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Non Compressive Myelopathies

Satish Khadilkar¹, Madhu Bala Singla¹, Sunila Jaggi²

Introduction

Medical myelopathies can lead to disabilities and reduction of quality of life rapidly and profoundly, often in the prime time of life. Hence the physician has to be up to date with the current knowledge of these disorders. Various studies on non-compressive myelopathies are available from India. Those undertaken before the MRI era¹² have discussed nutritional and infectious causes. Investigative facilities have now improved in India and newer studies are needed to redefine the profile of various aetiologies of non-compressive myelopathies in the Indian setting. The manuscript entitled “Etiological spectrum of non-compressive myelopathies in a tertiary care centre” by Kamble et al³ in this issue of JAPI is timely in this regard.

Clinical Syndromes

Non compressive myelopathies are clinically characterised by patterns of selective involvement of different anatomical structures of the spinal cord and these patterns help the etiological diagnosis. Some of the classical syndromes with their commonest causes are as follows. Complete spinal cord syndrome (eg. transverse myelitis), Brown Sequard syndrome (eg. multiple sclerosis), anterior spinal cord syndrome (eg. anterior spinal artery infarct), posterolateral cord syndrome (eg. vitamin B12 deficiency), central cord syndrome (eg. neuromyelitis optica), posterior syndrome (eg. posterior spinal artery infarct and tractopathies (eg. primary lateral sclerosis).

Aetiology

Causative factors of non-compressive myelopathies could be broadly grouped in inflammatory and non-inflammatory causes. In the inflammatory group, transverse myelitis is an important and a common cause.⁴ The other causes are infectious, demyelinating and vasculitic diseases. The non-inflammatory groups are of vascular, toxins and physical agents, degenerative, metabolic and inherited myelopathies.

In various studies on non-compressive myelopathies, the etiological spectra have varied according to populations studied and also in the time frame. In the more recent studies, the numbers of idiopathic cases are decreasing with discovery of new tests and better resolution of neuroimaging. In the western literature,
fluid (CSF) to differentiate between inflammatory and non-inflammatory aetiologies, as their treatment modalities are different. If there is evidence of inflammation, the next step is to search for the cause of inflammation as it can be due to demyelination, infectious and secondary to systemic immune conditions. Hence, further inquiry into history should be undertaken as mentioned in the algorithm before proceeding further and rest of the workup can be planned according to associated features pointing to demyelination, infections and systemic immune conditions. When no evidence of inflammation exists, consider non-inflammatory aetiologies like vascular, radiation, metabolic, inherited etc.

Imaging features should be carefully studied and these may point to some specific aetiologies and aid in planning further work up.

Role of Neuroimaging

Imaging has now become a vital and integral part of the work up of non-compressive myelopathies. The modalities include magnetic resonance imaging, digital subtraction imaging, etc. The imaging findings of some common aetiologies are shown in Fig. 1.

**Diagnostic Evaluation**

Evaluation of a patient with symptoms of myelopathy requires a comprehensive approach as the list of causes is huge. An algorithmic approach could be utilized (Algorithm 1). The first step is to perform an MRI of the spine to rule out a compressive aetiology which may need urgent intervention. Once compression is excluded, the next step is to confirm the evidence of inflammation by MRI spine contrast study and cerebrospinal fluid (CSF) to differentiate between inflammatory and non-inflammatory aetiologies, as their treatment modalities are different. If there is evidence of inflammation, the next step is to search for the cause of inflammation as it can be due to demyelination, infectious and secondary to systemic immune conditions. Hence, further inquiry into history should be undertaken as mentioned in the algorithm before proceeding further and rest of the workup can be planned according to associated features pointing to demyelination, infections and systemic immune conditions. When no evidence of inflammation exists, consider non-inflammatory aetiologies like vascular, radiation, metabolic, inherited etc.

