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White Matter Changes and Cognition: Where do we Stand?

Satish Khadilkar, Nikhil Kadam

White matter hyper intensities (WMH) of presumed vascular origin are often seen on brain magnetic resonance imaging (MRI) in older subjects and in patients with strokes and dementia. They are known to increase the risk of stroke. The presence of WMH on MRI in patients having dementia raises the issue of mixed dementia, but the relative contribution from vascular factors and ongoing neurodegeneration vary from case to case and need to be weighed in individual patients before a diagnostic label is used.

Historically, the finding of altered areas of white matter attenuation on computerized axial tomography was discussed in the late 1980s by Hachinski and colleagues. They described patchy low attenuation in the periventricular and deep white matter, which they referred to as “leukoaraiosis” literally translating as rarefaction of the white matter. In subsequent years, as MRI scans were used widely, the MRI signal changes were confirmed to be in the periventricular areas, deep white matter and are also seen to occur in the deep grey matter. Neuropathologically, subtle WMH on MRI were associated with microglial and endothelial activation while extensive WMH were associated with reduced density of glia and vacuolation. WMH are part of the spectrum of small vessel disease which includes lacunar (or small subcortical) ischemic and haemorrhagic strokes, micro bleeds, perivascular changes and brain atrophy.

Until recently, WMH were generally dismissed as inevitable consequences of “normal” advancing age. Many recent studies, however, indicate that they have important risk factor associations, emphasizing that they should not be overlooked. The effects of these on cognition are cumulative. Besides their direct effects on brain, WMH are believed to increase the risk of brain damage in the presence of other pathologies. The prevalence of WMH increases with increasing vascular risk factors, like hypertension, diabetes, smoking. Several studies suggest that exposure to vascular risk factors in midlife is associated with an increased risk of dementia. In particular, hypertension and diabetes are known to be associated with a faster decline in executive function and processing speed. Whether these risk factors also affect structural brain aging and cognitive performance in individuals without dementia remains unclear.

It is well recognized that vascular risk factors are common to the pathogenesis of both vascular dementia and Alzheimer’s dementia (AD). Apart from the occurrence of a clinical stroke, the mechanisms by which vascular factors increase the risk of AD or accelerate cognitive deterioration among patients with AD are not yet fully elucidated. WMH may not fully explain the impact of vascular factors on the brain. Other more subtle structural changes may exist and have consequences related to cognition and dementia. The vascular brain injury could act additively or synergistically with concomitant AD pathology to produce more severe cognitive dysfunction than either process alone. This interpretation is supported by extensive clinical-pathologic data indicating that subjects with both vascular disease and AD pathology show more severe cognitive impairment during life than those with pure AD or require less severe AD pathology to produce the same amount of cognitive impairment. The presence of vascular factor however does not question or negate the actual neurodegenerative mechanism that underlies “pure AD”.

Thus, the important question no longer is whether vascular factors contribute to dementia, but to determine their relative contribution to types of dementia in general population. This subject is analysed by Umasundar and colleagues in this issue of the journal. Authors have investigated the prevalence of important risk factors like hypertension and diabetes in patients having AD and compared with cognitively normal age, gender matched controls. The article narrates correlation of white matter abnormalities with aging and vascular risk factors as well as cognitive abnormalities. The authors conclude that periventricular white matter hyper intensities were significantly more in the hypertensive AD group, as compared to the non-hypertensive AD group. Deep white matter hyper intensities were seen only in the control group and their severity did not show an association with gender or the presence of hypertension and diabetes. The study revealed that deep white matter abnormalities are largely prevalent in an older, cognitively normal population, and not specifically associated with AD. This is in contrast to the previous studies which appear to suggest that deep white matter changes are more representative of true ischemic insults, than those in the periventricular regions. One of the limitations of this study is the sample size and perhaps a larger dataset will be necessary to validate these observations.

In practice, this means that a clinician treating a patient with AD should acknowledge that the patient’s symptoms could be due in part or could be precipitated by vascular risk factors. In a similar fashion, in patients with vascular-related dementia, accompanying neurodegenerative pathology could partly explain the clinical presentation. We need to take into account the respective influences of both vascular risk factors and neurodegenerative pathologies. The interplay of these two often has a role in the initial manifestation or
worsening of the patient’s symptoms. The therapeutic goal is to maximize the cognitive capacity of the patient for as long as feasible. Aggressively treating vascular risk factors could potentially thwart the cognitive deterioration. However, it has not been convincingly shown in a therapeutic trial that controlling vascular factors reduces the risk of AD.

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The Effect of Hypertension and Diabetes Mellitus on White Matter Changes in MRI Brain: A Comparative Study between Patients with Alzheimer’s Disease and an Age-matched Control Group

Uma Sundar1*, Abhilasha A Manwatkar2, Anagha R Joshi3, Prashant Bhandarkar4

Abstract

Background: White matter hyperintensities (WMH) on MRI brain in the periventricular and deep white matter regions are commonly seen in older persons with normal cognition and in patients with AD.

Aims: To compare presence and severity of WMHs in patients with AD with that in a cognitively normal control group, and to evaluate effect of presence of Hypertension and Diabetes on WMHs in both groups.

Material and Methods: Thirty four patients with AD were serially recruited from Neurology and Psychiatry OPDs. An age and gender matched cohort of 24 persons with MMSE over 27/30 from the community acted as controls. Vascular risk factors, MMSE and MRI brain were assessed in all. Fezekas’s and Pasquier grading of WMH and atrophy were done. Periventricular WMHs (PVWMH) and Deep WMH (DWMH) were assessed separately.

Results and Conclusions: Overall, Periventricular WMHs of grade 2 and over were seen in 19/34 patients, and in 7/24 controls (P value 0.044). Significantly higher grades of PVWMHs were seen in hypertensives as compared to non-hypertensives in the case group, and in women compared to men. In the control group, hypertension had no effect on severity of PVWMHs. Among both Diabetics and non-diabetics, no difference in PVWMHs was found between the case and control groups.

DWMHs were, conversely, seen only in the control group.

Overall, over a quarter of cognitively normal older persons had WM hyperintensities of grade 2 and over on MRI brain; 55% of AD patients had PVWMH of Gd 2 or over, and no DWMHs.

Background

The diagnosis of Alzheimer’s disease (AD) does not require that the MRI brain be free of old ischemic insults. If a patient presents with the classical features of memory loss progressing to a more general cognitive dysfunction, any minor ischemic changes on the MRI may be considered irrelevant except in the rare instance of dominant hippocampal infarcts. In the Indian population, subclinical lacunas and periventricular/deep white matter changes on the MRI are often picked up incidentally due to high prevalence of uncontrolled or undiagnosed vascular risk factors.1,2 The co-incident occurrence of these changes in a patient with AD possibly raises the concern of a diagnosis of mixed dementia and also impacts progression of severity of Dementia.3,4

This study is designed to see the effect of hypertension and diabetes mellitus on white matter changes in MRI brain of patients with AD, as compared to an age matched, cognitively normal control group.

Materials and Methods

This prospective observational comparative study was performed between known patients of Alzheimer’s diseases (AD) and healthy individuals (control) over 60 years of age. The patients of AD were diagnosed as per DSM-4 criteria, and recruited from Neurology and Psychiatry OPDs in a tertiary care public hospital over 11 months. Patients with prior recorded and clinically obvious strokes were excluded. For the control group, we included age and gender matched persons from the community with MMSE score over 27/30, who consented to participate in the study, and who had not had a previous clinical stroke.

All subjects underwent evaluation for vascular risk factors, viz., Hypertension and Diabetes Mellitus. Review of case records, BP recordings twice, and review of fasting and post prandial blood sugars and HbA1c levels, along with treatment details were noted, before concluding that subjects had either Hypertension or Diabetes. Current MMSE scores, and duration of illness were noted for the patient group.

MRI protocol included 3D flair sag, T2 axial, SWI axial, Diffusion axial, and T1 3D sequences.

Features noted included Fazekas’s score grades 0-3 in periventricular as well as Deep white matter, and grading of cerebral atrophy by Pasquier scale in the range of 0-4. Additionally, presence of any lacunes, gliosis, or micro hemorrhages (on GRE sequence) were noted. The films were independently read by 2 senior radiologists.

Our primary outcome measure was the evaluation of White matter hyperintensities in Periventricular and Deep white matter areas (PVWMH and DWMH) on MRI. The secondary
Table 1: Demographic variables, prevalence of diabetes, hypertension and MMSE scores in AD and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>AD (34)</th>
<th>Control (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>26 (76%)</td>
<td>8 (34%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Age groups</td>
<td>Mean ± SD</td>
<td>72 ± 6.36</td>
</tr>
<tr>
<td></td>
<td>&lt; 65</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>65 - 69</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>70 - 74</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>75 - 79</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>≥ 80</td>
<td>4</td>
</tr>
<tr>
<td>Hypertensive/Non-Hypertensive</td>
<td>16/18</td>
<td>12/12</td>
</tr>
<tr>
<td>Diabetics/Non-Diabetics</td>
<td>11/23</td>
<td>6/18</td>
</tr>
<tr>
<td>MMSE Score</td>
<td>&lt;= 15</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>&gt; 15</td>
<td>22</td>
</tr>
</tbody>
</table>

The prevalence of these comorbid conditions was statistically similar in the 2 study groups. In our study, both the duration and control of Diabetes and Hypertension were comparable in the AD and control groups. (Duration of Diabetes in control vs AD was 13.6 vs 14 yrs, and of Hypertension was 14.7 vs 16 yrs. Mean fasting sugar in control vs AD was 112 vs 140 mg%, and PLBS was 178 vs 192 mg%, whereas average BP was 154/90 mm Hg in control group and 150/90 mm Hg in AD group).

Overall, PVWMHs of grade 2 and over were significantly more prevalent in AD group (seen in 19/34 AD patients, and in 7/24 controls - P value 0.044). Among Hypertensives, significantly more subjects had worse PVWMHs of grade 2 and 3 in the AD group, than in the control group, as opposed to non-hypertensives where no such difference was found (Table 1). Among both Diabetics and non-diabetics, no difference in severity of PVWMHs was found between the AD and control groups. Among women, the AD group had significantly higher number of persons in the worse category of PVWMHs (Grade 2 and 3), than the control group. This was not seen among males (Table 2).

With regard to DWMHs, none in the patient group had Grade 2 or over changes, whereas 6/18 in the control group had Grade 2 or over changes (P value 0.002). Thus, significantly higher number of subjects were seen in worse category of DWMs, in the control group as compared to the AD group, in hypertensives as well as non-hypertensives, and in diabetics as well as non-diabetics.

No participants from control group had a cerebral atrophy score of 2 or more, while AD group had 18 (53%) with cerebral atrophy score of 2 or more. Due to this, cerebral atrophy score was significantly higher in AD group for the comorbid conditions.

**Discussion**

The presence of WM changes in patients with AD, with or without existing vascular risk factors such as Hypertension and DM, raises the concern of a diagnosis of mixed dementia, as well as adding a burden of subcortical Dementia (executive function abnormality) to the existing cortical dementia in AD. It is well recognized that vascular risk factors are common to the pathogenesis of both VaD and A.D. Subcortical vascular changes on MRI are usually gradual and progressive and not related to a particular index stroke. Their prevalence in AD patients, and possible contribution to cognitive dysfunction, was the subject of interest in this study.

The high prevalence of recognized as well as undiagnosed Hypertension and Diabetes in the general population in India has been documented in various population studies. We looked at the prevalence of Hypertension and Diabetes among our 2 study groups and evaluated the effect of these 2 variables on WMHs on MRI. These comorbid conditions were statistically similar in the 2 study groups.

In our study, among the 34 patients with AD, 15 had 0-1 Fazeka’s scores and 19 had Gd 2-3, in the PVWM, as compared to 17 and 7 with Gd 0-1, and 2-3 respectively, in the control group. This difference for higher grades of score in the AD group was significant (p = 0.047, OR = 0.32. 95% CI 0.107-0.9868). Conversely, when the DWM was considered, none of the patients with AD had the higher grades of Fazeka’s.
score, all 34 patients having only 0–1 grades; in the control group, however, 6/24 subjects had Gd 2–3 changes. This difference for higher grades of the score in the control group was again significant at a P value of 0.033(OR 24.24, 95%C I 1.29-454.6).

Clinicopathological and imaging correlations of the WM hyperintensities have been described.10,11 The available pathology describes periventricular WMH as having discontinuous ependyma, gliosis, loosening of the white matter fibers, and myelin loss around tortuous venules in perivascular spaces. The gliosis, demyelination, and fiber loss have been reported to worsen as the periventricular WMH worsens.12 In deep WMH, there was demyelination, gliosis, and axonal loss around perivascular spaces, with vacuolation and increased tissue loss as the lesions became more severe. The periventricular and Deep WM changes have been described as a continuum.15-14 Various studies have also shown correlation of WMH with vascular risk factors,15 and shown progression in severity with aging and cognitive decline over time.16,17

In our study, severity of PVWMHs was more marked in AD group, whereas severity of DWMHs was more in the control group. This calls into question the etiopathogenesis, links with vascular risk factors, and association with cognitive dysfunction, of PVWMHs and DWMHs, as separate entities. Studies have looked at the difference between periventricular and Deep WM hyperintensities, ascribing different etiopathogenesis to each. Smooth PVWMHs may be due to interstitial fluid leakage in periventricular area and are likely to be non-ischemic, whereas DWMHs and irregular PVWMHs have been postulated to be ischemic in etiology. Additionally, DWMHs are likely to be due to small vessel disease whereas irregular PVWMHs may result from chronic hemodynamic insufficiency.18-20 The higher prevalence of deep WMH in the control group as compared to the AD group could be due to higher prevalence of undocumented risk factors such as proximal carotid stenosis or higher lipid levels, in the control group.

In the control group with normal cognition, 7/24 (29.1%) and 6/24 (25%) subjects had higher grades of Fazekas’s scores in PVWM and DWM respectively. Half of the control population had Hypertension, and a quarter were Diabetic. Additional vascular risk factors which were operational were gender and age. Alcohol and tobacco abuse, high waist hip ratio, and lipid abnormalities could also have been contributory, but were not recorded in this study. In this control group, the presence of Hypertension did not influence development of worse DWMHs, as ¼ of the control group had Grade 2-3 DWMH in both the hypertensive and the non-hypertensive groups. Also, in the control group, the presence of Diabetes did not affect development of worse grade of DWMH (2/9 with Gd 2 or over in non-DM group as compared to 1/3 in Diabetic group- P 0.173, 95% C I -38.64-71.57). Similarly, 1/3rd of both genders had Grade 2-3 DWMH.

The correlation of WM abnormalities on MRI with aging and vascular risk factors on the one hand, and with progression of cognitive abnormalities on the other, is the subject of many ongoing studies. Medina et al have demonstrated significant decrease in white matter integrity in the posterior and deep white matter regions, on DTI-MRI studies, in AD and Mild Cognitive Impairment.21 Akisaki et al have demonstrated correlation between WMH and lower cognition in an elderly, diabetic Japanese population.22

The dichotomy between PVWMHs and DWMHs in our study, was of particular interest. Previous studies appear to suggest that DWMHs are more representative of true ischemic insults, than PVWMHs. Our study suggests that DWMHs are largely prevalent in an older, cognitively normal population, and not specifically associated with AD. It is possible that these MRI changes of WMHs would also correlate with severity and duration of AD; due to paucity of numbers, we did not subanalyse for WMH grading in relation with AD severity. Another limitation of our study was lack of volumetric analysis. Volumetric analysis of the hyperintensities would help to quantify the data, and better correlations with changes in cognitive scores over time would then be possible. Despite these limitations, we believe the study’s findings are applicable and generalisable to the Indian population.23

Conclusion

This study showed that over a quarter of cognitively normal, older Indian persons had WM hyperintensities of grade 2 and over on MRI brain.

Fifty five percent of patients with AD had PVWMHs of Gd 2 or over on MRI, significantly more than in an age-matched control group. PVWM hyperintensities were significantly more in the hypertensive AD group, as compared to the non-hypertensive AD group. DWMH were, conversely, seen only in the control group, but their severity did not show an association with gender, or the presence of Hypertension and Diabetes.

References

Correlation of Computed Tomography of Colonic Wall Thickening with Colonoscopy

Harshad Khairnar1*, Meghraj Ingle2, Shamsher Chauhan3, Nirav Pipalia1, Prabha Sawant4, Vikas Pandey5, Akash Shukla6

Abstract

Introduction: Computed Tomography of abdomen frequently shows bowel wall thickening with different grades and characteristic of thickening. The correlation of bowel wall thickening (BWT) with endoscopic findings is not well described in Indian population. Therefore we did this study to determine the correlation of BWT with endoscopic findings.

Methods: Its Prospective single center study with 85 Consecutive patients with age group more than 12 years with CT scan abdomen showing bowel wall thickening were included in the study. Colonoscopy was done subsequently within a span of 15 days with appropriate bowel preparation. Colonooscopic correlation was done in relation to site, degree and characteristic of thickening. Biopsies were taken at the site of visible abnormalities on endoscopy and from normal appearing mucosa in case of strong suspicious of disease.

Results: Total of 85 (37 men) consecutive symptomatic patients with colonic wall thickening on computed tomography underwent colonoscopy. The mean age group was 34.2 (SD±17.35) years. Endoscopy was normal in 20 patients (24%) and abnormal in 65 patients (76.5%). Patients with mild thickening were more likely to have normal endoscopy than those with moderate/severe thickening (19 versus 1 patient; p<0.001). The abnormality rate was similar across different bowel segments (left vs right side; 85.7% versus 76.5%, p<0.57). Out of 65 patients with endoscopic abnormality, 41 (62.12%) had tuberculosis, 10 (15.16%) had neoplastic pathology or sometimes it may be normal.1 Clinicians often see patients with or without abdominal complaints with imaging showing bowel thickening. Based on imaging findings such patients are often referred for endoscopic evaluation. However there is always a dilemma for doing diagnostic endoscopy as there are no definite guidelines published on this issue. This dilemma arises in patients with low index of suspicion for sinister pathology or in the elderly patients in whom invasive procedure can cause high procedure related complications. Some studies have tried to correlate CT reports of BWT with subsequent endoscopic findings.1,6-8 There is lack of published data from India. We conducted this study to determine whether a CT finding of BWT predicted a pathological findings on subsequent endoscopic evaluation of the reported site of BWT. We also sought correlation of degree and nature (regular versus irregular) of BWT on CT with endoscopic abnormalities.

Methods

This was a prospective observational study conducted between 1st June 2017 and 30th October 2017 at the Lokmanya Tilak Municipal Medical College Sion, Mumbai. 85 Consecutive patients with age group more than 12 years with CT scan abdomen showing bowel wall

Introduction

Bowel wall thickening (BWT) is an increasingly recognized entity on Computed Tomography (CT) of abdomen. It could represent inflammatory, infectious, ischemic or neoplastic pathology or in the elderly patients in whom invasive procedure can cause high procedure related complications. Some studies have tried to correlate CT reports of BWT with subsequent endoscopic findings.1,6-8 There is lack of published data from India. We conducted this study to determine whether a CT finding of BWT predicted a pathological findings on subsequent endoscopic evaluation of the reported site of BWT. We also sought correlation of degree and nature (regular versus irregular) of BWT on CT with endoscopic abnormalities.

Methods

This was a prospective observational study conducted between 1st June 2017 and 30th October 2017 at the Lokmanya Tilak Municipal Medical College Sion, Mumbai. 85 Consecutive patients with age group more than 12 years with CT scan abdomen showing bowel wall

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Received: 19.03.2018; Accepted: 01.12.2018
thickening were included in the study. Demographic data was collected for all patients. Patients with past history of gastrointestinal surgery for any bowel pathology, gastrointestinal malignancy, intestinal tuberculosis were excluded from the study. On CT BWT was graded as mild (3-5 mm), moderate (6-9 mm) and severe (>10 mm) in presence of satisfactory distention. For the purpose of correlation with endoscopy BWT on CT was categorized into following four segments (1) Right segment: which included Ascending colon, IC valve, Cecum and Terminal ileum. (2) Left segment: which included Descending and Recto-sigmoid colon. (3) Transverse colon. (4) Combination of segments: which included involvement of more than 1 segment including hepatic or splenic flexure. All scans were reported by two senior consultant radiologists (with at least 10 years of experience) from the Department of Radiology, LTMGH, Sion Hospital, Mumbai. Colonoscopy after written informed consent from each patient was done subsequently within a span of 15 days with appropriate bowel preparation using low volume (2 litre) split dose regime of PEG 3350 powder. Standard white light direct-view endoscope with a series of Q150 L (Olympus CF, Tokyo, Japan) was used to perform the procedure. Biopsies were taken at the site of visible abnormalities on endoscopy and from normal appearing mucosa in case of strong suspicious of disease. Histopathological examination confirmed the diagnosis. This study has been approved by institutional ethics committee and is accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Continuous variables were presented as a mean with standard deviation while categorical variables were presented as proportions. Categorical variables were compared by Chi-square test and Fisher Exact Test. P value of less than 0.05 was considered statistically significant.

Results

Total 105 patients were assessed for eligibility. 85 patients met inclusion criteria who underwent colonoscopy after written informed consent for the same.

Total of 85 patients who fulfilled inclusion criteria were included in the study. Out of these 37 (43.5%) were male and 48 (56.5%) were female patients. Mean age group was 34.1 ± 17.4 years. Pain in abdomen 74 (87%), Fever 28 (32%), Weight loss 25 (30%), Bleeding per rectum 13 (15.3%) and Diarrhea 12 (14.1%).

Table 1: Demographic profile of patients with BWT on CT scan

<table>
<thead>
<tr>
<th>Demographic profile</th>
<th>n=85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>37 (43.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>48 (56.5%)</td>
</tr>
<tr>
<td>Mean age</td>
<td>34.1 ± 17.4 years</td>
</tr>
<tr>
<td>Pain in abdomen</td>
<td>74 (87%)</td>
</tr>
<tr>
<td>Fever</td>
<td>28 (32%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>25 (30%)</td>
</tr>
<tr>
<td>Bleeding per rectum</td>
<td>13 (15.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (14.1%)</td>
</tr>
</tbody>
</table>

Table 2: Segment, characteristic and degree of thickening on CT scan

<table>
<thead>
<tr>
<th>Segment of thickening on CT</th>
<th>Total (N=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right segment</td>
<td>60 (69.5%)</td>
</tr>
<tr>
<td>Left segment</td>
<td>14 (16.5%)</td>
</tr>
<tr>
<td>Combination of segments</td>
<td>8 (10.5%)</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>3 (3.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic of thickening</th>
<th>Total (N=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>55 (64.7%)</td>
</tr>
<tr>
<td>Irregular</td>
<td>30 (35.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Degree of thickening</th>
<th>Total (N=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>37 (43.5%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>38 (44.8%)</td>
</tr>
<tr>
<td>Severe</td>
<td>10 (11.7%)</td>
</tr>
</tbody>
</table>

On Computed Tomography scan 60 patients (69.5%) had right side colonic thickening, 14 patients (16.5%) had left side thickening and 8 patients (10.5%) had a thickening involving multiple colonic segments. While isolated transverse colon thickening was seen in only 3 (3.5%) patient which was least common affected site. Distribution of degree and characteristic of thickening is as shown in Table 2.

When we studied degree of BWT, 37 (43.5%) patients had mild (<5 mm), 38 (44.8%) had moderate (6-9 mm) and 10 patients (11.7%) had severe thickening (10 mm or more) on CT scan. Those with mild thickening 19 out of 37 patients (51%) had normal colonoscopy. Out of 19 patients with mild thickening involving IC region 15 had normal endoscopic findings (Figure 2). In moderate to severe thickening group only 1 patient out of 48 had normal colonoscopy. In severe thickening group 5 patients had large polypoidal lumen occluding growth which turned out to be malignancy on histopathology (Figure 3). This correlation of degree of thickening on CT with endoscopic was statistically significant (P<0.001) (Table 3).

Out of 65 patients, 42 had lesions involving IC region. In 40 patients (95.2%) IC thickening was secondary to tuberculosis (Figure 3). Only one patient had cecal malignancy and the other one had Crohns disease involving terminal ileum and IC junction. Out of 10 patients with rectosigmoid lesion on endoscopy 9 had malignancy (Figure 4) and one patient had tuberculosis of rectum. The frequency of the diseases diagnosed on histopathology is as shown in Table 4.
Total 65 (76.47%) patients showed abnormal findings on endoscopy. 20 patients (23.53%) with BWT did not have any abnormality on endoscopy. The overall correlation of BWT on CT with endoscopic finding was seen in 65 patients (76.5%). It correlated more on left side compared to right side (85.7% versus 76.7%). However this correlation was not statistically significant (P value< 0.57). Correlation of multiple sites thickening was observed in only 50% of patients. While this was 100% when CT showed thickening involving transverse colon (Table 5).

12 out of 14 cases of malignancy (83.3%) on CT showed irregular thickening with or without loss of fat planes. In patients with intestinal tuberculosis 19.5% (8 out of 41 cases) had irregular, thickening on CT scan (p<0.05) (Table 6).

Discussion
In this study correlation of BWT on CT with abnormal findings on colonoscopy correlated well on left side compared to right side (85.7% versus 76.7%). Overall this correlation of BWT on CT and abnormal endoscopy at the exact same site was seen in 76.5% patients. CT finding of BWT with evident pathology was seen with highest frequency involving IC region (41 out of 65 i.e 62.12% patients). Tuberculosis was the commonest diagnosis in these cases (86% of the total IC pathology). Multiple sites thickening on CT had very poor correlation with endoscopy. Endoscopy was normal in 20 patients (24%) when CT showed BWT. The correlation of degree of thickness on CT with endoscopy was poor for mild thickening compared to moderate to severe thickening. Malignancy was seen most commonly involving rectosigmoid region. There was good correlation for malignancy on CT in respect to site, degree and the characteristic of thickening compared to other abnormalities on endoscopy. In India so far the studies of correlation of bowel wall thickening with endoscopy findings have been done for etiological purpose and for differentiating intestinal tuberculosis from Crohn’s disease. However when CT shows BWT, there are no studies...
for specific recommendation of further diagnostic evaluation. When there is low possibility of disease in presence of BWT on CT dilemma occurs for doing endoscopy. This study correlated BWT on CT with endoscopy in terms of site of thickening as well as characteristic and degree of thickening. This correlation was seen in 57.58% cases in a study by MM Uzzmann et al. Other studies done by Rockey et al, Moraitis et al and Wolff et al showed correlation in 67%, 72% and 74% cases respectively.6-8 These studies recommended endoscopic evaluation despite showing inconsistent correlation of BWT on CT with endoscopy and mostly dealt with malignant pathology. We showed that the correlation of BWT was better for left colonic pathology compared to right colon. Uzzmann et al also noticed the same observation.1 In his study it was 48.4% for right side compared to 62.4% on left side. Cai et al also showed an 81% correlation with rectosigmoid lesions but only 13% with cecal lesions.9 Similar findings were observed by Eskaros et al10 and Shin et al.11 Bowel wall thickness is measured as the distance from the outer colon wall edge (defined as interface between mesenteric fat and bowel wall) to the inner bowel edge which is demarcated by noting the interface between bowel wall and intestinal gas or contrast. Normal bowel wall thickness should measure approximately 3mm.9 The degree of BWT has been graded by Bharucha et al as mild (3-6mm), moderate (6-12mm) and severe (>12mm).3 In present study fifty percent of patients with mild thickening (less than 5mm) involving IC region had normal endoscopy. Most of these patients had nonspecific abdominal complaints. However in rest of the patients with mild thickening endoscopy has revealed some abnormalities. Thus despite inconsistent results of correlation as described by above mentioned studies colonoscopy should be done to rule out the abnormalities. Cai et al suggested that the relatively high mobility of cecum makes it more likely to collapse and give artificial pictures. In addition the effects of contrast agents are likely to induce less distention on the right colonic wall compared with left side, predisposing to more false positive readings.9 Furthermore there are differences in venous drainage pathways, hydrostatic pressures and collateral formation that could explain the inconsistent correlations between right and left colonic segments.

Conclusion

This study shows the correlation of site of bowel wall thickening on CT scan as well as the degree and characteristic of thickening. Degree of thickening on CT has good correlation of finding abnormalities on endoscopy especially when BWT is more than 5mm on CT scan.

As this is single center data the findings should be validated by other centers. Endoscopy would pick up only mucosal abnormalities. For deeper pathology involving muscularis and serosal layer which is involved in few diseases full thickness biopsy would be necessary as endoscopic biopsy could miss the diagnosis.

Abbreviations

CT: Computed Tomography, BWT: Bowel Wall Thickening, IC valve: Ileocecal valve, SRUS: Solitary Rectal Ulcer Syndrome, PEG: Polyethylene Glycol.

References

In Hypertension,

Zilarbi
Azilsartan Medoxomil 40/80 mg Tablets

Drop in BP, as it should be...

In newly diagnosed T2DM patients
Right from the start

Glipsov
Teneligliptin 20 mg Tablets

Morning to...Morning control

In Hypertension & Angina

S-Numlo
S(-)Amlodipine Tablets IP 2.5/5 mg

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RRI as Diagnostic and Follow up Indicator in Cirrhosis of the Liver with Hepatorenal Syndrome and Refractory Ascites

Arun Kumar C1*, Pavitra L1, Ajoy Krishnamurthy2

Abstract

Introduction: Hepatorenal syndrome (HRS) is a syndrome of functional renal failure occurring in patients with advanced liver failure in the absence of clinical, laboratory, or histological evidence of other known causes of renal failure. However HRS has always been considered to be potentially reversible. RRI (Renal Resistive Index) is an affordable, non invasive and easily available tool which can be used to detect the early onset of HRS. Large volume paracentesis and albumin infusion along with splanchnic vasoconstrictors are the mainstay in the treatment of refractory ascites. The cost of treatment with terlipresin is prohibitive for people in the rural areas but not so with noradrenaline. Therefore, noradrenaline should be an acceptable alternative, in a developing country, especially in Rural India.

Aim: The aims of this study were to determine the usefulness of RRI in diagnosis and follow up of HRS and to determine if large volume paracentesis with noradrenaline and albumin infusion can prevent patients from going into Hepatorenal syndrome.

Materials and Methods

- Type of study: Prospective Observational clinical study. Dept. Of Medicine MVJ MCand RH Hoskote.
- Patients with cirrhosis of liver, refractory ascites and an RRI of > 0.70 were included in the study.
- A protocol for LVP (Large volume paracentesis) was laid down and followed in each case. Follow up RRI was done on 2nd day, 7th day and after two months.

Results: 184 patients with cirrhosis of liver with tense ascites underwent RRI by USG Doppler. 53 patients with RRI of > 0.7 were included in the study, after fulfilling the inclusion and exclusion criteria of which 25 patients (Cases) gave informed consent; the remaining 28 who were not willing for LVP were considered as “controls”. The mean RRI of cases was 0.7617+ 0.0457; the follow up mean RRI of cases on the 2nd day, 7th day and after 2 months were 0.6821+0.0466, 0.6375+0.0311 and 0.6030 +0.0461 respectively, with the p value of 0.00001. In the control group the mean RRI was 0.7245+0.0174 and the follow up mean RRI on the 2nd day, 7th day and after 2 months were 0.7245+0.174, 0.7191+0.0148 and 0.7368+0.01944 respectively, with the p value of 0.2100.

Conclusion

- RRI is an affordable, non invasive and easily available tool which can be included as part of a routine Ultrasonographie evaluation in liver cirrhotics. The RRI can be used for assessing early onset of HRS and in follow up.
- Large volume paracentesis, Noradrenaline with Albumin infusion (5 gms/litre of ascitic fluid removed) is as effective as other costlier options for refractory ascitis.

Introduction

Hepatorenal syndrome (HRS) is defined as an unexplained kidney failure in a patient with liver disease and is a common complication of advanced cirrhosis.1 The pathogenesis of HRS is renal vasoconstriction. The intra renal arterial doppler is a non invasive tool used to study the extent of this vasoconstriction and the RRI is derived from it.2 Large volume paracentesis is the first-line therapy for refractory ascites in patients with cirrhosis and it has shown to be as effective as standard therapy.3 Paracentesis-induced circulatory dysfunction (PICD) is a disorder characterized by marked activation of the renin–angiotensin axis secondary to the further increase of an already established splanchnic arteriolar vasodilation.1 PICD is a frequent and potentially harmful complication of large volume paracentesis. In several studies4,5 Albumin is the most commonly used plasma expander; its safety and efficacy in preventing PICD is well demonstrated. In addition vasoconstrictor agents like noradrenalin (0.1-0.7mg/h) have also shown to reduce the incidence of PICD and preventing patients going into HRS. A combination of noradrenaline and albumin infusion has also been tried in order to increase glomerular filtration rate and renal plasma flow thereby improving the renal function and reversing the HRS.

