointestinal system, pancreatico-biliary tract, appendix. A. Lumbricoides can migrate and enter into the small orifices like bile duct and pancreatic duct. Other parasites that are known to infest the biliary tract are Clonorchis sinensis, Opisthorchis viverrini, Opisthorchis felineus, and Dicrocoelium dendriticum. Fasciola hepatica and F. gigantica can present as acute hepatic or chronic biliary tract infection. From the bile duct worm can rarely enter into the cystic duct, gall-bladder or intrahepatic bile ducts. Biliary ascariasis can present as biliary colic, cholecystitis, recurrent pyogenic cholangitis or liver abscess.

Role of ERCP/endoscopic ultrasonography

As in trans-abdominal ultrasound, endoscopic ultrasound can identify ascaris in the bile duct as echogenic linear structure without any acoustic shadow with central sonolucent line. Once the diagnosis of biliary ascariasis is established, worm can be extracted after small biliary sphincterotomy.

Conclusion

This report shows that in cases of biliary colic, suspicion of biliary ascariasis should be kept especially in highly endemic countries like India. It can mimic choledocholithiasis owing to folding of the worm inside the CBD. A careful examination using endosonography followed by ERCP for extraction usually gives the diagnosis.

References

Basidiobolomycosis - Miss Me; It Hurts You

Murali Alagesan\textsuperscript{1}, Joel Franklin\textsuperscript{2}, J Jayalakshmi\textsuperscript{3}, TM Subba Rao\textsuperscript{4}, V Chaithra\textsuperscript{5}

Abstract
Basidiobolomycosis is a subcutaneous infection of the limbs and trunk caused by \textit{Basidiobolus ranarum}. It is one of the under diagnosed infection which usually occurs in tropical areas. High index of clinical suspicion is needed to diagnose this condition. We hereby report a case of basidiobolomycosis in a 25 year old male who presented to us with a non healing ulcer in left thigh. Biopsy showed granulomatous inflammation with fungal infection suggestive of phycomycosis. Fungal culture grew \textit{Basidiobolus ranarum}. Patient was treated with oral itraconazole. The ulcer resolved completely after 3 months of treatment.

Introduction
\textit{Z}ygomycosis is an infection caused by fungal agents belonging to the phylum Zygomycota. These are saprophytic fungi and are found ubiquitously in the environment. The class Zygomycetes includes two fungal orders: Mucorales and Entomophthorales. They have different pathogenic potentials; the order Mucorales primarily affects the immunocompromised patients causing invasive diseases like rhino cerebral or pulmonary mucormycosis with high mortality, where as the order entomophthorales, which include \textit{Basidiobolus} and \textit{Conidiobolus} genera, cause chronic infection in the subcutaneous tissue in the immune competent individual.\textsuperscript{1} Basidiobolomycosis is caused by the fungus \textit{Basidiobolus ranarum}. Here we present a case of subcutaneous basidiobolomycosis which was misdiagnosed as mucormycosis by histopathological examination.

Case Details
A 25 year old male software engineer from Coimbatore was referred to us for intravenous amphotericin B, for the treatment of his non healing ulcer over the anterior aspect of left thigh as biopsy of the lesion was reported as mucormycosis. He had this lesion for the past 3 months which started as a painless nodular swelling (Figure 1A). He had consulted many clinicians earlier and was on multiple antibiotics, but his skin lesion progressively increased in size. He had no co-morbid illness and was apparently normal 3 month back. Ultra sonogram of the thigh was suggestive of abscess in subcutaneous plane. He underwent incision and drainage (I and D) of the abscess which resulted in a deep cavitatory lesion. Culture from the material during I and D was sterile. As the lesion was worsening (Figure 1B) he underwent another debridement. Gram’s stain, AFB stain of the tissue didn’t reveal any organisms and bacterial culture of the pus was sterile. Biopsy of the ulcer was performed and sent for histopathological examination (HPE). The HPE was reported as extensive ulceration and dense inflammation of dermis and subcutaneous area with fat necrosis and abscess formation composed of neutrophils and eosinophils along with thin walled broad aseptate fungal hyphae branching at right angles and surrounded by fibrosis and dense inflammation with giant cells. PAS stain was positive. Final report was foreign body granuloma with many fungal hyphae resembling mucormycosis. At this point we decided to re-evaluate the patient. On examination, he had a 3×1 cm linear non tender ulcer with surrounding induration on the left thigh (Figure 1C). His complete blood count showed total leukocyte count – 7400 (Neutrophils -50 %, Lymphocytes-34%, Eosinophils-4%, Monocytes-7%), ESR – 24 mm in 1 hour. His blood glucose, renal function test and liver function test were within normal limits. Human Immunodeficiency virus 1 and 2 were non-reactive. Since the history and clinical picture didn’t fit with a diagnosis of mucormycosis (the morphology of the lesion, duration of the ulcer), a second opinion of the slide was sought. The histopathology description (Figure 2A, 2B, 2C) included the presence of granulomas in dermis and subcutis associated with the presence of numerous eosinophils. There were also scattered abscesses and eosinophilic material surrounding the fungal hyphae resembling Splendore–Hoeplli phenomenon. A probable diagnosis of subcutaneous phycomycosis was suggested with a comment that fungal culture was required for confirmation. Additional biopsy specimen was collected aseptically for fungal culture from the edge of the lesion. On Sabouraud’s Dextrose Agar, furrowed creamy brown, heaped up, radially folded colonies grew after 3 days of incubation (Figure 3). Lactophenol cotton blue wet mount showed aseptate hyphae and smooth walled zygospores with characteristic conjugation beaks which confirmed the fungus to be \textit{Basidiobolus ranarum} (Figure 4). After the diagnosis of basidiobolomycosis was confirmed, the patient was started on oral Itraconazole 200 mg once daily for 3 months. The ulcer healed slowly and complete resolution of the lesion (Figure 1D) was seen after 3 months.

Discussion
Basidiobolomycosis is caused by \textit{Basidiobolus ranarum}, a saprophytic fungus present in soil, decaying fruit and vegetable matter as well as in the gut of amphibians and reptiles.\textsuperscript{2} It can cause a variety of clinical manifestations including subcutaneous zygomycosis, gastrointestinal zygomycosis and occasionally an acute systemic illness. The subcutaneous form is a granulomatous infection of the skin and subcutaneous tissues characterized by the formation of firm, painless, disciform nodule generally on the
Conclusion

This case is presented to insist on the importance of clinical correlation of histopathology reports along with proper sampling and appropriate microbiological test while treating rare infections.

References

Hyponatremia Due to Secondary Adrenal Insufficiency

Anuj Sarma

Abstract

Hyponatremia is a common electrolyte seen in critical care patients. The rapid diagnosis to the cause of hyponatremia is crucial as delay may lead to poor outcome especially in elderly group of patients. Among the variety of cause of hyponatremia, secondary adrenal insufficiency is a overlooked cause. Here I present two cases in which hyponatremia got corrected once adrenal insufficiency was detected and treated.

Introduction

Hyponatremia is defined as plasma Na+ concentration <135 mm and is a very common disorder in patients admitted in ICU. The causes include euvolemic, hypovolemic, hypervolemic hyponatremia. Among the euvolemic cause, adrenal insufficiency is a important consideration which requires high degree of suspicion in order to detect early and treat properly.