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**Role of Neuroimaging**

Imaging has now become a vital and integral part of the work up of non-compressive myelopathies. The modalities include magnetic resonance imaging, digital subtraction imaging, etc. The imaging findings of some common aetiologies are shown in Fig. 1.
angiography and sometimes the computerized myelography. Various specific imaging characteristics of cord lesions have been documented in different conditions which help in narrowing the diagnostic possibilities and at times give an accurate diagnosis as mentioned in Algorithm 1. In addition, persistent enhancement of cord lesion for more than 2 months with dorsal subpial and central canal enhancement (Tridet sign) is seen in neurosarcoidosis. Surprisingly, Kamble and colleagues report that both their multiple sclerosis patients had long segment lesions. This is distinctly unusual and calls for more diagnostic scrutiny of such patients.

Conclusions

As can been seen from the above discussion, a wide variety of diseases present with non-compressive myelopathies. A detailed history and clinical examination coupled with the appropriate work up can lead to the final diagnosis in majority of cases. Neuroradiology and serological markers have increased our diagnostic accuracy. The study by Kamble et al is important as provides the current spectrum of non-compressive myelopathies in Kota region. More studies are needed to define the pattern of existing and newly recognised conditions like the Myelin oligodendrocyte antibody (MOG) syndrome in India. Regional as well as multicentric national studies are clearly required to elucidate the prevalence of various aetiological subsets in India.

References

Etiological Spectrum of Non-compressive Myelopathies in Tertiary Care Centre

Sumit Kamble1*, Vijay Sardana2, Dilip Maheshwari3, Bharat Bhushan3, Piyush Ojha1

Abstract
Aims: To study the clinical, radiological, cerebrospinal fluid profile of non-compressive myelopathy and to study various etiologies of non-compressive myelopathies in causation of quadriplegia and paraplegia.

Study Design: Observational study.

Place and Duration of Study: Department of Neurology, Govt. Medical College, Kota in year 2015 and 2016.

Methodology: All the patients presented with myelopathy and MRI spine not showing any significant compression included in study. To know the etiology of non-compressive myelopathy patients were investigated including routine blood tests, cerebrospinal fluid analysis and visual evoked potentials, MRI of the brain, and immunological, infectious, and metabolic profile based on the pattern of involvement.

Results: The study had 80 patients with a median age of 38 years and male: female ratio 1.5:1. Patients were divided into acute myelopathy and chronic myelopathy. Forty four patients presented with acute myelopathy whereas 36 patients had chronic myelopathy. The causes of Acute myelopathy were post infectious myelitis (13), neuromyelitis optica spectrum disorder (NMOSD) (6), multiple sclerosis (MS) (2), connective tissue disorders (1), acute disseminated encephalomyelitis (4) and idiopathic (18). The causes of Chronic myelopathy were Vitamin B12 deficiency (8), MS (2), mixed connective tissue disease (1), Copper deficiency (1), hepatic myelopathy (1), radiation (1), hereditary spastic para/spastic myelopathy (1) and idiopathic (21).

Conclusion: Underlying etiology like demyelinating, infectious/post infectious, autoimmune or nutritional was found in 52% patients of non-compressive myelopathy.

INTRODUCTION
Non-compressive myelopathy have varied etiology ranging from infectious, nutritional, demyelinating, toxic, heredo-familial to degenerative conditions. The causative etiology is somewhat different in India as compared to the western countries. In India infectious, para-infectious and nutritional causes predominate over demyelinating and hereditary causes. There are multiple studies on the etiological spectrum of non-compressive myelopathies in past, however there has been only few Indian study post era of newer diagnostic criteria and post discovery of neuromyelitis optica (NMO) spectrum disorders. The previous studies from India were carried when serological test for NMO was not available1,2. This study was carried out in an attempt to determine the etiological spectrum of non-compressive myelopathies in a tertiary care hospital.

Material and Method
It was an observational study carried out in the Department of Neurology, Government Medical College, Kota, from January 2015 to December 2016, and the data were collected prospectively. The study was aimed to determine the causes of non-compressive myelopathies, and to study the clinical and radiological features of non-compressive myelopathies.