In an earlier study done by Moshin et al6 it was seen that patients with RI ≥0.77 had massive ascites when compared to patients with RRI <0.77 and this was statistically significant (P = 0.02). This finding confirmed that elevated RRI is seen in patients who have worsened in their disease. These findings were observed in other studies done earlier by Götzberger et al7 (0.74 vs. 0.67, P < 0.01), Celebiet al8 and Rivolta et al.9
A study conducted by Goyal et al. revealed that patients with cirrhosis and ascites showed significantly increased RRI (0.72 ± 0.02) when compared to cirrhosis without ascites (0.62 ± 0.06). Elevated RRI >0.70 was present in 16% (8/50) patients in the group with cirrhosis alone and in 60% (30/50) patients in the group who had cirrhosis and ascites.

In this study we used LVP, Noradrenaline and Albumin for the treatment of HRS while monitoring with the RRI. We believe that this is the first study in INDIA using RRI as a criteria for diagnosis and follow up.

Aim of the Study
1. To determine usefulness of RRI in diagnosis and follow up of HRS.
2. To determine if large volume paracentesis, noradrenaline and albumin infusion can prevent patients from going into Hepatorenal syndrome.

Materials and Methods
This study was a descriptive observational prospective study and conducted in MVJ Medical College and Hospital Hoskote Bangalore in the year 2014-16 (over a period of two year). The Study was approved by the Institution’s Research and Ethical Committee Board and informed consent for the trial was obtained from each person. The inclusion criteria were Patients > 18 years diagnosed to have cirrhosis of liver with refractory ascites clinically and sonologically. RRI >0.7 was also taken as inclusion criteria.

Duplex Doppler evaluation of the renal arteries was done using a 3.5-MHz convex transducer (GE Voluson 730 Pro).

The patients were asked to fast at least 4 h before examination to reduce masking by intestinal gas. Doppler signals were taken from interlobar arteries and arcuate arteries in both kidneys. Colour doppler ultrasound was used to help to identify the arteries. A train of at least three similar, sequential time-velocity waveforms of Doppler signals was obtained at each point of measurement during suspended respiration. The RI was calculated with the formula RI = (peak systolic velocity – end diastolic velocity)/peak systolic velocity (Figure 1). Patients were excluded if it was not possible to measure the RI in two different places in each kidney due to massive ascites or masking by gas. Inter-observer variability was kept to the minimum by having the same ultrasonologist perform the Doppler studies and patients with RRI >0.7 were included in the study.

The exclusion criteria were patients with other acute infections and potentially or overt cardiovascular instability, Diabetes mellitus, Hypertension, Suspected or overt malignant disease, Patients with nephropathies, or with pathomorphological findings in ultrasound like decreased kidney size, reduction of renal parenchymal width and significant renal parenchymal hyperechogenecity, Peripheral vascular thrombosis, mesenteric vascular thrombosis, Hypertension, Sensitivity to adrenaline, Hypotension (systolic BP <90mm Hg) and INR >2 after repeated correction with FFP.

Protocol for LVP Using Nor-Adrenaline
Large volume paracentesis (4 lit) was done over a period of 1 to 2 hrs. Albumin (5g/L) was given i.v. Noradrenalin infusion rate was adjusted to keep the systolic blood pressure around 110 mmHg for a period of 24 hrs. Patient’s vital signs were monitored in the ICU for 24 hours and Patients were instructed not to get up from the bed for 24 hours. Post paracentesis RRI was measured on day 2, day 7, and after 2 months.

The data was systematically collected, compiled and statistically analysed using IBM SPSS 22.0 Software to draw cross-tabs and make relevant conclusions. Differences between groups were analyzed by students t test and p < 0.05 was considered significant.

Results
For the purpose of making comparisons, the study population was divided into two groups of cases and controls. 184 patients with cirrhosis of liver with tense ascites underwent RRI by USG Doppler. 53 patients with RRI > 0.7 were included in the study. After fulfilling the inclusion and exclusion criteria of which 25 patients (Cases) gave informed consent; the remaining 28 who did not consent for LVP, were considered as controls (Fig 2). While both cases and controls received standard treatment(diuretics, aldosterone antagonists and salt restriction) for cirrhosis of liver with ascitis, only cases received LVP along with noradrenaline and albumin infusion. In our study 84% of the patients were males of the age group 30-50 years.

The mean RRI of cases was 0.7617±0.0457; the follow up mean RRI of cases on the 2nd day, 7th day and after 2 months were 0.6821±0.0466, 0.6375±0.0311 and 0.6030 ±0.0461
only improved the RRI, a surrogate indicator of Renal function, but also improved the eGFR, Serum creatinine and portal vein diameter.

Studies (Table 2) which compared noradrenaline with terlipressin have found noradrenaline to be equally efficacious. We used nor-adrenaline as a vasopressor to avoid PICD and also for its cost benefit compared to telipressin. The RRI was used to determine the presence of HRS and for follow-up. Our study showed that LVP with noradrenaline and albumin infusion resulted in reversal of HRS in 100% of the cases. In the controls where LVP was not done there was 100% recurrence of HRS. 3 patients died in the controls because of worsening HRS. No deaths were noticed in the cases till 60 days.

Discussion

HRS is a disease associated with rapid clinical deterioration and high mortality. Therefore early detection and treatment improves survival rates in individuals with HRS. Liver transplant, which most cannot afford, is the only treatment which could revert HRS. Of the alternative treatment options, LVP with vasopressors and albumin may give some temporary relief.

As shown in Table 2 LVP with noradrenaline and terlipressin was carried out in most studies. In a developing country like India the cost of treatment with terlipressin is prohibitive and may not be affordable to all. The prevalence of cirrhosis in the rural Indian population is 0.2-0.5% [13]. Most of these patients will progress to developing refractory ascites. This large rural population belong to the low socio-economic strata, unable to afford or access Terlipressin. Nor-adrenaline has been shown to be equally efficacious and a cheaper, cost effective alternative.

No study to date has used the RRI for diagnosis, nor for follow up. While large studies have measured RRI as part of the investigation for cirrhosis with ascites, no standards have been laid down for what we should take as abnormal. The figure of >0.70 RRI has been used by us as per Goyal's study [10] but we still don't know what the RRI is in the normal population. However, using the RRI we have been able to show a significant difference in the values over a 2 month follow-up period. These differences are held also for the eGFR, Serum Creatinine and for the portal vein diameter. All three of these values indicating improvement in the kidney and liver function.

Larger studies need to be done using the RRI both for diagnosis and for follow-up. Using Nor-adrenaline in the protocol of LVP would benefit far more patients at a far lesser cost.

Conclusion

RRI is an affordable, non invasive and easily available tool which should be included as part of a routine Ultrasonographic evaluation in liver cirrhotics, for early detection of HRS and for follow-up.

LVP along with Noradrenaline with Albumin infusion (5 gms/litre of ascitic fluid removed) is as effective as other costlier options.
Diabetes mellitus (DM) is becoming a potential epidemic in India with more than 62 million diagnosed diabetics and an increase of nearly 2 million per year. Poor adherence to medication regimens increases the probability of adverse outcomes in type 2 diabetes patients. Therefore, improving medication adherence is a growing priority to control this epidemic. Hence, this study was conducted to determine the level of adherence to medication in Type II diabetic patients and to study the various factors affecting adherence to medication and the relationship between the severity of diabetes with the adherence categories.

Methods: A cross-sectional study was conducted at medicine outpatient department (OPD) of a tertiary care hospital, New Delhi among 200 type 2 diabetic patients for duration of 2 months using a predesigned and pretested semi-structured interview schedule and diabetes medication adherence was assessed by Morisky’s medication adherence scale questionnaire.

Results: Out of 200 participants, 32.5% were found to have high adherence while 34.5% and 33% had moderate and low adherence. Factors found to be associated with adherence were age, educational status, longer duration of disease and presence of glaucometer. Almost four-fifths of the patients (79.5%) had poor plasma glucose control.

Conclusion: There is a need to focus on improving adherence among type 2 diabetes patients and strengthening health care systems for regular supply of medicines and provide health education to the patients and their families emphasising the need of adherence to medications.
Table 1: Socio-demographic profile of the participants (N=200)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td></td>
</tr>
<tr>
<td>18-40</td>
<td>45 (22.5)</td>
</tr>
<tr>
<td>41-60</td>
<td>122 (61)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>33 (16.5)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74 (37)</td>
</tr>
<tr>
<td>Female</td>
<td>126 (63)</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
</tr>
<tr>
<td>Hindu</td>
<td>173 (86.5)</td>
</tr>
<tr>
<td>Muslim</td>
<td>21 (10.5)</td>
</tr>
<tr>
<td>Sikh</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>60 (30)</td>
</tr>
<tr>
<td>Just literate</td>
<td>14 (07)</td>
</tr>
<tr>
<td>Primary</td>
<td>33 (16.5)</td>
</tr>
<tr>
<td>Middle</td>
<td>34 (17)</td>
</tr>
<tr>
<td>High/Intermediate</td>
<td>42 (21)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
</tr>
<tr>
<td>Unemployed / retired</td>
<td>11 (5.5)</td>
</tr>
<tr>
<td>Employed</td>
<td>88 (44)</td>
</tr>
<tr>
<td>Homemaker</td>
<td>101 (50.5)</td>
</tr>
<tr>
<td>Per capita annual income</td>
<td></td>
</tr>
<tr>
<td>Less than 20,000</td>
<td>39 (19.5)</td>
</tr>
<tr>
<td>20,001 – 40,000</td>
<td>72 (36)</td>
</tr>
<tr>
<td>40,001 – 80,000</td>
<td>44 (22)</td>
</tr>
<tr>
<td>More than 80,000</td>
<td></td>
</tr>
<tr>
<td>Socio-economic status</td>
<td></td>
</tr>
<tr>
<td>Upper / upper middle</td>
<td>53 (26.5)</td>
</tr>
<tr>
<td>Middle</td>
<td>45 (22.5)</td>
</tr>
<tr>
<td>Upper lower</td>
<td>91 (45.5)</td>
</tr>
<tr>
<td>Lower</td>
<td>11 (5.5)</td>
</tr>
</tbody>
</table>

Adherence to prescribed medications was measured by Morisky’s medication adherence scale (MMAS). In this study, moderate adherence was considered to be statistically significant at 95% confidence level.

Results

A total of 200 patients were included in the study out of which 74 (37%) were males and 126 (63%) were females. The mean age of the participants was 49.8 ±10.5 yrs with majority (61%) of participants belonging to 41 to 60 years age group. Nearly half of the participants (51%) belong to lower socio-economic class and one third of the participants (30%) were illiterate.

Table 1 shows the socio-demographic characteristics of study participants.

The socio-demographic factors that were found to be significantly associated with adherence to medications among Type II Diabetes mellitus patients were age more than 40 years and educational status of high school and above (Table 3). Among the clinical factors, those having longer duration of disease more than 5 years had higher medication adherence and this association was statistically significant (p = 0.002). Among the therapy related factors, presence of glucometer was found to be significantly associated with good medication adherence (p < 0.001). Those patients spending more than Rs. 1000 per month on diabietic medications (68.7%) were found to have good medication adherence than those patients who were spending less or no amount (16.7%). Regarding health seeking behaviour, those patients who stayed at a distance of more than half an hour from hospital (80.6%) had good medication adherence as compared to those who stayed near (56%).

Discussion

Adherence to prescribed medications is essential for metabolic control and reduced complications. The present study showed that nearly 1/3rd (32.5%) patients were adherent while the remaining two thirds (34.5% and 33%) were moderately adherent and non-adherent to anti-diabetic medications which is similar to the findings reported from a hospital in Pune where 40.95% patients had good adherence whereas 37.14% had medium adherence and 21.90 % had low adherence. (8) A study on medication adherence conducted in a tertiary hospital of South India in 2015 reported non-adherence in 54.6% patients which was higher than our study findings. (9) Another study conducted in a diabetic clinic in Bangalore reported a non-adherence rate of 61% while 21% were adherent and 18% were moderately adherent. (10) Humera Sarwar et al. in their study conducted in different hospitals of Hyderabad reported that 14.3% patients were adherent while 45.7% and 40%
Table 2: Clinical characteristics and adherence to medication among diabetic patients (N = 200)

<table>
<thead>
<tr>
<th>Disease related parameter</th>
<th>Total (N = 200)</th>
<th>High adherence (N = 65)</th>
<th>Medium adherence (N = 69)</th>
<th>Low adherence (N = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of disease since diagnosis (yrs)</td>
<td>125 (62.5)</td>
<td>43</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>51 (25.5)</td>
<td>13</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>5-10</td>
<td>24 (12)</td>
<td>9</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Treatment taken</td>
<td>Oral OHA + Insulin</td>
<td>39 (19.5)</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>OHA = Insulin</td>
<td>Yes</td>
<td>96 (48)</td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td>No</td>
<td>104 (52)</td>
<td>39</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>Glycaemic control (HbA1c)</td>
<td>&lt; 6.5 gm/dl</td>
<td>15 (7.5)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>6.5-8.0 gm/dl</td>
<td>76 (38)</td>
<td>26</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>8.0-10.0 gm/dl</td>
<td>75 (37.5)</td>
<td>24</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>&gt; 10 gm/dl</td>
<td>34 (17)</td>
<td>8</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>Hypertension (HTN)</td>
<td>99 (49.5)</td>
<td>32</td>
<td>37</td>
</tr>
<tr>
<td>Ischemic heart disease (IHD)</td>
<td>02 (1)</td>
<td>02</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>HTN + IHD</td>
<td>07 (3.5)</td>
<td>03</td>
<td>02</td>
<td>02</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>03 (1.5)</td>
<td>00</td>
<td>01</td>
<td>02</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>23 (11.5)</td>
<td>09</td>
<td>06</td>
<td>08</td>
</tr>
<tr>
<td>Others</td>
<td>02 (1)</td>
<td>00</td>
<td>02</td>
<td>00</td>
</tr>
<tr>
<td>None</td>
<td>89 (44.5)</td>
<td>27</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>Number of hospitalisation due to DM</td>
<td>None</td>
<td>117 (88.5)</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>One</td>
<td>20 (10)</td>
<td>5</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>&gt;1</td>
<td>3 (1.5)</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>18.5 – 22.9</td>
<td>45 (22.5)</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>23 – 24.9</td>
<td>41 (20.5)</td>
<td>15</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>&gt;25</td>
<td>114 (57)</td>
<td>35</td>
<td>39</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 4: Association between adherence to medication and plasma glucose control (N = 200)

<table>
<thead>
<tr>
<th>Adherence pattern</th>
<th>Number of patients (N)</th>
<th>Plasma Glucose status Controlled (N, %)</th>
<th>Plasma Glucose status Not controlled (N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>65</td>
<td>20 (30.8)</td>
<td>45</td>
</tr>
<tr>
<td>Medium</td>
<td>69</td>
<td>14</td>
<td>55</td>
</tr>
<tr>
<td>Low</td>
<td>66</td>
<td>7</td>
<td>59</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>41 (20.5)</td>
<td>139 (79.5)</td>
</tr>
</tbody>
</table>

χ² = 8.17, p = 0.017

patients were moderately adherent and non-adherent to medications. Another study by Shobhana et al. reported a very high rate of non-adherence of 75% and this difference from our study findings could be due to improved patient awareness and availability of anti-diabetic medications over the years. Improved adherence reported in our study could also be due to the fact that half of the study population belonged to middle and upper middle class with good purchasing power and in case of non-availability of medicines in government hospital, adherence was maintained by buying the medications.

Various studies advocate that people with diabetes have difficulty managing their medication regimens - oral hypoglycaemic agents or insulin, as well as other aspects of self-management. In our study, roughly 20% of respondents were prescribed injectable medication along with oral therapy which makes it even more difficult for the patient to comply with, thereby leading to ineffective plasma glucose control. 55.5% patients suffered from a co-morbid condition such as hypertension accounting for 89.1% of the total complications which is slightly higher than the study findings reported in Nepal where hypertension accounted for 70.62% of the total complication.

The effect of age on adherence was found in our study population with significantly higher rate of adherence among patients aged more than 40 years which is similar to the findings of study conducted by Sander D. Borgsteede et al. However, in a study conducted in Egypt, higher adherence was found in younger age group with less adherence in elderly and middle age group.

Some of the factors thought to influence compliance include social and psychological components like knowledge and understanding including communication, quality of the patient – healthcare provider interaction and patient satisfaction, social isolation and social support including the effect of the family, health beliefs and attitudes and factors associated with the illness and the treatment including the duration and the complexity of the regimen. In our study, it was found that a strong association exists between compliance to medications and literacy levels. Illiteracy can interfere with understanding of the disease and medication to some extent and various studies show that the risk of non-adherence is very high when patients cannot read and understand basic written medical instructions. Other factor found to promote adherence was presence of glucometer at home which helps in maintaining plasma glucose control.

According to our study findings, plasma glucose control was better among patients that adhered with their antidiabetic medication compared with their non-adherent counterparts and this finding is similar to the findings of Saith et al. Hence, it can be concluded...
that if diabetic patients adhere with their appropriately prescribed anti-diabetic medication, glycaemic outcome will be improve. Hence, clinicians attending to type 2 diabetic patients should inquire rationally for medication adherence at every clinical encounter with diabetic patients. This will prevent the clinician from attributing lack of response to medications as therapeutic failure rather than medication adherence problems.  

The present study had some limitations. Adherence was assessed using self-reported questionnaire, so there could be potential inaccuracies in patients’ responses. The patients included in the study had diabetes mellitus for different duration of time which may affect their perceptions and response to questions on treatment adherence. The study was conducted in a single clinic and caution should be exercised in extrapolating the results. However, ours is a leading tertiary care centre and if poor adherence rates are seen here, then situation would be worse in other centres.  

Conclusion

From this study, it is seen that adherence to medication was poor and as a result, plasma glucose control was poor in majority of patients. Hence, there is a need to focus on improving adherence among type 2 diabetes patients as it leads to better clinical outcomes and less complications in such patients. The factors found to be associated with non-adherence were younger age (<40 years), low education status, lesser duration of disease and absence of glucometer. It was found that those patients who were dependent on government healthcare system for medications were less adherent to medications. Thus, there is a definite need to improve health care systems for regular supply of medicines and provide health education to the patients and their families emphasising the need of adherence to medications. Other factors related to side-effects or unavailability of drugs leading to non-adherence should be looked into and solutions should be found to improve adherence among diabetic patients.  

References


Dr. Vithalrao Nadgouda Best All India Annual Thesis Award

1. The award is open to the physicians from various medical institutions / hospitals from India within one year of passing the MD / DNB examination in Medicine / General Medicine / Internal Medicine as on the last date for submission of the application for the above award 31st May 2019.
2. There shall be two awards: the first award shall comprise of Rs. 15,000/- along with a certificate and the second award shall comprise of Rs. 10,000/- along with a certificate.

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Dr. Mangesh Tiwaskar
Hon. General Secretary

Dr. A. M. Bhagwati
Jt. Secretary
SCRATCHING
gives pleasure
But Inflicts PAIN & INFLAMMATION
Compliance of WHO Guideline on Dengue Management among Indian Patients: An Intervventional Quality Improvement Study
Anu Balkrishnan¹, Prasan K Panda², RM Pandey³, Ashutosh Biswas⁴, Praveen Aggarwal⁵, Naval K Vikram⁶, Lalit Dar⁷, Naveet Wig⁸

Abstract
Introduction: Dengue fever management is guided by WHO guideline, the recent one being 2009; however, compliance to the guideline is difficult to assess and in India there is no data on it. The present study, a longitudinal pre-post interventional quality improvement study, was done to determine the compliance to the guideline on dengue patients before and after resident physicians' training during two peak seasons and their impact on survival.

Methods: This study was conducted in a tertiary health care centre in North India over 18 months. Data of hospitalized patients who admitted with dengue fever diagnosis in a peak season was collected in the form of quality indicators as described by the WHO-2009 guideline on dengue. Resident physicians were then given appropriate training about the guideline during the off season. Data of new dengue patients in next peak season after resident training was collected and compared with the baseline by standard statistical tests.

Results: The post-intervention compliances of all components increased (total mean score by giving one point to each of the quality indicators reached 7.9 from 6.4). The compliance to individual indicator also increased: the admission criteria (baseline, 44% to post-intervention, 52%, p = 0.37), classification criteria (91.7% to 96%, p = 0.33), correct staging/triage (42.9% to 86%, p < 0.01), vitals monitoring (85.7% to 92%, p = 0.28), correct usage of bolus fluids (34.3% to 69.5%, p < 0.01), crystalloid as choice of fluid (100% in both groups), proper fluid titration (26.2% to 56%, p < 0.01), hematocrit monitoring (95.2% to 98%, p = 0.42), platelet transfusion when indicated (65.5% to 58%, p = 0.39), antibiotic use when required (61.5% to 80%, p = 0.03), and discharge criteria (100% in both groups). The mortality decreased from 7.1% (baseline) to zero (post-intervention). The median duration of hospital stay also reduced by 1 day.

Conclusions: The study affirms that the compliance to WHO guideline on dengue management in India can be further improved by regular physician training on the guideline. Simultaneously, this educational intervention not only improves patient outcomes but also direct proper resource utilization especially platelet transfusion and antibiotic use. Furthermore, every hospital/institute should have an internal quality improvement program like this to improve the management of dengue patients. Future studies are needed to understand various barriers to 100% implementation of the guideline.

Introduction
Dengue fever is an arboviral disease caused by Flavivirus continues to be one of the commonest tropical diseases. WHO notified it as a major international health concern because of increasing frequency of epidemics, co-circulation of multiple serotypes, and occurrence of dengue hemorrhagic fever in new areas.¹ WHO descriptions of dengue and their guidelines have been started in 1975, followed by revision in 1986, 1997, and 2009. The management comprises nothing but aggressive body fluid balance and continuous monitoring of clinical-laboratory parameters. Various studies from Malaysia, Indonesia, and Thailand to assess the outcome of practicing WHO guideline have shown the reduced rate of the complications, mortality, and costs of the treatment.２,³ Studies done in Nepal and Puerto Rico show limited knowledge of physicians regarding the management and sub-optimal compliance to the present guideline.４,５ However, a study from Singapore identifies no major gaps in knowledge but proves wide variations in the management practice.⁶

The development and publication of guidelines often do not lead to changes in clinicians’ bedside practices in a timely fashion. Adopting or de-adopting new evidence based practices among health care persons are sometimes found to be delayed, without any clear reasons.⁷ Though we have many guidelines describing protocol based management of dengue fever, actual scenario is found to be different from the ideal one. Fear and panic among common people and health communities lead to admission of maximum cases in the hospital, increased prophylactic transfusion of blood components, and improper hydration and unnecessary use of antibiotics which further cause over utilization of resources, burden to health system, iatrogenic complications, and economic losses. Repeated education/training is the only old known method to overcome this hurdle. Hence, learning has to be adopted again and again on a protocol based approach.

There is no data in India with regard

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Received: 09.04.2018; Accepted: 16.11.2018
to the compliance of WHO guideline on management of dengue fever. Assessing the physician’s approach to the management and ensuring the compliance to the guideline is the need of the hour to combat dengue fever. We hypothesize that the baseline compliance of the treating physician to WHO-2009 guideline is highly variable at a referral hospital/institution in India. To increase the compliance, we educate them through an interventional program. The study is a pre- and post-interventional study. Primary objective of the study is to determine the guideline compliances by seeing admitted patients’ document/file at baseline and at post-intervention phase and compare them. Secondary objective is to determine the outcomes with respect to the mortality and hospital stay.

Methods

Study settings and participants

The prospective interventional quality improvement study (time series design) was conducted in the department of Emergency and Internal medicine at a tertiary level health centre, North India, during September, 2013 to March, 2015. This chosen time period was of importance with respect to the seasonal occurrence of dengue fever. The disease was usually precipitated by rainfall, temperature, and the degree of urbanization. In India, September to February was the peak time for this. Therefore, pre-intervention phase was chosen in one peak season, post-intervention season was in the next peak season, and intervention phase (education phase) was in between. Included patients were admitted ones who fulfilled the criteria for dengue fever as per WHO-2009 guideline. Dengue fever was defined as an acute febrile illness with two or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leukopenia) and occurrence at the same location and time as other confirmed cases of dengue fever. Only laboratory confirmed cases were included (Table 1). Excluded patients were children (age of < 12 years), pregnant, co-infected patients, and those had taken partial treatment from other hospital.

Sample size

Target sample had been calculated based on proportion of properly managed dengue patients. Out of the broad four aspects of the management i.e. fluid management, platelet transfusion, proper monitoring, and other medications, it was expected that fluid or platelet transfusion was less properly managed. Assuming that 30% of the patients were properly managed for fluid and blood transfusion separately; to estimate this with an absolute precision of 10% and confidence interval (CI) of 95%, calculated sample size was 84. Thus a maximum of 84 or all the patients admitted with dengue fever during a season, whichever was the least was considered as the required sample size for the study. Same applied to the post-intervention phase also.

Interventions

Study conducted in three phases of equal time period over 18 months: baseline phase, intervention phase, and post-intervention phase. Resident physicians were chosen for intervention/training because of their lead role during the outbreak management among other staffs (e.g. nurses, technicians) involved in the team work. They were post-graduate trainee of the hospital/institution. Every six months, a new batch of 5-10 residents had entered to the post-graduate education of the institution and at one point of time 50-60 residents were there. New residents were not directly managing the patients, usually accompanied with senior residents and consultants. Intervention delivered in the department were educational programs based on the prevalent WHO guideline. Programs aimed to create awareness and inculcate the guideline among the residents through four training sessions. Two open forums on the same were also being conducted for all staffs involved in the management to further increase the efficiency of management. Training were designed and delivered by the investigators. Emphasis was laid on the accuracy, relevance, layout, and technique of presentation. Content of the training material was kept simple, meaningful, and interesting. Different methods were used to deliver the content using appropriate audio-visual aids. Multiple mock sessions of the presentation were held for validation. Residents were not told about the ongoing study to prevent the bias of documenting properly in patient files even if the guideline was not followed. Blinding was possible because of academic interest of the topic and it was part of educational curriculum to be completed in an academic year.

Outcomes

Compliance with each of the components of the guideline was measured in both phases after seeing individual patient file by applying a standardized checklist/questionnaire which included patient demographics, comorbidities, vital signs, laboratory parameters, and 11 quality indicators (admission criteria, dengue classification, triage into correct stage, vitals monitoring, usage of bolus fluids, crystalloid as choice of fluid, correct fluid titration, hematocrit (Hct) monitoring, proper use of platelet transfusion, use of antibiotics, and discharge criteria). Criteria for admission included all severe dengue patients, dengue with warning signs, and dengue with co-morbidities or in social isolation. Dengue was classified into dengue fever with or without warning signs (DW & DF respectively) and severe dengue (SD) (Table 1). Dengue was staged (triaged) into 3 phases- febrile, critical, and recovery phases. Critical phase included the fluid leak phase where aggressive

Table 1: Criteria for dengue case classification and levels of severity (WHO 2009)

<table>
<thead>
<tr>
<th>Probable dengue</th>
<th>Warning signs</th>
<th>Severe dengue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live in / travel to dengue endemic area</td>
<td>Abdominal pain or tenderness</td>
<td>Severe plasma leakage:</td>
</tr>
<tr>
<td>Fever with any 2 of the followings</td>
<td>Persistent vomiting</td>
<td>• Shock</td>
</tr>
<tr>
<td>1. Nausea, vomiting</td>
<td>Clinical fluid accumulation</td>
<td>• Fluid accumulation with respiratory distress</td>
</tr>
<tr>
<td>2. Rash</td>
<td>Mucosal bleed</td>
<td>Severe bleeding (as evaluated by clinician)</td>
</tr>
<tr>
<td>3. Aches and pains</td>
<td>Lethargy/restlessness</td>
<td>Severe organ involvement</td>
</tr>
<tr>
<td>4. Tourniquet test positive</td>
<td>Liver enlargement ≥2 cm</td>
<td>• Liver: AST or ALT ≥ 1000</td>
</tr>
<tr>
<td>5. Leukopenia</td>
<td>Increase in haematocrit (Hct) with rapid fall in platelets</td>
<td>• CNS: Impaired consciousness</td>
</tr>
<tr>
<td>6. Any warning sign</td>
<td></td>
<td>• Heart and other organs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confirmed dengue (important when no sign of plasma leakage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Dengue NSI antigen demonstration (ELISA) or</td>
</tr>
<tr>
<td>✓ Dengue RNA detection (PCR), or</td>
</tr>
<tr>
<td>✓ Dengue IgM positive (ELISA), or</td>
</tr>
<tr>
<td>✓ A fourfold or greater change in reciprocal IgG in paired sera</td>
</tr>
</tbody>
</table>

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Journal of The Association of Physicians of India • Vol. 67 • April 2019
fluid management was required with frequent clinical and Hct monitoring. In the recovery phase patient may develop fluid overload and pulmonary edema if fluid therapy was continued without titration/tapering. Here we assessed how many patients were staged/triaged correctly. Monitoring of vital signs included pulse rate, respiratory rate, blood pressure, pulse pressure, jugular venous pulsations, capillary filling, and urine output. Fluid bolus was defined as 20 mL/kg fluid infused over 30-minutes in critical phase patients. Four hourly monitoring of Hct was assessed. Platelet transfusion was correctly indicated when total platelet count was < 10X10^9/L or there was a major bleed from any body parts. Discharge criterion was fulfilled when patient was afebrile, with subsided warning symptoms, with stable vitals, and with recovered complications.

**Statistical Methods**

The data storage and analysis were performed using Microsoft excel and STRATA SE 11 respectively. For categorical variables, frequency and percentage were calculated and compared with help of the chi-square test or Fisher’s exact test. Continuous variables were expressed as mean± standard deviation (SD) and compared with unpaired student t-test and Mann Whitney test. A p value of less than 0.05 was considered significant.

**Ethics approval and consent**

The study protocol was approved by the institutional review board. Data collection procedures were completed with ensuring the subject confidentiality. Verbal consent was obtained from all the residents for the educational training.

**Results**

**Participant flow**

A total of 138 patients were screened, but 134 patients were assigned, allocated, and analyzed in the study. Four patients were excluded because they had partial treatment from outside hospital and with complications during admission. The study was in two groups; pre-intervention phase of six months having 84 patients and post-intervention phase of six months having 50 patients (Figure 1). The second phase could not reach to the appropriate sample size because of low prevalence of dengue patients in that season.

**Baseline data**

Baseline characteristics were comparable in the pre- and post-intervention groups (Table 2). Among different categories of dengue, half of cases were DF (n=49/84 [58.3%], n=24/50 [48%] in both groups respectively) followed by DW cases (n=24/84 [28.6%], n=16/50 [32%]) and then SD cases (n=11/84 [13.1%], n=10/50 [20%]). When compliance was expressed in qualitative forms viz. good (> 90%), average (70-90%), poor (50-69%), and very poor (< 50%), at baseline, good compliance was found only in three quality indicators- correct classification, Hct monitoring, and discharge criteria. Very poor compliance was found in four indicators- admission criteria, correct staging of patients, usage of bolus fluid, and correct fluid titration.

**Primary outcome variable: compliance with the guideline**

When a total score was calculated by giving one point to each of the quality indicators except the discharge criteria and choice of fluids as crystalloid (each 100% in both the groups) and compared, it showed a mean increase from 6.4 in pre-intervention group to 7.9 in post-intervention group. Compliance to major quality indicators improved at post-intervention and four indicators- staging of the patients, adequate usage of bolus fluids, fluid titration, and usage of antibiotics improved to a significant level (Table 3).