Case Report

1. 71 yr. old male, known diabetic, presented to ICU with generalised weakness for last 2 weeks along with confusion and irrelevant talk for last 3 days. There is no history of fever, headache, vomiting. On examination patient in altered sensorium, pulse-80/min, BP-130/80 mmhg, chest, cvs-normal, JVP not raised, plantar bilateral flexor, neck rigidity absent, perabdomen-normal; edema of absent. There is no past history steroid medication or drug abuse. Investigation revealed- Na+-118.5 mg/dl, K+-3.42 mg/dl, serum osmolality-252.04 mos/kg, urinary osmole-312 mos/Kg, urinary spot Na+72 mmol/l. TSH-3.79 mIU/L, T3-1.6 nmol/l, T4-1.28 nmol/l. LFt, RFT is normal. CVP was 8 cm water, Abg-normal. Echocardiogram patient in altered sensorium, pulse-80/min, BP-130/80 mmhg, chest, cvs-normal, JVP not raised, plantar bilateral flexor, neck rigidity absent, perabdomen-normal; edema of absent. There is no past history steroid medication or drug abuse. Investigation revealed- Na+-118.5 mg/dl, K+-3.42 mg/dl, serum osmolality-252.04 mos/kg, urinary osmole-312 mos/Kg, urinary spot Na+72 mmol/l. TSH-3.79 mIU/L, T3-1.6 nmol/l, T4-1.28 nmol/l. LFt, RFT is normal. CVP was 8 cm water, Abg-normal. Echocardiogram patient conscious,vitals normal, no edema, normal JVP, normal CVP, urine spot na>20. The causes now included 1. Hypothyroidism 2. Siadh 3. Adrenal insufficiency. Hypothyroidism was ruled out as patient had normal thyroid function. The next possibility was adrenal insufficiency. Serum cortisol morning (8 am) was sent which showed level of 25.2 nmol/l (normal range 123-626 nmol/l), and the evening sample of 23.5 nmol/l (46.2-389 nmol/l). ACTH level sent came to be 13 pg/ml. The patient is now diagnosed to be a case of secondary adrenal insufficiency and treated with hydrocortisone injection. Gradually the sensorium of the patient improved and sodium level reached normal level in next 3 days. The patient is discharged on tablet prednisolone and is now on regular follow up.

2. 70 yr old female came to hospital with weakness, reduced appetite for 10 days and decreased sensorium for last 2 days. No past history of fever, headache, vomiting, over the counter drugs or steroid medication. On examination patient conscious,vitals normal, no edema, JVP not raised, per abdomen normal. Blood investigation revealed Na+116.1 nmol/l, K+4.59 mmol/L, urine osmolality 332.02 mosm/kg, serum osmolality of 224.0 mosm/kg, urine spot Na+158 mmol/L. TSH-3.56 mIU/L. Abg normal, CVP-7 cm water. USG abdomen, X-ray chest, MRI brain-normal study. Echo-normal study. Serum cortisol morning-78 nmol/l (range 123-626 nmol/l), evening-40.2 nmol/l (range 46.2-389 nmol/l). Serum ACTh-21 pg/ml, serum aldosterone-2.17 ng/dl, plasma renin-0.84.

Patient was diagnosed to be case of hyponatremia due to adrenal insufficiency and treated with hydrocortisone injection following which sensorium improved and sodium level reached to normal range.

Case Discussion

In both the cases mentioned above, patient both elderly group, presented with altered sensorium, weakness, loss of appetite, and on investigation found to have very low sodium. Despite correcting initially with hypertonic saline, the sensorium and sodium level did not improve. On further elucidating the cause secondary adrenal insufficiency was detected and treated promptly leading to quick recovery.

Hyponatremia is a common disorder occurring in 22% of hospitalised patients. It is subdivided diagnostically into 3 groups based on history and volume status, hypovolemic, euvolemic, hypervolemic. Among the euvolemic condition, secondary adrenal insufficiency is an important cause of hyponatremia. Secondary adrenal insufficiency is a condition associated with deficient production of ACTH. The symptoms include weakness, fatigue, weight loss, loss of appetite. Laboratory investigation findings include hyponatremia, low to normal ACTH, normal renin and aldosterone levels.

The mechanism leading to hyponatremia in adrenal insufficiency are multifactorial-this include

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1. Cortisol feeds back negatively on CRH and ACTH, an inhibitory effect that is removed with adrenal insufficiency.3,5
2. Cortisol deficiency results in increased hypothalamic secretion of corticotropin releasing hormone (CRH), an ADH secretagogue.5,7
3. In addition, cortisol appears to directly suppress ADH secretion.6,7 Thus, ADH levels increase when plasma cortisol levels are low. The increase level of ADH causes water retention and hyponatremia.

**Conclusion**

In summary a high degree of suspicion is needed to detect cortisol deficiency especially in elderly group who may present with nonspecific symptoms of weakness, lethargy, reduced appetite and hyponatremia as happened in both the above cases.

**Acknowledgement**

I want to thank almighty God, Chief Medical Director of Down town Hospital Dr N.N. Dutta Sir and all hospital teachers, sister and staff, my wife Dr. Gargee Borthakur, my daughter Tapashya Borthakur, my parents Hari Prasad Sarma and Bharati Sarma, my sister Jubita Sarma, my parents in law Sushil Chandra Borthakur and Gayatree Borthakur and the great Dr. Michael De Bakey whose inspiration, blessings gave me strengths in writing this case report.

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**Posterior Reversible Encephalopathy Syndrome in Dengue Fever**

**Sarkar S1, Chakraborty AP2, Roy MK3**

**Abstract**

Dengue, an arthropod born disease can present with mild febrile illness to life threatening dengue haemorrhagic fever but posterior reversible encephalopathy syndrome(PRES) which usually seen in hypertensive emergencies is rare in the setting of dengue. We are presenting a case where a patient presented with dengue, developed PRES.

**Introduction**

Dengue is an important arthropod borne disease worldwide with 50-100 million infections occurring each year.1 Disease caused by dengue ranges from a relatively mild febrile illness to a life-threatening condition characterised by extensive capillary leak.

Posterior Reversible Encephalopathy Syndrome (PRES) usually occurs in the setting of hypertensive emergencies, characterised by bilateral increase in T2 signal intensity in the white matter on MRI usually concentrated in the posterior part of the hemispheres. Findings are of white matter edema which normalizes over several weeks.2 The incidence of neurological manifestations is rare in dengue. Here we present a case of dengue fever with posterior reversible encephalopathy syndrome.

**Case Report**

A 68 years old non diabetic and non-hypertensive homemaker presented with history of continuous fever without chills for 5 days and altered sensorium since 2 days and one episode of generalised tonic clonic convulsions 1 day before admission. There was no history of headache, vomiting, antecedent exanthematous illness, vaccination, ear discharge, intake of drugs, no bleeding manifestations.