Patients presenting with acute or chronic paraparesis or quadriplegia consistent with myelopathy (with or without coexisting neuropathy, radiculopathy or encephalopathy,) were included in the study. Patients were excluded from the study if (a) Magnetic resonance imaging (MRI) of spine showing spinal cord compression explaining patient’s neurologic dysfunction, (b) Patients of myelopathy who did not undergo MRI of the spinal Cord or did not give consent (c) diagnosis consistent with motor neuron disease (MND) and (e) degenerative Cerebellar ataxias associated myelopathy. All the Patients were evaluated clinically including onset, duration, and progression of neurological symptoms and history related to any clue to etiology of myelopathy like history suggestive of connective tissue disorders, toxin, high risk behavior or malignancy or treatment of malignancy. Patients were also looked for evidence of systemic disease or malignancy in the general and systemic examinations.

All patients underwent relevant routine biochemical analysis including complete hemogram, liver function tests, renal function tests serum electrolytes, thyroid profile, urinalysis and appropriate neuroimaging studies were carried out in all the patients. All cases with no obvious clinically significant compression visible on MRI which can explain the symptoms underwent further investigations which included serum HIV, VDRL, ESR, X-ray chest, collagen disease profile (ANA, RA factor, anti-dsDNA, and ant phospholipid antibody).

*Senior Resident, †Senior Professor & Head, ‡Associate Professor, Department of Neurology, Government Medical College, Kota, Rajasthan; †Corresponding Author
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Venereal disease research laboratory

polymerase chain reaction (PCR) and oligoclonal bands (OCBs); viral, immunoglobulin G (IgG) index and further CSF investigations like ADA differential counts, protein, and sugar.

Fluid (CSF) analysis included routine using 1.5 Tesla MRI. Cerebrospinal potentials (VEPs). MRI was done (AQP4 - IgG) and visual evoked levels, antibody against aquaporin-4 (NMO spectrum disorder (NMOSD) was based on 2010 Revised McDonald Criteria. NMO spectrum disorder (NMOSD) was diagnosed based on 2015 International Panel for NMO Diagnosis criteria.²

Results

Eighty patients with diagnosis of non-compressive myelopathy were included in study, out of which 48 were male and 32 were females with male: female ratio 1.5:1. Mean age of study population was 38 years. Demographic and clinical profile of 80 patients summarized in Table 1.

Acute-subacute myelopathy was diagnosed in 44 (55%) patients. The median age was 33 years (range, 6–65 years). The common causes were NMOSD, multiple sclerosis (MS), connective tissue disorders, post infectious myelitis, acute disseminated encephalomyelitis (Table 2). No etiology was found in 17/44 (36.36%) patients. Other diagnostic criteria’s like for NMOSD diagnostic criteria and Revised McDonald Criteria.

A non-compressive myelopathy usually affects patients in the prime of their life. In our study median age of the study population was 38 years, with slight male predominance with male: female ratio 1.5:1. Similar results were seen in previous studies done in India like Prabhakar et.al.² which had mean age of 34 years.

In previous studied done in India, the most common cause of non compressive myelopathy was Acute transverse myelitis (ATM). In study from eastern India by Das et. al. had 82 patients enrolled between July 1994 and June 1996,¹ the most common cause of non-compressive myelopathy was ATM 24 (29.3%), and etiology was not found in 23 (28.0%) patients. In another study from North India by Prabhakar et.al., the most common cause of non-compressive myelopathy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (60%)</td>
</tr>
<tr>
<td>Female</td>
<td>32 (40%)</td>
</tr>
<tr>
<td>Motor manifestations</td>
<td></td>
</tr>
<tr>
<td>Quadriaparesis</td>
<td>54 (67.5%)</td>
</tr>
<tr>
<td>Paraparesis</td>
<td>24 (30%)</td>
</tr>
<tr>
<td>Bilobal weakness</td>
<td>1 (1.25%)</td>
</tr>
<tr>
<td>Monoparesis</td>
<td>1 (1.25%)</td>
</tr>
<tr>
<td>Sphincter involvement</td>
<td>52 (65%)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>9 (11.25%)</td>
</tr>
<tr>
<td>Optic neuritis/atrophy</td>
<td>3 (3.75%)</td>
</tr>
<tr>
<td>Type of myelopathy</td>
<td></td>
</tr>
<tr>
<td>Acute-Subacute</td>
<td>44 (55%)</td>
</tr>
<tr>
<td>Chronic</td>
<td>36 (45%)</td>
</tr>
<tr>
<td>Relapsing myelopathy</td>
<td>3 (3.75%)</td>
</tr>
<tr>
<td>Symmetrical</td>
<td>63 (78.75%)</td>
</tr>
<tr>
<td>Asymmetrical</td>
<td>17(21.25%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Etiology of acute to subacute myelopathy(n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
</tr>
<tr>
<td>NMOSD</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
</tr>
<tr>
<td>Infectious/post infectious myelitis</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3: Imaging and cerebrospinal fluid profile of acute-to-subacute myelopathy</th>
</tr>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>MRI</td>
</tr>
<tr>
<td>LEM</td>
</tr>
<tr>
<td>No signal change</td>
</tr>
<tr>
<td>CSF</td>
</tr>
<tr>
<td>Protein &gt;45 mg/dL</td>
</tr>
<tr>
<td>OCBs</td>
</tr>
</tbody>
</table>