Admission criteria was averagely followed in both groups, however, in a subgroup analysis, it was not followed in majority of EHS patients (n=35/52 [67.3%], n=12/16 [75%] respectively). Majority of patients were in either febrile or critical stages in both the groups (febrile stage, n=45/84 [53.6%] and n=23/50 [46%]; critical stage, n=39/84 [46.4%] and n=24/50 [48%]; recovery stage, n=0/84 and n=3/50 [6%] respectively). Choice of fluid was crystalloid in all cases with 0.9% normal saline (90% of total fluids), ringer lactate (7.4% total fluids), and 5% dextrose normal saline (3.6% total fluids). No colloid other than albumin [n=3 (3.6%)] was used in the study. Oral fluids were used in all the patients along with intravenous fluids. Even though the adequacy of oral fluids was low at the time of initiation of fluids, they were monitored well and oral intake was increased with time along with titration of fluid therapy. Compliance to the platelet transfusion showed a downward trend from 65.5% to 58% (p=0.39). In subgroup analysis, excluding the beneficiaries of Employee Health Scheme (EHS) of the hospital, it improved but non-significantly from 56.3% to 58.8% (p=0.83). About other blood component transfusions, packed RBC transfusions were used correctly in 40% cases of severe mucosal bleeding with low or normal Hct (n=6/15) and FFP was correctly in 100% cases of prolonged prothrombin time (n=2/2). Antibiotics were prescribed without

![Enrollment](image-url)
Table 2: Comparison of baseline characteristics in between pre- and post-intervention groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-intervention (n=84)</th>
<th>Post-intervention (n=50)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)*</td>
<td>26.7 ± 10.2</td>
<td>30.2 ± 10.6</td>
<td>-</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>1:6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated co-morbidities</td>
<td>13.1%</td>
<td>10%</td>
<td>0.06</td>
</tr>
<tr>
<td>Pulse rate (per minute)*</td>
<td>89.6 ± 13.6</td>
<td>90 ± 11.8</td>
<td>0.51</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)*</td>
<td>40.1 ± 10.1</td>
<td>37.5 ± 9.4</td>
<td>0.52</td>
</tr>
<tr>
<td>Respiratory rate (per min)*</td>
<td>16.1 ± 4.9</td>
<td>15.4 ± 4.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)*</td>
<td>13 ± 2.2</td>
<td>12.7 ± 2.3</td>
<td>0.48</td>
</tr>
<tr>
<td>Hematocrit (%)*</td>
<td>39.1 ± 7</td>
<td>39.4 ± 6.6</td>
<td>0.77</td>
</tr>
<tr>
<td>Total WBC count (x10^3/µL)*</td>
<td>4200 (1200-37400)</td>
<td>4200 (12000-40900)</td>
<td>0.71</td>
</tr>
<tr>
<td>Platelet count (x10^9/L)*</td>
<td>44000 (500-252000)</td>
<td>24500 (5000-195000)</td>
<td>0.10</td>
</tr>
<tr>
<td>ESR (mm/ 1st hour)*</td>
<td>8 (2-64)</td>
<td>18 (4-117)</td>
<td>0.40</td>
</tr>
<tr>
<td>Prothrombin time (sec)*</td>
<td>13.5 ± 1.9</td>
<td>12.5 ± 2.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Blood urea (mg/dl)*</td>
<td>20 (10-116)</td>
<td>22.5 (10-303)</td>
<td>0.99</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)*</td>
<td>0.9 (0.4-7)</td>
<td>0.9 (0.4-10.2)</td>
<td>0.96</td>
</tr>
<tr>
<td>Serum sodium (meq/L)*</td>
<td>13.5 ± 5</td>
<td>137.2 ± 5.1</td>
<td>0.16</td>
</tr>
<tr>
<td>Serum potassium (meq/L)*</td>
<td>3.9 ± 0.7</td>
<td>4.3 ± 0.7</td>
<td>0.99</td>
</tr>
<tr>
<td>SGOT (IU/L)*</td>
<td>94 (21-1003)</td>
<td>106 (21-3178)</td>
<td>0.09</td>
</tr>
<tr>
<td>SGPT (IU/L)*</td>
<td>59 (13-1526)</td>
<td>71 (16-1980)</td>
<td>0.06</td>
</tr>
<tr>
<td>ALP (IU/L)*</td>
<td>190 (74-770)</td>
<td>210 (74-1298)</td>
<td>0.51</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)*</td>
<td>0.6 (0.2-2.8)</td>
<td>0.6 (0.2-5.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum Albumin (mg/dl)*</td>
<td>3.8 ± 0.5</td>
<td>3.5 ± 0.6</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*Vital signs include pulse rate, respiratory rate, blood pressure, pulse pressure, jugular venous pulsations, capillary filling, and urine output.

Discussion

The quality improvement study represents an in-depth document evaluation of WHO-2009 guideline compliance in the management of dengue patients before and after resident physician’s educational programs. Compliance, assessed using the quality indicators, improves significantly for the correct staging/triage, use of bolus IV fluids, titration of fluids, and usage of antibiotics. It does not improve for the proper use of platelet transfusion, however, improves non-significantly after excluding the EHS populations. There is non-significant improvement in the remaining indicators such as admission criteria, dengue classification, vital signs monitoring, and Hct monitoring. There is 100% compliance in both groups for the choice of fluid usage and the discharge criteria. Mortality and hospital stay improve when guideline compliance increases. The study affirms that the established guideline is yet to be implemented fully (100%) in a research institution/tertiary care hospital. To our knowledge, no studies use similar quality indicators comprising the major parts of the guideline like the present study in determining the compliance except few studying individual criterion. More importantly, document evaluations guiding an institute for the internal quality improvement program are not studied in previous studies. We will discuss few important indicators in details.

According to the guideline, recommended first-line intravenous fluid is crystalloid which was followed in 100% cases in this study. Although crystalloid is not superior to colloid when blood pressure increment is concerned, but colloid takes longer time to make recover in patients with low pulse pressure. Rate of intravenous fluid administration should be at stepwise increments or decrements with at least 4–6 hourly Hct monitoring during the critical phase. This was performed in > 95% cases in both groups. However, overall fluid titration (that includes clinical monitoring in association with Hct monitoring) was not performed well in all patients. This was only in 1/4th of patients and increased significantly after education programs to more than half of patients. Similarly fluid bolus (20 mL/kg) was very poorly performed in pre-intervention groups (1/3rd patients) and significantly improved after the education programs (2/3rd). Hence, the present study describes very poor compliance of fluid management and compliance improves after the educational training.

Platelet transfusions did not show much improvement even with education and it showed the possibility of a fear factor among patient populations and treating team in withholding the transfusions in patients with thrombocytopenia without any definitive indications. Studies have showed the futility of prophylactic platelet transfusions. A case control study by Prashantha et al showed that prophylactic platelet transfusion in clinically stable DF patients was associated with significant delay in platelet recovery and increased...
duration of hospitalization, although it was not harmful in terms of morbidity or mortality.\textsuperscript{16} More importantly platelet as a hospital resource material should not be misutilized considering extra load during a dengue outbreak. Human behavioral factors may have significant role on this; a future study on this is need of the hour.

As dengue is a tropical disease, it can be seen as a co-infection with other tropical diseases and co-infections such as with malaria, enteric fever, scrub typhus, or leptospirosis. These co-infections have been reported in the literature and thus antimicrobials use can be justified in such cases.\textsuperscript{17,18} However, prophylactic antibiotics are not advocated. Compliance to the rational antimicrobials use (prescribed when indicated) are not priori studied in dengue cases. The present study showed significant 18.5% absolute improvement in the compliance after the education, but the baseline irrational use of antimicrobials was 38.5% which outlined again the misutilization of resources. Hence barriers to the guideline adoption have to be determined again.

Both morbidity (or hospital stay) and mortality among dengue patients had improved after the educational training on the guideline. There were no deaths in post-intervention group despite of higher number of severe dengue cases compared to the pre-intervention group. Therefore, compliance to the guideline definitely improves the outcome. This has also been studied by Magpusao and Mayurasakorn et al who showed significant improvement of the case fatality ratio of dengue cases after providing the education to the physician.\textsuperscript{2,13}

For a training program to be successful, it should be convenient, relevant, focused, and delivered to the target population. We had targeted the relevant population (i.e. resident physicians). The individual duties of treating team members may vary, but the resident is the front runner and backbone of the whole patient management, especially in Indian tertiary care institutions. Henceforth, these facts reinforce the strength of the study design and relevance. Furthermore, we observed other obstacles in providing higher compliance rates among individual quality indicators including lack of adequate man power (resident doctor was the only provider many-a-times), delay in response time by medical personnel in an overcrowded Indian hospital setting, practical limitations in implementing training programs to all physicians at a time, difficulty in monitoring in a busy emergency ward, and lack of appropriate means and devices for continuous and accurate surveillance of compliance to the guidelines. Our institute continues to work towards meeting the goals set for this education programs and overcoming barriers.

This study has notable limitations. First, the study location is a referral hospital. Therefore it is difficult to generalize the findings in the whole country/world where primary care delivering hospitals are much more. However, the success of this program is most likely attributable to its focus on quality indicators of the prevalent guideline and proper documentation of the treatment, which should be independent of medical locations and applicable to all hospital-based responders as well. Hence, implication of this study is widespread. Second, the skill retention is a major question as this will determine the frequency at which doctors should be re-educated. Third, we did not measure other variables as discussed above including the contribution of other medical personnel, training of nursing staff, immediate availability of intensive care, overburdened residents, their behaviour, and other unknown factors. These may have blunted the improvement in individual indicator’s compliance post-training. Identifying and rectifying all these variables could have led to a better rate of compliance in the study. Henceforth, this study encourages having a large study/program for each institute to target an adequate compliance (100%) to the guideline.

In conclusion, the study affirms that the education training improves the guideline compliance which should be upto the mark in dengue endemic country like ours. The documentation quality, evaluated after training the medicine residents (who are usually the front runner of the dengue management team), may be used as an assessment tool for the internal quality improvement program to determine the guideline compliance. Furthermore, this study may prevent resource misutilization like the platelet transfusions or antibiotic uses. Future studies should assess the efficacy of these training programs (i.e., skill retention) and find out various barriers for achieving 100% compliance rate of the prevalent guideline.

References

Predictors of Severity in Scrub Typhus

Ritin Sharma1, Sanjay K Mahajan2*, Balraj Singh3, Rajiv Raina4, Anil Kanga5

Abstract

Aims: To study predictors of severity in patients of scrub typhus admitted in a tertiary care hospital.

Material and Methods: Total 92 patients of scrub typhus were included in the study. The diagnosis was established by presence of IgM antibodies by Indirect Immunofluorescence Assay (IFA) test which is currently the reference standard for the diagnosis of scrub typhus. The clinical and laboratory profile, course in hospital, and outcome were documented. Factors associated with severe disease were analyzed.

Observations: Fever (100%), cough (37%), headache (33%), vomiting (31%), altered sensorium (23%), diarrhea (18%), abdominal pain (16%), myalgia (14%), and seizures (3%) were common clinical features. An eschar was present in 23% of patients. Common laboratory findings included elevated transaminases (61%), thrombocytopenia (39%), and leukocytosis (30%). Severe sepsis was present in 33% patients. Septic shock was present in 4% patients. Presence of one or more organ failure was seen in 34% of patients. The overall case-fatality rate was 4%. Factors significantly associated with organ failure (severe disease) were leucocytosis (p < 0.001), hyperbilirubinemia (p < 0.001), high SGOT levels (p 0.030), hypoalbuminemia (p < 0.001), high urea levels (p < 0.001), and high creatinine levels (p 0.012). Among the criteria used to classify severity of scrub typhus, presence of one or more organ failure was significantly associated with mortality (p 0.004).

Conclusion: Scrub typhus can manifest with potentially life-threatening complications such as meningoencephalitis, septic shock, ARDS, acute liver failure, acute kidney injury, severe thrombocytopenia. Leukocytosis, hyperbilirubinemia, transaminitis, hypoalbuminemia, and uremia were associated with organ failure and were significantly associated with morbidity and mortality.

Introduction

Orientia tsutsugamushi and Rickettsia species are important cause of non-malarial febrile illness in Southeast Asia preceded only by dengue.1 Among rickettsioses, scrub typhus is most common followed by Indian tick typhus.2 The incubation period for symptoms ranges between 6 to 21 days from exposure. Patients may present with sudden fever, chills, headache, backache, profuse sweating, vomiting and enlarged lymph nodes. A macular or maculopapular rash may appear on the trunk, and later it may extend to the arms and the legs. An eschar at the wound site is the single most useful diagnostic clue.3 The Indirect Immunofluorescence Assay (IFA) test is currently the reference standard for the diagnosis of scrub typhus.4

Treatment with doxycycline is associated with a rapid abatement of fever and this effect has even been considered almost diagnostic. Azithromycin is also effective and is easier to administer, given its shorter treatment duration, and less gastrointestinal side effects. It is suitable for use in pregnancy and for children.5

The symptoms of scrub typhus are usually mild and its clinical course is uneventful. However, some patients experience severe or fatal events. Serious complications include pneumonitis, acute respiratory distress syndrome, acute renal failure, myocarditis, and septic shock. Mortality rates in untreated patients range from 0-30%.6

In the studies of scrub typhus in Indian Literature, the diagnosis is based on Weil Felix test or IgM ELISA. In present study the diagnosis of scrub typhus was done by Indirect Immunofluorescence Assay (IFA) test which is currently the reference standard for the diagnosis of scrub typhus however the test is expensive and requires considerable training.4

Methods

The study was conducted among all adult (age ≥ 18 yrs.) patients of scrub typhus admitted to wards of a tertiary care hospital from July 1st 2015 through June 30th 2016.

Inclusion Criteria

1. Patients diagnosed as Scrub typhus with IFA.
2. Age ≥ 18 years.

Exclusion Criteria

Patients of scrub typhus with co-infections and pregnant patients were not included.

Operational Definitions

Scrub typhus

A patient showing clinical features consistent with scrub typhus and IgM antibodies by IFA

Severe Disease

A case of scrub typhus with criteria fulfilling severe sepsis or septic shock or evidence of organ system failure was defined as severe disease and a case of scrub typhus leading to mortality was defined as a poor outcome.

1 Resident, 2 Associate Professor, Department of Medicine, 3 Associate Professor & Incharge Epidemiology Unit, Department of Community Medicine, 4 Professor, Department of Medicine, 5 Professor, Department of Microbiology, I.G. Medical College, Shimla, Himachal Pradesh; *Corresponding Author

Received: 04.03.2018, Revised: 21.09.2018, Accepted: 01.12.2018
1. Cardiovascular: Arterial systolic blood pressure <90 mm Hg or mean arterial pressure <70 mm Hg that responds to administration of IV fluids.

2. Renal: Urine output <0.5 ml/kg per hour for 1 hour despite adequate fluid resuscitation.

3. Respiratory: Paco₂/Fio₂ ≤250 or, if lung is the only dysfunctional organ, ≤200.

4. Hematologic: Platelet count <80,000/µl or 50% decrease in platelet count from highest value recorded over previous 3 days.

5. Unexplained metabolic acidosis: pH ≤7.30 or base deficit ≥5.0 mEq/L and plasma lactate level >1.5 times upper limit of normal.

### Septic shock

Defined as Sepsis with hypotension (arterial blood pressure <90 mm Hg systolic) for at least 1 hour despite adequate fluid resuscitation.

Or

Need for vasopressors to maintain systolic blood pressure ≥90 mm Hg or mean arterial pressure ≥70 mm Hg.
Organ system failure

Neurologic: Glasgow Coma Score < 6 (in absence of sedation)

Cardiovascular:
- Heart rate < 54 beats per min
- Mean arterial blood pressure < 49 mm Hg (systolic blood pressure < 60 mm Hg)
- Ventricular tachycardia, ventricular fibrillation, or both

Pulmonary:
- PaCO2 > 50 mm Hg (acutely)
- Ventilator or continuous positive airway pressure dependence on the second day of organ dysfunction

Hepatic:
- Jaundice (bilirubin > 6 mg/100 dL)
- Coagulopathy (Prothrombin Time, 4 sec greater than control, in the absence of anticoagulation)

Renal:
- Urine output < 479 mL/24 hr or < 159 mL/8 hr
- Serum BUN > 100 mg/100 dL
- Serum creatinine > 3.5 mg/100 dL

Hematologic:
- White blood count < 1, 000 cells/mm3
- Platelets < 20,000 platelets/mm3
- Hematocrit < 20%.

A brief history regarding presenting complaints, relevant past history, and personal history was recorded. Patients were subjected to general and systemic examination. Hematological and biochemical investigations were done as a part of fever workup. Patients were subjected to imaging studies where indicated.

IgM Indirect Immunofluorescence Assay (IFA)

An IFA for the detection and semi quantitative determination of IgM class antibody against Orientia tsutsugamushi in human serum or plasma was done using kit manufactured by Fuller Laboratories.

Data was collected from time of admission to discharge / death. We entered data on Microsoft excel spreadsheet and was analyzed using Epi Info 7.1.5 for windows. We did descriptive analysis for baseline characteristics of patients.

The study was cleared by Institutional Ethics Committee.

Results

Total 92 admitted patients of scrub typhus aged from 18 years to 80 years were included in the study. Seventy eight (85%) patients were in age group of 18-60 years. Out of 92 patients, 72% were females and 28% were males with the ratio of female to male 2.5:1. Fever was present in all cases, however high grade fever was present in 27% patients. The clinical details of patients are given in Table 1.

The comparison of hematologic and biochemical findings in patients with organ failure and without organ failure is given in Table 2.

Among hematological findings, there was significant difference in mean hemoglobin (p = 0.021) and mean hematocrit (p = 0.001) in patients with organ failure and without organ failure. Among biochemical abnormalities, hyperbilirubinemia (p < 0.001), mean SGOT (p = 0.030), mean serum albumin (p < 0.001), mean serum creatinine (p = 0.012) were significantly different among patients in organ failure group and in patients without organ failure.

The distribution of patients by severity of disease i.e. SIRS, Severe Sepsis/Septic shock and organ failure is given in Table 3.

SIRS was present in 76% of patients and severe sepsis was present in 33% patients, 26% were females and 50% were males. Out of components of severe sepsis thrombocytopenia was present in 37%, hypotension in 21%, acute lung injury was noted in 4% patients.

Septic shock was present in 4% patients, 8% were males, and 3% were females. SIRS, severe sepsis, septic shock all were more common in male patients.

The Organ failure (defined as dysfunction of any of organs) was present in 34% patients, and was common in males. MODS was (two or more organ failure) was present in 5% patients and all were females.

The outcomes of patients by severity of disease i.e. SIRS, Severe Sepsis/Septic shock, organ failure is given in Table 4.

When Severe Sepsis criteria were applied, there were 4 ICU admissions in both severe sepsis and non-severe sepsis group (RR=2.1, 95% CI=0.6-7.7). In non-severe sepsis group ICU admissions were due to ventilator support required in patients due to poor GCS. There were 2 deaths in each group (RR=2.1, 95% CI=0.3-14.0).

When organ system failure criteria were applied, there were 5 ICU admissions in patients with organ failure group and 3 in patients without organ failure group (RR=3.3, 95% CI=0.8-12.8). All 4 deaths were in patients with organ failure (RR=Undefined, 95% CI=Undefined). Among the criteria used to define severity, evidence of organ failure was most significantly associated with ICU admission (p=0.071) and mortality (p=0.004).

Discussion

Scrub typhus is a febrile disease that is endemic in Asian-Pacific areas, including the Korean Peninsula. It is a clinically important disease because of its high incidence in areas of endemicity and associated with many serious complications.

In our study 85% of patients were in age group of 18 to 60 years, people of this age group are mostly involved in agricultural activities or visit the forest/grass fields to collect grass for feeding their cattle. About half (49%) of patients in our study were in the age group of 21-40 years, Sharma et al reported highest incidence of scrub typhus in the age group of 30-40 years. The higher incidence in female may be due to the fact that females in this region actively participate in the agricultural or horticultural work. The typical working position of females in a squatting position, with bare hands in the fields or cutting grass predisposes them for exposure to infected mites which inhabiting soil and scrub vegetation. Mahajan et al in their study noted that more than 2/3rd of patients were female.

In this study, duration of symptoms at presentation was 7-14 days in 56% of patients, < 7 days in 31.5% patients, >14 days in 12.0% of patients. Our State is a hilly state and majority of patients present late to a healthcare facility, leading to emergence of complications and poor outcome. The distribution of various clinical features of scrub typhus in our study were similar to a study by Tsay et al. Eschar was present in 23% patients in our study and was lesser than other studies. This may be
due to reason that eschar is seen less frequently in South Asians, especially those who are dark skinned.

The target cells for *O. tsutsugamushi* are endothelial cells and macrophages. It disseminates into the multiple organs through endothelial cells via hematogenous and lymphogenous routes and predominantly locates in the macrophages of the liver and spleen. Disseminated vasculitis with perivasculitis is the hallmark of scrub typhus, and involvement of the brain and lungs are the most important factors in any fatal outcome.

Complications of scrub typhus, defined as severe disease were septic shock, renal dysfunction, altered sensorium, jaundice, thrombocytopenia, myocarditis and death. Among hematological parameters anemia, leukocytosis and thrombocytopenia were associated with severe disease. Raised SOTG levels were associated with organ failure. Mean albumin level was low in patients with organ failure. Lee et al concluded that hypoalbuminemia in scrub typhus was closely related to the frequency of various complications.

Raised serum creatinine was associated with organ failure. The pathophysiology of acute renal failure is associated with prerenal azotemia due to renal hypoperfusion in cases of shock or volume depletion. Hypoalbuminemia is common with rickettsial diseases and is reported to be due to the leakage of plasma albumin into the perivascular space because of widespread vascular damage. Second, disseminated intravascular coagulation is considered another pathophysiological trait of renal failure. Third, acute tubular necrosis might cause renal failure because of the direct invasion of *O. tsutsugamushi* into a renal parenchyma. Mahajan et al reported renal dysfunction as a significant mortality risk factor. In Table 2 urea to creatinine ratio (mean) in our study was 33.3 in patients with organ failure suggesting that intrinsic renal disease was main pathogenic process for renal dysfunction. In Table 4, organ failure was significantly associated with mortality, however combining severe sepsis and an organ failure criterion to define severity allows detecting patients with poor outcome early and their early management.

Severe sepsis was present in 33% and septic shock was present in 4% patients. Incidence of septic shock in scrub typhus varies in literature. Vikrant et al reported septic shock in 3% of patients however Kumar et al reported septic shock in 22% of patients.

Patients with severe sepsis and organ failure were more likely to get ICU admission. Among the criteria used to classify severity of scrub typhus, organ failure was significantly associated with mortality. Possibly it is because that organ failure cut off values used to define organ failure were more stringent and severe sepsis being a less severe manifestation of scrub typhus in same spectrum of disease process. In a study by Varghese et al, shock requiring vasoactive agents, CNS dysfunction, and renal dysfunction were independent predictors of mortality. Hence presence of organ failure should alert physician towards severe disease. Strict monitoring and ICU care should be provided to such patients to prevent multiple organ failure and mortality.

**Limitations**

This study had some drawbacks. The data about previous treatment received in peripheral hospitals before admission was not available. This study was conducted in a tertiary care centre, so more severely affected patients requiring intensive management were included in the study, resulting in increased number of patients with severe disease as compared to Primary Health Services.

**Conclusion**

**Scrub typhus can manifest with potentially life-threatening complications such as**

- meningoencephalitis, septic shock, ARDS, acute liver failure, acute kidney injury, severe thrombocytopenia.
- Leukocytosis, hyperbilirubinemia, transaminitis, hypoalbuminemia, and uremia were associated with organ failure and were significantly associated with mortality.

**Financial Assistance**

IFA was done as a part of Project No. GIA/32/2014-DHR Dated 22-10-2014, funded by Indian Council of Medical Research.

**References**

Dengue Encephalopathy in Hadoti Region: Clinical Presentation, Diagnostic Evaluation, Management and Outcome

Manoj Saluja1, Yogesh Kumar Swami2*, Saurabh Chittora3, Hemant Vimlani1

Abstract
Background: Dengue viral infection is common worldwide. Recent studies have shown dengue viral infection causing encephalopathy, with high morbidity and mortality. Dengue encephalopathy patients usually present with altered sensorium, elevated lab parameters and high antibody titres at the time of admission. Dengue infection was very common and virulent in Hadoti region during August to November 2017 and many patients presented with encephalopathy.

Aims: To study the clinical presentation, lab parameters and other diagnostic features, management and outcome of patients of dengue fever with encephalopathy in Hadoti region in August to November 2017.

Settings and Design: The study was done in Govt Medical college Hospital Kota and other multi-speciality hospitals of Kota. Study population comprised of 60 patients presenting with febrile illness and thrombocytopenia, serologically proved to be having Dengue fever. Among these 60 patients, 30 patients had encephalopathy who presented with altered sensorium, seizures or any other neurological symptoms and remaining 30 had no signs and symptoms of encephalopathy.

Results: Among 30 patients with encephalopathy and positive serology (NS1/IgM/ IgG), fever and altered sensorium was most common symptom, while amongst patients without encephalopathy fever with chills and generalised body ache was more common clinical feature. Convulsions and respiratory distress were very common among encephalopathy patients. Out of 30 encephalopathy patients 16 patients (53%) had convulsions, 14 (46%) had respiratory distress, 17(56%) had shock and 3 patients (10%) had hemiplegia. 2 patients also had visual blurring and dysarthria. Mean duration between appearance of fever and altered sensorium was 4.6 (±2.1) days. Most of patients with encephalopathy had deranged hepatic (bilirubin, SGOT, SGPT), renal (urea, creatinine, decreased urine output) and coagulation parameters (PT/INR, bleeding manifestations). 9 (30%) patients died and 21(70%) patients improved with complete recovery (except 3 hemiplegic patients).

Conclusions: Increased incidence of dengue fever with encephalopathy in the recent years, in the absence of single sensitive test for detecting dengue encephalopathy, variable CSF and MRI Brain features, and associated high morbidity and mortality poses a big problem for clinician. This study may be helpful in focussing on early diagnosis and aggressive initial management which can influence final outcome.

Introduction

RNA virus of family Flaviviridae that spreads by Aedes mosquitoes is responsible for dengue fever. Approximately 2.5 billion people are at risk primarily in the densely populated areas of tropical and subtropical countries, with an estimated infection load of 50 million worldwide annually. According to the World Health Organization (WHO), India is considered in endemicity category A, in which dengue is a major public health problem. Presentations in symptomatic patients include undifferentiated viral fever, dengue fever, and dengue hemorrhagic fever. Expanded dengue spectrum includes unusual manifestations like neurological, hepatic, renal, and other isolated organ involvement.

Common clinical features are fever, arthralgia, headache, petechial spots, rashes and hemorrhagic manifestations. Dengue virus is considered as a non-neuropotrop virus. However, increasing number of studies and case reports of central nervous involvement (CNS) involvement are being reported. The CNS manifestations can be attributed to three factors (a) neurotropic effect, (b) secondary to systemic manifestation, and (c) postinfectious sequelae including immune-mediated reactions. Numerous neurological manifestations are reported like encephalopathy, encephalitis, Guillain Barre syndrome, transverse myelitis, acute disseminated encephalomyelitis, and myositis. These neurological complications are rare and its pathogenesis is controversial. Few theories states that dengue neurological manifestation is secondary to systemic manifestation (Encephalopathy), but recent evidence is in favour of dengue neurotropism, because dengue virus and dengue IgM antibodies has been discovered in CSF of encephalopathy patients which suggests that dengue virus is capable of central nervous system infection. Dengue fever associated with encephalitis has high morbidity and mortality and only few studies or case series has been published regarding dengue encephalitis. This study may be useful in early detection of dengue fever patients with encephalopathy (which might be encephalitis) using clinical features and laboratory parameters in resource limited countries which are

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Received, 28.03.2018; Accepted: 05.01.2019
having maximum number of dengue cases, so that early diagnosis of dengue encephalopathy and timely supportive therapy can reduce or avoid morbidity and mortality. We present a total of 30 cases of dengue fever with encephalopathy.

Material and Methods

This epidemiological prospective study was done Govt Medical College Hospital Kota and other multispecialty hospitals of Kota.

This study included total of 60 patients serologically proved to be having dengue fever. Among which 30 patients had encephalopathy (or encephalitis) who presented with altered sensorium, seizures or any other neurological symptoms. Rest 30 patients of dengue fever without encephalopathy served as control.

The diagnosis of dengue fever was based on clinical features, (fever, headache or bodyache, altered sensorium, hemorrhagic manifestation, jaundice, and shock) and positive serum NS1/IgM / IgG antibodies. The diagnosis encephalopathy was based on clinical features (Low GCS, altered sensorium, headache, and seizures or any other neurological deficits), MRI brain findings (Hyperintense areas) and CSF study (Cell count, protein and sugar).

The detailed medical history, age, area of residence, and clinical features were noted. Consciousness was assessed by Glasgow coma scale (GCS). Systemic manifestations such as lymphadenopathy, hepatosplenomegaly, jaundice, Cardiac, Renal and Respiratory findings were also recorded.

The laboratory tests included complete blood examination (hemoglobin, hematocrit, WBC counts, platelet counts), blood sugar, blood urea, serum creatinine, bilirubin, SGOT, SGPT, prothrombin time, INR, and Dengue serum antibodies. Electrocardiogram, Chest X-ray (PA view) done in all patients, and CT scan and/or MRI brain, Cerebrospinal fluid analysis (analyzed for protein, sugar, cells) were carried out in as much as possible patients of encephalopathy group.

Exclusion criteria

Patients with previous liver or kidney failure and recent cerebral events (stroke, meningoencephalitis), malaria, and hepatitis were excluded.

Results

Among 30 patients of proved dengue fever with altered sensorium, seizures, or any other neurological symptoms suggestive of encephalopathy/encephalitis, 22 patients were male and 8 were female. All patients presented with fever with or without chills. Headache, vomiting, pain abdomen were also prominent features. Detailed symptomatic profile of encephalopathy group and controls is given in Table 1.

Most common clinical features in patients with encephalopathy were fever with altered sensorium. Clinical features like seizures, shock, generalised weakness and shortness of breath were significant.

All 30 patients had altered sensorium, among which 19 patients required intubation and ventilator support and 2 patients required BIPAP support, 9 patients were maintained on oxygen supply by face mask.

Neurological examination

All encephalopathy patients presented with altered sensorium, 11 patients had exaggerated DTR, 12 patients had extensor plantar reflex, rest all had normal DTR and normal plantar reflex.

Hepatic dysfunction was found in most of patients as deranged transaminases or bilirubin levels. 14 patients (46%) also had renal impairment as deranged urea/creatinine or decreased urine output. All patients had thrombocytopenia of varying degree. Detailed lab results are analysed in Table 2.

All 30 encephalopathy patients had severely deranged liver enzymes (SGOT, SGPT), coagulopathy (Raised PT, INR), severe thrombocytopenia and positive serology (NS1/Ig-M /Ig-G), 3 patients required CRRT for Acute Kidney Injury for short period of time. 16 patients had generalized seizures, 14 patients had respiratory distress out of which 2 patients had ARDS and 1 patient had hemoptyis.

7 patients (23%) had hyponatremia and required IV sodium. CSF study showed high protein and normal cell counts in 10 patients and normal protein and cell count in 14 patients (CSF was not done in 7 patients).

MRI Brain study

MRI brain was done in 23 patients, out of which-

1. 4 patients had diffuse cerebral edema
2. Hyperintensities in temporal lobes/thalamus or pons seen in 10 patients, among which 6 patients had hyperintensities in thalamus, 3 patients in temporal lobes and 1 patient’s MRI shows diffuse cerebral atrophy and multiple small infarct
were administered as indicated. Among all patients with low GCS were intubated to protect the airway and majority of them extubated after 5-7 days. 9 patients were on prolonged ventilation who died later due to refractory septic shock and MODS due to secondary bacterial sepsis. CRRT done for 3 patients with AKI (Acute kidney injury) having oliguria/anuria, Pulmonary edema, Hyperkalemia and severe metabolic acidosis.

Neurological complications are rare and its pathogenesis is controversial, few theories states dengue neurological manifestation is secondary to systemic manifestation (Encephalopathy), but recent evidence is in favour of dengue neuro tropism, because dengue virus and dengue IgM antibodies has been discovered in CSF of encephalopathy patients which suggests that dengue virus is capable of central nervous system infection.

In our study the features of encephalitis (headache, altered sensorium, and seizures) in majority of patients were seen more commonly after 4-7 days of onset of fever. Among the four dengue serotypes (DEN-1 to DEN-4) DEN-2 and DEN-3 have highest propensity to neurological complications.11,12

Cam BV et al, and Hendarto SK et al, have reported the encephalopathy incidence ranging from 0.5% to 6.2%. Kankirawatana et al., found that 18% of children with suspected Encephalitis in Thai hospital were found to have dengue infection.

The patients who died in encephalopathy group (9 out of 30 patients), all of them presented with – low GCS, seizures, headache. Hence patients with dengue fever with predominance of these clinical features and severely deranged lab parameters are probably manifesting encephalopathy which has high morbidity and mortality, so early diagnosis and aggressive management should be given to prevent anticipated complication.

In case of dengue Encephalitis diagnosis can be made either by detection of virus in CSF (viral culture / PCR) or immune response by the body (Ig-M antibodies in CSF). The gold standard method is viral culture which is difficult and time consuming. Regarding CSF IgM and IgG antibodies, Puccioni-Sohler M et al.,13 and Cristiane Nascimento Soares14 have shown that these antibodies can be seen in CSF but the absence will not rule out encephalitis. In our study CSF IgM and IgG was not done because the sensitivity of this test found to be very low and was thought to be financial burden for those patients.

CSF study in encephalopathy group showed high protein and normal cell counts among 10 patients and normal protein and normal cell count among 13 patients but serum IgM and IgG were positive in all patients. These findings are similar to that of viral encephalitis. Brain imaging- MRI is the modality of choice which shows the findings consistent with viral encephalitis include cerebral edema, white matter changes, necrosis and brain atrophy. Encephalitis features in brain (Hyperintense areas) can be seen in global pallidus, temporal lobes,15,16 thalamus,17 hippocampus,18 pons, and spinal cord.19 Among 30 dengue patients with encephalitis, 20 patients recovered completely at the end of 1 month (independent for activities of daily living), and 9 patients died (due to severe sepsis with MODS).