General survey showed the patient had tachycardia (110/min), hypotension (80/60 mmHg), high respiratory rate (34/min), elevated temperature (101.2°F), a puffy facies and poor GCS (7/15). Patient had no focal weakness, deep tendon reflexes were normal but the plantar response was bilaterally extensor. Sensory and cerebellar

**Fig. 1: NCCT brain was normal**

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we considered the possibility of Dengue above treatment. In this background sensorium even after 5 days of the showing expected improvement in lymphocytes), rest being normal. mg/dl with a cell count of 15/μl (all also sent and report was awaited. CSF normal limits. IgM Leptospira was out to be positive. Chest X-ray and NS1 antigen and IgM antibody came II antibodies were negative. Dengue Malarial parasite, MPDA and HIV I and 156 U/L; Se Bilirubin – 0.68 mg/dl). (AST - 96 U/L, ALT - 109 U/L, ALP – 151 mg/dl and creatinine – 3.1 mg/dl), deranged hepatic transaminases pre-renal azotemia (serum urea – 151 mg/dl and creatinine – 3.1 mg/dl), deranged hepatic transaminases (AST - 96 U/L, ALT - 109 U/L, ALP – 156 U/L; Se Bilirubin – 0.68 mg/dl). Malarial parasite, MPDA and HIV I and II antibodies were negative. Dengue NS1 antigen and IgM antibody came out to be positive. Chest X-ray and USG of whole abdomen were within normal limits. IgM Leptospira was also sent and report was awaited. CSF study revealed raised protein – 179 mg/dl with a cell count of 15/μl (all lymphocytes), rest being normal.

Meanwhile, patient was not showing expected improvement in sensorium even after 5 days of the above treatment. In this background we considered the possibility of Dengue encephalitis and at this stage patient was haemodynamically stable and an MRI Brain was done. It showed (Figure 2) - Multiple long TR hyper intensities in bilateral parieto-occipital cortex with subcortical white matter; no diffusion restriction, no contrast enhancement, no GRE blooming. MRI findings were consistent with Posterior Reversible Encephalopathy Syndrome (PRES).

Patient was put on supportive treatment only and showed gradual improvement in the sensorium over the next 2 days. Vital signs and general condition also improved and patient started to take food orally. Blood parameters and biochemistry gradually normalized. Blood Culture, IgM Leptospira reports came negative, ANA (by Hep2) was sent and came negative.

A repeat MRI (Figure 3) was done 2 weeks later and it showed complete resolution of the above findings.

**Discussion**

Despite extensive research, the pathogenesis of Dengue fever posterior reversible encephalopathy syndrome is not fully understood but endothelial dysfunction and failure of cerebral auto regulation play a key role. The brain edema is the result of active exocytosis of water rather than simply a passive leak from vessels subjected to high pressures. CSF pressure and protein may be elevated to more than 100mg/dl without any cellular reaction. Strongly associated conditions like hypertensive emergency, systemic lupus erythematosus, chronic kidney disease, immunosuppressive therapy, use of chemotherapeutic agents like tacrolimus, cyclosporine, vincristine and interferon alpha were all excluded in our patient. This case is important as never in the course of her disease our patient had accelerated hypertension and PRES occurring in the background of Dengue Shock syndrome is probably not reported elsewhere. It points towards a possible similar pathogenesis between the two; of endothelial dysfunction which invites further research.

**Conclusion**

Out of the various manifestations of dengue fever posterior reversible encephalopathy syndrome can be an atypical and rare presentation.

**References**


Myocardial Infarction in a Patient with a Rare Coronary Anomaly

Arindam Basu¹, Angshumitra Bandyopadhyay², Santanu De³, Kajal Ganguly⁴

Abstract
Congenital anomalies of the coronary arteries include anomalies in the origin, distribution and termination of the coronary arteries. Common anomalies included under this heading includes abnormal origin of a coronary artery from a different sinus, or from another coronary artery, passage in between two great arteries, or drainage into a cardiac chamber. Dual origin of a coronary artery constitutes an extremely rare form of such congenital coronary anomalies. Although such anomalies are common with the right coronary artery (RCA), those with the left anterior descending coronary artery (LAD) are rarely reported.

Introduction
Congenital anomalies of the coronary arteries have an incidence of < 1.3%. Of them, anomalies involving the RCA are although encountered often, those involving the left system, particularly the LAD are rarely, if ever, reported. Different researchers have put the incidence of Dual origin of LAD at different figures, mostly < 1%. Also, this rare anomaly has been subclassified based on their angiographic characteristics. Reports of acute coronary syndrome in these patients are very rarely reported.

Case Report
A 75 year old male, non-diabetic and non-hypertensive, presented to the Cardiology emergency at 2 AM with the complaints of acute onset of chest pain of 2 hours duration. Initial ECG done in the emergency revealed Inferior wall ST elevation myocardial infarction. The resident on duty admitted the patient to the ICCU. His vitals revealed bradycardia with a pulse rate of 52/min and a blood pressure of 92/70 mm Hg. There was significant residual angina but no dyspnoea, and the ECG showed a < 50% ST segment resolution. 2D- Echo showed hypokinesia of the infero-posterior wall with borderline depressed LV systolic function, with an LVEF of 50%. Blood biochemistry revealed an Hb level of 11.2gm/L and a creatinine level of 1.3 mg/dl, with an eGFR of 41.67ml/min. Patient was taken up for coronary angiography the next day.

Coronary angiography revealed the LMCA originating from the left sinus and branching into a small left anterior descending branch and a relatively larger circumflex branch. The LAD coursed normally till about the middle of the anterior inter-ventricular groove, giving off three diagonals and a large septal branch, and then the LAD suddenly seemed to disappear. The right coronary artery showed a tight lesion in the proximal part and an intermediate lesion in the mid part. The surprising part was that an aberrant branch of the RCA originating from the proximal part coursed back towards the anterior inter-ventricular groove and followed the course of a normal LAD from the middle of the groove till the apex and wrapped around towards the inferior surface of the LAD. This aberrant vessel was of a similar calibre as that of the native LAD, was longer and gave rise to a few septal branches.

The RCA proximal lesion was identified as the culprit lesion and this was dilated and a DES of size 3.5mm x 32mm placed and inflated at 14 atmospheric pressure. The procedure was uneventful.

The patient was initially observed in the ICCU for a day more and later, shifted to the general ward. He was released on the 5th post operative day and was found to be doing reasonably well on his first follow up visit 1 week later. Considering the aberrant distribution of his coronaries he was asked to undergo a CT coronary angiography, to rule out any further obstruction to the course of LAD. The CT coronary angiography confirmed the diagnosis of Dual LAD (Figure 1).

Discussion
Congenital coronary anomalies are rare and reported to occur in 0.64 – 1.3% of patients undergoing angiography. They may or may not be associated with underlying coronary artery disease. Particularly, anomalies concerning LAD (its origin, course and distribution) are rare, although such anomalies are common with RCA.

Dual LAD (also known as dual anterior interventricular artery) had been reported to occur with an incidence of 1% by Morettin as well as Spindalo-Franco et al. The term Dual LAD is an unusual coronary artery anomaly proposed by Spindola in 1983, who also classified these into four angiographic types (recently, the number of types of Dual LAD has been increased to six) (Table 1).