(VDRL) test were done depending upon clinical scenario. Ultrasound abdomen and computerized tomography scans of thorax and abdomen were done in patients suspected to have systemic disease or malignancy.

Case Definitions

Myelopathy can cause considerable morbidity due to either paraparesis or quadriaparesis. Many studies are done in the past in India about etiological spectrum of non-compressive myelopathy however only few studies are done after the discovery of aquaporin-4 antibodies and after newer proposed diagnostic criteria’s like for NMOSD diagnostic criteria and Revised McDonald Criteria.

Discussion

serum vitamin B12 level, copper level, angiotensin converting enzyme (ACE) levels, antibody against aquaporin-4 (AQP4-IgG) and visual evoked potentials (VEPs). MRI was done using 1.5 Tesla MRI. Cerebrospinal fluid (CSF) analysis included routine investigations like total count, differential counts, protein, and sugar. Further CSF investigations like ADA, immunoglobulin G (IgG) index and oligoclonal bands (OCBs); viral polymerase chain reaction (PCR) and venereal disease research laboratory

Table 1: Clinical and demographic profile (n=80)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
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</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (60%)</td>
</tr>
<tr>
<td>Female</td>
<td>32 (40%)</td>
</tr>
<tr>
<td>Motor manifestations</td>
<td></td>
</tr>
<tr>
<td>Quadriaparesis</td>
<td>54 (67.5%)</td>
</tr>
<tr>
<td>Paraparesis</td>
<td>24 (30%)</td>
</tr>
<tr>
<td>Bilobal weakness</td>
<td>1 (1.25%)</td>
</tr>
<tr>
<td>Monoparesis</td>
<td>1 (1.25%)</td>
</tr>
<tr>
<td>Sphincter involvement</td>
<td>52 (65%)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>9 (11.25%)</td>
</tr>
<tr>
<td>Optic neuritis/atrophy</td>
<td>3 (3.75%)</td>
</tr>
<tr>
<td>Type of myelopathy</td>
<td></td>
</tr>
<tr>
<td>Acute-Subacute</td>
<td>44 (55%)</td>
</tr>
<tr>
<td>Chronic</td>
<td>36 (45%)</td>
</tr>
<tr>
<td>Relapsing myelopathy</td>
<td>3 (3.75%)</td>
</tr>
<tr>
<td>Symmetrical</td>
<td>63 (78.75%)</td>
</tr>
<tr>
<td>Asymmetrical</td>
<td>17(21.25%)</td>
</tr>
</tbody>
</table>

Table 4: Etiology of chronic myelopathy (n=36)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>2(5.5%)</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
<td>8(22.2%)</td>
</tr>
<tr>
<td>Copper deficiency</td>
<td>1(2.7%)</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>1(2.7%)</td>
</tr>
<tr>
<td>Hepatic myelopathy</td>
<td>1(2.7%)</td>
</tr>
<tr>
<td>Radiation</td>
<td>1(2.7%)</td>
</tr>
<tr>
<td>Hereditary spastic paraparesis</td>
<td>1(2.7%)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>21(58.3%)</td>
</tr>
</tbody>
</table>
were ATM (54.4%) and B12 deficiency. However these studies were done before serological test for AQP4-IgG was available. Some of these cases could have been MS or NMOSD. According to Transverse myelitis consortium working group (TMWG), ATM is classified according to Idiopathic and secondary to diseases like MS, NMOSD and connective tissue disorders. So in our study rather than making broad diagnosis of ATM, patients were classified according to etiology of ATM, because treatment and prognosis differ according to etiology of ATM.