Comparative study of patients who survived and died on the basis of various parameters are given in Table 3. Among all patients, 24 patients were given mannitol/dexamethasone, and 16 patients also received inj. acyclovir. Inj. Acyclovir found to be beneficial in dengue encephalopathy patients, most probably due to cross reactivity with viral antigen, however exact reason is not known.

Discussion

Dengue is endemic to over 100 countries and approximately 2.5 billion people are at risk. It is estimated that 50–100 million infections and 25,000 fatalities occur worldwide every year. World health organization (WHO) surveillance shows that global incidence is increasing.2 The primary vector is the mosquito Aedes Aegypti. Dengue fever has varying clinical presentation ranging from asymptomatic infection to life threatening hemorrhagic fever and dengue shock syndrome. Complications of dengue fever are common and usually related to renal and hepatic dysfunction. In our study almost all patients had severely deranged liver enzymes (SGOT, SGPT), coagulopathy (Raised PT, INR), severe thrombocytopenia and positive serology (NS1,Ig-M and Ig-G). Patients were managed conservatively as per WHO guidelines. In the patients with hemorrhagic diathesis, platelet concentrate and/or fresh frozen plasma were administered as indicated. Among all patients with low GCS were intubated to protect the airway and majority of them extubated after 5-7 days. 9 patients were on prolonged ventilation who died later due to refractory septic shock and MODS due to secondary bacterial sepsis. CRRT done for 3 patients with AKI (Acute kidney injury) having oliguria/anuria, Pulmonary edema, Hyperkalemia and severe metabolic acidosis.

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Brain imaging- MRI is the modality of choice which shows the findings consistent with viral encephalitis include cerebral edema, white matter changes, necrosis and brain atrophy. Encephalitis features in brain (Hyperintense areas) can be seen in global pallidus, temporal lobes,15,16 thalamus,17 hippocampus,18 pons, and spinal cord.19 Among 30 dengue patients with encephalitis, 20 patients recovered completely at the end of 1 month (independent for activities of daily living), and 9 patients died (due to severe sepsis with MODS). CSF culture or PCR for viral detection in CSF was not done. But all patients proved to be having dengue serum antibodies are managed conservatively according to WHO guidelines. More research is necessary for the changing trend of host immunological response and dengue viral characteristics as more patients with dengue viral infection in recent years are presenting with encephalopathy.

In Hadoti region mortality rate was high among dengue encephalopathy patients as comparative to other studies may be due to more virulent strain of dengue virus or delayed reach to health care centre.

Conclusion

Increased incidence of dengue fever with encephalopathy in the recent years, in the absence of single sensitive test for detecting dengue encephalitis, variable CSF and MRI Brain features, and associated high morbidity and mortality, this study may be helpful in focussing on early diagnosis and aggressive initial management which can influence final outcome.
Glucose Monitoring in Critically Ill: Is Absence of “Stress Hyperglycaemia” a Cause for Concern?

Vijayashree Gokhale1*, Tanvi Batra2, Shalaka S Shinde3, Shipra Gulati3, Arjun Lal Kakrani4

Abstract

Aim: To study variations in glucose levels over 48 hours in critically ill patients by capillary blood glucose done on glucometer and compare the same in different categories of patients based on various diseases, as well as their correlation with sepsis and diabetes mellitus. To compare the same result in subgroups of patients with the readings of continuous glucose monitoring.

Material and Methods: We studied 50 critically-ill patients (Age ≥ 18 years), admitted in medical ICU (on mechanical ventilation/ionotropic supports/in sepsis) in a teaching hospital in semi-urban Maharashtra. Critical illness was defined as any physiological instability leading to disability or death within minutes or hours, based on neurological assessment, respiratory system involvement and cardiovascular involvement.

Capillary blood sugar levels were done 4 hourly using ‘NIPRO’ glucometer. Site was rotated. 5 patients had simultaneous continuous glucose monitoring, using I-Pro bio-sensor.

Results: Total 50 patients were included in the study. The data was collected and tabulated. Analysis showed that all critically ill patients showed some higher than normal recordings of blood sugar, which till now has been attributed to ‘stress-hyperglycaemia’. This may be absent or blunted in sepsis. In the critically-ill patients with primary involvement of gastrointestinal tract, meal-unrelated fluctuations were seen. In critically-ill patients with CNS and CVS involvement, lowest BSL recordings were seen (meal unrelated) at 2 am.

Conclusion: We concluded that that patients who develop hypoglycaemia may have an equally bad prognosis or even worse than those who develop hyperglycaemia during the period of critical illness. CGM devices record tissue glucose levels continuously, and may be useful as a ‘tissue hypoglycaemia’ alert.

Introduction

The critically ill patient is extensively monitored. Heart rate, blood pressure, SpO2, and ECG is routine in level 1 ICU. ABG and electrolytes are monitored for patients on ventilator. Blood glucose however is monitored only in diabetics, especially in DKA. Mild hyperglycaemia encountered in non-diabetic patients is labelled as “stress hyperglycaemia” and left alone, which often comes to normal in 24–48 hours. Studies on treatment of “stress hyperglycaemia” with short acting insulins did not show any additional benefits. The most common complication of critical illness is sepsis, leading to multi-organ failure and death. Glucose is the most important carbohydrate fuel in the body. In the fed state, the majority of circulating glucose comes from the diet; in the fasting state, gluconeogenesis and glycolysis maintain glucose concentrations. The latter is true in most of the critically ill patients, where the majority of circulating glucose comes from the diet. In the fed state, glucose is the most important carbohydrate fuel in the body. In the fasting state, gluconeogenesis and glycolysis maintain glucose concentrations. The latter is true in most of the critically ill patients, where the majority of circulating glucose comes from the diet.

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patients. Glucose can be monitored as venous blood glucose, capillary blood glucose by glucometer, and continuous tissue glucose monitoring. While venous blood glucose and capillary blood glucose are comparable, a lag period of approximately 1-2 hours is seen with tissue glucose. But it is tissue glucose levels which form the internal milieu of organs, where cellular metabolism takes place. In Mammalian cells, glucose provides primary source of energy for brain as well as renal medulla, and is the sole provider of energy for red blood cells and retina. Total consumption of glucose in a 70 kg person is 160g, the brain uses 120g out of this. In the critically ill patient, “stress hyperglycaemia” may be the body’s safeguard against ‘hypoglycaemia’ and a blunted response should be an indication to monitor glucose levels.

**Aims and Objectives**

To study variations in glucose levels over 48 hours in critically ill patients by capillary blood glucose done on glucometer.

To compare the blood glucose levels over 48 hours in disease wise classification of patients

Patients with and without sepsis

Diabetics and non-diabetics

Compare glucometer evaluation and continuous glucose monitoring graphs in a small subset of patients

**Materials and Methods**

50 critically ill patients on admission to Medical intensive care unit of a teaching hospital in semi-urban Maharashtra were serially included in the study. Capillary blood glucose was measured 4 hourly for a duration of 48 hours using NIPRO glucometer. 5 patients had simultaneous continuous glucose monitoring, using I-Pro biosensor.

Data was recorded in proforma.

Statistical analysis was done using Microsoft excel and Epi-info software. The frequency distribution and graph were prepared for the variables. The categorical variables were assessed using Pearson chi-square. Mantel Haenzel Odds Ratio (OR) and corresponding 95% Confidence Interval (CI) were calculated for dichotomous variables.

**Results**

Our study included critically ill patients aged above 18 years, maximum being in 40-60 years age group. 56% were males, 44% females. In our study, average capillary BSL of critically ill patients (time and day matched) ranged between 150 - 163 mg/dl, a variation of only 13 mg%, suggestive of ‘stress-hyperglycaemia’. On graphic representation, the highest readings were at 2 pm and 10 pm, corresponding to post prandial blood sugar.

On segregating patients according to their primary system involvement, different patterns emerged. Gastrointestinal patients showed maximum meal-unrelated fluctuations, while in patients with primarily renal involvement, lowest average was 128 (at 2 am) and highest 180 (at 6 am). Patients with CNS critical-illness, mostly strokes, showed a low of 125 (at 2 pm, day 1) and a high of 190 (at 2 pm on day 2), indicating a time

![Fig. 1: Line diagram comparing average BSL over 48 hours according to type of diseases in study group](image)
delay for development of ‘stress-hyperglycaemia’), and low sugars in acute phase.

Patients with CVS critical illness also showed a low sugar level of 125 (at 2 am), and a high sugar level of 170 (at 2 pm). The dip at night may be significant.

In the Sepsis versus non-sepsis analysis, patients with sepsis had BSL ranging between 140-160 mg/dL, while the non-sepsis group had BSL between 150-180 mg/dL. This may point towards a ‘blunted stress-hyperglycaemia’ response in sepsis, and ‘tissue hypoglycaemia’ as a possibility.

Continuous glucose monitoring done in only 5 patients simultaneously, due to cost restraints, showed marked hyperglycaemia in 3 patients who were diabetic, but showed lower sugars in patient of fulminant hepatitis and erratic high and low in patient with sepsis; However, the low and high sugar levels did correspond in the 2 methods of estimation, albeit with a lag period in CGM.

**Discussion**

In studies by C. Dana, et al and Xu Li, Ma Y, Chen, et al bedside capillary glucose monitoring in intensive care was comparable with laboratory venous blood glucose.

Krinsley JS, Falciglia M, et al, Umpierrez GE, Freire AX, et al studied hyperglycaemia in heterogeneous population of critically ill, and found “admission diagnosis” and “admission hyperglycaemia” to be risk factors.

Egi M, Bellomo R, et al and Christiansen C, Toft P, et al studied hyperglycaemia, both acute and chronic in diabetics and non-diabetics, while Paul E. Merik, Rilando Bellomo felt “stress hyperglycaemia is an essential survival response”.

In a study by Suleiman M, Hammerman H et al, impaired glucose metabolism and fasting glucose emerged an independent risk factor in patients with acute Myocardial Infarction.


The Metabolic group, mostly diabetics, showed hyperglycaemia as expected, and were on treatment with insulin. Stegenga ME, et al felt “Diabetes does not alter mortality or homeostatic and inflammatory responses in patients with severe sepsis.”

Significant hypoglycaemia was not seen in any of our patients.


Roosmarijn TM, Jan Hendrik Leopold et al, in their studies with Continuous Glucose monitoring, had mixed opinions regarding efficacy.

Whereas Carol Lorenco, Yenny Leaf et al felt there is better accuracy in real-time Continuous Glucose Monitoring in patients with Septic Shock.

**Conclusions**

A majority of our patients showed borderline hyperglycaemia, probably ‘stress-hyperglycaemia’.

On segregating patients according to primary system affected, fluctuating and ‘meal-unrelated’ hyperglycaemia emerged in patients with gastrointestinal disease, most marked in CGM records of patient with fulminant hepatitis. Sepsis patients showed overall lower average glucose levels than in those without sepsis, as also seen in CGM graph.
Limitations of Study
Small sample size, CGM could not be done in every patient due to costs.

Clinical Implications
Critically ill patients may have fluctuating glucose levels, depending upon the primary system or organ involvement. In sepsis, there may be ‘blunting of the stress-hyperglycema’ response, making patients prone to ‘hypoglycemia’ and increased mortality. Continuous Glucose monitoring in sepsis gives an idea of overall glucose trend, and can act as a ‘hypoglycemia alert’.

References

Prevalence of HIV Associated Neurocognitive Disorder using Modified Mini Mental State Examination and its Correlation with CD4 Counts and Anti-retroviral Therapy

Sachin Kumar¹, Dandu Himanshu², Ruchika Tandon³*, Virendra Atam⁴, Kamal Kishore Sawlani², Sudhir Kumar Verma³

Abstract
Introduction: HIV Associated Neurocognitive Disorder (HAND) is still prevalent even in the ART (Anti-Retroviral Therapy) era. It may have some association with CD4 counts and Anti-Retroviral Therapy. The prevalence of HAND in HIV-patients, was, therefore studied in the context of ART and CD4 counts.

Methods: Modified Mini Mental State Examination scores of 200 (65% males) HIV-positive patients and 200 controls were analyzed in the context of ART and CD4 counts.

Results: Maximum number of participants were educated between 8th-12th class (89.5%), aged between 25-50 years (81.5%) and a higher proportion of males had a CD4 count <500 (69.2%) (p=0.007). Using 3MS, 21% patients (mean 76.24±1.51) and none of the controls were found to be neurocognitively impaired. Mean scores of patients with CD4 counts<500(82.54±5.58) were lesser in comparison to those of patients with CD4 counts>500 (p<0.001). Those with an ART duration of <48 months had a lower score in comparison to those with an ART duration of >72 months (p=0.005).Most decrease from maximum value was seen in similarities (48.3 %), second recall (36.1 %), repetition (33.4 %), copying two pentagons (28.3 %), read and obey

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Received: 15.11.2017; Accepted: 12.12.2018
(24.0%), mental reversal (22.7%) and first recall (21.3%) parameters of Modified Mini Mental State Examination.

Conclusions: HAND was less prevalent in the present study in comparison to past literature. CD4 counts and ART duration had an inverse association with the degree of cognitive impairment. The parameters of Modified Mini Mental State Examination showing maximum impairment may be compiled to form a short screening questionnaire.

Introduction

HIV (Human Immunodeficiency Virus) disease is a major problem and much prevalent disease worldwide, more so in the low and middle income countries. According to the United Nations Programme on HIV and AIDS (UNAIDS) estimate, there were approximately 36.9 million people living with HIV/AIDS (Acquired Immunodeficiency Virus) in 2015. India has the third highest number of people living with HIV disease in the world. There has been a steady decline in number since 2007 with numbers coming down from 2.23 million to 2.12 million in 2015.

HIV enters the central nervous system (CNS) after initial infection and is responsible for a range of neuropsychiatric complications directly or through associated immune activation. Brain-related problems in HIV patients include HIV-associated neurocognitive impairment (HAND) and opportunistic infections.

Cognition is a mental process involved in judging, knowing, learning, perceiving, recognizing, remembering, thinking, and understanding that leads to the awareness of the world around us. It is involved in acquisition and understanding of knowledge, formation of beliefs and attitudes and in the decision making and problem solving. Among these cognitive domains, the HIV infection most prominently affects motor functioning, attention, processing speed, executive functioning, and memory and this HIV related neurocognitive impairment can be classified into asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD), depending on the disease severity. HAND is an important cause of morbidity. Hence, it is necessary to study the prevalence of HAND in people living with HIV disease (PLHIV), to employ some interventions to manage this complication. HIV-associated neurocognitive impairment may be more severe in people at their extremes of age and in those with more severe disease, measured through lesser CD4 counts and the more time since the onset of HIV disease.

Neurocognition can be tested by various methods and Mini Mental State Examination (2S) and Modified Mini Mental State Examination (3MS) are two such methods. Among Mini Mental State Examination and Modified Mini Mental State Examination, Modified Mini Mental State Examination is an expanded version, which has been found to be better in predicting functional outcome in a previous study.

King George's Medical University (KGMU), Lucknow, India, is a tertiary care center in North India, which serves as a referral center to patients suffering from HIV disease from North India and also some patients from other parts of the country as well.

Table 1: Modified mini mental state examination scores of patients with HIV disease in relation to the CD4 counts and duration of ART

<table>
<thead>
<tr>
<th>SN</th>
<th>Predictor</th>
<th>3 MS score</th>
<th>Mean</th>
<th>SD</th>
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<tr>
<td>1</td>
<td>CD4 count</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>⩽500 (n=125)</td>
<td>82.54</td>
<td>5.58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;500 (n=75)</td>
<td>88.44</td>
<td>3.99</td>
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<td></td>
<td>t=8.003; p&lt;0.001 using t-test</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>Duration of ART (n=182)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less than 48 months (n=82)</td>
<td>83.10</td>
<td>5.76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48-72 months (n=39)</td>
<td>85.15</td>
<td>6.40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More than 72 months (n=61)</td>
<td>86.11</td>
<td>5.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F=4.415; p=0.05 using ANOVA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hence, we assessed the prevalence of HIV Associated Neurocognitive Disorder (HAND) in HIV patients presenting to the outdoors of King George's Medical University, Lucknow, India and the factors affecting HAND in the PLHIV. The presence of co-morbid depression may also affect the cognition assessment in these patients and this was also studied.

Materials and Methods

The study was conducted in the Department of Medicine, KGMU, Lucknow, India on HIV positive patients visiting the outdoors of KGMU, Lucknow, India, from September 2015 to September 2016.

Participants

Patients with HIV disease aged more than 18 years and in full GCS (fully oriented to time, place and person) without any signs of meningial irritation, raised intracranial tension or a history of head injury, were included in the study. All the patients giving consent for the study were included. Those people, who were educated below 8th standard, were excluded from the study. Age, sex and educational status matched healthy control participants, who gave consent for the study, were also included. The controls were taken from among hospital staff members, whose HIV status was shown to be negative.

Procedure

The Modified Mini Mental State Examination test was used to assess the cognitive functions of 200 patients suffering from HIV disease according to the NACO testing guidelines. Since, previous researchers have shown that at a cut off of 79, the sensitivity and specificity of detecting cognitive impairment is between 98-100 and 70-81 respectively, hence, we chose a cut off of 79 for defining cognitive impairment. The patients were defined as cognitively impaired, if they had a total 3MS score of <79. The test was administered to the patients by means of personal interview by the investigator, who is a resident doctor and were confirmed by another investigator who is a neurologist. Once enrolled, the history and examination of the patients was noted. History of the patients was also taken, in particular regard to any opportunistic infections and subsequent treatment taken in the past. Laboratory investigations were done at ART center as per the NACO programme, which included hemoglobin, complete blood counts, serum electrolytes, renal and hepatic function tests and some additional tests like serum vitamin B12 levels and thyroid function tests. Those participants, who had vitamin B12 levels
of less than 200 or deranged thyroid function tests, were excluded from the study. A CT scan of the head was also done and those with an abnormal CT head were excluded from the study. Patient’s health questionnaire-9 (PHQ-9) was also administered to these patients for the assessment of depression as it could be a confounding factor. All the patients who were found to be moderately severe or severely depressed were excluded from the study. Two hundred age, sex and education matched healthy controls were also included in the study. A written informed consent was taken from all the study participants. The study was approved by the institutional ethical committee of King George’s Medical University, Lucknow, India (Approval number: 77th ECM II B-Thesis/P6).

Data analysis
The data was analyzed using Microsoft IBM SPSS version 20 (Statistical Package for the Social Sciences). The means, medians and standard deviations were calculated for different demographic variables. The means and standard deviations were calculated for Modified Mini Mental State Examination total score and different individual parameters of Modified Mini Mental State Examination. Frequency and percentage was calculated for different demographic and clinical parameters and significance was tested between frequencies of different variables using Chi square tests. For comparison among different means, T-test and ANOVA were used.

Results
Out of 200 patients, 65% were males and the remaining were females. Sixteen (8%) patients [7 (5.4%) males and 9 (12.6%) females] were of <25 years of age, 21 (10.5%) patients [14 (10.8%) males and 7 (10%) females] were of >50 years of age, but maximum patients [163 (81.5%) with 109 (83.8%) males and 54 (77.1%) females], belonged to an age group between 25-50 years (p=0.056). Most of the patients [179 (89.5%), 121 (93.1%) males and 58 (82.9%) females] had an education between 8th-12th standard and only 17 (8.5%) [8 (6.2%) males, 9 (12.9%) females], were graduates and 4 (2%) [1 (0.8%) male, 3 (4.3%) females], were postgraduates (p=0.056). CD4 counts of <500 were observed in 90 (69.2%) males and 35 (50%) females [125 (62.5%) total cases] and the remaining people had CD4 counts of >500 (p=0.007) (using Chi-square tests).

The median CD4 count of the cases was 429. Using Modified Mini Mental State Examination, neurocognitive impairment was seen in 42 (21%) of the HIV patients (mean score 76.24±1.51) and 158 (79%) HIV patients were not found to have a neurocognitive impairment (mean score 87.02±4.15).

There were 200 controls. Mean Modified Mini Mental State Examination score of controls was 87.62±4.23 (p-value for difference from
The 3 MS score of patients with HIV disease in relation to CD4 counts and the duration of antiretroviral therapy is mentioned in Table 1.

There were 18 patients, who were not on ART, as they were new patients with a high CD4 count, in whom ART had not yet been started, in accordance with the National guidelines of India, who had a mean Modified Mini Mental State Examination score of 86.13±5.43. The median CD4 count of these patients was 579.

The mean of different parameters of Modified Mini Mental State Examination in HIV patients and healthy controls is mentioned in Figure 1. The differences in between means were also calculated using independent samples T-test and the p-values are depicted in Figure 1.

Of the 15 parameters of Modified Mini Mental State Examination, for all except one item (three stage command) the mean scores were lower than normal value. The mean scores ranged between 2.99±0.10 (Registration) and 14.74±0.67 (Temporal orientation) (Figure 1).

The percentage decrease from maximum value of different parameters of Modified Mini Mental State Examination is mentioned in Figure 2.

The maximum decrease from the highest achievable value was seen in similarities (48.3 %), second recall (36.1 %), repetition (33.4 %), copying two pentagons (28.3 %), read and obey (24.0 %), mental reversal (22.7 %) and first recall (21.3 %) parameters of Modified Mini Mental State Examination (Figure 2).

The relationship of different parameters of 3 MS score with CD4 counts and the duration of ART is depicted in Table 2.

### Discussion

Around two-thirds of all patients were male and the remaining were females. This is consistent with the previous studies and may be either because the disease is more prevalent in the male population or because males may be utilizing the health resources to a greater extent in comparison to the females.20,21 In our study, maximum people had an education between 8th and 12th standard and the graduates and post graduates were very less and this may be due to the fact that lesser education might be a risk factor for HIV disease and as such the disease prevalence is higher in underprivileged community. This fact is also in accordance with the previous studies.22 However, significantly higher proportion of males had a CD4 count ≤500, which may be because, the disease may be more advanced in males as compared to the females due to increased chances of acquiring disease due to high risk behaviour.

**HAND in different studies** worldwide has been shown to be seen in approximately 50% of all HIV infected individuals, with some studies showing a prevalence of as high as 85%.23,24 In different studies published mainly from Southern and Western parts of India, a very low prevalence of HAND (<10%) is reported. But a study conducted in Chennai and Bangalore in India, showed the prevalence to be between 50 to 60%. Clade C virus, a natural variant of the Tat protein, which promotes viral replication directly, has been shown to be greater in India, which could explain the low prevalence of HAND in India.25 In our study, around one-fourth of all patients with HIV disease were found to be neurocognitively impaired when tested using Modified Mini Mental State Examination, which could be explained by the presence of Clade C virus in India.

In the present study, those patients who had higher CD4 counts and a greater duration of ART, were found to have a lesser neurocognitive impairment, which shows that lesser burden of disease and early initiation of ART prevents neurocognitive decline in these patients. It was also observed that HIV-infected individuals who never experienced low CD4 cell counts were relatively protected from neurocognitive impairment in comparison to those with a history of severe immune-suppression. A possible pathogenic mechanism suggested could be that a lower level of CD4 T-cells may allow a greater entrance of viruses inside the Central Nervous System. Similar observations have been there in some previous studies, though there are a few studies, which are not in accordance with this finding.26-31 Those who were not on ART had
a very high Modified Mini Mental State Examination score, probably because most of these patients were having a higher CD4 count and were new patients and had probably not experienced a nadir of CD4 counts. According to the national guidelines of India till September 2016, ART was started only if CD4 count was below 350 cells/cc or if the patient was in clinical stage 3 or 4 of WHO staging. So, better immune competence might be the reason for these patients having a higher Modified Mini Mental State Examination score.

There are certain domains of cognitive functioning like motor functioning, attention, processing speed, executive functioning, learning, verbal memory, reasoning, verbal fluency which may be more often affected in patients suffering from HIV disease and certain domains like naming and visuospatial functions may be relatively preserved in these patients depending on the severity of cognitive deficit.13-33 However, some studies have detected impairment of visuospatial functions in HAND.33 Hence, testing for these particular domains of cognitive function using advanced neurocognitive tests would be a better choice for detecting HAND. It took around ten to twelve minutes to administer Modified Mini Mental State Examination to these patients. However, for screening purposes, we may need a smaller test, which takes lesser time to screen for cognitive dysfunction.

Since, certain parameters of Modified Mini Mental State Examination like similarities, second recall, repetition, copying two pentagons, read and obey, mental reversal and first recall were found to be most affected in patients suffering from HIV disease in our study, so, it is proposed that a shorter version comprising these parameters may be a useful tool for screening patients for HAND.

References

DREEM Study: Students’ Perceptions of Learning Environment in a Medical College in Mumbai, India

Sandeep Bavdekar¹, Sushma Save²*, Ashwin Pillai³, AM Kasbe²

Abstract

**Purpose:** This study was carried out to assess medical education environment (MEE) at our institution and to determine if there is an association between the assessment scores and factors such as gender, residence, family educational background and medium of instruction during school years.

**Methods:** Students appearing for the final qualifying examination were enrolled in the cross-sectional survey after obtaining written informed consent. Demographic data and personal information such as place of residence, parental education and medium of instruction was collected. The Dundee Ready Education Environment Measure (DREEM) Questionnaire was used for assessment of MEE. The numerical variables were described in terms of mean and standard deviation, median and inter-quartile range and percentages. Independent t-test, one-way Anova, Mann-Whitney test and Kruskall–Wallis test were the analytical tests used depending upon the number of groups and characteristics of the data.

**Results:** Fifty-five students were enrolled in the study. The overall DREEM score was 119+/-22 (Median 116), 46(83.64%) reported overall positive perception. Students’ perception of atmosphere (SPA) scored highest as compared to other domains. Teacher-centered teaching with emphasis on factual learning, authoritarian teachers, boredom in the course and lacking support systems were some of the problem areas identified on the basis of students’ perceptions. There was a significant difference in Students’ academic self-perception (SASP) and students’ social self-perception scores between students coming from urban and rural backgrounds.

**Conclusions:** Students reported an overall positive perception of MEE. Problem areas and research priorities were identified leading to a preparation of an action plan.

Introduction

Medical education (ME) is a highly demanding world over. ME and professional conduct as aspects of university life are considered very complex and stressful.¹ Medical students need to develop wide-ranging skills and aptitudes to meet the healthcare needs of the patients and society that they intend to serve. The education environment (EE) defined as everything that is happening in the classroom, hospital, wards, department, faculty, university is known to affect students’ performance² and a conducive EE should ideally nurture intellectual activities and progression, while at the same time boosting friendliness, cooperation, collaboration and support.³,⁴

Studies carried across the world to assess ME environment, identify problem areas⁵ and help implement corrective measures. Some of them have shown that perception of MEE may be affected by factors such as gender,³,⁴,⁷,¹⁰ year of study,⁵,⁸ or nativity¹⁰ among others. No information was available about the EE at our institution. In absence of such data, the faculty members carry on the teaching activities without knowing, let alone understanding the students’ perceptions and needs related to the EE. In addition, students admitted to medical courses in our institution come from diverse backgrounds: rural or urban, with different family educational backgrounds, having studied in English or vernacular-medium schools from the various states of India. It was postulated that the same MEE could be perceived differently by students coming from different backgrounds.

Hence, a study was undertaken to assess the MEE in the institution and to determine if an association exists between the assessment scores and factors such as gender, residence, family educational background and medium of instruction during school years.

Material and Methods

This cross-sectional survey was carried out over a period of 6 months after obtaining approval from the institutional ethics committee. The students studying at the medical college for medical graduate course (MBBS), who had completed their training up to the III MBBS and had appeared for the final qualifying examination in 2014 or 2015 were enrolled after obtaining written informed consent. Information regarding demographic and other personal information such as age, gender, place of residence prior to entry into the medical college and medium of instruction in secondary school was collected in an anonymous manner.

They were then requested to complete the Dundee Ready Education Environment Measure (DREEM) Questionnaire. The DREEM instrument is a 50-item inventory, consisting of five subscales:²

1. Students’ perception of learning (SPL): 12 items, maximum score 48: [Item numbers: 1, 7, 13, 16, 20, ...]

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⁵Corresponding Author
Received: 19.08.2018; Accepted: 25.12.2018
Table 1: Definition of factors whose association with DREEM scores was studied

<table>
<thead>
<tr>
<th>Category</th>
<th>Options</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residence</td>
<td>Urban (Including city, town, metropolis)</td>
<td>Place of residence for majority of school years (1st-10th standard: Area with a municipality or cantonment board or a place satisfying the following three criteria simultaneously: a minimum population of 5,000; at least 75% of male working population engaged in agricultural pursuits; and a density of population of at least 400 per sq. km. (1,000 per sq. mile))</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td>Residence characteristics not satisfying criteria for urban area</td>
</tr>
<tr>
<td></td>
<td>Post-graduation</td>
<td>Holding a post-graduate degree from a University</td>
</tr>
<tr>
<td>Highest educational status of any parent</td>
<td>Secondary School Certification (SSC)</td>
<td>Completed and passed the SSC examination (or equivalent) completing 10 years of schooling</td>
</tr>
<tr>
<td></td>
<td>Primary Education</td>
<td>Completed a minimum of four years of schooling</td>
</tr>
<tr>
<td></td>
<td>Literate</td>
<td>A person who can both read and write with understanding in any language irrespective of receiving or not receiving any formal education. A person who is blind and can read in Braille is treated to be literate</td>
</tr>
<tr>
<td></td>
<td>Illiterate</td>
<td>Not able to read and write in any language</td>
</tr>
<tr>
<td>Medium of Instruction during secondary schooling</td>
<td>English</td>
<td>Medium of instruction English throughout 6 years of secondary schooling (5th-10th Standard)</td>
</tr>
<tr>
<td></td>
<td>Other than English</td>
<td>Medium of instruction other than English for any period during secondary schooling (5th-10th Standard)</td>
</tr>
</tbody>
</table>

Table 2: Total DREEM score and domain-wise scores

<table>
<thead>
<tr>
<th>Domain</th>
<th>No. of items</th>
<th>Max. score possible</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Mean score as %Max. score</th>
<th>Students with positive perceptions no., %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPL</td>
<td>12</td>
<td>48</td>
<td>27.15 (6.78)</td>
<td>28</td>
<td>56.56</td>
<td>36, 65.45</td>
</tr>
<tr>
<td>SPT</td>
<td>11</td>
<td>44</td>
<td>25.27 (5.12)</td>
<td>24</td>
<td>57.43</td>
<td>39, 70.91</td>
</tr>
<tr>
<td>SASP</td>
<td>8</td>
<td>32</td>
<td>19.56 (5.17)</td>
<td>20</td>
<td>61.13</td>
<td>39, 70.91</td>
</tr>
<tr>
<td>SPA</td>
<td>12</td>
<td>48</td>
<td>30.18 (5.71)</td>
<td>29</td>
<td>62.88</td>
<td>48, 87.27</td>
</tr>
<tr>
<td>SSSP</td>
<td>7</td>
<td>28</td>
<td>17.03 (3.51)</td>
<td>17</td>
<td>60.82</td>
<td>42, 76.36</td>
</tr>
<tr>
<td>DREEM score</td>
<td>50</td>
<td>200</td>
<td>119 (22)</td>
<td>116</td>
<td>59.50</td>
<td>46, 83.64</td>
</tr>
</tbody>
</table>

SPL: Student’s perception of Learning; SPT: Student’s perception of teaching; SASP: Student’s perception of atmosphere; SPA: Student’s perception of atmosphere (SPA): 12 items; maximum score of 48; [Item numbers: 11, 12, 17, 23, 30, 33, 34, 35, 36, 42, 43, 49] | 22, 24, 25, 38, 44, 47, 48] |
| b. Students’ perceptions of teachers (SPT): 11 items; maximum score 44; [Item numbers: 2, 6, 8, 9, 18, 29, 32, 37, 39, 40, 50] |
| c. Students’ academic self-perceptions (SASP): 8 items; maximum score of 32; [Item numbers: 5, 10, 21,26, 27, 31,41,45] |
| d. Students’ perceptions of atmosphere (SPA): 12 items; maximum score of 48; [Item numbers: 11, 12, 17, 23, 30, 33, 34, 35, 36, 42, 43, 49] |
| e. Students’ social self-perceptions (SSSP): 7 items; maximum score of 28; [Item numbers: 3, 4, 14, 15, 19, 28, 46] |

The total score of all subscales was 200.

The students were requested to read each statement carefully and respond using a 5-point Likert-type scale ranging from strongly agree to strongly disagree. The items were scored as follows:

Strongly agree (SA): 4, Agree (A): 3; Uncertain (U): 2; Disagree (D): 1, Strongly Disagree (SD): 0. Nine of the 50 items (item numbers 4, 8, 9, 17, 25, 35, 39, 48 and 50) were negative statements. These negative items were scored in reverse for analysis so that the higher the score, the more positive the feedback, or the more incorrect perception. Thus, the negative items were scored in the reverse order as Strongly agree (SA): 0, Agree (A): 1; Uncertain (U): 2; Disagree (D): 3 and Strongly Disagree (SD): 4.