Type I: Running in the anterior interventricular sulcus (AIVS), the
Table 1: Spinaldo-Franco classification of dual LAD

<table>
<thead>
<tr>
<th>Type</th>
<th>S-LAD Origin</th>
<th>S-LAD Course</th>
<th>L-LAD Origin</th>
<th>L-LAD Course</th>
<th>Origin of major Diagonal vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Proximal LAD</td>
<td>Proximal AIVG</td>
<td>Proximal LAD</td>
<td>Proximal AIVG</td>
<td>Epicardial course on the left ventricular side of the proximal AIVG, reentering the distal AIVG</td>
</tr>
<tr>
<td>II</td>
<td>Proximal LAD</td>
<td>Proximal ATVG</td>
<td>Proximal LAD</td>
<td>Proximal LAD</td>
<td>Epicardial course on the right ventricular side of the proximal AIVG, reentering the distal ATVG</td>
</tr>
<tr>
<td>III</td>
<td>Proximal LAD</td>
<td>Proximal AIVG</td>
<td>Proximal LAD</td>
<td>Proximal LAD</td>
<td>Intramyocardial course in the proximal septum, then either emerging epicardially in the distal AIVG, or terminating intramyocardially as septal perforator arteries</td>
</tr>
<tr>
<td>IV</td>
<td>LMCA</td>
<td>Proximal AIVG</td>
<td>RCA</td>
<td>Proximal AIVG</td>
<td>Epicardial free wall course anterior to the infundibulum of the right ventricle traversing to the distal AIVG, or intramyocardial course within the septal crest emerging epicardially in the distal AIVG</td>
</tr>
<tr>
<td>V</td>
<td>LCS</td>
<td>Proximal AIVG</td>
<td>RCS</td>
<td>Proximal AIVG</td>
<td>Intramyocardial course within the septal crest emerging epicardially in the distal AIVG</td>
</tr>
<tr>
<td>VI</td>
<td>LMCA</td>
<td>Proximal AIVG</td>
<td>RCA</td>
<td>Underneath the RVOT</td>
<td>Underneath the RVOT in the area of the interventricular septum</td>
</tr>
</tbody>
</table>

Fig. 1: 3D reconstructed image of the CT coronary angiography of this patient

Conclusion

Dual LAD is an extremely rare variety of coronary artery anomaly; however, it has very little clinical significance in the absence of stenosis. When affected by obstructive disease, it can be subjected to revascularization by surgery. Familiarity with the types can help the surgeon avoid an incorrectly placed arteriotomy. Even though it confers an additional ischemic protection to the anterior wall, patients may still be exposed to the danger of an ischemic event affecting the other territories of the heart, as occurred in this case, or rarely, even the anterior wall may be affected by a myocardial infarction.

References

Better performers have

Volibo

No indications for GI therapy

VoliboM
Leeches are blood sucking annelid worms with ability to expand or contract their bodies. They are mainly found in shaded humid places such as swamps, lakes, slow streams etc. Hirudo medicinalis have been commonly used for medicinal purposes in Europe while Hirudo granulosa leeches are most common and abundant in India for the purpose.

Mature adult leeches on an average grow 5 centimeters in length; they are brown, greenish brown with a darker tone on the dorsal side. Worm has two suckers, one at each end. Anterior sucker has tripartite jaws, and on them about 100 sharp teeth, used to incise the host, where blood feeding takes place. Hind suckers mainly act as leverage. Incision leaves a mark that is an inverted Y inside a circle resembling Mercedes Benz logo.

Saliva of leech contains 60 different proteins and many pharmacologically active biological substances. They are injected in the host while sucking the blood and are responsible for the local anesthetic, analgesic, anticoagulant (hirudin), platelet aggregation inhibitor activity (Apyrase, collagenase etc.), and vasodilatation. Leech applications are not generally painful due to a local anesthetic effect. Adult worm can consume blood up to ten times their body weight in a single meal with 5-15 ml being the average volume taken. They drop off in 20 minutes or so because of tumescence after a full meal. The amount of blood could be controlled by prescribing appropriate number of these bloodletting leeches and if needed to constantly replace them.

Detailed description of leech therapy is found in the text of Sushruta Samhita (1000 BC) by Sushruta. He described six non-poisonous leeches and indicated the medical conditions where they were useful. Lord Dhanvantari (Nepal stamp, 1977) is traditionally shown with 4 hands. Here his left lower hand holds leeches. No other stamp or cancellation is issued on leech/s to the best of my knowledge during medieval and early modern period, leeches were used as part of bloodletting to maintain balance of four humors. Legendary Arabic physician Avicenna in his –Canon of Medicine (1020 AD) has discussed hirudotherapy in a comprehensive manner.

The use of leeches became very widespread in the 18th and 19th Century in Europe. However, Jan Baptista van Helmont (1579-1644) physician and chemical philosopher, presiding over medicine claimed that bloodletting was a dangerous waste of patient’s vital strength. The use of leeches became less widespread towards the end of the 19th Century.

Medical leech made an international comeback in 1970. Their use was pioneered by Russian surgeons who started it in tissue flap surgery. Today they are used in microsurgery to release or drain congested blood in wound sites. Plastic surgeons use them in challenging skin grafts. They have also been used in traumatic hand/fingers reattachment and reconstructive surgery. Their preference in these areas is because of the precision with which they can be applied. Regular post procedure checks for bacterial infection, prolonged bleeding is necessary. Used leeches are destroyed and discarded after procedure.

Medicinal leeches are grown in special biological farms meeting the conditions of sterility. In 2004, US FDA approved French firm to market leeches. They are typically stored in hospital refrigerator for plastic and re-constructive surgeons.

Leeches indeed have a place in the field of medicine, however disgusting they may seem at times.
Abstract

Diagnosis of cough poses a common dilemma during consultations at primary care settings in India. This Expert Opinion document presents a diagnostic algorithm for primary care physicians to distinguish between cough conditions that can be treated at the community level and potentially serious cough that requires specialist care. The etiology and diagnostic work-up primarily depends on cough classification based on its duration as acute (<3 weeks), subacute (between 3 and 8 weeks), and chronic (>8 weeks). A targeted screening of numerous causes of cough through salient history, including smoking status, environmental exposure, and medication use is recommended. Aggressive investigations are recommended with presence of “red flag” signs. Confirming the diagnosis by monitoring treatment response is essential. If cough persists, frequent causes of acute cough such as infections, asthma, cardiac disease, and foreign body aspiration often overlap with causes of subacute and chronic cough. For cough duration >2 weeks, pulmonary tuberculosis should be ruled out. Subsequently, asthma, gastroesophageal reflux disease, upper airway cough syndrome, environmental cause, or post infectious cough should be suspected. Refer to specialist care if cardiac cause is suspected. Patients would be treated empirically after considering overlapping etiologies. Thus, this diagnostic strategy could bring in greater accuracy in the clinical assessment of cough and accelerate the process of appropriate referrals to specialty care.

Background

Cough is a sudden and repetitively occurring protective reflex, which helps clear the large breathing passages from fluids, irritants, foreign particles, and microbes. Normally, cough acts as a defense mechanism for the airways and the lungs; however, in some conditions, it may become excessive and potentially harmful to the airway mucosa. The prevalence of cough in India is 5%-10%. It is one of the most common presenting complaints (30%) at the primary care setting. Cough may adversely affect the quality of life, sleep, and productivity at work. Cough may also lead to urinary incontinence and depression.