The overall score was interpreted as follows (2): 0-50: Very poor; 51-100: Plenty of problems; 101-150: More positive than negative; 151-200: Excellent

The description of factors whose association with DREEM score was studied, is provided in Table 1.

Statistical Plan: The data from respondents was entered in the Excel Sheet. It was presented using descriptive statistics (frequency and percentages for gender, place of residence prior to entry into the medical college, medium of instruction in secondary school and highest educational qualification of parents). The numerical variables (domain and total scores as per DREEM inventory) were described using mean and standard deviation and median and inter-quartile range (IQR). The data was checked for normal distribution by the Sapiro-Wilk test. It was decided to apply the independent t-test for comparison between two means variables (gender, place of residence prior to entry into the medical college, parental educational status and medium of instruction in secondary school) if the data were normally distributed. Similarly it was decided to use Mann-Whitney test if the data were non-parametric and there were two groups (or Kruskall-Wallis test, if there were to be more than two groups) for non-parametric data (PSPP 1.0.1 free software).

Results

Sixty participants were approached. Fifty-five (Response rate: 91.67%, Males 29, 52.73%) consented to participate and were enrolled. Their age ranged from 22-28 years, 43(78.18%) were from the urban background and 39(70.91%) studied with English as the medium of instruction. Parents of 49(89.01%) students studied over SSC. The total DREEM score ranged from 63-158 with a mean total DREEM Score being 119±22 (Median score 116). Forty-six (83.64%) reported overall positive perception (mean Total DREEM score over 100). Data regarding Total DREEM score and domain-wise scores is depicted in Table 2. The mean score as percentage of the maximum possible score ranged from 56.56% (SPL) to 62.88% (for SPA). Similarly, the number of students reporting positive perceptions for various domains ranged from 39 (65.45%) for SPL to 46 (87.27%) for SPA.

Table 3 lists all the items in the instrument and the mean scores for each item. The three items that were highly rated were ‘I have good friends in this course’, ‘the teachers are knowledgeable’ and ‘I am confident about passing this year’. None of the items was scored as over 3.5

Table 4 lists the scores of items across the various domains that were marked at an average of 2 or less. There were 9 such items, with three from the domain of Students’ perception of teachers (SPT). The lowest scored item referred to the perception of authoritarianism
Table 3: Scoring of each item in the DREEM questionnaire

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Item statement</th>
<th>Score</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPL: Students’ Perception of Learning</td>
<td>1</td>
<td>I am encouraged to participate during teaching sessions</td>
<td>2.80(0.76)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>The teaching is often stimulating</td>
<td>2.40(0.83)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>The teaching is student centred</td>
<td>2.09(1.01)</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>The teaching helps develop my competence</td>
<td>2.38(1.01)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>The teaching is well focused</td>
<td>2.43(0.94)</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>The teaching helps to develop my confidence</td>
<td>2.31(0.98)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>The teaching time is put to good use</td>
<td>2.40(0.89)</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>The teaching over emphasizes factual learning*</td>
<td>1.49(0.90)</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>I am clear about the learning objectives of the course</td>
<td>2.35(1.08)</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>The teaching encourages me to be an active learner</td>
<td>2.36(0.91)</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>Long term learning is emphasized over short term learning</td>
<td>2.38(1.10)</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>The teaching is too teacher-centred*</td>
<td>1.75(1.11)</td>
</tr>
<tr>
<td>SPT: Students’ Perception of Teachers</td>
<td>2</td>
<td>The teachers are knowledgeable</td>
<td>3.15(0.65)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>The teachers espouse a patient-centred approach to consulting</td>
<td>2.49(0.79)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>The teachers ridicule the students*</td>
<td>2.18(0.86)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>The teachers are authoritarian*</td>
<td>1.45(0.81)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>The teachers have good communication skills with patients</td>
<td>2.71(1.12)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>The teachers are good at providing feedback</td>
<td>2.16(1.12)</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>The teachers provide constructive criticism here</td>
<td>2.16(0.96)</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>The teachers give clear examples</td>
<td>2.44(0.90)</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>The teachers get angry in teaching sessions*</td>
<td>2.00(1.07)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>The teachers are well prepared for their teaching sessions</td>
<td>2.62(0.73)</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>The students irritate the teachers*</td>
<td>1.91(0.95)</td>
</tr>
<tr>
<td>SASP: Students’ Academic Self-perception</td>
<td>5</td>
<td>Learning strategies that worked for me before continue to work for me now</td>
<td>2.13(1.04)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>I am confident about passing this year</td>
<td>3.02(0.87)</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>I feel I am being well prepared for my profession</td>
<td>2.22(1.12)</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Last year’s work has been good preparation for this year’s work</td>
<td>2.60(0.85)</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>I am able to memorise all I need</td>
<td>1.93(1.10)</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>I have learnt a lot about empathy in my profession</td>
<td>2.64(1.01)</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>My problem solving skills are being developed here</td>
<td>2.40(0.97)</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>Much of what I have to learn seems relevant to a career in healthcare</td>
<td>2.6(0.95)</td>
</tr>
<tr>
<td>SPA: Students’ Perception of Atmosphere</td>
<td>11</td>
<td>The atmosphere is relaxed during ward teaching</td>
<td>2.42(1.08)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>This college is well time tabled</td>
<td>2.62(1.03)</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>Cheating is a problem in this college*</td>
<td>1.99(1.27)</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>The atmosphere is relaxed during lectures</td>
<td>2.65(1.04)</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>There are opportunities for me to develop interpersonal skills</td>
<td>2.85(0.76)</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>I feel comfortable in class socially</td>
<td>2.98(0.89)</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>The atmosphere is relaxed during class/seminars/tutorials</td>
<td>2.69(0.94)</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>I find the experience disappointing*</td>
<td>2.42(1.15)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>I am able to concentrate well</td>
<td>2.56(0.86)</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>The enjoyment outweighs the stress of the course</td>
<td>2.29(0.98)</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>The atmosphere encourages me as a learner</td>
<td>2.29(0.88)</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>I feel able to ask the questions I want</td>
<td>2.42(0.99)</td>
</tr>
<tr>
<td>SSSP: Students’ Perception of self-performance</td>
<td>3</td>
<td>There is a good support system for students who get stressed</td>
<td>1.95(0.85)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>I am too tired to enjoy the course*</td>
<td>2.22(1.08)</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>I am rarely bored in this course</td>
<td>1.87(1.06)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>I have good friends in this course</td>
<td>3.31(0.63)</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>My social life is good</td>
<td>2.85(0.83)</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>I seldom feel lonely</td>
<td>2.18(1.14)</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>My accommodation is pleasant</td>
<td>2.65(1.27)</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate standard deviation; *Negative items whose scores were reversed for analysis

Table 4: Questions that scored low

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Question</th>
<th>Score Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPL: Students’ Perceptions of Learning</td>
<td>25</td>
<td>The teaching over-emphasizes factual learning</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>The teaching is too teacher-centered</td>
</tr>
<tr>
<td>SPT: Students’ Perceptions of Teachers</td>
<td>9</td>
<td>The teachers are authoritarian</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>The teachers get angry in teaching sessions</td>
</tr>
<tr>
<td>SASP: Students’ Academic self-perception</td>
<td>27</td>
<td>I am able to memorize all I need</td>
</tr>
<tr>
<td>SPA: Students’ Perception of Atmosphere</td>
<td>17</td>
<td>Cheating is a problem in this college</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>There is good support system for students who get stressed</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>I am rarely bored in this course</td>
</tr>
</tbody>
</table>

regression analysis, it was noted that the SASP and SSSP scores were significantly different among students from urban and those from rural backgrounds.

Discussion

This study showed that an overwhelming majority (83%) of students who received training at our institution had overall positive opinion about learning, teachers and atmosphere and academic and social self-perceptions through the under-graduate learning period. The students’ perception of atmosphere scored the highest among all the domains. The overall mean DREEM score of 119 generally conveys a positive attitude with a definitive scope for improvement. The SPL, SASP and SPA scores were in the category of “more positive perception”, while SPT scores were interpreted as “moving in the right direction”. The SSSP scores could be labeled as “not too bad”. It is worth noting that for all the domains, the scores were in the category one-notch below the highest one. The problems perceived by students included over-emphasis on
Table 5: Analysis of scores for each domain with reference to independent variable

<table>
<thead>
<tr>
<th>Grouping Variable</th>
<th>Domain</th>
<th>Mean, SD</th>
<th>Median, IQR</th>
<th>t/z</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female/Male)</td>
<td>SPL</td>
<td>26.79, 6.84</td>
<td>26.52, 6.81</td>
<td>29.09, 9.00</td>
<td>25.00, 11.00</td>
</tr>
<tr>
<td></td>
<td>SPT^</td>
<td>26.62, 4.50</td>
<td>26.00, 5.26</td>
<td>26.00, 7.00</td>
<td>24.00, 7.50</td>
</tr>
<tr>
<td></td>
<td>SPA</td>
<td>29.92, 5.88</td>
<td>30.31, 5.52</td>
<td>30.09, 9.00</td>
<td>29.00, 9.00</td>
</tr>
<tr>
<td></td>
<td>SASP</td>
<td>18.27, 5.67</td>
<td>20.72, 4.66</td>
<td>19.00, 11.25</td>
<td>22.00, 7.50</td>
</tr>
<tr>
<td></td>
<td>SSSP</td>
<td>16.58, 3.13</td>
<td>17.59, 3.62</td>
<td>16.50, 5.25</td>
<td>18.00, 5.00</td>
</tr>
<tr>
<td></td>
<td>All Domains</td>
<td>119.08, 22.22</td>
<td>121.14, 20.89</td>
<td>120.50, 34.00</td>
<td>118.00, 25.00</td>
</tr>
<tr>
<td>Place of Residence (Urban/Rural)</td>
<td>SPL</td>
<td>26.65, 7.05</td>
<td>28.58, 5.78</td>
<td>26.00, 11.00</td>
<td>29.00, 12.00</td>
</tr>
<tr>
<td></td>
<td>SPT^</td>
<td>25.51, 4.40</td>
<td>29.08, 5.66</td>
<td>25.00, 6.00</td>
<td>30.00, 11.00</td>
</tr>
<tr>
<td></td>
<td>SPA</td>
<td>29.63, 5.23</td>
<td>31.92, 6.88</td>
<td>29.00, 8.00</td>
<td>32.50, 10.50</td>
</tr>
<tr>
<td></td>
<td>SASP</td>
<td>18.53, 5.02</td>
<td>23.25, 4.03</td>
<td>19.00, 9.00</td>
<td>24.00, 6.75</td>
</tr>
<tr>
<td></td>
<td>SSSP</td>
<td>16.47, 3.22</td>
<td>19.42, 3.15</td>
<td>16.00, 5.00</td>
<td>19.50, 5.25</td>
</tr>
<tr>
<td></td>
<td>All Domains</td>
<td>116.79, 20.69</td>
<td>132.25, 19.99</td>
<td>111.00, 29.00</td>
<td>129.50, 35.00</td>
</tr>
<tr>
<td>Medium of Instruction (English/Vernacular)</td>
<td>SPL</td>
<td>26.49, 6.78</td>
<td>28.50, 6.80</td>
<td>26.00, 11.00</td>
<td>29.00, 12.25</td>
</tr>
<tr>
<td></td>
<td>SPT^</td>
<td>25.46, 4.33</td>
<td>28.31, 5.65</td>
<td>25.00, 6.00</td>
<td>27.50, 10.75</td>
</tr>
<tr>
<td></td>
<td>SPA</td>
<td>29.31, 5.09</td>
<td>32.13, 6.55</td>
<td>29.00, 7.00</td>
<td>32.50, 10.50</td>
</tr>
<tr>
<td></td>
<td>SASP</td>
<td>17.84, 5.09</td>
<td>21.56, 4.95</td>
<td>19.00, 9.00</td>
<td>22.50, 9.00</td>
</tr>
<tr>
<td></td>
<td>SSSP</td>
<td>16.87, 3.47</td>
<td>17.69, 3.28</td>
<td>16.00, 6.00</td>
<td>18.00, 4.00</td>
</tr>
<tr>
<td></td>
<td>All Domains</td>
<td>116.87, 20.16</td>
<td>128.19, 22.70</td>
<td>114.00, 27.00</td>
<td>126.00, 44.50</td>
</tr>
<tr>
<td>Parental Education (Above SSC/Above SSC or below)</td>
<td>SPL</td>
<td>25.33, 7.58</td>
<td>27.29, 6.74</td>
<td>24.50, 15.00</td>
<td>27.00, 10.00</td>
</tr>
<tr>
<td></td>
<td>SPT^</td>
<td>26.50, 4.32</td>
<td>26.27, 4.99</td>
<td>26.50, 9.00</td>
<td>25.00, 7.00</td>
</tr>
<tr>
<td></td>
<td>SPA</td>
<td>30.00, 6.72</td>
<td>30.14, 5.88</td>
<td>30.00, 10.00</td>
<td>29.00, 9.00</td>
</tr>
<tr>
<td></td>
<td>SASP</td>
<td>22.17, 4.58</td>
<td>19.24, 5.19</td>
<td>24.00, 9.00</td>
<td>19.00, 8.00</td>
</tr>
<tr>
<td></td>
<td>SSSP</td>
<td>18.67, 4.59</td>
<td>16.92, 3.24</td>
<td>17.50, 8.00</td>
<td>17.00, 6.00</td>
</tr>
<tr>
<td></td>
<td>All Domains</td>
<td>122.67, 23.75</td>
<td>119.86, 21.29</td>
<td>124.50, 45.00</td>
<td>118.00, 30.00</td>
</tr>
</tbody>
</table>

SPL: Student’s perception of Learning; SPT: Student’s perception of teaching; SPA: Student’s perception of atmosphere; SASP: Student’s Academic self-perception; SSSP: Student’s social self-perception; ^: Failed Shapiro-based test of normality; t/z value; Mann-Whitney U test used; *: Statistically significant, P< 0.05

Table 6: Linear regression analysis

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variable</th>
<th>t/z</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Students’ Perception of Learning (SPL)</td>
<td>Gender</td>
<td>-0.87</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Stay</td>
<td>0.83</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>Education medium</td>
<td>0.90</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>Parental education</td>
<td>1.32</td>
<td>0.19</td>
</tr>
<tr>
<td>Students’ Perception of Teachers (SPT)</td>
<td>Gender</td>
<td>-1.11</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>Stay</td>
<td>1.81</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Education medium</td>
<td>1.11</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>Parental education</td>
<td>1.31</td>
<td>0.20</td>
</tr>
<tr>
<td>Students’ Perception of Atmosphere (SPA)</td>
<td>Gender</td>
<td>-0.17</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>Stay</td>
<td>0.59</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>Education medium</td>
<td>1.29</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Parental education</td>
<td>0.97</td>
<td>0.34</td>
</tr>
<tr>
<td>Students’ Academic self-perception (SASP)</td>
<td>Gender</td>
<td>1.22</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Stay</td>
<td>2.10</td>
<td>0.04^</td>
</tr>
<tr>
<td></td>
<td>Education medium</td>
<td>-0.08</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Parental education</td>
<td>0.31</td>
<td>0.76</td>
</tr>
<tr>
<td>Students’ social self-perception (SSSP)</td>
<td>Gender</td>
<td>0.75</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>Stay</td>
<td>2.71</td>
<td>0.01^</td>
</tr>
<tr>
<td></td>
<td>Education medium</td>
<td>-1.27</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Parental education</td>
<td>0.15</td>
<td>0.88</td>
</tr>
<tr>
<td>All Domains</td>
<td>Gender</td>
<td>-0.18</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>Stay</td>
<td>1.75</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Education medium</td>
<td>0.67</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Parental education</td>
<td>1.08</td>
<td>0.29</td>
</tr>
</tbody>
</table>

*: Statistically significant; P< 0.05; SPL: Student’s perception of Learning; SPT: Student’s perception of teaching; SPA: Student’s perception of atmosphere; SASP: Student’s Academic self-perception; SSSP: Student’s social self-perception

This is the first study of its kind conducted at our institution and this effort should help the institution plan and implement measures that will improve the overall educational environment. It has tried to determine if predictive factors unique to Indian settings had any impact on perceptions. India is a multi-religious, multi-ethnic, multi-linguistic, multi-cultural society with economic diversity. Students coming from diverse backgrounds (rural vs. urban, varying parental educational status and differing medium of instruction) are admitted to the MBBS course at our institution through selection on the basis of a state-level entrance examination and a nation-wide entrance examination. This is probably the first study to determine if the scores differ based on any of these characteristics. In fact, in contrast to most other studies, our study has tried to look at these predictive characteristics. As the students with rural background have scored significantly higher for SASP and SSSP domains, it appears that they are not unduly awed by the metropolitan city and are able to cope with learning in a large institution in such a city.

We have decided to share the results of this study with the institution head, institution’s Academic Committee and its Medical Education and Teaching Technology Unit as well as with teachers. We also intend to hold focused group discussion with respondents to obtain more information regarding the students’ perceptions and the reasoning behind them. For example, we intend to get the details regarding their perception of cheating. We need to know the situations in which students have encountered cheating (marking attendance, holding training sessions, assessment of performance or any other) before we plan corrective steps. Medical teachers in our institution do receive training regarding adult learning processes, making sessions interactive, effective use of media through workshops. However, the students’ perceptions indicate that...
there is a scope for improvement and there is a need to make the teaching student-centered with greater emphasis on participatory and experiential learning. It needs to be probed why students find the course boring: is it not stimulating enough because of its content or is it presented in an uninteresting manner. It is possible that after deliberations, a need would be felt to increase the hours provided for problem-based learning (PBL). At the same time, students seem to be facing stress and feel that the support systems are deficient. This issue has been reported in other studies\textsuperscript{11-13} as well and it appears that medical colleges need to provide added attention to this issue so as to meet students' expectations. Our institution has a preceptor program, wherein newly admitted students during the first year of training are assigned to a group of senior students and a faculty mentor. Although, the first year of the MBBS course is most stressful and it is hoped that after spending one year at the institution, students would find their own friends and social support; it appears from the study that the preceptor program needs to be extended through the fifth year of training.

The study had its share of limitations. We could interview only 55 of the 95 eligible individuals due to logistic problems, as some of them were not visiting the institution. Thus, they were unavailable for interview. The methodology of self-reporting questionnaires is associated with response bias,\textsuperscript{11} although the response rate in the study was 92%. The DREEM questionnaire used for the study has not been validated in Indian settings though it has been used worldwide across cultures in medical,\textsuperscript{14-18} dental colleges,\textsuperscript{19-22} and institutions offering other healthcare courses,\textsuperscript{23} including Indian ones.\textsuperscript{9,14,24-26} for assessing students’ perceptions. Thus, it is now considered a valid and reliable tool and is accepted globally for measuring the medical education environment.\textsuperscript{6,16,27-28}

It can be stated that validation of the instrument in Indian settings is a research priority. The authors intend to undertake a follow-up study and report its impact after corrective measures are implemented. In fact, medical colleges should carry out such surveys periodically to determine the perceptions of students and this feedback can be used to identify problem areas and plan and implement corrective strategies. The Indian studies should also try to determine association of lower scores with certain locally- and nationally-relevant social, economic and educational background risk factors; so that focused interventions can be planned.

References

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Metformin HCl 500 mg SR + Glipizide 1 mg + Voglibose 0.2 mg

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Metformin HCl 500 mg SR + Glimperide 1 mg + Voglibose 0.3 mg

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**Ecosprin® AV 150/20**
(Enteric Coated Aspirin 150 mg + Atorvastatin 20 mg)
Level of Health Literacy Among Type 2 Diabetic Persons and its Relation to Glycemic Control

Anbarasan S1*, Anil Gurtoo2, Srinivaasan M3, Musafir Khan AP3

Abstract
Introduction: Health literacy is the degree to which an individual can obtain, process, understand and communicate about health related information to make informed health decisions. Our aim was to study the influence of Diabetic health literacy in affecting the glycemic control in Diabetic patients.

Methodology: This is a Cross sectional Analytical study in 200 diabetic patients. Diabetic Knowledge Test developed by Michigan Diabetic Research and Training Center was modified after appropriate permission and was used to measure health literacy, HbA1C was used as a measure of glycemic control.

Results: In the study population, Median HbA1C was 9 gm% with Interquartile Range (IQR) of 6.10-11.80 in low health literacy group, 7.80 with an IQR of 5.95-9.32 in marginal health literacy group and 6.20 with an IQR of 5.38-7.90 in adequate health literacy group (P Value <0.001). After adjusting for socio demographic characteristics, Linear regression analysis showed that HbA1C decreased by 0.385 for every one point increase in Questionnaire score [Std.error 0.60, 95% C.I. “-0.502 to -0.267, P Value <0.001]. The Odds of achieving adequate glycemic control was 0.309 in marginal health literacy group and 0.205 in low health literacy group. (95% C.I.=0.092-0.455). On applying Pearson’s correlation between answer score and HbA1C, we got correlation coefficient “r”=-0.417 indicating a strong negative correlation. We also found that patients with low health literacy had higher chances of developing hospitalizations (P=0.027), Neuropathy (P =0.001) and retinopathy (P=0.049).

Conclusions: This study shows that inadequate health literacy is an independent predictor of glycemic control and complications. Development of strategies to communicate more effectively with patients who have poor health literacy are needed at the patient clinician level and the patient system level and should be based on a deeper understanding of the needs and competencies of patients with poor health literacy.

Introduction

Health literacy represents the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health1. Health literacy is a measure of patients’ ability to read, comprehend, and act on medical instructions and the concept of health literacy becomes particularly important with management chronic diseases like diabetes, hypertension etc since these diseases need a better understanding by the patients2. Though there is abundant body of literature available on the importance of the concept of health literacy, there are only limited studies which measure the direct association between the level of health literacy and the outcome of chronic diseases like Diabetes or Hypertension. In spite of enormously growing researches on identifying better drugs for treatment of diabetes, little emphasis has been given by both researchers and clinicians in improving health literacy of these patients which is very simple and cost effective. In this study, we are measuring the possible correlation between the level of health literacy in Type 2 Diabetics and its relation to the outcome of the disease.

Materials and Methods

It is a cross sectional, analytical study carried over a period of 18 months. We included 200 patients. Our inclusion criteria was, all Type 2 diabetic patients with disease duration of 5 years or more. Institutional ethical committee clearance was obtained. Newly diagnosed patients and those with renal failure, cardiac failure and stroke were excluded from the study. Patients with stroke are known to have minimal cognitive dysfunction and minimal cognitive impairment is common even in minor strokes. And also impairment in cognitive functions occurs in patients with cardiac failure and renal failure and so these patients were also excluded from the study.

Methodology

A total of 200 type-2 diabetic patients who met the appropriate selection criteria were included in the study. After obtaining informed consent, detailed history and physical examination including anthropometric measurements were carried out. The Diabetic Knowledge Test (DKT), developed by the Michigan Diabetes Research and Training center for measuring functional literacy in diabetic patients was modified and used after obtaining appropriate permissions from the Michigan University- [Grant Number P30DK092926]. The initial portion of the questionnaire which can be used both for patients on oral

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Received: 30.07.2017; Accepted: 20.12.2018
Patients were classified as having adequate glycemic control if their HbA1c is 7 or less, Marginal if HbA1c is between 7.1-8, Poor if HbA1c is between 8.1-10 and very poor if HbA1c is more than 10.

**Statistical Analysis**

Continuous variables are presented as means SD or median (IQR) if the data was skewed. Data was checked for normality before statistical analysis using Shaiipro Wilk test. Normally distributed continuous variables were compared using ANOVA. Kruskal Wallis test was used for those variables that were not normally distributed (skewed distribution). Categorical variables were analyzed using the Chi Square test. Pearsons Correlation was used to measure the correlation between HbA1c and responses scored in questionnaire. Regression analysis was used to analyse the direct association between HbA1c and score in questionnaire after other characteristics were controlled. For all statistical tests, a P value less than 0.05 was taken to indicate a significant difference.

**Results**

The mean age of the study population was 54.95 years with a standard deviation of 9.59 years. Out of total 200 patients 113 (57%) patients were females and rest 87 (44%) were males. Mean age of females was 54.95 years with a standard deviation of 9.15 and mean age of males was 55.21 years with standard deviation of 10.18 years. There was no statistically significant association between age (One way ANOVA) of the patients or sex(Chi Square test) of the patients with their level of health literacy in our study.

Since the number of very low health literacy group was very small (0.5%), it was merged with the low health literacy group.

**Demographic parameters and level of health literacy**

The relationship between various demographic parameters like age and sex is given in the following table (Table 1). An important observation we got here is that the formal literacy status of the study population did not have a significant association with the level of health literacy.

**Health literacy and glycemic control**

The association between the level
health literate individuals and 6.20 in adequate health literate individuals. Because of skewed distribution, Kruskal Wallis test was applied and it was found that there was a statistically significant relationship (P Value <0.001) between health literacy and glycemic control.

Total number of questions answered correctly by the patient (Q Score) and their HbA1C levels, both are absolute numbers (Continuous Variables). So the correlation between HbA1C and the Q Score was assessed with the help of Pearson’s Correlation. We found that there is a strong negative correlation between HbA1C and the Q Score. Pearson Product Moment Correlation (PPMC) coefficient “r” was -0.417. It indicates a strong negative correlation. The correlation is statistically significant. (P Value <0.001).

Since HbA1c and the scores in the questionnaire are both continuous variables, we applied linear regression analysis to study the relationship between them after adjusting for socio-demographic characteristics. The linear regression coefficient (Beta) was “-0.385”, which means that for every one point increase in the Questionnaire score, HbA1c decreased by 0.385 (Standard error of coefficient Beta was 0.060 and 95% confidence interval of Beta was “-0.502 to -0.267”). Statistical significance (P Value) of the regression was <0.001.

Odds of achieving adequate glycemic control was analysed in various levels of health literacy. It was found that patients with low health literacy were less likely to achieve adequate glycemic control (HbA1C <7 gm%) than patients with adequate health literacy. (Odds Ratio=0.205, 95% C.I=0.092-0.455). It was also seen that patients with marginal health literacy were less likely to achieve adequate glycemic control than patients with adequate health literacy (Odds Ratio 0.309, 95% C.I=0.160-0.594).

Table 2: Odds of achieving adequate glycemic control

<table>
<thead>
<tr>
<th>Level of health literacy</th>
<th>N</th>
<th>Glycemic control</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate</td>
<td>86</td>
<td>Adequate 59 (69.6%)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Marginal</td>
<td>72</td>
<td>Adequate 29 (40.3%)</td>
<td>0.309</td>
<td>0.160 - 0.594</td>
</tr>
<tr>
<td>Low</td>
<td>42</td>
<td>Adequate 13 (31%)</td>
<td>0.205</td>
<td>0.092 - 0.455</td>
</tr>
</tbody>
</table>

Table 3: Diabetic complications and health literacy

<table>
<thead>
<tr>
<th>Level of health literacy</th>
<th>Frequency/%</th>
<th>Frequency/%</th>
<th>Frequency/%</th>
<th>P value (Chi square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate</td>
<td>19 (45.20%)</td>
<td>23 (31.90%)</td>
<td>19 (22.10%)</td>
<td>0.027</td>
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<tr>
<td>Marginal</td>
<td>18 (42.90%)</td>
<td>8 (11.10%)</td>
<td>24 (27.90%)</td>
<td>0.001</td>
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<tr>
<td>Low</td>
<td>18 (42.90%)</td>
<td>16 (22.20%)</td>
<td>22 (25.60%)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Table 3: Diabetic complications and health literacy

Diabetic complications and health literacy

On studying the association between complications of Diabetes and health literacy, we found that the hospitalizations for various diabetes related complications increased as the level of health literacy decreased. The level of health literacy also had significant impacts on the development of health literacy and glycemic control was analyzed by Chi Square test and it was found that the glycemic control improves as the level of health literacy increases (Significance value P <0.001).

The mean score in the questionnaire (DKT) gained by patients in low health literacy group was 5.33 with a standard deviation of 0.72, 7.99 in patients with marginal health literacy with a SD of 0.813, and 12.14 in patients with adequate health literacy with a SD of 1.77.

HbA1c is a continuous variable, and it was found that the distribution of HbA1c was skewed in the study population. So median was calculated with an Interquartile Range (IQR). The median HbA1c was 9 in low health literate individuals, 7.80 in marginal
of neuropathy and retinopathy. The results are depicted in Table 3.

The association between health literacy and compliance of the patients to various advices given in clinic was analyzed by Chi Square Test. It was found that, there exists a statistically significant association between the level of health literacy and the compliance with physician’s advice. Patients with low health literacy were more likely to be less compliant with diet than marginal or adequate health literacy (P value- 0.002). Also patients with low health literacy fails to perform adequate exercises than persons with good health literacy (P value <0.001). Patients with low health literacy were also found more likely to be less compliant with their medications prescribed (P Value <0.001).

Discussion

Health literacy is defined as, “The degree to which individuals can obtain, process, understand and communicate about health-related information needed to make informed health decisions.” Patients with poor health literacy not only have limitations in reading labels on a pill bottle or interpreting blood sugar values or doing schedules or comprehending appointment slips, but also may have difficulties in processing oral communication and conceptualizing risk. In the context of a health care system in which scientific advances and market forces place a greater technical and self-management demands on patients, poor health literacy may be a particularly important barrier to chronic-disease care. Low health literacy has been consistently associated with worse diabetes knowledge in a variety of settings including ambulatory and hospitalized older patients.

The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025. Schillinger et al reported that inadequate health literacy was associated with nearly twofold increased odds of poor glycemic control compared with adequate health literacy (adjusted odds ratio: 2.03; 95% CI: 1.11–3.73; p = 0.02). Strategies to minimize the hazards of this growing epidemic should include promotion of health literacy.

Recognizing that low health literacy is common and associated with many facets of diabetes care – including important outcomes – strategies to address health literacy should be developed, tested and promoted. The foundation of these strategies rests with the principles of clear health communication, including assessment of understanding, use of plain language, emphasizing few key points and using effective printed materials. As advocated by ADA in its position statement in January 2015, patient-centered communication style that incorporates patient preferences, assesses literacy and numeracy, and addresses cultural barriers to care should be used. Considering low health literacy, the American College of Physicians Foundation (ACPF) developed the ‘Living with Diabetes Guide’ as a resource for patient education and also to promote goal setting and shared decision making in diabetes care.

This study throws light upon the importance of health literacy in management of diabetes mellitus. For health care professionals, the prevalence of poor health literacy and the strength and consistency of the association between health literacy and diabetes outcomes should serve as a call to action. Development of strategies to communicate more effectively with patients who have poor health literacy are needed at the patient-physician level, and the patient-system level and should be based on a deeper understanding of the needs and competencies of patients with poor health literacy.

Recommendations and Conclusions derived from this study

- The results of this study shows that, there is an urgent need for incorporating programs to improve health literacy in Diabetic management programs to overcome the devastating consequences of this disease.
- For the health care providers, this study reminds about the importance of imparting proper education to the patients in addition to the medications.
- For the Government and policy makers, this study tells the need of incorporating health literacy in school education. This can reduce the incidence of chronic diseases as a whole and improve the well being of the society, improve their productiveness, reduce the cost spent in health care and can improve the GDP of the Nation.
- Direct involvement of patients in developing educational materials may empower them to improve their health, while assuring that the content effectively educates them.
- Research to develop effective office-based communication strategies and efforts to more widely apply chronic-disease management programs for patients with poor health literacy should be supported.

References

Inducible Amp C Beta-lactamase Producing *Pseudomonas aeruginosa*: Predominant Resistance Mechanism and a Threat in a Tertiary Care Teaching Hospital

Nandini MP¹, Navaneeth BV²*

Abstract

**Background:** Antibiotic resistance to multiple antibiotics among *P aeruginosa* are on rise due to acquisition of various beta-lactamase enzymes. *P aeruginosa* possessing such enzymes can cause major break down in therapy and are responsible for substantial clinical challenges.

**Objectives:** To know the antibiotic susceptibility pattern, common resistance mechanisms of *P aeruginosa* and document baseline antibiotic resistance data to implement effective infection control program.

**Methods:** A total of 200 *P aeruginosa* was isolated between January - June 2015 from various clinical samples of both hospitalized and outpatients. Antibiotic susceptibility testing was done by Kirby-Bauer disc diffusion method to ceftazidime, cefepime, cepiprome, piperacillin -tazobactam, cefoperazone-sulbactum, ciprofloxacin, gentamicin, amikacin, imipenem and piperacillin. ESBLs, inducible chromosomal and non-inducible plasmid Amp C beta-lactamase and metallo-beta-lactamase presence was investigated.