The existing international guidelines on cough diagnosis and management are tailored to specialty care, and they do not address challenges encountered in developing countries like India. In our setting, a large proportion of patients (68.7%) with cough are treated empirically without a definite diagnosis. Cough is a common manifestation of tuberculosis in India, with an incidence of 2.79 million. Diagnosis of pulmonary tuberculosis is missed in about 25% of the cases.

Following the recommended diagnostic criteria for cough management appears to be one of the major challenges faced by the primary care physicians in India. The diagnostic tests are either unavailable in the primary care setting or the patients cannot afford them; additionally, there is a longer waiting period for definitive diagnosis. Another concern is rampant self treatment of cough with overthecounter medications. Thus, a symptom based approach would help mitigate these challenges for general practitioners (GPs) in India. A simple and specific algorithm can help GPs distinguish between conditions that could be managed with empirical treatment at the community level and potentially serious illnesses that require specialist care.

Hence the objective of this consensus document was to provide a structured and systematic approach for diagnosis of cough in the Indian scenario and to assist primary care physicians in effective cough management.

The Process

Experienced pulmonologists from across India discussed the existing national and international guidelines, current evidence on cough diagnosis and management, and the applicability of these guidelines for diagnosis of cough in the Indian primary care setting. Based on literature review, clinical practice, and feasibility, a simple holistic step-by-step approach for the diagnosis and management of cough as a symptom was proposed. The recommendations were finalized on the basis of the consensus among the experts. This consensus document is the first attempt toward providing a simplistic algorithm for diagnosing cough in India.

Diagnostic Approach Toward Cough

The recommended systematic approach toward cough diagnosis is presented as an algorithm. It involves...
Cough is classified into 3 categories on the basis of its duration in adults: acute (<3 weeks), subacute (between 3 and 8 weeks), and chronic (>8 weeks).

**Duration of cough**

Cough can set in due to infectious causes such as sinusitis, influenza, pneumonia, and infective bronchitis. Based on a survey in Indian patients visiting primary care clinics, upper and lower respiratory tract infections were the cause of cough in 12.2% and 8.1% of patients respectively.

Other causes of acute cough could be asthma, congestive heart failure, and pulmonary embolism (Table 1). 13,14 In the same Indian survey, these noninfectious causes for cough were observed in 7.4% (asthma) and 0.5% (congestive heart failure) patients in the primary care settings. 3 Cough syncope is another cause of acute cough that should be aggressively investigated, especially in the elderly population, as it may have a cardiac or neurological origin. 15 Foreign body aspiration (FBA) and pharyngeal incoordination should also be suspected in case of acute cough in children. 16 Bronchoscopy is indicated if the medical history indicates FBA, as it requires referral to specialist care. 17

Acute cough of viral origin should be treated empirically and may not require aggressive investigations unless it is characterized by “red flag signs (Table 2)”.

The expert group recommended that, in the primary care setting, the following red flag signs (Table 2) are important and relevant for any decision regarding diagnostic investigations or referral to a specialist:

**Table 2: Red flag signs**

- Hemoptysis
- Prominent dyspnea
- Systemic symptoms such as weight loss, fever, sore throat
- Hoarseness of voice
- History of tuberculosis (self or in a person who is in close contact)
- Immunosuppressive state
- Smokers’ cough especially in patients >35 years of age
- Cough syncope

When cough is not associated with an obvious respiratory infection, the evaluation of patients is similar to that for chronic cough.

**Chronic cough**

Chronic cough could have multiple etiologies. Figure 1 shows the most common diseases observed in clinical practice in the primary care setting. 22

**Clinical history and physical examination**

Personal history taking is the key to identifying the cause of chronic cough. It should elicit history of smoking, exposure to irritants, and use of cough-inducing medications such as Angiotensin Converting Enzyme Inhibitors (ACEIs), β-blockers, and Amiodarone.

In case of such history, reconsidering the medications such as ACEIs, β-blockers, or Amiodarone, smoking cessation, and prevention of exposure to irritants may relieve the cough (elaborated in Figure 2A). 23 Persistence of cough after discontinuation of ACEIs raises the possibility of gastroesophageal reflux disease (GERD), postnasal drip, and asthma.

**Table 1: Causes of acute cough**

- Upper respiratory tract infections (bacterial or viral)
- Pneumonia
- Asthma
- Congestive heart failure
- Pulmonary embolism
- Foreign body aspiration

**Fig. 1: Causes of chronic cough**

ACE inhibitor; Angiotensin-converting enzyme inhibitor; GERD: Gastroesophageal reflux disease; TB: Tuberculosis

**Table 2: Red flag signs**

- Hemoptysis
- Prominent dyspnea
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- Smokers’ cough especially in patients >35 years of age
- Cough syncope

History of tuberculosis infection (self or in a person who is in close contact) is the India-specific addition made by the expert group, especially for the primary care setting. Similarly, expert group suggested that smokers’ cough be considered especially in patients >35 years of age as a red flag sign. In addition, the red flag signs in pediatric age group are neonatal onset cough, abnormal voice or crying and cough while feeding (with dysphagia) and vomiting. 18

**Subacute cough**

For a cough that has begun with an upper respiratory tract infection and has lasted for 3 to 8 weeks, the most common conditions to consider are postinfectious cough, bacterial sinusitis, postnasal drip, and asthma. 19 Most causes overlap with causes of acute and chronic cough. Patients with subacute cough are recommended to be first treated symptomatically.

**Postinfectious cough**

Postinfectious cough is the most common etiology of subacute cough. Approximately 12% to 48% of adult patients with subacute cough have postinfectious cough. 19,20 A self-limiting cough that persists after viral or virus-like infections is termed as postinfectious cough. It lasts for no more than 8 weeks, and the chest radiograph is generally normal. The causative pathogens observed are *Mycoplasma pneumoniae* and *Bordetella pertussis*. 21 Pathogenesis of postinfectious cough is unclear; however, the attributes are inflammation, epithelial damages of upper and lower airways, increased mucus secretion, and an increased reactivity of airways.
Key Messages: Clinical history and physical examination

Symptom-oriented physical examination (including cough sounds) is performed for the following:
- Classification of cough
- Identification of etiological factors
- Evaluation and ruling out of common causes of cough, e.g., gastroesophageal reflux disease, cough variant asthma
- Provisional diagnosis
- Referral to a Cardiologist, if required

Key Message

- A history of intake of Angiotensin-Converting Enzyme Inhibitors will help diagnose drug-induced cough

Other differential diagnoses of cough

Pulmonary tuberculosis

Pulmonary tuberculosis should be suspected if cough persists beyond 2 weeks after the initiation of initial treatment and presence of suggestive signs and symptoms. The National Strategic Plan emphasizes on early diagnosis and management of patients with tuberculosis who seek care from healthcare providers.24

All presumptive tuberculosis patients should be evaluated for sputum smear examination (spot–early morning or spot–spot). If the first sputum smear is positive and patient is not at risk for drug-resistant tuberculosis, it is categorized as microbiologically confirmed tuberculosis (Figure 2B).24

Asthma

Asthma (25%) and nonasthmatic eosinophilic bronchitis (10%) are among the common causes of chronic cough. Asthma was diagnosed among 7.4% of patients presenting with cough in an Indian study conducted with primary care providers.26 Although rarely performed in the Indian primary health care setting,27 spirometry can be employed to establish the diagnosis of asthma.28
Gastroesophageal reflux disease

GERD, singly or in combination with other conditions, can cause chronic cough. In patients with normal chest radiographic findings, GERD is the most likely cause of cough. However, accurate diagnosis of GERD-induced chronic cough is a major challenge. In addition, the consensus regarding the causal relationship between reflux and cough and the diagnostic approach to establish GERD etiology is lacking.

Cough due to GERD can be ruled out by administering proton pump inhibitor therapy and monitoring the patient; if the patient improves, the diagnosis is confirmed as GERD. However, it takes approximately 3 months for true GERD-related cough to improve. Chronic cough could be related to GERD if cough occurs at night time and/or postprandially, when the patient reclines, not in association with activity, and/or without the presence of postnasal drip.

Key Messages
- Specialized investigations* may be required to rule out gastroesophageal reflux disease
- If empirical treatment for asthma or coughvariant asthma for approximately 4 weeks provides no relief, treatment with proton pump inhibitors for gastrointestinal reflux disease may be added.

* pH testing, pH impedance testing, and/or an upper endoscopy

Upper airway cough syndrome

Upper airway cough syndrome (UACS) is the cause of chronic cough in around 30% of patients, but disease pathogenesis is unclear. UACS is difficult to diagnose and treat because it often coexists with other disorders that contribute to chronic cough. In most cases, UACS is diagnosed on the basis of its clinical symptoms and the patient’s response to treatment with an H1 receptor antagonist.

In patients for whom a specific etiology of chronic cough is not apparent, empirical treatment can be initiated for about 15 days if UACS is considered as the etiology.

Key Messages
- Signs of upper airway cough syndrome:
  - History suggestive of allergic rhinitis, nasal examination
  - Postnasal drip
  - A cobblestone appearance of the posterior part of the pharynx

Environmental factors

Environmental pollutants can cause airways to become hyperactive. Irritants such as sulfur, ozone, nitrous oxides, and indoor air pollution because of biomass combustions can cause chronic cough and asthma as the exposures are persistent.
Chronic cough may set in because of multiple causes, which, in turn, may have overlapping symptoms posing challenge in the differential diagnosis. Asthma, UACS, and GERD, alone or in combination, were reported to be responsible for 93.6% of the cases of chronic cough in Brazil, which were named as “pathogenic triad of chronic cough.”39 In addition to the overlapping etiologies, smoking, asthma, and allergic rhinitis were found to be the risk factors for cough among the elderly in a Korean cross sectional study. Moreover, comorbidities, constipation, and uncontrolled diabetes mellitus had positive associations with cough in the elderly.40 The comorbidities may contribute to respiratory symptoms and, consequently, to poor asthma control. In addition, the presence of comorbidities complicates diagnosis. Cardiovascular disease or left ventricular failure can cause symptoms of breathlessness and cough.41 Hence, thorough history, physical examination, and investigations such as electrocardiogram and imaging play a crucial role in accurate diagnosis. Given the overlapping etiologies, asthma, GERD, and UACS should be managed with empirical treatment. Referral to a specialist is recommended if cough persists.

Figure 2C shows the approach for diagnosing common etiologies of chronic cough such as asthma, GERD, UACS, and postinfectious causes.

**Table 3: Approach to cough in primary care setting in India**

<table>
<thead>
<tr>
<th>Cough type Duration</th>
<th>Acute &lt;3 weeks</th>
<th>Subacute Between 3 and 8 weeks</th>
<th>Chronic &gt;8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult population</td>
<td></td>
<td>Postinfectious cough</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric population</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diagnostic objective</td>
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<tr>
<td>Investigations</td>
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<tr>
<td>ACEI: angiotensin-converting enzyme inhibitor; ESR: erythrocyte sedimentation rate</td>
<td></td>
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</tr>
</tbody>
</table>

### Overlapping etiologies

Although rare (0.5%), cough is one of the presenting symptoms of cardiac failure with pulmonary congestion. In elderly patients, patients with past history of myocardial infarction, congestive heart failure, and in patients with paroxysmal nocturnal dyspnea, dry irritating cough, a cardiac cause, should be suspected and the patient should be referred to a specialist immediately.35

**Key Messages**

- Primary care providers should consider environmental factors as one of the important etiological factors for chronic cough.
- Diagnostic investigations are not recommended at primary care settings for suspected gastroesophageal reflux disease, and upper airway cough syndrome.
the primary care setting. Empirical management and preventing exposure

Box 1: Recommendations for differential diagnosis of cough for the primary care setting

- Cough may be treated empirically and may not require aggressive investigations unless it is characterized by "red flag signs" or persists for >2 weeks.
- Pulmonary tuberculosis should be excluded if the cough persists for >2 weeks after the initial treatment with suggestive signs and symptoms.
- Upper airway cough syndrome, gastroesophageal reflux disease, and cough-variant asthma should be diagnosed based on medical history and nasal examination and treated empirically. Referral should be considered for spirometry and other specialized lung function tests.
- Cough of cardiac origin should be suspected based on history of cardiac illness, the use of angiotensinconverting enzyme inhibitors, β-blockers, and amiodarone, and the presence of orthopnea and/or dyspnea, and the patient should be referred to a specialist.
- Environmental factors should be considered as one of the significant causes for chronic cough.
- Any neonatal cough, until an etiology is established, should be suspected for pneumonia. Referral for bronchoscopy is advised if foreign body aspiration is suspected.

to cough-inducing factors such as medications (ACEIs, β-blockers, and Amiodarone), smoking, and environmental irritants are recommended for cough >2 weeks old for patients with a normal chest radiograph and absence of red flag signs. If cough persists with suggestive symptomatology, pulmonary tuberculosis should be excluded and the diagnosis should be established on the basis of 2 sputum acid-fast bacilli smears and ESR. A chest radiograph can be repeated in case of sputum smear-negative patients. Patients in whom pulmonary tuberculosis is ruled out, asthma, GERD, UACS, or postinfectious cough should be suspected. If feasible, patients should be referred for spirometry to establish diagnosis of asthma. Chest radiographs can be repeated if cough persists after initial diagnostic work-up and treatment. In case the radiological findings persist, the patient should be referred to a specialist, where further investigations such as computed tomography scan, bronchoscopy, peak expiratory flow, or cardiac studies may be performed.

To conclude, this diagnostic algorithm will facilitate early diagnosis and better management of patients with cough in India at a primary care level. Compliance to this recommended approach will aid in reducing the overall burden of the disease associated with cough at the community level and encourage appropriate referrals to specialty care for definitive treatment. A similar algorithm for the treatment at primary care setting will be a suitable addon to this symptomatic approach for diagnosis of cough.

Disclosure

The expert meetings were done in association with Abbott Healthcare Pvt. Ltd. The views expressed and discussed in the meetings and stated in this consensus article are the views of the authors and not of Abbott Healthcare Pvt. Ltd.