**Results:** Twenty five percent isolates were from the intensive care unit, 41.5% from in patients and 33.5% from outpatients. Inducible, non-inducible Amp C beta-lactamase, ESBLs and MBLs producers was 47.5%, 4%, 26% and 19% respectively. Highest resistance was recorded to cephahlosporins (44% - 56.5%). Least resistance to colistin (2%), imipenem (19.5%) and amikacin (21.5%). Resistance to piperacillin-tazobactam, ciprofloxacin, gentamicin and cefoperazone-sulbactam was 24%, 31.5%, 32%, and 36.5% respectively. Multi-drug resistance were 37.5%. Overall resistance pattern were higher among ICU and inpatient than outpatient isolates.

**Conclusion:** Inducible Amp C beta-lactamases was found to be predominant resistance mechanism followed by ESBL and MBL among *P aeruginosa*. Resistance was high to cephahlosporins and among hospitalzed patients. Usage of cephahlosporins could be risk factor for inducible resistance. Colistin, imipenem and amikacin as first line with piperacillin-tazobactam as alternative may be preferred antibiotics in treating *P aeruginosa* infections. Calls for screening, monitoring and infection control measures.

Introduction

*Pseudomonas aeruginosa* nosocomial infections have become a worldwide healthcare issue especially in intensive care units.¹ *P aeruginosa* is notorious for its stubbornness in the hospital settings, and multidrug resistance mechanisms are frequently seen in such hospital isolates.² There are two antibiotic resistance mechanisms among *P aeruginosa*. One is by mutation in the intrinsic gene (intrinsic resistance) and the second is by acquiring antibiotic resistant genes from other bacteria. Further, acquired resistance in the form of over expression or by plasmid transfer of resistance genes, impart resistance to broad spectrum of antibiotics leading to increased frequency among clinical and environmental strains.³ Usually these resistance are mediated by enzymes like extended spectrum bet-lactamases (ESBLs), Amp C beta-lactamases and metallo-beta-lactamases (MBLs).⁴ Detection of such enzymes and timely report to the prescribing hands become crucial as the presence of these enzymes makes treatment of infection both hard and costly. Hence a preliminary attempt was undertaken to document their occurrence and to prepare a base line data for an effective infection control program.

Material and Methods

ESIC-MC and PGIMS, Rajajinagar, Bengaluru is a tertiary care 500 bed teaching hospital. It is a closed system of health care delivery system where only patients insured under ESIC scheme represents the patient population. This study was an extension of a postgraduate dissertation work. The study period was from January – June 2015. Clinical specimens belonging to patients who stayed at least 3 days in hospital [ICU and in patients] and of all outpatients [irrespective of their previous hospitalization status] were included. Only one isolate per patient with clinical significance was considered. Institutional ethical clearance was obtained. *P aeruginosa* were isolated and identified from various clinical samples (pus, urine, sputum, throat, vaginal and wound swab, body fluids like ascitic, cerebro spinal and pleural fluid) submitted to diagnostic microbiology by standard methods.⁵ Antibiotic susceptibility test was performed by Kirby- Bauer’s
Detection of ESBL by combined disc diffusion method: A disc of ceftazidime (30 µg) alone and a disc of ceftazidime-clavulanic acid (30/10 µg) was placed at distance of 25 mm apart on a lawn culture of the test isolate on Muller-Hinton Agar (MHA) plate and incubated overnight (18 hrs) at 37°C. When there is an increase of >5mm in inhibition zone diameter around combination disc of ceftazidime-clavulanic acid versus ceftazidime disc alone was considered an ESBL producer (Figure 1).

Detection of inducible chromosomal Amp C beta-lactamase by disc antagonism test: A disc of cefoxitin (30 µg) and other beta lactam discs (cefotaxime, ceftriaxone, ceftazidime) were placed at a distance of 25 mm apart on a lawn culture of test isolate on MHA plate and incubated overnight at 37°C. If radius will be smaller by 4 mm or more, then antagonism will be considered (Figure 2).

Detection of non-inducible plasmid mediated Amp C beta lactamase by Amp C disc test: Briefly, 0.5 McFarland suspensions of ATCC 25922 Escherichia coli were inoculated on the surface of MHA plate. A 30µg cefoxitin disc and a sterile plain disc inoculated with several colonies of the test organism was placed just beside the cefoxitin disc almost touching it, with inoculated disc face in contact with the agar surface. After overnight incubation at 37°C, the plates were examined for either an indentation or a flattening of the zone of inhibition, indicating enzymatic inactivation of cefoxitin (positive result), or absence of a distortion (negative result) (Figure 3).

Detection of MBL by EDTA disc synergy test: Overnight culture of the test strain was suspended to the turbidity of a McFarland no 0.5 tube and used to swab inoculate a MHA plate. After drying, a 10 µg imipenem disc and EDTA disc (1.5 mg) placed at a distance of 10mm from it. After overnight incubation, the presence of an enlarged zone of inhibition was interpreted as MBL positive (Figure 4).

Detection of MBL by MHT: The surface of a MHA plate was inoculated evenly using a cotton swab with an overnight culture suspension of ATCC 25922 Escherichia coli, which was adjusted to one-tenth turbidity of McFarland no 0.5 tube. After brief drying, an imipenem disc was placed at the center of plate and imipenem resistant test strains from overnight cultured plates was streaked heavily from the edge of the disk to the periphery of the plate and incubated over night at 37°C. The presence of a distorted inhibition zone was interpreted as MBL positive - confirmatory for MBL (Figure 5).

The data were analysed using Microsoft Excel.

Results

A total of 200 P aeruginosa were isolated during the study period. Fifty (25%) were from the intensive care unit, 83 (41.5%) were from inpatients and 67 (33.5%) were from outpatients. Seventy six (38%) isolates were from females and 124 (62%) isolates were from males. Isolation from pus, sputum, miscellaneous, urine and blood was 61 (30.5%), 49 (24.5%), 46 (23%), 35 (17.5%) and 4 (2%) respectively. Isolates of P aeruginosa revealed 47.5% of inducible and 4% of non inducible plasmid mediated Amp C beta-lactamases. ESBLs and MBLs were 26% and 19% respectively (Table 1).
Detection of inducible and non inducible plasmid mediated Amp C beta-lactamases was high among ICU (60% and 4%) and inpatient isolates (49.3% and 4.8%) compared to outpatient isolates (32.8% and 2.9%). ESBL detection rate among ICU (28%), inpatients (21.6%) and outpatient isolates (29.8%) were nearly similar. Detection of MBL was high (32.8%) among outpatient isolates compared to inpatients (13.2%) and ICU isolates (10%). Two percent of ICU isolates were MBL positive by MHT whereas none could be found positive among inpatient and outpatient isolates by MHT (Table 1).

Highest resistance of 56.5% was noted to ceftazidime. Least resistance was recorded to colistin (2%), imipenem (19.5%) and amikacin (21.5%). Resistance to piperacillin-tazobactam, ciprofloxacin, gentamicin and cefoperazone-sulbactam was 24%, 31.5%, 32%, and 36.5% respectively. Resistance to ceftipime and cefepime were 44% and 53% respectively. Multi-drug resistant was found to be 37.5%. Overall resistance pattern were higher among ICU and inpatient isolates than outpatient isolates (Table 2).

### Discussion

ESBLs are enzymes that mediate resistance to third generation cephalosporins (ceftaxime, ceftazidime, ceftriaxone) and are inhibited by beta-lactamase inhibitors (clavulanic acid, tazobactam, sulbactam), cefamycins (cefoxitin) and carbapenems (imipenem, meropenem). In the present study we observed 26% are ESBL producers which is high compared to studies from other parts of India revealing 19.4% - 21% as ESBL producers. Although ESBLs among P. aeruginosa is uncommon compared to other common Gram negative bacteria like E. coli and K. pneumoniae, the present increasing trend suggest possible horizontal gene transfer among P. aeruginosa and insists for better monitor and control measures.

Amp C beta-lactamases mediate resistance to cefamycins (cefoxitin), third and fourth generation cephalosporins, beta-lactamase inhibitors and are susceptible to carbapenems. P. aeruginosa produces both inducible chromosomal Amp C and non-inducible plasmid mediated AmpC. In the present study, 47.5% were inducible and 4% were non-inducible plasmid mediated Amp C beta-lactamase producers. In contrast, study from Varanasi reveals only 7% as inducible and 52.4% were non-inducible Amp C beta-lactamase. Besides, usage of cefepimycins in hospitals activates and hyper produces inducible Amp C enzymes. High cephalosporins resistance (44% - 56%) and inducible as a predominant resistance mechanism in the present study possibly indicates pressure of cephalosporins (personal interactions with clinician’s reveals frequent preference of cephalosporins) as an inducing antibiotic in the hospital environment. However, studies at one side show increase occurrence of Amp C beta-lactamase production in P. aeruginosa with use of inducers (like imipenem) and the other side without antibiotic inducers (mutational induction of Amp C gene). Further studies are needed in the present setting to understand the relation between use of inducing antibiotics and the occurrence of high inducible resistance among P. aeruginosa.

MBL is the most common carbapenem resistance mechanism in P. aeruginosa. Both beta-lactam and beta-lactamase inhibitors are ineffective against MBL producers. The present study records 19% isolates as MBL producers. However, studies from India ranges from 8% to 74.5% MBL producers among P. aeruginosa. Report from the global epidemiology of carbapenem-resistant P. aeruginosa documents that the geographical prevalence of MBL genes not only increasing steadily but also varies from country to country. Besides, the present study records 37.5% as multi-drug resistance seen in MBL producers. The appearance of MBL producing multidrug-resistant P. aeruginosa is a challenge in bringing the clinical infection under control and needs monitoring.

Overall resistance pattern in the present study were higher among ICU and inpatient isolates than outpatient isolates indicating a much antibiotic pressure in hospitalized patients. A study on trends of antibiotic resistance of P. aeruginosa from wound infections reveals a decreasing trend in resistance to ciprofloxacin, ceftazidime and carbapenems among in patients isolates due to reduced antibiotic usage.
whereas no change among outpatient isolates.\textsuperscript{24} Colonization pressure, cross transmission and exposure to multiple antibiotics have been identified to be important risk factors for the resistance acquisition of \textit{P. aeruginosa}.\textsuperscript{25} The present study reveals a higher resistance to cephalosporins (44\% to cefpirome, 53\% to cefepime and 56.5\% to ceftazidime). However, status of colonization, cross transmission between patients and the load of all individual antibiotics used in the present study was not known. Although each resistance mechanism is related to a specific class of antibiotics, multiple mechanisms mediate variably resistance to each class of antibiotics and vary from country to country.\textsuperscript{26} Further studies also have to be carried out to look into other resistance mechanisms such as loss or reduced outer membrane protein channels and over production of active efflux pumps.

To conclude, inducible Amp C beta-lactamase was found to be predominant mechanism of resistance and a cephalosporins usage may be risk factor among \textit{P. aeruginosa}. Colistin, imipenem and amikacin as first line and piperacillin–tazobactam and ciprofloxacin as an alternative could be useful antibiotics. The laboratories need to prepare for colonization pressure in ICU for quantifying the risk of new resistance acquisitions, to select suitable antibiotics, to establish appropriate control measures and to monitor the resistance trends.

\section*{Acknowledgement:}

The authors thank the Heads of ESIC institution and the RajivGandhi University of Health Sciences, Bengaluru for granting permission to conduct this work.

\section*{References}

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Association of Sonographically Assessed Visceral and Subcutaneous Abdominal Fat with Insulin Resistance in Prediabetes

Jalees Fatima, Nikhil Gupta, Ritu Karoli, Ashok Chandra, Shruti Jagirdaar, Raghav Arora, Neha Pandey

Abstract

Introduction: Visceral abdominal Fat, not Subcutaneous Abdominal Fat better correlates with insulin resistance. Hence the present study was undertaken to study the association of sonographically assessed visceral and subcutaneous abdominal fat with insulin resistance in patients with pre-diabetes.

Material and Methods: It was a hospital based cross sectional study done in prediabetes subjects. All the subjects were called fasting overnight and were given a structured questionnaire designed by investigator. Fasting and postprandial blood sugar, lipid profile, Hb1Ac and fasting insulin levels was done in every subject. Ultrasound assessment of subcutaneous and visceral abdominal fat, fatty liver and fatty pancreas was done.

Results: Seventy Five patients (males 35 and females 40) were studied. Twenty nine patients had fatty liver and 40 patients had fatty pancreas. Among all sonographic parameters visceral abdominal fat thickness (VAF) showed a significant positive correlation with insulin resistance (p< 0.05). Subcutaneous abdominal fat thickness (SAF) had a positive though statistically non significant correlation with insulin resistance. Visceral abdominal fat thickness correlated best with fatty pancreas and had a significant positive correlation with insulin resistance.

Conclusion: Fatty pancreas and visceral abdominal fat prove to be two important indices which mark the risk of insulin resistance thus may be considered an important predictor for screening of metabolic syndrome.

Introduction

The prevalence of diabetes in adults aged 20–79 years was estimated to be 8.8% in 2015 and predicted to rise to 10.4% in 2040. Of 371 million diabetic people worldwide 63 million are Indian. Prediabetes is a continuum between normal health and diabetes. This is characterized by increased fasting plasma glucose, as well as impaired glucose tolerance. Diabetes mellitus (DM), prediabetes and insulin resistance (IR) are important causes of morbidity and mortality, particularly due to their cardiovascular complications.

Abdominal (Central) obesity is a significant health problem associated with glucose intolerance, insulin resistance, metabolic perturbations, hyperinsulinemia, and progression to type 2 diabetes mellitus. Insulin resistance is associated with increasing BMI and metabolic syndrome. However, normal-weight individuals may also be insulin resistant, suggesting that overall adiposity is not the sole determinant of insulin resistance. Measurement of intra-abdominal visceral fat accumulation is an important step for the assessment of atherosclerosis risk. The distribution of abdominal fat as visceral and subcutaneous fat is a dimension of obesity that is not properly assessed by anthropometric measurements.

CT or MRI imaging techniques are gold standard for assessment of abdominal fat distribution. However their disadvantages are exposure to high levels of radiation, high costs and technical difficulties. Ultrasonography has been proven to be a useful alternative to computed tomography in measuring intra-abdominal fat and predicting visceral obesity.

There is scarce data regarding abdominal fat distribution (visceral and subcutaneous) and its association with insulin resistance in prediabetes population. Henceforth this study was undertaken to study the association of sono-graphically assessed visceral and subcutaneous abdominal fat with insulin resistance in patients with prediabetes.

Material and Methods

The present study was conducted on patients coming in OPD and indoor of department of medicine, Era’s Lucknow medical College, Lucknow. It was a crosssectional study and data was collected for 1 year between June 2016 to June 2017. Ethical approval was obtained from ethical committee of Era’ Lucknow Medical College. Written and informed consent was taken for participating in the study from the subjects. Subjects included were prediabetes patients diagnosed according to the ADA criteria. Diabetes mellitus, ascites, patients admitted in ICU or terminally ill were excluded from the study. Subjects were taken by random sampling. All the subjects were called fasting overnight and were given a structured questionnaire designed by investigator. Fasting and postprandial blood sugar, lipid

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Received: 10.01.2018; Accepted: 15.01.2019
profile, HbA1c, fasting insulin levels and ultrasound abdomen was done in every subject. Fasting insulin level was done by chemiluminescence magnetic immune assay and insulin resistance was measured by homeostasis model assessment (HOMA-IR) method and was calculated by the formula: Fasting serum insulin (mU/ml) × fasting serum glucose (µmol/L)/22.5. A Low HOMA-IR values <3 indicated mild insulin resistance, whereas >5 indicated severe insulin resistance and values between 3-5 indicated moderate insulin resistance.

Ultrasonography assessment of abdominal adiposity

1.5 MHz convex and 11 MHz linear probe was used for measurement of subcutaneous fat thickness, visceral fat thickness and grades of fatty liver and fatty pancreas. Visceral abdominal fat thickness was defined as the distance between the anterior wall of the aorta and the posterior surface of the rectus abdominal muscle. Subcutaneous abdominal fat thickness was measured by placement of a 7.5-MHz probe perpendicular to the skin on the epigastrium. The thickness of the subcutaneous fat was defined as the distance between the anterior surface of linea alba and the fat–skin barrier. Fatty liver and fatty pancreas grading was done according to the standard criteria accepted by the American Gastroenterology Association. Fatty liver (in the absence of alcohol intake) Grade 1 (mild steatosis): slightly increased liver echogenicity with normal vessels and absent posterior attenuation. Grade 2 (moderate steatosis): moderately increased liver echogenicity with partial dimming of vessels and early posterior attenuation. Grade 3 (severe steatosis): diffusely increased liver echogenicity with absence of visible vessels and heavy posterior attenuation. Fatty pancreas grade A and B: Non-fatty pancreas, pancreatic echogenicity is equal to renal cortical echogenicity. C: Mild fatty pancreas, pancreatic echogenicity is definitely lower than retroperitoneal fat. D: Moderate fatty pancreas, pancreatic echogenicity is slightly lower than retroperitoneal fat. E: Severe fatty pancreas, pancreatic echogenicity is equal to retroperitoneal fat.

Statistical analysis

Statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 20 statistical analysis software. Baseline demographic and lipid profile were described in mean ±SD for continuous variables and n (%) for categorical variables. Student’s t test for continuous variables and the χ² test for categorical variables were used for analyzing the significance of differences between groups by gender difference. Pearson correlation was performed to assess correlation of insulin resistance with subcutaneous fat and visceral fat. P values <0.05 were considered significant.

Results

Total 75 patients were enrolled for the study. Out of 75 patients 35 were males and 40 were females. Baseline characteristics of all subjects are expressed as Mean ± Standard Deviation and Range (Minimum and Maximum) in Table 1. Mean Fasting Insulin and mean HOMA-IR were 10.2±8.1 (4.5-25.56) and 3.56±0.58 (1.2-3.8) respectively. Among 75 cases 20 (28.57%) had normal vessels and absent posterior attenuation. Fatty liver (in the absence of alcohol intake) was no significant difference in mean subcutaneous abdominal fat in both these groups. Mean visceral abdominal fat was more in fatty pancreas group (140.5±21.09 cm²) than in non fatty pancreas group (129.06±22.09 cm²) and this difference was statistically significant (p=0.05) however there was no significant difference in mean subcutaneous abdominal fat in both these groups. Insulin resistance had positive correlation with visceral fat which was statistically significant (p=.035). Correlation of Insulin resistance with subcutaneous fat was weakly positive but statistically insignificant (p=.098) (Table 3). On bivariate analysis of other risk factors with insulin resistance HDL-C had a statistically significant negative correlation with insulin resistance (R=-0.258, P=0.026) and serum triglycerides had a statistically significant positive correlation with insulin resistance (R= 0.261, P=0.024). Rest all the parameters were statistically insignificant (Table 4).

Discussion

The global prevalence of prediabetes is estimated to be 7.3% in 2017 and will further rise to 8.3% in 2045. Insulin resistance is associated with increasing BMI and central obesity. Although insulin resistance is correlated with BMI, it is more strongly associated with abdominal obesity, a key component of the metabolic syndrome. A recent study observed that association of visceral fat was stronger with insulin resistance but association for subcutaneous fat and the ratio of VAF/SAF was less strong. 22

The Framingham Heart Study (FHS) examined the association between abdominal fat distribution assessed by CT and various metabolic risk factors. In a large community-based primarily white population, both SAF and VAF were significantly associated with fasting plasma glucose and insulin resistance. The associations were stronger with VAF than with SAF. VAF but not SAF contributed significantly to risk factor variation after adjustment for BMI and waist circumference. It is recognized that overaccumulated visceral fat tends to act as a dysfunctional adiposity that induces excess storage of ectopic fat (muscle, epicardial, and liver fats). Consequently, abnormal free fatty acid metabolism may trigger dysfunctional release of adipokines. Accumulation of those ectopic fats influences the metabolic profile and was no significant difference in mean subcutaneous abdominal fat in both these groups. Mean visceral abdominal fat was more in fatty pancreas group (140.5±21.09 cm²) than in non fatty pancreas group (129.06±22.09 cm²) and this difference was statistically significant (p=0.05) however there was no significant difference in mean subcutaneous abdominal fat in both these groups. Insulin resistance had positive correlation with visceral fat which was statistically significant (p=.035). Correlation of Insulin resistance with subcutaneous fat was weakly positive but statistically insignificant (p=.098) (Table 3). On bivariate analysis of other risk factors with insulin resistance HDL-C had a statistically significant negative correlation with insulin resistance (R=-0.258, P=0.026) and serum triglycerides had a statistically significant positive correlation with insulin resistance (R= 0.261, P=0.024). Rest all the parameters were statistically insignificant (Table 4).

### Table 1: Baseline characteristics of study subjects

<table>
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<th>Mean ± SD</th>
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<td>Age (Year)</td>
<td>40.77±9.7</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>24.2±6.0</td>
<td>18-29</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>90.46±10.6</td>
<td>76-90</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120.6±3.6</td>
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<tr>
<td>DBP (mmHg)</td>
<td>77.1±3.9</td>
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</tr>
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<td>Fasting plasma glucose (mg/dl)</td>
<td>99±10.5</td>
<td>68-120</td>
</tr>
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<td>2 h plasma glucose (mg/dl)</td>
<td>175.4±15.3</td>
<td>141-199</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.58±0.14</td>
<td>5.0-6.0</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>180.3±14.9</td>
<td>155-225</td>
</tr>
<tr>
<td>Serum triglyceride (mg/dl)</td>
<td>117.1±24.7</td>
<td>75-168</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>45.4±9.04</td>
<td>32-70</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>119.5±16.7</td>
<td>98-158</td>
</tr>
<tr>
<td>Fasting insulin (mU/L)</td>
<td>10.2±8.1</td>
<td>4.5-25.56</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.56±0.58</td>
<td>1.2-3.8</td>
</tr>
</tbody>
</table>

- Significant at p < 0.05


eventually increases the risks for developing metabolic syndrome, whereas subcutaneous fat has been recognized as a “healthy adiposity,” which may not adversely impact the development of metabolic syndrome. In particular, prospective studies have provided evidence that VAF is an independent predictor of pre-diabetes and diabetes. 

Our results are consistent with previous work in finding an association between SAF and VAF and indices of glucose metabolism, and in finding an association for VAF than for SAF—with the benefit that our study is based on a highly feasible one-dimensional assessment of VAF and SAF with ultrasonography rather than on methods requiring expensive equipment and offline interpretation of results, such as the two- or three-dimensional imaging with CT or MRI. As we know that diabetes has an inexorable decline in beta cell function so we focused on prediabetic state which is potentially reversible state of diabetes. The Asian Indian population has a unique phenotype. They are thin outside fat inside (TOFI) meaning that the persons with normal BMI and apparently not so obese may be having metabolically abnormal fat deposition in their visceral compartment. Our study showed that visceral fat has statistically significant correlation with insulin resistance whereas waist circumference has positive but statistically insignificant correlation with insulin resistance in prediabetes. Therefore visceral fat may be significant predictor of insulin resistance and metabolic syndrome in this population. To substantiate this statement further studies with larger population are needed.

A limitation of this study is its cross-sectional design. It is a single centric study with a small sample size. Our study participants are north Indian we cannot generalize our results to other populations.

Conclusion

Insulin Resistance had statistically positive correlation with visceral abdominal fat. HDL-C and triglycerides were found to be correlated with insulin resistance. Fatty pancreas and visceral abdominal fat prove to be two important indices which mark the risk of insulin resistance thus may be considered an important predictor for screening of metabolic syndrome. Further studies in a larger population are needed to elucidate the role of visceral fat in the development of insulin resistance which is the key component in the pathophysiology of metabolic syndrome.

References

Medical Research in Medical College in India: Current Scenario and Ways to Improve it

Kanjaksha Ghosh¹, Kinjalka Ghosh²

Abstract

Background: Medical colleges should be the engines of medical research in India however sadly it is far from that.

Materials and Methods: Articles published in English literature from 1990’s were reviewed along with personal experience of more than 30 years of interacting with various medical institutions of India.

Results: Six to ten medical colleges publish more than 60% of research papers in indexed journals out of existing 450 medical colleges in India. There are many reasons why there is very little or poor quality research in medical colleges in India. Poor mentorship, severe patients load, lack of research interest, lack of funding and lack of multicentric co-ordinates research activity, lack of incentive for research, are some of the reasons.

Discussion and Conclusion: Many of the reasons cited above for good quality research needs are correction. However generous funding should be available as a research fund to the medical colleges both by state and by central government. Both undergraduate and postgraduate curricula needs to be modified to reflect that good medical research is part of good medical practice.

Introduction

Medical Colleges are engines of medical research anywhere in the world. There are more than 450 medical colleges in India churning out more than 60000 medical graduates in the country. Out of these 60000 graduates at least 40% of them do various postgraduate degrees, diploma or fellowships. In addition to 450 medical colleges there are at least equal number of corporate hospitals where postgraduates medical curriculum are available in many of them. Sadly such a big medical manpower spread across their vast country contributes very little for research activity. One of the research papers¹ cites that top 6 colleges published more than 56% of total research papers since 1990s. Several scathing criticism on nature of medical research in medical colleges in India has been published.¹-⁵ These papers not only pointed out poor quality of research but also academic dishonesty, plagiarism, publications in non-indexed substandard medical journals without review as some such shortcomings. Even the mere output of research from these colleges are meagre.

It may be argued that each year thousands of candidates are completing there MD, MS, MCH, DM degrees where writing a dissertation is a must. So why at least a good number of these dissertations are not finding their way to good publications? Let us now see what It takes to develop a good research infrastructure and do our medical colleges have it?

Scenario in India and Solution

First and foremost is the need for a good mentor with a track record of good research capability. Sadly most of the medical college faculties will fall short of it. More over even if there are good faculty they are transferred so often that they cannot develop a good research base in any medical college. Secondly there has to be a tradition of research in a college so that from the beginning MBBS students and later MD / MS students are in contact with the research ambience of the Institute. In fact few of the medical colleges where such ambience has already been developed publish maximum number of research papers. Colleges should incentivize good research both at student as well as faculty level. Though Medical Council of India (MCI) have let down the rules of selection and promotion of medical college faculties where a minimum number of research papers need to be published for such a job or promotions. Many such papers are published in predatory journals on paying money.⁶

Patient’s load and low number of faculties in medical colleges are real challenges as well as opportunities. Where load of patients are very high it is often difficult to concentrate on research. In addition many faculties in medical colleges are extremely busy practitioners and their private practice definitely in some way compromise their time to do research (There are notable exactions to all role tough) and not uncommonly takes precedence over all other activities.

Modern medicine is laboratory based and the progress in laboratory medicine including imaging techniques is happening by leaps and bounds. Though many corporate hospitals are using these techniques most of the medical colleges do not. They outsource these investigations on a case by care basis. This approach severely compromise research capability. Arunachalam⁷ has pointed out that a large amount of dissertations that our students churn out are little more than copycat research with very little original thinking in it. Out of many

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Received: 30.03.2018; Accepted: 16.11.2018
subjects, the students are taught in MBBS curricula only community medicine devotes one or two chapters on research methodology in the form of elementary medical statistics and epidemiology. However most of the students show little interest in these classes. Medical ethics, patient’s consent etc are important components of medical research today but very few colleges teach these subjects at undergraduate or post graduate levels. Poor teaching and lack of adequate number of faculties have been pointed out by early workers as one of the reasons why research output itself is poor in medical colleges. After the research work is done ability to write the research paper in a short but engaging and inimitable style makes their research paper publishable. This quality of writing do not appear suddenly but requires long practice. Without good mentoring most of the dissertations of medical postgraduates do not see the light of the day.12-13

Having a good medical record section in a medical college can provide a veritable treasure trove for medical research. Sadly however medical record section of most medical colleges are poorly maintained. Hardly any trained medical statistician are recruited by the college for these record sections. More over the basic material i.e. patients case sheets are so poorly written that very little can be extracted from these records for retrospective studies or follow up studies. In the current era of digitization the whole hospital and its record system needs to be digitized as one of the minimum important step for medical research. Digitisation improve patient care, prevents medical litigation by providing clear record and of course support research activity.

If we look at some of the best medical journals of the world i.e. The lancet, BMJ, Annals of Int Med., JAMA or The New England Journal of Medicine, it can be easily seen that Randomized control trials (RCT) accounts for a very large number of quality papers. To produce these kind of research which is collaborative, multicentric and multispecialty with a good medical statistician who develops the programme with requisite number of patients having proper statistical power to do the trial is lacking in Indian scenario. This kind of trials could be properly done by big funding agencies like DBT, DST, ICMR, DHR etc. or by International funding agencies. Without a properly developed infrastructure or staff base the medical colleges could ill afford to take part in these kind of trials.

Pharmaceutical companies who develop novel products are keen to give such kind of trials. Unfortunately Indian pharma companies till recently developed very few novel products on its own. Hence new trials by these companies are merely repetition trials on drugs which already underwent extensive trial abroad. Moreover because of various reasons doing RCT in India is not easy because of red tapism and involvement of multiple agencies for required permission to carry out such trials.

So what could be the solution? First and fore most the faculty of the medical colleges should feel an urge to do good quality medical research irrespective of incentives given i.e. the desire to pursue the unknown should be incentive enough. As many of the current faculty have poor idea of how to conduct good research, they themselves need research methodology training.

This could be organized by community medicine department of the medical colleges and junior faculty at least (i.e. Assistant and Associate Professors) should be urged to attend. This course should also have a segment on “How to write and criticize a research paper”. National funding agencies for medical research much encourage such activities.

Medical research in a medical college should be built on day to day challenges and experiences rather than doing similar kind of work as copycat research already conducted and published from elsewhere. Medical records should be digitized with proper access codes. Students should be reared in a research environment not forgetting what our great William Osler said “Wards are greatest of research laboratories”.

Without money no good research is possible now a days. Hence there Should be research funds in each medical college. This fund could be developed through donations by ex-students or well wishers of the society, grateful patients etc through legacy and other instruments of donation. This is regularly seen for IITs but unfortunately not for medical colleges in our country. Every faculty should be encouraged to write and compete for project funding at state DST level and at national government or non government funding level.

Faculty should be rewarded for publishing good quality research papers or for bringing completely funded research project to the hospital.

ICMR and DHR has already started giving small funds for MD/DM/MS/ MCh/DDS/MDS dissertation. It has also set up a network of laboratories inside many medical colleges.

Advantage should be taken by the faculties of the respective medical colleges with such laboratories. Now a days most of the faculty attend at least one national / international conferences a year or every two years. Attempts should be made to forge alliance with similar medical workers to develop multicentric research activities. These kind of research activities are more likely to be funded. In addition big cities have ICMR/ DBT / CSIR / BARC centres. The scientists from such centres are very eager to do good quality research. Medical College faculties should talk or actively look for collaborations with these scientists.

In fact few medical colleges are actively utilizing such opportunities already. Traditional Medicine from India has a lot to offer to modern medicine. Hence this is also a relatively unexplored area with immense possibilities for funding and research. MCI needs to revamp its curricula at various levels as the phenomenal advances of modern medicine in different areas of biological research makes such a change necessary more often.

Medical Colleges now needs non-medical scientists cadre in different subjects. Unless MCI forces this necessity to medical colleges this will never happen. Modern research needs basic scientists in addition to doctors. AIIMS has research scientist post at various departments. Where financial crunch does not allow implementation for such posting, ICMR / CSIR / University faculty can be provided honorary adjunct faculty post. This will not only solve such problem but also will bring high power basic science centres in the country within close vicinity of medical colleges for
collaborative research of higher quality. Several authors have suggested different solutions to address the problem. Research oriented medical education, improving quality of the faculty, reducing patient load, funding for project, workshop, hand holding by eminent research organization etc.

In a recent editorial Bandewar et al have raised certain important question regarding putting emphasis only on research and nothing else for recruitment and promotion of medical teachers as self-defeating because a medical teacher teaches, manages patients either in the ward or in the laboratory and in addition is asked to do research. Hence ideally they need to be assessed in all the three domains. However when it comes to research there is no doubt that we have to improve it for our medical teachers without any compromise on quality.

One of the challenges which we and our previous generation of teachers faced was lack of good quality indexed national medical journals. Now many of our national journals are indexed and are published by well established international publishers, so our access to publications has definitely increased. If we are ready to make changes, our medical colleges can become the engine of medical research in the country in near future.

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**FELLOWSHIP OF THE INDIAN COLLEGE OF PHYSICIANS (FICP) AT APICON 2019 AT KOCHI**

The following members were awarded the Fellowship of the ICP at Kochi, APICON 2019

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4. Dr. Anand P. Ambali, Vijayapura
5. Dr. Mohd. Sajid Ansari, Lucknow
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Tuberous Sclerosis with Bilateral Angiomyolipoma

Rajendra Singh Jain¹, Ibraheem Khan²

A 26 years old female presented with bilateral dull aching flank pain and hematuria for last two months. There was no h/o headache, vomiting, seizure, trauma, abnormal behaviour, cognitive decline or bladder-bowel involvement. Her father and brother also had similar skin lesions on forehead and face. General physical examination revealed multiple adenoma sebaceum and a forehead plaque on her face (Figure 1A).