References


CBNAAT: Cartridge Based Nucleic Acid Amplification Test; ESR: Erythrocyte Sedimentation Rate

Fig. 3: Combined algorithm for diagnosis of cough


Varicella Zoster Virus and Neurological Complications

Khichar Shubhakaran
Professor Neurology, Dr. S. N. Medical college, House No. E-22/13, Umed Hospital Campus, Jodhpur, Rajasthan

Sir,

I read an interesting case report published in Aug 2018 issue of JAPI (Vol 66 page no. 103) by Chouhan and colleagues. Herpes zoster is a major health burden affecting individuals of any age. Here I would like to share my views and experience:

1. Recently we had a patient who presented as Guillain Barre Syndrome which was diagnosed post varicella zoster sequela and treated successfully.
2. There were also two patients who had 6th nerve palsy as a complication of herpes zoster ophthalmicus.

Case 1: A 23 year right handed young female presented with history of diplopia of two days duration, after an event of herpez ophthalmicus of right first division of trigeminal nerve of approximately 3 weeks duration which was treated with acyclovir along with other supportive treatment. On examination patient had diplopia in left lateral gaze and on inspection was found to have left 6th nerve palsy. There was no history of any immune compromise state. The patient was investigated specially the magnetic resonance imaging (MRI) of brain and orbit, and cerebrospinal fluid examination, which were within normal limits. The patient was given intravenous methyl prednisolone 1 gm intravenous infusion for 5 days followed by a short course of oral methyl prednisolone, and the patient had an excellent recovery.

Case 2: A 55 year right handed male patient who was a known case of late onset diabetes of 5 years duration, had history of herpes zoster of left ophthalmic (V1) division of the trigeminal nerve of 13 days duration, which was treated with acyclovir along with other supportive treatment. On examination patient had diplopia of two days duration, after an event of left ophthalmic (V1) division of trigeminal nerve of approximately 3 weeks duration which was treated with acyclovir along with other supportive treatment. On examination patient had diplopia in left lateral gaze and on inspection was found to have left 6th nerve palsy. There was no history of any immune compromise state. The patient was investigated specially the magnetic resonance imaging (MRI) of brain and orbit, and cerebrospinal fluid examination, which were within normal limits. The patient was given intravenous methyl prednisolone 1 gm intravenous infusion for 5 days followed by a short course of oral methyl prednisolone, and the patient had an excellent recovery.

There are different views and observations in different studies. According to some studies the neurological deterioration like herpes zoster myelitis can be prevented with oral antiviral therapy even after a delay in diagnosis. While others observed no benefit of oral antiviral on ocular complications of herpes zoster ophthalmicus, which has been ascribed by others to a late starting of initial treatment.

So the aim of this correspondence is that varicella zoster is a preventable disease and it’s complications can be reduced by early recognition of varicella zoster and its effective treatment thereby reducing the burden on the society.

References


Prevalence of Associated Co-morbidities Influencing Choice of Migraine Prophylaxis in a Headache Clinic

Uma Sundar1, Sameer Shrirangwar2
1Professor, LTNMCH, Mumbai, Maharashtra; 2Senior Resident, TMC, Mumbai, Maharashtra

Sir,

The choice of migraine prophylaxis medication is often dictated by associated co-morbidities, leading to contra-indication to a particular prophylactic medication, or a desirable side-effect of another. Amitryptiline would be preferred in associated insomnia, depression and neuralgic pain, whereas Divalproex or Topiramate would be preferred in associated Epilepsy and bipolar mood disorder. Beta blockers would be chosen if there is associated Angina or Hypertension, but avoided in presence of asthma or brittle Diabetes.

We conducted a prospective observational study to assess burden of associated co-morbidities in Migraine, with serial recruitment of subjects from the Neurology and Headache clinics of a large teaching hospital. All patients with newly diagnosed or previously diagnosed Migraine, requiring prophylactic medications (2 or more migraine episodes per month, causing significant disability despite abortive medications), were included. There were no exclusion criteria. Migraine was defined as per the International Classification of Headache Disorders (ICHD)-2 criteria for Migraine with and without aura.

Evaluation of co-morbidities was done by interview, clinical examination on more than 2 visits, checking of lab data, EEG, X-rays, ECG, 2DEcho, and MRI brain. Depression was diagnosed as per DSM-4 criteria by standard interview format.

Windows SPS v 16 was used for analysis.

The study included 212 patients (162 women). There were 29 patients under 20 yrs of age, 91 in the 21-30, 69 in the 31-40, 20 in the 41-50 and 3 in the over 50 years age group. Migraine with aura was seen in 59/212 (27.8%) patients. Migraine duration was under 1 year in 40.5 % patients, and over 4 years in 12.2% patients. Among women older than 40 yrs (23/162), only 12 were newly diagnosed. The commonest trigger for headache was bright light and the commonest associated symptom was nausea.

Regarding co-morbidities, we found that Diabetes was present in 2.3% (5/212), Obstructive airway disease in 3.3% (7/212), Cardiac failure in 0.4% (1/212), Depression in 3.7% (8/212), associated vestibular symptoms in 33.4%(71/212), syncope/seizure in 33.4%(71/212), syncope/seizure in 33.4%(71/212), syncope/seizure in 33.4%(71/212), syncope/seizure in 33.4%(71/212), syncope/seizure in 33.4%...
2.3% (5/212), Ischemic heart disease in 0.9% (2/212), and hypertension in 4.7% patients (10/212). Depression among chronic migraineurs has been well documented. Among the 5 women (all under 40 yrs) with syncope / seizure, 3 had had more than 1 adult onset generalized tonic clonic seizure, with a normal epilepsy-protocol MRI brain and EEG; the other 2 had syncope with a normal EEG, normal MRI brain with angiogram and normal Tilt table testing response. The syncope was attributed to a complicated or basilar Migraine.

Depression and vertigo were both significantly commoner in women over 40 years as compared to younger women. (P 0.03, OR 3.58, 95% CI 1.12-11.41, and P < 0.0001, OR 3.78. 95% C I 2.10-6.81 resp.). The higher rates of Depression among older women could be related to longer Migraine duration, and higher prevalence of chronic vertigo.

Among the 50 men migraineurs, co-morbidities were significantly fewer (1 each had Diabetes, hypertension and asthma), probably due to their lower mean age (24 years - range 13-32).

References


Exertional Heat Stroke - Golden hour is the Key to Success: A Report from Peripheral Military Hospital of Northern India

Amol Patel1, Dharmesh Soneji2, Deepak Mulajker3, Manali Patell

1Med. Specialist and Med Oncologist, 2Consultant Med. and Medical Oncology, HOD, MDTC, Army Hospital Research and Referral, New Delhi; 3Med. Specialist and Med. Oncologist, Command Hospital, Western Command, Pune, Maharashtra; 4Associate Consultant, Critical Care Medicine, VPS Rockland Hospital, Qutub, New Delhi

Sir,

Exertional heat stroke (EHS) is an acute medical emergency with poor outcomes if not treated in time. We present our experience of treating nine patients of EHS and their successful outcome from peripheral hospital of northern India.

Total of 24 patients brought post exercise with heat related illness in the month of August and September. Out of these cases, nine were diagnosed as EHS with median age of 30 years (range: 18-36). The median rectal temperature was 104.5°F. The baseline clinical features and laboratory parameters are listed in Table 1. All patients were delirious at presentation with seizures in 18% of cases. Treatment started immediately with aggressive and rapid evaporative cooling. Patients were made naked, covered with wet cotton sheet and continuously cold water was splashed. Combination of other methods were used for non-responding patients with ice packs put over inguinal and axillary regions. Gastric lavage with ice cold water used for one patient. Continuous rectal temperature monitoring done and temperature brought to 99°F within 45 minutes to one hour. Fluid management was an integral part of management. Urine output of 50 ml/hr was maintained. Three patients had decreased urine output of < 30 ml/hour. They were treated with high ceiling diuretic inj Furosemide 10 mg to prevent myoglobin induced renal failure.

One patient had acute renal failure requiring haemodialysis for 6 weeks. All patients survived without any residual functional or neurological impairment. One patient suffered from rebound hyperthermia during the course of treatment. Three patients went on to develop mild hypothermia which recovered subsequently, possibly benefitting with mild hypothermia.

Six patients (66%) developed hypocalcaemia and lactic acidosis. Delirious patients were sedated using inj. Diazepam (88.89%), and non-responders were treated with (66.67%) continuous Inj. Propofol infusion for 12 to 16 hours. All patients recovered completely and were discharged from the hospital at mean 9 days of hospitalisation.

Rapid cooling is the treatment for EHS. Ice Cold Water Immersion is the method of choice but it is not readily available and practical issues are associated with it. In practice, combination of various methods is used. Deshwal et al reported clinical and biochemical parameters of 78 patients of EHS. All patients were paratroopers and evaporative cooling method was used immediately upon reception of patient. They also reported similar experience with no mortality. Tong et al reported 26.5% of mortality among 68 patients of exertional heat stroke with infections.

Time to start treatment is the most important factor in deciding outcome as it is for acute myocardial infarction. Immediate start of treatment improves outcomes.

We highlighted importance of the golden hour concept of heat stroke management. Evaporative cooling is the field method of cooling and can be used where ice water immersion facility is not available. The end point of cooling is matter of debate, the lower threshold of 99°F should be prospectively studied in future clinical studies.

Table 1: Baseline Clinical features

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
<th>Patient 8</th>
<th>Patient 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal temperature (°F)</td>
<td>104.3</td>
<td>105.1</td>
<td>106</td>
<td>104.2</td>
<td>104.5</td>
<td>105.4</td>
<td>105.9</td>
<td>104.3</td>
<td>104.2</td>
</tr>
<tr>
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<td>+</td>
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<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Systolic BP (&lt; 90 mmHg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Seizure</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Delirium</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Oliguria (&lt;30 ml/hour)</td>
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<td>-</td>
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<td>-</td>
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<tr>
<td>Respiratory symptoms</td>
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<td>Heat acclimatisation</td>
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<td>Done</td>
<td>Not done</td>
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<td>Alcohol consumption (night before exercise)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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</tr>
</tbody>
</table>

# Delirium in the form of violent behaviour, incoprehensible or irrelevant speaking; + Present, - absent
Hemophagocytic Lymphohistiocytosis (HLH) with Unusual Trigger

Anirban Mandal1, Puneet Kaur Sahi2

1Department of Pediatrics, Sitaram Bhartia Institute of Science and Research, New Delhi; 2Department of Pediatrics, All India Institute of Health Sciences, New Delhi

Sir,

We read with much interest the article by Babu Raj et al., published in the recent (March, 2018) issue of your journal but at the same time would like to make the following comments, which would benefit the general readers of JAPI.

The authors describe a 34 year old male with subarachnoid hemorrhage and left cerebellar contusion following an assault. He developed fever, skin rash, pancytopenia, splenomegaly, hepatitis, hypertriglycerideremia, hyperferritemia and evidence of hemophagocytes in the bone marrow. A diagnosis of Hemophagocytic Lymphohistiocytosis (HLH) was made and the patient was successfully managed with appropriate therapy.

Firstly, the authors state “Unusual trigger” for his HLH and though they suggest Epstein-Barr virus (although tested negative) and Phenytoin as the possible triggers they do not define any! We do agree with the authors partially. The patient had dysuria and his urine culture grew Enterococcus faecalis. Enterococcus being already known as a trigger for HLH, the authors should have considered it as the most plausible of all probable triggers in this case.

Secondly, a possibility of parvoviral infection was considered on the basis of erythroblasts showing “large basophilic intranuclear inclusions and cytoplasmic budding” but the typical inclusion bodies seen in parvoviral infection are eosinophilic. Moreover, with a strong suspicion of parvoviral infection they should have considered doing PCR based tests in this case to confirm the diagnosis when parvovirus IgM came to be negative. As the interpretation of the serological tests for parvovirus are often complicated by false negative results.

Thirdly, the authors have stated to use the “HLH-2004” criteria for diagnosis of HLH in the index patient but the aforementioned criteria requires a hemoglobin (Hb) of < 9 gm/dl and an absolute neutrophil count (ANC) of <1000/mm3 to diagnose anemia and leukopenia respectively. But the patient had an Hb of 9.1 gm/dl and a total leucocyte count of 1600/mm3 (ANC not mentioned).

Fourthly, the patients abnormal CSF findings were attributed to “a diagnosis of SAH / ? Partially treated bacterial meningitis” but HLH with CNS involvement can also give rise to a similar picture. An MRI of the brain with gadolinium could have helped in this case.

Though it is not mentioned we presume that such a patient of assault with subarachnoid hemorrhage may have received blood component therapy. This is of special interest in this case as the patient had fever, skin erosion and cytopenias along with hemophagocytes in the bone marrow. All of these could be seen in transfusion-associated graft-versus-host-disease (TA-GVHD) which is very difficult to differentiate from HLH without a skin biopsy.

References


Reply from Author

Aravind Duruvusal
Postgraduate, Dept. of General Medicine, Sri Ramchandra Medical College & Research Institute, Porur, Chennai, Tamil Nadu Sir,

I would also want to thank Anirban Mandal and Puneet Kaur Sahi for reading the case report and raising questions.

Firstly, we have not mentioned EBV as a probable cause, its Parvovirus as a probable cause. Enterooccus is a rare cause for HLH and in the case cited, occurred in a patient with AML post allogeneic transplant and was associated with bacteremia. Here, in our patient, a patient had Enterococcus growth in urine culture, but blood culture was sterile.

Secondly, parvovirus has been associated with multiple inclusion bodies. There are many case reports wherein Patients with Parvovirus infections whose inclusion bodies are basophilic. I would completely agree with them that PCR should have been done for this Patient, we also wanted to do a PCR for Parvovirus but could not be done due to logistic issues.

Thirdly, we have not stated that we have used “HLH -2004” criteria for diagnosis. We have used 2009 Diagnostic criteria for diagnosis.

Fourthly, HLH with CNS involvement was not considered because we had done an MRI with gadolinium enhancement for this patient, which showed only a resolving SAH and it did not fit in with classical findings associated with CNS involvement in HLH.

Finally, Patient did not receive any blood components, PRC was not required because Hemoglobin was never below 9 mg/dl. So the question of GVHD does not arise here.

References

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