Her neurological examination (MMSE -26/30) and biochemical investigations were unremarkable except the urine which showed RBC cells 10-15 /cubic mm without microalbuminuria and sugar. Contrast enhanced CT-abdomen revealed huge heterogeneously enhancing mass lesions with fat density in both kidneys, right and left kidney measuring 22.3 x 22 mm and 67 x 34.8 mm respectively.

Fig. 1: (A) revealed-Adenoma sebaceum: multiple skin lesion on face (red arrow) and a forehead plaque (black arrow). (B) Contrast enhanced CT-abdomen revealed huge heterogeneously enhancing mass lesions with fat density in both kidneys, right and left kidney measuring 22.3 x 22 mm and 67 x 34.8 mm respectively.

Fig. 2: Magnetic resonance imaging (MRI) brain with contrast showed (a) subependymal nodules in foramen of monro (b,e) Subependymal nodules: dotting the ependymal surface of the ventricles. The lesions were isointense to gray matter on T2 and DWI image (c) White matter abnormalities : high signal on FLAIR images (d) Cortical and subcortical tubers: central signal loss with a high signal peripheral rim in parietal on FLAIR (f) Subependymal giant cell astrocytomas (SEGA): incompletely calcified, or enhancing lesion.

Diagnosis of tuberous sclerosis was made on the basis of recommendations of the 2012 International Tuberous Sclerosis Complex Consensus.¹ Our patient had atypical presentation despite all radiological findings of tuberous sclerosis, large forehead plaque and the positive family history of skin lesions without any neurological sign and symptoms.

References

Hyperdense Middle Cerebral Artery Sign

Uday Mahajan¹, Sujeet Raina², Rajesh Sharma³

Postgraduate Student, Assistant Professor, Professor, Dr. Rajendra Prasad Govt. Medical College, Tanda, Kangra, Himachal Pradesh

Received: 15.04.2017; Accepted: 20.08.2018

A 62 year male presented to the emergency of our hospital at 8.20 am with history of sudden onset weakness right half of body and deviation of face towards left since 7.50 am of the same day. Patients had no history of headache, seizures, nausea, vomiting or faecal incontinence. He was a known hypertensive with poor compliance to medication. He was a not a known diabetic and was a non-smoker. At the time of presentation his pulse was 62 beats/ minute and was regular. His blood pressure was 164/90 mmHg. Nervous system examination revealed global aphasia; right 7th supranuclear palsy and features of upper motor neuron hemiparesis on right side. The NIH stroke scale was 15. Detailed cardiovascular examination was normal. Rest of the examination was within normal limits. A clinical diagnosis of stroke was kept with a deficit of right side UMN hemiparesis with right seventh supranuclear palsy with global aphasia. Non contrast CT revealed a hyperdense middle cerebral artery on left side with a CT density of 67 HU. The findings refer to the radiological sign of ‘hyperdense middle cerebral artery sign’.

The ‘hyperdense middle cerebral artery sign’ (HMCAS) is the focal increased attenuation of the middle cerebral artery on CT and is the direct visualization of occlusive thrombotic material within the lumen. It is an earliest visible sign of middle cerebral artery ischaemic stroke and is visible long before parenchyma changes appear. The sign has a high specificity (90-100%) but low sensitivity about 30%.¹,² The frequency of disappearance of HMCAS following intravenous thrombolysis as well as intra-arterial thrombectomy is determined by location (proximal versus distal), length and volume of middle cerebral artery thrombus.³,⁵

References


1Postgraduate Student, 2Assistant Professor, 3Professor, Dr. Rajendra Prasad Govt. Medical College, Tanda, Kangra, Himachal Pradesh

Fig. 1: Hyperdense MCA sign. Noncontrast axial CT scan of the brain showing hyperattenuation of the left middle cerebral artery (arrow)

Prof. Milind Y. Nadkar
Editor-in-Chief, JAPI
Treatment of Pulmonary Embolism with Chemotherapy in a Case of Newly Diagnosed Osteosarcoma

Agrima Mian¹, Aayush K Singal¹, Sameer Bakhshi², Rita Sood¹, Naval K Vikram¹, Animesh Ray¹

Abstract
A 21-year old female, recently diagnosed with osteosarcoma of right humerus, presented to the emergency with history of fever, productive cough, chest pain and progressive respiratory distress for six days. Initial investigations suggested pneumonia but she did not respond to parenteral antibiotics. CT pulmonary angiogram revealed bilateral pulmonary artery embolism. Thrombolysis was performed using alteplase, which failed to improve the clinical condition. In view of underlying malignancy, a possibility of tumour-embolism was considered and she was started on chemotherapy for osteosarcoma. There was dramatic improvement in her respiratory symptoms after the first chemotherapy cycle, along with radiological resolution of the embolism. This case highlights the importance of suspecting tumour embolism in a known case of malignancy with respiratory distress.

Introduction
Patients with an underlying malignancy are prone to develop hypercoagulable state and subsequent pulmonary thromboembolism. Rarely, the embolus may consist of tumour cells and hence, will not respond to thrombolysis and anticoagulation. There have been very few cases reported till date, of an osteosarcoma being described as a cause of pulmonary tumour embolism. Most of these patients had a fatal outcome. Accurate ante-mortem diagnosis and successful treatment for the embolism has been rare.

Case Report
A 21- year old female presented to medical emergency with complaints of fever, productive cough, chest pain and progressively increasing respiratory distress for six days. She had been diagnosed with right proximal humerus osteosarcoma 20 days back and was treatment naïve.

At admission, she was normotensive but had tachycardia (heart rate of 120/min), tachypnea (respiratory rate of 40/min) and hypoxemia (resting oxygen saturation at room air of 74%). Investigations revealed neutrophilic leucocytosis and arterial blood gas analysis suggested respiratory alkalosis with type I respiratory failure. Chest radiograph revealed multiple bilateral ill-defined air space opacities with a right-sided wedge shaped opacity in the lower zone (Figure 1).

Considering the clinical possibility of community acquired pneumonia, she was started on intravenous antibiotics and high flow oxygen by mask. She did not show significant response to the initial treatment. The electrocardiogram on day 2 showed changes suspicious of pulmonary thromboembolism (sinus tachycardia, a right axis deviation, a RV strain pattern and T wave inversion in chest leads V1-V4).

Computed Tomography Pulmonary Angiogram (CTPA) done on Day 2 revealed a large saddle shaped thrombus involving both right ascending and descending pulmonary artery and left descending pulmonary artery along with parenchymal infarcts (Figure 2A).

Echocardiogram revealed dilated right atrium and ventricle, with a 23x9 mm mobile thrombus prolapsing into the right ventricle, causing moderate right ventricular dysfunction, mild tricuspid regurgitation with severe pulmonary artery hypertension. Anticoagulation with low molecular weight heparin (1 mg/kg BD) was started. One hundred milligrams of Recombinant-tissue plasminogen activator (alteplase) was administered for thrombolysis on day two of hospitalization.

Despite thrombolysis, her respiratory distress continued to worsen, mandating non-invasive bi-level positive pressure ventilation (Table 1). Venous Doppler scan of bilateral lower limbs was normal. Upper limb Doppler revealed thrombosis. 

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Received: 28.12.2018; Accepted: 28.01.2019
of right brachial and axillary vein. A repeat CTPA done three days later showed no change in the thrombus burden (Figure 2B).

Lack of response to anticoagulation and thrombolysis raised the suspicion of tumour embolism. Surgical thrombectomy could not be performed due to poor performance status and high surgical risk. She was started on ifosfamide-etoposide based chemotherapeutic regimen (ifosfamide 3000 mg/m2 IV OD and etoposide 75 mg/m2 IV OD Day 1-4).

After the 4-day chemotherapy cycle, the respiratory distress started improving. By day 7 oxygen saturation was stable on room air. Post chemotherapy CTPA showed significant resolution of pulmonary embolism and 60% recanalization of pulmonary artery (Figure 2C). PET scan revealed FDG-uptake in the residual thrombus in the left descending pulmonary artery with multiple sub-parenchymal and subpleural cavitory lesions attributable to pulmonary infarction, along with FDG avid primary right humeral mass with standardized uptake value (SUV) comparable to the residual thrombus (Figure 3).

The diagnosis of pulmonary tumour embolism was confirmed and patient was discharged after first cycle of chemotherapy. At the time of preparation of this manuscript, the patient has completed the six-course chemotherapy and a resection surgery for the osteosarcoma has been performed.

**Discussion**

Venous thromboembolism is a well-recognized occurrence in malignancy, and up to a fourth of cases occur in patients with diagnosed cancer. Tumour embolism is a lesser known entity, most frequently described with epithelial solid tumours (breast, lung, gastro intestinal tract and hepatocellular carcinoma). Pulmonary tumour embolism secondary to sarcoma is uncommon, and a comprehensive search revealed only 21 cases reported with osteosarcoma.

The Virchow’s triad describes the three primary factors for thrombogenesis as endothelial
dysfunction, stasis or turbulence in blood flow and hypercoagulability. Thrombogenesis in malignancy can occur via all the above mechanisms. While benign venous thrombi are composed of activated platelets, fibrin mesh and macrophages; tumour emboli are composed of viable tumour cells. Thrombus arising from solid tumours. Although FDG avidity can be seen in inflammatory cells comprising bland thrombi as well, a recent study by Sharma et al identified cut-off SUVmax of 3.63 to differentiate benign from tumour thrombi with a sensitivity of 72% and specificity of 90%. Histological diagnosis is gold standard, though utility is limited to surgical embolectomy and autopsy. On histology, the tumour emboli are usually concentric and cellular, compared to the non-concentric and serpentine thromboemboli.

Treatment of pulmonary tumour embolism includes chemotherapy for the primary malignancy, and/or surgical embolectomy (attempted in three of the reported cases). The diagnosis of tumour embolism in our case was considered after the patient failed to respond to anti-coagulation and thrombolysis. However, high clinical index of suspicion along with use of modalities such as 18 –FDG PET and Fusion PET-CT can help in early differentiation from bland venous thromboembolism. This is important as unnecessary thrombolysis and life-long anti-coagulation can be avoided. Physicians should remember pulmonary tumour embolism when encountered with a case of malignancy presenting with unexplained hypoxia, more so in absence of clinical response to routine management of thromboembolic disease.

Acknowledgements
We acknowledge Dr. Ashu Seith Bhalla, MD, Department of Radiodiagnosis, and Dr Rakesh Kumar, Department of Nuclear Medicine, All India Institute of Medical Sciences for the radiological investigations.

References
Massive Lower Gastrointestinal Bleeding Due to Fulminant Necrotizing Amebic Colitis: A Diagnostic and Therapeutic Challenge

Sanjay Chandnani, Suhas Udgirkar, Samit S Jain, Nikhil Sonthalia, Qais Contractor, Pravin M Rathi, Anirudh Chapekar

Abstract
Acute fulminant necrotizing amebic colitis rarely presents with massive life-threatening lower gastrointestinal bleeding without diarrhea. Diagnosis is difficult as colonoscopy is suboptimal due to active bleeding, stool testing is often negative and a positive serology cannot confirm the diagnosis. We herein report a case of a 39-year-old male who presented with profuse bleeding per rectum, without associated significant antecedent history of fever or diarrhea. Colonoscopy was inconclusive as active bleeding obscured the vision. Computed tomography of abdomen revealed non-specific thickening of the caecum. Emergency laparotomy with right hemicolectomy and temporary ileostomy was performed. Microscopic examination of colonic mucosa revealed Entamoeba histolytica trophozoites with erythrophagocytosis suggestive of fulminant amebic colitis. Intravenous metronidazole was given subsequently and patient recovered completely. Ileocolonic anastomosis was done after closing the ileostomy three months later. This case highlights this exceedingly rare presentation of fulminant amebic colitis which poses a diagnostic challenge and can be life threatening without early surgical intervention.

Introduction
Amebic colitis caused by Entamoeba histolytica is a common cause of diarrhea in the tropics. Fulminant necrotizing amoebic colitis (FNAC) is an uncommon but life-threatening complication which can lead to perforation, peritonitis, toxic megacolon, bloody diarrhea and a high mortality (40-89%) if not recognized early. It is common in endemic areas, among travelers visiting endemic areas and is often misdiagnosed as Inflammatory Bowel disease initially. Even after appropriate antibiotics mortality rate remains high because of delayed diagnosis and systemic complications. We here report a rare case of FNAC presenting with acute massive life threatening lower gastrointestinal bleeding treated with emergency colectomy and antibiotics.

Case Report
A 39-year-old male presented with acute onset massive bleeding per rectum for one day, associated with dizziness and altered sensorium. For two days prior to presentation he had history of low grade fever with increased stool frequency (3-4 per day). There was spontaneous passage of only fresh blood mixed with clots as well as passage of blood mixed stools on the day of presentation. There was no history of abdominal pain, peri-anal pain, straining during defecation, finger evacuation, increased defecation time, mass coming out of per rectum, weight loss, anorexia, urgency or tenesmus. There was no previous history of diarrhea, constipation, abdominal distension, or feeling of lump. Patient had pulmonary tuberculosis 3 years ago, which was treated with anti-tubercular drugs. He was a chronic alcoholic taking 30 gm alcohol/day since last 10 years. On examination patient was drowsy with pulse rate 132/min, blood pressure 90/60 mm of Hg and had peripheral cool extremities. He had pallor with mild generalized abdominal tenderness with no evidence of any lump or organomegaly. On per rectal examination external skin tag was present with normal anal tone and finger was stained with blood. Proctoscopy revealed blood clots in the rectum. Patient was initially resuscitated with intravenous colloids, inotropes and moist oxygen inhalation. Laboratory investigation revealed hemoglobin of 5.2 gm%, leucocyte count of 22,500/cumm, serum Alanine transaminase of 65 IU/L, Aspartate transaminase of 60 IU/L, Alkaline Phosphatase 280 IU/L and Serum creatinine 1.7 mg%. Serum anti-HIV antibodies were negative. Rest of the laboratory tests were unremarkable. After initial resuscitation, blood transfusion and hemodynamic stabilization, urgent colonoscopy was performed. There was poor visibility due to large amount of fresh and altered blood from caecum till rectum. Subsequently contrast enhanced computed tomography (CECT) of abdomen with angiography was done which revealed concentric, segmental, intramural wall thickening of ileocecal (IC) junction, caecum and proximal ascending colon (approximately 1.3 cm wall thickness) and inflamed appendix with periolic and peri appendiceal fat stranding (Figure 1 A, B). There were also discrete heterogeneously enhancing lymph nodes, about 10.9 x 11 mm in size in the right iliac fossa. There was no evidence of active contrast blush. There was no evidence...
of air under the diaphragm, perinephric air or paraspinous air suggestive of luminal perforation. Stool microscopic examination did not show evidence of ova, cyst or parasite. Serum ELISA for Entamoeba histolytica antibody was positive. In view of colonic thickening, persistent bleeding per rectum, hemodynamic instability and requirement of multiple transfusions (6 units in total), exploratory laparotomy was performed. Intra-operative findings revealed thickened IC junction with perforated retrocecal appendix and multiple ulcers in the caecum which was the site of bleed. Right hemicolecotomy with ileostomy was done. He is doing well at 6 months follow up.

Discussion

Amebiasis is a water and food borne protozoal disease infecting as much as 10% of the world’s population and is responsible for 40,000-100,000 deaths annually. It mainly affects the colon and the liver. It has predilection for both sexes in childhood but males are affected more than females in adults. There is a bimodal age of distribution with peaks at 2-3 years and 40 years. Ameboma occurs in 1.5% of infected patients and carries a mortality of 0.5%. Stool routine microscopy is the most commonly employed diagnostic test which has a poor sensitivity of 25-60%. Antigen detection in stool is more sensitive but not widely available. Fulminant necrotizing amoebic colitis affects 6-11% of symptomatic patients. It can be complicated by microscopic sealed off perforation or can cause macroscopic perforation resulting in generalized peritonitis. Mortality is high if not treated urgently. Ameboma is a mass of granulation tissue with peripheral fibrosis and a core of inflammation related to chronic amebic infection usually found in the cecum and ascending colon. Colonization with other bacterium like Clostridium species, malnourishment, chronic alcohol intake, chronic corticosteroid use, male sex, age >60 yrs., associated liver abscess, abdominal pain, leukocytosis, hyponatremia, hypokalemia, hypoalbuminemia are factors associated with FNAC. All layers of the colon can be involved which can lead to toxic megacolon and perforation. Close differential diagnosis includes severe attack of IBD, carcinoma colon, other infectious colitis and ischemic colitis. Misdiagnosing and treating it as IBD with steroids can lead to toxic megacolon and perforation. Close differential diagnosis includes severe attack of IBD, carcinoma colon, other infectious colitis and ischemic colitis. Misdiagnosing and treating it as IBD with steroids can lead to toxic megacolon and perforation.
Especially in India, in the recent years, epidemics in tropical countries.

Perforated retrocecal pocket on CECT abdomen suggestive of intraperitoneal air or paraspinal air evidence of air under the diaphragm, with inflamed appendix. There was no intramural thickening of terminal ileum, as evident from abdominal CT revealed concentric ring enhancement. Perforation was ruled out on FNAC. However, in our case, abdominal CT scan revealed concentric ring enhancement of terminal ileum, cecum, proximal ascending colon with inflated appendix. There was no evidence of air under the diaphragm, retroperitoneal air or paraspinal air pocket on CECT abdomen suggestive of perforation. Perforated retrocecal appendix was found intraoperatively. This highlights the need for high index of suspicion and low threshold for surgical exploration in cases of FNAC. The treatment of amoeboma includes antibiotics and agents for eliminating intestinal cysts. Early surgery is life saving and it is to be performed as two staged procedure. Primary resection anastomosis is contraindicated because of high risk of suture breakdown. There is high incidence of gangrene with anastomotic leaks if resection anastomosis is done primarily. Early surgery includes aggressive resection of bowel and exteriorizing the bowel ends i.e., right hemicolectomy with ileostomy and mucus fistula. Hartmann’s procedure has been advocated by some in elderly toxic patients.

In conclusion, acute FNAC presenting as massive lower gastrointestinal bleed without significant antecedent diarrhea is an exceedingly rare complication of intestinal amebiasis. Pre-operative diagnosis is often difficult as stool testing is often negative and colonoscopy is suboptimal in view of active bleeding. High degree of clinical suspicion and timely operative intervention is critical in managing this life threatening condition.

References


Encephalitis Due to Dengue Virus Infection Mimicking Japanese B Encephalitis: Two Case Reports

Rathindranath Sarkar¹, Rudrajit Paul², Indranil Thakur², Ratul Ghosh⁴, Shyamaprasad Singh⁴, Avinash Mani⁴, Tanmay Jyoti Sau³, Goutam Lahiri⁶

Abstract

Dengue virus induced encephalitis is a very rare entity and its full clinicoradiological profile is still unknown. We here report two cases of dengue encephalitis from Eastern India. The first one is a 20 year old female and the second one is a 13 year old boy. Both of them presented with altered consciousness and seizures. Blood and CSF study for dengue IgM were positive. MRI of brain showed T2 hyperintensity in the Thalami along with similar changes in other parts of the brain. Both patients responded to conservative therapy but residual neurological deficit were variably present. Relevant literature pertaining to dengue encephalitis have also been discussed.

Introduction

Dengue virus is a vector-borne ssRNA flavivirus causing periodic epidemics in tropical countries. Especially in India, in the recent years, dengue infection has become quite common and has caused a number of outbreaks during the high mosquito breeding seasons. Also, in the recent years in India, along with these outbreaks, atypical features of dengue infection have become quite common. Dengue is not primarily known to be a neurotropic virus. But recently, a few cases of central nervous system affection in dengue infection have been reported. These neurotropic features may or may not coincide with the other more classical clinical features of the
laboratory tests revealed hemoglobin of 15.2 gm/dl (Hct.: 48), total leukocyte count (TLC) of 8000/cmm and platelet count of 130000/cmm. Blood urea and electrolytes were normal. HIV, Hepatitis B, C and CMV serologies were negative. Malaria antigen test was negative. Liver function test showed normal bilirubin with SGOT 120 IU/L and SGPT 98 IU/L. However, on the next day, repeat blood counts showed a platelet count of 70000/cmm. Then, a dengue NS1 test was done which was positive. RT-PCR from CSF for Japanese B virus was also positive. Dengue IgM from CSF was also positive. CSF RT-PCR for Jap-B and PCR for HSV were negative.

For this patient, the platelet count decreased only slightly up to 100000/cmm on the 5th day before recovering quickly. The haematocrit increased up to 50 on the 4th day. However, the unconscious state persisted for three weeks. The seizures were also difficult to control and required triple drug therapy with levetiracetam, sodium valproate and clobazam. After recovery, the patient had residual rigidity of lower limbs and occasional urinary incontinence. At two months’ follow up, these problems, along with memory loss, were persisting.

In both of these cases, actual dengue viral isolation from CSF could not be attempted due to lack of facilities. But based on the available test results, they were diagnosed as encephalitis due to virus. Hence, a high degree of clinical suspicion is needed to diagnose this rare complication of dengue. We here report two such rare manifestations from Eastern India.

The Case Reports

Case 1

A 20 year old female from Howrah, West Bengal presented with low grade fever for three days and altered consciousness for one day. She had no skin rash, body ache, joint pain or any symptoms pertaining to any other system. On examination, there was no neck rigidity, pupils were equally reactive and plantar responses were flexor. Blood pressure was 100/60 mm of Hg with pulse of 110/min. Her Glasgow coma scale score at admission was 11. Other systemic examinations were normal. After admission, an initial CT scan was normal and CSF study showed 12 cells/cmm (all mononuclear) with a protein level of 70 mg/dl (N: 15—45). She had three episodes of generalized tonic-clonic seizures (GTCS) after admission, which were controlled with levetiracetam. Initial laboratory tests revealed hemoglobin levels and CSF protein level of 90 mg/dl. His initial laboratory tests showed hemoglobin of 13 gm/dl (Hct.: 43), TLC 9000/cmm and platelet count of 130000/cmm. Urea, electrolytes, liver function test and viral serologies were all normal. Blood and urine culture were negative. After admission, the patient gradually developed high fever (102—104ºF) along with left sided focal seizures. Malaria antigen test was negative. MRI scan of brain showed hyperintensity in right thalamus and right fronto-parietal cortex. Both areas showed diffusion restriction. Blood for dengue IgM was sent which came positive. Dengue IgM from CSF was also positive. CSF RT-PCR for Jap-B and PCR for HSV were negative.

The patient was discharged after two weeks. Her only complaint then was profound fatigue. At 5 months’ follow up, there is no residual neurodeficit or memory impairment. But the generalized fatigue was still present and she was being maintained on levetiracetam.

Case 2

A 13 year old boy from Hooghli, West Bengal, presented with acute onset headache followed by unconsciousness for two days. He had no history of fever to start with but at the time of admission, he had a temperature of 100ºF. There was slight neck rigidity and rigidity of lower limbs at presentation. There was no bleeding manifestation. Blood pressure was 90/60 mm of Hg. There were no abnormalities in the other systems on examination. His GCS score was 6. Initial CSF study showed 50 cells/cmm (all mononuclear) with normal sugar, chloride and ADA levels and CSF protein level of 90 mg/dl. The affected areas showed marked hyperintensities in cerebellum. Both areas showed diffusion restriction. Blood for dengue IgM was sent which came positive. Dengue IgM from CSF was also positive. CSF RT-PCR for Jap-B and PCR for HSV were negative.

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dengue virus infection.

Discussion

Encephalopathy and/or encephalitis due to dengue virus infection are very rare. The presenting manifestations are protean and range from headache, drowsiness, neck rigidity, hyperreflexia to seizures and coma. These manifestations along with fever may occur in a number of conditions and hence, dengue virus and/or its serological identification from both blood and CSF are needed for confirmation. This neurological complication of dengue is more commonly reported in children and adolescents.

In a study from Vietnam, out of a series of patients with CNS infection, only about 4% were due to dengue. Thus, even in endemic regions, dengue is a rare cause of encephalitis. This rarity, along with lack of other typical clinical features, often delay the diagnosis. Out of those diagnosed with dengue encephalitis in the Vietnam study, 57% had no characteristic clinical feature of dengue at admission. In both of our cases too, the initial features of dengue like body ache, rash or high fever were absent. Thus, clinical diagnosis or even suspicion of dengue encephalitis is often delayed.

The pathogenesis of dengue induced cerebral dysfunction is still unknown. While dengue is primarily not a neurotropic virus, the isolation of the virus and its antibodies from CSF point to CNS invasion. Non-encephalitic causes of CNS dysfunction like liver failure, cerebral edema etc. are also important causes of altered consciousness in dengue infection. The outcome and long-term sequelae of dengue encephalitis are usually favourable with most authors reporting significant recovery. However, residual deficits, like our cases, are also seen.

Some viral encephalitic syndromes have characteristic MRI brain changes which can help in a presumptive diagnosis. In Japanese B encephalitis, the characteristic changes are T2 hyperintensities in thalami, basal ganglia and cerebellum. Since the entity of dengue encephalitis is a newly described intensity, the characteristic MRI changes have not yet been standardized. Some authors have described globus pallidus hyperintensity. Others have described JE-like hyper-intensity in thalami and cerebellum. In some cases, no changes were found. In our cases, we found thalamus involvement along with cerebellum in one and high parietal cortex in the other. Rarely, dengue encephalitis has been documented to cause extensive T2 hyperintensities in thalami, brainstem and cortical white matter. Thus, no particular region of the brain is preferentially involved.

Since Geographical locations like ours are endemic for both JE virus and dengue virus infection, such similarity in MRI changes may create a dilemma and viral isolation from the CNS remains the only way for differentiation. PCR or viral culture from CSF has better specificity. But for clinical purposes, such tests are not always available. Hence viral serology (IgM) from CSF is a good surrogate marker. Also, as our case shows, presence of raised haematocrit and/or low platelet count in a febrile encephalopathy should prompt a search for dengue infection.

Although both the viral infections have no definite treatment, but differentiation is important to prognosticate the patients. Clinical experience with dengue encephalitis is much less compared to JE. But dengue encephalitis has much better prognosis.

Conclusion

As dengue virus infection is becoming a wider public health problem in India, clinicians should be aware of the potentially serious neurological manifestations of the virus and its imaging similarity with Japanese encephalitis B.

References


Fig. 2: MRI brain for case 2 showing FLAIR hyperintensities in right thalamus and adjacent parietal cortex along with restriction of diffusion in the same regions (red arrow)
Abstract
Tumor induced osteomalacia (TIO) is a paraneoplastic syndrome which is mostly caused by a phosphaturic mesenchymal tumour mixed connective tissue variant (PMTMCT). These tumours do not have any specific site predilection but their presence in cranial compartment is very rare. Two cases of TIO secondary to phosphaturic mesenchymal tumour at the skull base are described ahead, one of which was in the posterior fossa and the other in middle cranial fossa. Early diagnosis and complete excision of PMT is essential in preventing morbidity secondary to osteomalacia. This case report stands distinct in highlighting a rare site of a phosphaturic mesenchymal tumour and the need to keep a high index of suspicion in cases of TIO especially wherein localization of the tumour is unsuccessful.

Case Summary 1
A 53-year-old female presented with longstanding history of bilateral hip and knee joint pain, along with low backache. Though she took symptomatic treatment for 5 years, she never had satisfactory relief. She had started developing proximal muscle weakness along with walking difficulty. Biochemical tests showed low level of serum phosphorus. Bone densitometry showed osteopenia and two MRI scans of bilateral hip joints done over a period of one year showed nonspecific osteoporotic changes and pathological fracture of neck of femur. Serum fibroblast growth factor-23 (FGF-23) level was 725 RU/ml, which was high compared to reference value of 180. High FGF-23 was suggestive of tumour induced osteomalacia but tumour was not evident on MRI of the neck, chest, abdomen and pelvis. To help in localization, a Somatostatin receptor positron emission tomography PET-CT scan was done and it revealed a tumour in the left jugular foramen region involving posterior skull base and part of occipital condyle (Figure 1). Contrast enhanced MRI of the brain showed an homogenously enhancing extraaxial tumor in the region of jugular bulb (Figure 2). Surgical excision of tumor was necessary to reverse the symptoms of osteopenia and in view of the subtle neurological deficits. Pre-operative embolisation of feeders from ascending pharyngeal and occipital artery was performed and surgical excision of tumor was carried out with retromastoid craniotomy. A completely extradural bony tumour was seen in the jugular region with occasional involvement of outer dural surface. Total excision of tumour was possible.

Histopathological examination revealed neoplastic tissue containing giant tumor cells composed of oval to short fusiform cells arranged in sheets and fascicles within a vascularised stroma. The neoplastic cells contained scant cytoplasm and uniform bland appearing nuclei. It also showed trabeculated osteoid and reactive fibroblast proliferation without evidence of sarcomatous change. Diagnosis of phosphaturic mesenchymal tumor of skull base was made.

Post-operative dynamic CT scan of cervico-vertebral junction showed no instability. Patient’s serum phosphorus level started improving. At last follow-up after 6 months, serum phosphorous was 2.7 mg/dl and FGF-23 levels were 135 RU/ml.
had normalized. Tumor and his serum phosphorus (2.1 mmol/L) remained normal. The patient did not have recurrence of symptoms. On 6 months follow up, the patient was well with no neurological deficit and was able to walk without assistance. PET CT scan showed a small osteopenic lesion at the base of middle cranial fossa. MRI scan revealed homogeneous enhancement on administration of gadolinium. It was isointense on T1 weighted images and hyperintense on T2 weighted images and revealed homogeneous enhancement on administration of contrast (Figure 3). CT scan showed erosion of petrous temporal bone adjacent to the tumor. Presumptive diagnosis of a bony tumor was made. Navigation guided craniotomy and tumor excision was performed to discriminate a functional tumor from a bony lesion. Selective venous sampling was done to rule out metastasis. Histological examination confirmed the diagnosis of PMT without sarcomatous change. On 6 months follow up, the patient did not have recurrence of symptoms and his serum phosphorus (2.1 mg/dl) and FGF-23 (215 RU/ml) levels had normalized.

Discussion

PMTMCTs are responsible for TIO. These tumors secrete FGF-23, which inhibits phosphate reabsorption from renal tubules. This leads to hypophosphatemia, reduced calcitriol production, impaired bone metabolism, osteomalacia and impaired healing of fractures. In contrast to Parathormone (PTH), it has no effect on calcium metabolism, its action is not blocked by a PTH antagonist, and its effects do not appear to be mediated by cyclic AMP. Often such patients have long history of nonspecific symptoms of bone pain, weakness, fatigue or pathological fracture due to osteomalacia. Diagnosis of PMT is often delayed. The 2 cases reported here too had long history of bilateral hip and knee joint pain. Old age and menopause were considered causative reasons for symptoms before detailed investigations lead to final diagnosis. The diagnosis of TIO should be suspected from the clinical picture of an acquired hypophosphatemia and osteomalacia/rickets in association with renal phosphate wasting, absence of proximal tubular defects and an inappropriately low plasma calcitriol concentration. Serum levels of FGF-23 are elevated in PMT [3]. However localisation of tumor is challenging. They are generally located in appendicular skeleton or sinonasal region. Intracranial location of PMTMCCT is uncommon [3, 4] and intracranial tumors are unlikely to manifest as paraneoplastic syndrome. Therefore cranial compartment is often excluded from screening for tumor localisation leading to delayed diagnosis.

Recent studies have tested and defined a systematic approach to tumor localisation in patients, in whom there was a failure of initial localization of the tumor or in cases wherein re-localization was needed viz. recurrence or metastases. A multimodality approach was employed. Functional imaging studies included whole body 111In-octreotide single photon emission computed tomography (SPECT) and, if necessary, whole body 18-fluorodeoxyglucose PET/CT and anatomic imaging i.e. CT, MRI. Selective venous sampling was performed to discriminate a functional mass when multiple suspicious lesions were discovered.

Mathis et al. reviewed intracranial PMTs and found that all 8 reported cases of intracranial PMT were in the anterior cranial fossa except one case where tumor was in cavernous sinus. No case report in present literature describes occurrence of PMT in posterior fossa. Histologically these tumors are of mesenchymal origin with or without aggressive sarcomatous change.

Intracranial PMTs are often confused with meningioma, hemangiopericytoma and esthesioneuroblastoma on imaging. They are often neurologically silent so correlation between tumor and osteomalacia should be established before surgery.

After surgical excision of tumour, serum phosphate levels should normalize within a week. Serum FGF-23 level rapidly falls down after excision of tumor however it does not normalize and achieves a level which is just above normal. Complete excision of PMTs is the treatment of choice whenever feasible. Stereotactic radiotherapy may represent a viable treatment option for patients who are not ideal candidates for surgery or refuse surgery. However the effects manifest in a delayed phase and the pros and cons of radiation must be taken into account prior to initiation.

Conclusion

Early diagnosis and complete excision of PMTs is necessary for avoiding morbidity effects of TIO. There has been a better understanding of this condition in recent years leading to fairly early diagnosis and effective treatment. Clinicians must be aware of cranial location of PMTs as well and should include skull base and brain imaging in evaluation of a patient with TIO.

References


Fig. 3: MRI showing tumor located in the middle cranial fossa and based on anterior surface of petrous part of temporal bone with homogeneous enhancement on administration of contrast.
DRESS Syndrome

Priyansh Jain¹, Sneha Garg¹, Vinod Kumar Sharma¹, Sanjiv Maheshwari²

Abstract
Carbamazepine was and still used extensively in clinical practice in varied indications can cause adverse drug reaction shaving diverse clinical manifestations of variable severity. “Drug Reaction with Eosinophilia and Systemic Symptoms” (DRESS) syndrome is a severe, potentially life-threatening, acute adverse drug reactions, typically characterized by a long latency period from drug exposure. DRESS syndrome is characterized by the presence of fever, coetaneous eruptions, lymphadenopathy, internal organ involvement (such as hepatitis, carditis, interstitial nephritis, interstitial pneumonitis, etc.) and haematological abnormalities, mainly leucocytosis, eosinophilia and sometimes atypical lymphocytosis.
We report a clinical case of DRESS syndrome with liver injury, evaluated with the RegiSCAR scoring system as a “definite case” possibly induced by carbamazepine in a patient.

Introduction
Carbamazepine is an iminostiblinderivativederivative chemically related to the tricyclic antidepressants synthesized in 1953 by Walter Schindler. It is still one of the most commonly used anti-epileptic even though newer antiepileptic drugs (AEDs) with good efficacy and tolerability are available. Varied incidence of adverse reactions to carbamazepine is reported from clinical studies.¹ Serious adverse reactions to carbamazepine affecting the hematopoietic system (aplastic anaemia, agranulocytosis), skin (Stevens-Johnson syndrome/ toxic epidermal necrolysis) and cardiovascular system (heart failure, rhythm disorders) have been observed. Cutaneous reactions induced by carbamazepine may have diverse clinical manifestations and variable severity.

The Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a severe, potentially life-threatening acute adverse drug reaction, typically characterized by a long latency period (2–6 weeks to 3 months) from drug exposure. The term was introduced by Bocquet et al in 1996.² This clinical entity has been previously described as “anticonvulsant hypersensitivity syndrome”, “drug-induced hypersensitivity syndrome”, “drug-induced delayed multi organ hypersensitivity syndrome”, or more simply “hypersensitivity syndrome”. Although few drugs including aromatic anticonvulsants (carbamazepine, phenytoin and phenobarbital), salazosulfapyridine, dapsone and minocycline have been more frequently associated with DRESS syndrome, reports on various groups of drugs blamed for inducing the syndrome have been emerging. DRESS syndrome is an immune mediated idiosyncratic reaction. Genetic predisposition, defective drug detoxification and accumulation of toxic metabolites and reactivation of herpes virus family have been proposed to be involved in the pathogenesis. Cutaneous eruptions, lymphadenopathy, symptomatic or asymptomatic internal organ involvement (for example hepatitis, carditis, interstitial nephritis, interstitial pneumonitis, etc.) and haematological abnormalities, mainly leucocytosis, eosinophilia and sometimes atypical lymphocytosis are the major clinical features. Each clinical feature may be of variable onset and degree, leading to confusion and delay in diagnosis.
Two sets of diagnostic criteria have been independently introduced by the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) study group³ and the Japanese consensus group to aid in the diagnosis and classification of suspected cases. Although rare, the syndrome may lead to potentially fatal consequences, reported in 10–50% of cases, hence, we report a case of DRESS syndrome.

Case Presentation
A 40 year old male was admitted to hospital with a history of generalised swelling all over the body and reddish discoulouration of skin associated with rashes for 2-3 days. The skin rash was accompanied by nausea, vomiting, fever up to 39.7 °C and Acetaminophen was taken as antipyretic. Approximately 2-3 months ago treatment with Carbamazepine for seizure disorder (? generalised tonic clonic seizures). The patient’s past, family, personal and drug histories were unremarkable.

Physical examination revealed a very weak pulse, with a non-recordable blood pressure, axillary temperature of 38.8 °C, liver span of 14 cm and generalized non tender lymphadenopathy. He had facial oedema, angular cheilitis and maculopapular exanthema progressing to exfoliative erythroderma. No clinical signs of herpes simplex infection provoked by fever were observed.

His ESR was 20 mm/1 hr., total leucocyte counts were 51.8 x 10⁹/L with lymphocytic predominance (47%) along with presence of atypical lymphocytes and moderate eosinophilia (11.5%). His routine biochemistry showed mild azotemia (blood urea – 91 mg/dl and serum creatinine – 1.4 mg/dl) and mild transaminitis (AST- 114 IU/L and ALT- 132 IU/L). His arterial blood gas analysis was unremarkable. Serological assays for hepatitis B and C virus, human immunodeficiency virus were negative. Antinuclear antibodies were also negative. Blood, urine and stool cultures were negative. Chest radiography and electrocardiography were normal. Abdominal ultrasonography showed hepatomegaly with normal echotexture.

Application of the RegiSCAR scoring system yielded a score of 8 and the clinical case was designated as a “definite case” of DRESS syndrome (Table 1). Carbamazepine was withdrawn immediately and patient was taken on sodium valproate.

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Received: 25.10.2018; Accepted: 22.122.2018
Enlarged lymph nodes

- No/U
- Yes

Eosinophils, if leukocytes <4000

- 10–19.9%
- ≥20%

Atypical lymphocytes

- No/U
- Eosinophils
- 700–1499/µL
- ≥1500/µL

Eosinophilia

- No/U
- 0
- 2

Skin involvement

- −2
- Yes

Rash extent (>50% BSA)

- No/U
- Yes

Rash suggesting DRESS

- No
- U
- Yes

Biopsy suggesting DRESS

- No
- U
- Yes/U

Organ involvement

- No/U
- 0
- 2

Liver

- Yes

Kidney

- Yes

Lung

- Yes

Muscle/heart

- Yes

Pancreas

- Yes

Other organ(s)

- No/U

Resolution ≥ 15 days

- No/U
- Yes
- −1
- 0

Evaluation other potential causes:

- Serological tests like ANA, HAV/HBV/HCV, Chlamydia, Mycoplasma, Blood culture, etc.
- Negative or Positive ≥ 3 of above

Final score:

- <2: No case
- 2–3: Possible case
- 4–5: Probable case
- >5: Definite case

U = unknown/unclassifiable

Table 1: Scoring system of RegiSCAR for diagnosing DRESS and case estimation

<table>
<thead>
<tr>
<th>Score</th>
<th>−1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥ 38.5°C</td>
<td>No/U</td>
<td>Yes</td>
<td>−1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarged lymph nodes</td>
<td>No/U</td>
<td>Yes</td>
<td>0</td>
<td>1</td>
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<td>Eosinophils, if leukocytes &lt;4000</td>
<td>700–1499/µL</td>
<td>≥1500/µL</td>
<td>10–19.9%</td>
<td>≥20%</td>
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<td>Atypical lymphocytes</td>
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<td>Skin involvement</td>
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<td>2</td>
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<td>Rash extent (&gt;50% BSA)</td>
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<td></td>
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<tr>
<td>Rash suggesting DRESS</td>
<td>No</td>
<td>U</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Biopsy suggesting DRESS</td>
<td>No</td>
<td>Yes/U</td>
<td></td>
<td></td>
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<td>Organ involvement*</td>
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<td>Muscle/heart</td>
<td>No/U</td>
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<td>Pancreas</td>
<td>No/U</td>
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<td>Other organ(s)</td>
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<td>Resolution ≥ 15 days</td>
<td>No/U</td>
<td>Yes</td>
<td>−1</td>
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</table>

Discussion

Persistence or even paradoxical aggravation of symptoms despite removal of offending drugs is a unique feature of DRESS syndrome, and strict monitoring of haematological and biochemical values was performed for the accurate management of DRESS syndrome. Patient improved and was discharged on 14th day along with a course of corticosteroids for 3 months duration with gradual tapering with regular follow ups which were unremarkable.

Carbamazepine follows a metabolic pathway common to all hydroxylated aromatic compounds. It is metabolized by the liver cytochrome P-450 (CYP) enzyme system with the formation of intermediate arene oxides, and the epoxide hydroxylase is responsible for detoxifying these metabolites. It is speculated that hereditary or acquired abnormalities in the production and/or defective metabolite detoxification in some individuals may predispose to DRESS syndrome. Arene oxides are capable of binding to cell macromolecules producing cell damage or a secondary immunologic response. Moreover, carbamazepine is an enzyme inducer and can induce its own metabolism with auto induction of CYP3 A4 and CYP B6. Reactivation of herpes virus infections and co-administration of other drugs may also be implicated in the liver and other organ involvement in DRESS syndrome. The viral serological studies carried out in our patient were negative. Patch testing and lymphocyte transformation test although useful but were not performed in our case because of not affordability. Results from various studies indicate that the test has high specificity but limited sensitivity. Patch testing following DRESS syndrome can be performed after careful evaluation of the risk-benefit ratio for the individual patient due to the possibility of reactivation of cutaneous lesions. The investigation of some genetic markers in drug hypersensitivity patients is a promising tool for their screening and safe evaluation. Recently, genotyping for HLA markers has found a strong association between HLA*31:01 and carbamazepine-induced DRESS syndrome in Europeans.

The reported case of carbamazepine-induced DRESS syndrome presents the difficulties in the etiological assessment and management of severe multi organ adverse drug reactions in poly morbid patients with poly pharmacy. Newly developed autoimmune diseases and permanent visceral organ failure have been observed in patients with DRESS syndrome after the acute stage with a reported incidence of 11.5%. Early recognition of DRESS syndrome is essential to prevent considerable morbidity and mortality. Aromatic anticonvulsants, especially carbamazepine are the commonest cause of DRESS syndrome. Patients on carbamazepine which is increasingly used as a mood stabilizer must be carefully monitored for adverse drug reactions including DRESS syndrome.

References

Cross-sensitivity of Levetiracetam and Carbamazepine Induced Skin Rash

Samhita Panda

Abstract

Antiepileptic drugs (AEDs) are fairly commonly associated with drug induced rash that can be mild to life threatening. Aromatic AEDs are often linked to these skin reactions unlike newer non-aromatic ones such as levetiracetam (LEV), lacosamide and zonisamide. Drug rash including drug-induced hypersensitivity syndrome is a rare complication of LEV use. We report a case of maculopapular skin rash due to LEV with cross-sensitivity with CBZ which has not been reported till date.

Introduction

Drug induced rash is a common adverse effect of antiepileptic drugs (AEDs).¹ The AED-induced skin reactions vary from benign urticaria, maculopapular eruptions and acute generalized exanthematous pustulosis to more life-threatening conditions like toxic epidermal necrolysis (TEN), Steven Johnson Syndrome (SJS) and drug reaction with systemic symptoms syndrome (DRESS).

Most of the skin reactions occur in relation to aromatic AEDs such as phenytoin (PHT), carbamazepine (CBZ) and phenobarbitone.²-⁴ While most implicated AEDs belong to the older generation, some of the newer ones such as oxcarbazepine (OXC) and lamotrigine (LTG) are also frequently linked to skin reactions. Compared to these, valproate (VPA), levetiracetam (LEV), lacosamide and zonisamide (ZSM) are rarely associated with skin related adverse events. Till date, there are only a few case reports of LEV-induced skin rash including DRESS.⁵-⁹ Here, a case of maculopapular skin rash, most probably an adverse effect related to LEV exposure with cross-sensitivity with CBZ is reported.

Case Report

A 35-year-old lady presented with two episodes of generalized tonic-clonic seizures 4 months apart. There was brief cephalic aura following which she had behavioural arrest, eye and head deviation to left and stiffness of body. Electroencephalograph showed intermittent diffuse cerebral dysrhythmia, more over the right hemisphere. Magnetic resonance imaging showed only asymmetric dilatation of right temporal horn without any evidence of mesial temporal sclerosis. She was initiated on CBZ with gradual up-titrination to dose of 600 mg per day. Apart from initial sedation, she did not have any recurrence of seizures. She reported after 8 weeks with slowly progressive maculopapular, pruritic rash over the body for 12 days. She had consulted a dermatologist 2 days prior to visit and had been suggested the possibility of CBZ-induced drug rash. On examination, there was a red, maculopapular rash over the face, neck, limbs and torso which was confluent at places (Figure 1). There were no pustules or lesions involving the mucosa, palms or soles. There was no periorbital or perioral edema. Abdomen was soft and no hepatosplenomegaly was noted. Chest examination was non-contributory. Complete blood count showed hemoglobin- 13.7 g/dl, total leucocyte count- 10,800/ cu mm and absolute eosinophil count- 326/µL (normal 100-1000/µL). The Naranjo score was 6. Considering a late-onset CBZ-induced drug rash, CBZ was stopped. She was treated with steroids, antihistaminics and topical steroids.

LEV was started in view of its relative safety. The rash subsided completely. However, she re-visited after 4 weeks with re-appearance of pruritic, maculopapular rash over limbs and face with desquamation of skin over the groin folds. No mucosal involvement or periorbital swelling was noted. The IgE level was 57 KIU/L (normal<150 KIU/L). Naranjo score was 7. Since the patient was on no other medication, LEV was implicated for the drug rash and early TEN. It was stopped and she was subsequently put on Clobazam on which she has remained seizure free for the past 3 years.

Discussion

Hypersensitive skin reactions to AEDs have been known since first reports by Silber et al in 1934.² The spectrum includes benign conditions such as urticaria, maculopapular eruptions and acute generalized exanthematous pustulosis, to serious dermatologic disorders namely SJS, TEN and DRESS or drug induced hypersensitivity syndrome (DIHS).³ TEN is characterized by erythema, bullous detachment and necrosis of the epidermis and mucous membranes, sepsis and even death. SJS is characterized by fever, flu-like symptoms, blistering and peeling of skin, sepsis, dehydration and multiple organ failure. SJS involves less than 10% of the body surface unlike TEN which involves more than 30%. DRESS or DIHS, first described with phenytoin and named by Bouquet comprises of rash, fever, swelling, eosinophilia and organ dysfunction effecting the liver, kidneys, heart or lungs. Compared to SJS and TEN, hypersensitivity syndrome has less remarkable mucosal involvement.¹ The mortality is 4% in SJS, 10% in DRESS and 30% in TEN.

Drug induced skin reactions occur in upto 10% patients on at least one AED.¹ ¹⁴ In a retrospective study on 300 patients with epilepsy, 95% of hypersensitive reactions occured with CBZ, PHT, LTG and OXC with 86% observed less than 3 months after initiation of medicines. Elderly patients and those of female gender had higher risk to develop drug reactions. Non-aromatic drugs such as VPA, LEV, vigabatrin and topiramate were rarely associated with skin rash.¹ Amongst the newer
AEDs, LTG is the exception with high incidence of drug hypersensitivity. Rarely, VPA co-medication with LTG may be a risk factor for drug rash due to the inhibition of uridine diphosphate glucuronyltransferase. The present case exemplifies the rare situation of LEV-induced generalized exanthema occurring as cross-sensitivity to CBZ. LEV is a pyrrolidine compound with unclear mechanism of action. It does not influence the voltage gated sodium channels, GABA mediated transmission or calcium currents. It may regulate exocytosis and neurotransmission by binding to the synaptic vesicle protein 2A in the synaptic plasma membranes in the central nervous system. It selectively prevents hyper-synchronization of epileptiform burst firing and propagation of seizure activity without affecting normal neuronal excitability.

Like valproic acid, LEV has low frequency of rash compared to PHT, CBZ, LTG and ZSM in a retrospective study on 15 AEDs. Only a few scattered case reports on LEV-induced rash are present in literature. Overall, only 0.8% of patients develop rash after LEV. On rare occasions, drug induced skin reactions have occurred after introducing LEV as a substitute for rash due to other AEDs. One patient, who had already experienced maculopapular skin rash with lamotrigine and phenytoin given sequentially, developed rash with angioedema after the first dose of LEV. Similar eruption of morbilliform, pruritic rash after LEV was noted in another patient who had previous rash due to combination of phentoin and oxcarbazepine. Our patient is the third such case demonstrating cross-sensitivity to another aromatic AED, i.e. carbamazepine. In a study of 3793 consecutive Chinese patients with epilepsy, 3.61% (137) developed rash and only 18 patients had rash to two or more AEDs. High rates of cross reaction was noted amongst aromatic AEDs, specifically CBZ and PHT, CBZ and LTG and CBZ and OXC unlike with LEV.

While most drug hypersensitivity syndromes are idiosyncratic and not dose related, some of the drug reactions have a genetic basis. As such, the increased risk of drug reaction may be informed to the first degree relatives. Once having a drug hypersensitivity, one should avoid other aromatic AEDs and opt for non-aromatic compounds. However, in rare circumstances as in our case, a safe option like LEV may produce such a hypersensitive exanthema. Desensitization by gradual dose escalation and using other alternatives such as clobazam and mast cell stabilizers may be done.

**Conclusion**

Levetiracetam with its unique mode of action in focal and generalized epilepsies is a major component of antiepileptic drug armamentarium which has been considered relatively safe compared to older AEDs. However, recent reports have shed light on adverse effects not previously documented. Drug rash is a rare complication of LEV use and substitution with LEV should be done slowly under supervision in patients who previously developed AED induced rash.

**References**


![Fig. 1: Maculopapular reddish exanthematous eruption over A. The limbs and B. Perioral regions, sparing mucosal membranes](image-url)
Female Genital Mutilation

Jayant Pai-Dhungat

WHO defines genital mutilation (FGM) as procedures that intentionally alter or cause injury to the female genital organs for non-medical reasons.

The procedure has no health benefits for girls or women. It involves removing and damaging healthy female genital tissue and interferes with natural functions of women’s bodies.

More than 200 million girls and women alive today have been cut in 30 countries in Africa, Middle East and Asia and also migrants from these countries. FGM is therefore a global concern. WHO has created more detailed Types I-IV and subtypes in classification which varies depending upon how much tissue is removed:

- **Type-I** FGM includes removal of the clitoral hood and glans (clitoridectomy).
- **Type-II** is removal of inner and outer labia.
- **Type-III** FGM includes closure of vulva (infabulation). This “sewn and closed” is known among Arabs as “Pharaonic” (infabulation) and *Sunna circumcision* and refer to the tradition of Muhammad. It should be noted that FGM practice in North Eastern Africa are pre-Islamic. Practice became associated with Islam because of its focus on female chastity and seclusion. It is not mentioned in Quran or in other religious scripts. In infabulation a small hole is left for the passage of urine and menstrual flow. Defibulation needs to cut open later to allow sexual intercourse and childbirth. Sometimes the women goes through repeated opening and closing procedures. Increasing immediate and long-term risks.

- **Type IV** FGM is other harmful procedures like piercing, incising and cauterization.

Immediate complications include, bleeding, infection, shock and death and at times tetanus. Long term consequences include UTI, bladder cysts, vaginal and menstruation problems, keloids, sexual problem, increased risk of child birth complications. There are scores of psychological problems resulting from FGM.

FGM is internationally recognized as violation of human rights of women. It reflects deep-rooted sexual inequality, and constitutes an extreme form of discrimination against women, attempting to control her sexuality. WHO strongly urges medical professionals not to perform FGM.

The reasons for genital mutilation vary from one region to another as well as over the time. Most commonly cited reasons for FGM are where it is a social norm; the pressure to confirm to what others do and have been doing, as well as fear of being rejected by the community, are strong motivations to perpetuate the practice.

FGM aims to ensure premarital virginity and marital fidelity, and help her resist extramarital sexual acts. It is associated with cultural ideals of femininity and modesty. Practitioners may not distinguish between religion, tradition and chastity making it difficult to interpret the data.

Since 1997, great efforts have been made to counteract FGM, through research, work within communities, and changes in public policy. WHO/UNICEF launched the first evidence based guidelines for management of health complications (May, 2016). Guidelines were developed based on systematic review of best available evidence on health interventions for women living with FGM.

Thankfully prevalence of FGM has now decreased in most countries. Research showed that if practicing communities themselves decide to abandon FGM, the practice can be eliminated very rapidly.
Physiotherapists as Public Health Promoters: Will it be Mirage or Legitimacy in India?

Sandul Yasobant, Satyajit Mohanty

Physiotherapists have been involved not only in clinical practices but also in preventive healthcare services. It has been recently realized that physiotherapists can make an important contribution to preventive health care through health promotion and screening. Different nations have utilized physiotherapists as skilled human resource in various ways, such as engaging in increasing movement ability, improving function and promoting physical fitness through physiotherapy works force in Israel or engaging in primary healthcare team in Ontario etc. Evidences suggest that physiotherapists usually practice health promotion activities less or more as of their normal routine activities such as assisting patients to increase physical activity, smoking cessation and cardiothoracic exercise advices and further also willing to act as health promoters if given a chance with appropriate training.

In India, there is no such legalized authorized government body nor council to monitor these budding professionals and many “Satyagrahas” currently going on to formulate a Physiotherapy Council. On other hand, the current National Health Policy 2017 also states lack of skilled human resources for effective implementation of national health programs. If given a chance; these skilled health professional (physiotherapists) could have engaged as public health promoters as one of the many stakeholders. It must advocate for its role by demonstrating to other health care providers, governments and policy makers how physiotherapy can contribute to the health promotion approach. It is also clear that current educational knowledge of Indian physiotherapists need to be improved by introducing a special module on “Health Promotion & Practices in Physiotherapy” in the course curriculum as done in Australia. Specific rules & regulations need to be developed in collaboration with national governing bodies to establish a clear cut guideline within their domains, for engaging physiotherapists in the field of health promotion.

In the last few decades, there has been a call for reorientation of health services towards health promotion and prevention. Furthermore linking of health promotion with physiotherapy could be one step in attaining this goal. Physiotherapists in education, practice, and research settings can participate in the advancement of health promotion not only to the mainstream but to the forefront of public health practices. Factually, physiotherapists have taught patients how to manage illness; however in the future, the focus must be on teaching people how to remain healthy, if the current health policy targets this issue. Physiotherapists must have an evidence-based understanding of the significant effect that can be made through health promotion interventions and communicate this understanding to the public at large. Thus, Physiotherapists could become role models in national perspective and should have confidence in addressing broader health issues.

Losartan Induced Acute Urticaria

Ankita Srivastava, AD Mathur

Losartan is an antihypertensive drug that belongs to the class of angiotensin receptor blockers (ARB). Earlier, it was supposed to be free from adverse effects like cough and angioneurotic oedema, that are commonly seen with angiotensin converting enzyme inhibitors (ACE-I). Later, however, few cases of angioedema, urticaria and anaphylaxis have been reported with losartan too. Losartan is a widely prescribed drug in India, however, losartan induced urticaria has rarely been reported from the Indian subcontinent. We therefore report this case of urticaria caused by losartan which was confirmed with oral rechallenge.

A 23 year old male patient presented to the dermatology OPD with complaints of generalized, reddish, itchy skin eruption for one day. He reported that he developed these lesions one hour after taking single tablet (first dose) of losartan that was prescribed by physician for hypertension. On examination, multiple, small-to-large wheals were present all over the body. There was no swelling around eyelids or lips. There was no difficulty in breathing, throat discomfort, pain abdomen, fever and cough. There was no wheezing, hypotension and mucosal involvement. Based upon the clinical signs and symptoms, a diagnosis of acute urticaria was made. Because of strong temporal association with intake of losartan, losartan was stopped and antihypertensive therapy was changed to amlodipine. Patient was started on oral steroids and antihistamines and recovered in one week.

Taking into consideration the rarity of losartan induced urticaria, absence of any life-threatening features and cardioprotective and renoprotective action of losartan, we decided to rechallenge the patient with losartan. An informed consent was taken, and patient was given 25 mg of losartan orally after i.v cannulation, keeping...
A Reversible Case of Chronic Arsenicosis due to Homeopathy Medicine

Jaydeep Majumdar1, Sarmishta Mukhopadhyay2, Akhilesh Chandraker3, Sarbani Sengupta4, Bhaskar Ghosh5
1Post Graduate Trainee, General Medicine, 2Endocrinologist and Physician, Senior Divisional Medical Officer, 3Rheumatologist and Physician, Additional Chief Health Director, 4Neurologist, Additional Chief Health Director, BR Singh Hospital and Center for Medical Education and Research, Kolkata, West Bengal

Sir,

A 44 year old lady, homemaker, residing in south 24 parganas district of West Bengal presented with generalised weakness, weight loss, intermittent diffuse pain abdomen, anorexia, nausea, off and on diarrhoea for eight months. She also noticed darkening of her complexion for six months. Since last 4 months, she had intermittent headache of varying duration, frequency and intensity with tingling and numbness of all four limbs. She was normotensive, non-diabetic without any other significant co-morbidities. She was a non-vegetarian without any history of substance abuse. Her past medical records revealed that she was a patient of chronic anxiety disorder for which she was treated by homeopathy medicine.

On clinical examination she was found to be thin built (BMI-21 kg/m²) with mild pallor, bilateral pitting pedal edema with stable vitals. There was diffuse hyperpigmentation of whole body with painless non-itchy brownish spotty rain drop like pigmentation over face, particularly forehead and also in trunk. There was also hyperpigmentation and hyperkeratosis of the palms but not soles. Neurological examination showed (Figure 1) preserved higher mental function, bilateral papilledema showing (Figure 1) preserved higher mental function, bilateral papilledema and bilateral flexor planter response. Gastrointestinal examination revealed non-tender enlarged liver with 16 cm span, mild splenomegaly and mild

References

ascites. Other system examination were non-contributory.

Investigations showed mild microcytic hypochromic anaemia (Hb-9.2 g/dl, MCV-78 fl, MCH-26 pg, MCHC-31.3 g/dl), low serum iron (27.5 mcg/dl), low TIBC (84.4 mcg/dl), high serum ferritin (808.6 ng/ml), raised transaminases (AST-40 IU/L, ALT-98 IU/L), low serum total protein (4.6 g/dl), low serum albumin (1.9 g/dl), globulin (2.7 g/dl) and raised alkaline phosphatase (789 IU/L).

All other haematological and biochemical reports are normal. Serological tests including HBsAg, anti HCV, HIV and VDRL were negative. Serum ceruloplasmin, tissue transglutaminase, autoimmune hepatitis profile (ANA, ASMA, LKM-1) were normal. Hormonal profile including TSH (2.23 μIU/ml) and serum cortisol (18.77 μg/dl) were normal.

USG abdomen showed enlarged liver with altered echogenicity. Ascitic fluid examination revealed high SAAG ascites. Fundus photography was suggestive of papilledema with evidence of haemorrhage. MRI brain, MR angiography and MR venography of brain were normal. CSF study was within normal limit. Upper GI endoscopy with biopsy of second part of duodenum was suggestive of non-specific duodenitis. Nerve conduction velocity of all four limbs was suggestive of sensorimotor neuropathy.

Unexplained, apparently unrelated multi-system involvement including chronic diarrhoea, presence of liver disease, peripheral neuropathy, idiopathic intracranial hypertension (pseudotumor cerebri) and characteristic skin lesions suggested chronic arsenicosis. Arsenic level in hair was found to be 1.06 μg/g (N=0.02-0.2 μg/g) and arsenic level in nail was 1.24 μg/g (N=0.02-0.5 μg/g) with normal arsenic content (0.03 mg/l) of the drinking water of the locality.

History was revisited and thorough scrutiny of past medical records revealed that the patient was taking arsenicum album for her anxiety depressive disorder for last one year. The drug was discontinued. Six months later the patient came back with disappearance of all skin lesions, reversal of features of neuropathy, subsidence of diarrhoea, marked improvement of papilledema and normalization of altered liver function along with disappearance of ascites.

Arsenic toxicity from improper use of homeopathy medicine is reported in literature. Pseudotumor cerebri due to arsenic therapy in acute promyelocytic leukemia is also reported. Learning point is that apparently harmless homeopathy medicine may cause multi-system involvement. It emphasizes the importance of drug history in clinical medicine. Reversal of symptoms and signs after drug withdrawal is the greatest proof and most rewarding.

Conclusion

Meticulous history taking and thorough scrutiny of past medical records is often helpful in reaching diagnosis to especially multisystem disorders. Many popular and herbal medications contain heavy metals which should be taken into consideration while taking drug history of the patient. Clinicians must consider these drugs apart from potable water as a potential source of arsenic poisoning.

References

Elections of API, ICP and PRF

(Full details circular No. 1 & 2/2019)

Election for Governing Body of API, Faculty Council of ICP and Board of PRF are announced for following posts:-

**Governing Body of API:**
- President-Elect: One; Vice President: One; Hon. Treasurer: One; Elected Members: Six and Zonal members eight (one from each zone)

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

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

Separate nominations must be submitted for each post.

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

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

**Requirements for eligibility for the contests of**

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

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

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

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

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

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

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

Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 31st May 2019. For every post on the Governing Body / Faculty Council / Board of PRF, the nomination must be accompanied by a sum of Rs. 2,950/- (Rupees two thousand five hundred only) non refundable in the form of Demand Draft payable at Mumbai. The nomination paper NOT accompanied by the Bank Draft of Rs. 2,950/- will be deemed invalid.

**Important**

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

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

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

**DEAD LINES OF ELECTION PROCEDURE**

- Last date to receive the nomination at API Office: 31st May 2019
- Last date for withdrawal: 20th June 2019
- Last date to receive ballot papers at API Office: 31st August 2019

The full API circular No. 2/2019, ICP circular No. 1/2019 and Board of PRF 1/2019 are on API and JAPI website

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

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

5.2.1.1 Minimum experience of 10 years after Post Graduation.

5.2.1.2 Continuous membership of the Association of Physicians of India for not less than 7 yrs.

5.2.1.3 Should have made a significant contribution to research / teaching / development in the field of medicine.

5.2.1.4 Should have contributed to API by way of scientific or Organizational works.

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

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

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

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

- The Proposer / Seconder should not propose / second more than 3 nominees for award of ICP in a particular year.
- It is responsibility of the Nominee / applicant to get the proposal completed by the proposer and seconder along with the citation.
- API Membership No. of the proposer / seconder should be entered by the proposer / seconder themselves.
- The proposer should satisfy the requirements for proposal as under:-
  - The Nominee is a life member of API
  - The Nominee has completed 10 years after post-graduation
- The Nominee should read the Form carefully before filling the columns, to project their achievements appropriately.
- The Nominee should list their achievements in appropriate columns.
- Proof of qualifications, publications, honours, awards, must be submitted as supporting data. The supporting data should be numbered parwise (eg 1., 2., 3., etc). For more than one supporting documents, the numbering should be in alphabets (eg 1 (a), (b), (c), etc).
- No hand written applications will be accepted.
- One original and seven Xerox copies to be submitted
- Last date for receiving application form is 31st May, 2019.

Dr. Mangesh Tiwaskar
Hon. General Secretary

Dr. A.M. Bhagwati
Jt. Secretary

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

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

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

3. **Date of Birth**

4. **Address Residence**

5. **Address Office**

6. **Tel.:**

7. **Fax:**

8. **Mobile**

9. **E-mail:**

10. **Postgraduate degree in Medicine**

11. **Year of passing**

12. **Institute**

13. **University**

14. **Other Professional Qualifications**

15. **Year**

16. **Speciality / Subjects**

17. **University / Institute**

18. **Certificates Attached**

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

20. **Name of Hospital / Clinic / Organisation & Location**

21. **Number of Beds (if applicable)**

22. **Period Served year wise (From-To)**

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

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

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

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

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

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

   b) **Organisation**

   c) **Year**

   d) **Attach title page / Abstract as Appendix**
9. **Research work** (list below)

<table>
<thead>
<tr>
<th>Title of Award</th>
<th>Organisation</th>
<th>Year</th>
</tr>
</thead>
</table>

(a) Research sanctioned & funded by Research Agency

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

Attach Letter of sanction.

Attach title page / Abstract

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

<table>
<thead>
<tr>
<th>Post held in Organisation / Meeting</th>
<th>Name of Organisation / Meeting / CME</th>
<th>National / Zonal / Under API/ICP</th>
<th>Year</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Speaker / Chairperson / Other</th>
<th>Title of Talk / Session</th>
<th>Name of Meeting</th>
<th>Year</th>
</tr>
</thead>
</table>

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

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

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

(c) Service in Rural Areas

<table>
<thead>
<tr>
<th>Service</th>
<th>Evidence</th>
</tr>
</thead>
</table>

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

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

Last date for receiving the application form is 31st May 2019.

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

Citation

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

Name ____________________________________________  Name ____________________________________________

Membership No. ________________________________  Membership No. ________________________________

Signature Proposer __________________________________  Signature Seconder ________________________________

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