In our study patient was diagnosed as post-infectious ATM if had a clear history of febrile illness within 30 days preceding onset of myelitis. Serological test for infection were done according to history of febrile illness. All serological tests could not be done for all infections due to financial limitation. Most common infection preceding ATM in our study was Dengue infection, which was seen in 8/13 post infectious ATM. This patient had preceding Chikungunya infection. In others exact etiological infection could not be found out in 4/13(30.76%) patients. In study done by Marchioni et al. specific serological evidence of infection was found only in 5.7% patients in post infectious neurologic syndromes.

NMOSD was seen in 6/44 patients with acute to subacute myelopathy. It was most common cause of LETM (6/14, 42.8%). The median age of presentation of NMOSD was 36 years with strong female preponderance (5/6). Most common location of myelitis was cervico-dorsal cord (100%). In retrospective Indian study of 44 patients with NMOSD, the most common location of myelitis was cervico-dorsal cord (77.5%) like seen in our study, however the median age of presentation was 26.5 years. Post discovery of aquaporin-4 antibodies, a multicenter study done in 288 patients showed the common causes of acute non compressive myelopathy were NMO (17.0%), MS (10.8%), and para infectious (17.3%). Etiology was not found in 45 (15.6%). So post discovery of aquaporin 4 antibodies, more and more patients who were previously diagnosed as idiopathic or remained undiagnosed are now being diagnosed as NMOSD and MS.

In our study, the most common cause of chronic non compressive myelopathy was Vitamin B12 deficiency. The common causes of Vitamin B12 deficiency in our patients were secondary to strict vegetarian diet, alcohol consumption and malnutrition and. Antiparietal antibody could not be done due to financial reasons. The most common type of presentation of Vitamin B12 deficiency was Myeloneuropathy. T2 hyperintense signal of cord were seen in 3/8 patients and were most commonly located to posterior and lateral column in both cervical and thoracic region. Most common cause of Vitamin deficiency was pernicious anemia in study of 143 patients of Vitamin deficiency was pernicious anemia in study of 143 patients. Vitamin deficiency may be dietary insufficiency. Other causes of chronic myelopathy were primary progressive MS, hepatic myelopathy, copper deficiency, radiation and Hereditary spastic paraparesis, however majority of chronic myelopathies were idiopathic.

**Conclusion**

This study showed that non-compressive myelopathy primarily affects patients in third to fourth decade of life. Patients are in there prime of life and are predominately earning members of family. Various causes of non-compressive myelopathy were found in 52% of patients; however etiology remained undiagnosed in 48% of patients. The common cause of acute to sub-acute myelopathy includes post infectious myelitis, NMOSD and MS whereas most common cause of chronic myelopathy was Vitamin B12 deficiency. Etiology could not be found out in 48% patients, however paraneoplastic panel, antibodies against myelinoligodendrocyte glycoprotein (anti-MOG) and complete infectious panel were not done in patients and there was no long term follow up, as some etiologies could have been found out on follow up. The study help us to understand better the etiological spectrum of non-compressive myelopathy.

**References**

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Outcome of HIV Related Kidney Diseases Treated with Combined Antiretroviral Therapy (cART)

Jai Prakash¹, Mohd. Iqbal²*, Prem Shankar Patel², Suraj Prakash³, Shyam Sundar⁴, Usha Singh⁵

Abstract

Introduction: The safe and effective treatment of HIV-associated renal diseases with cART can decrease the progression to ESRD and also improve the morbidity and mortality secondary to renal failure.

Material and Methods: HIV positive patients with clinical kidney disease were the subjects of this study. The diagnosis of HIV was established using immunochromatographic assays. The patients were subjected to meticulous history, physical examination, laboratory investigations and kidney biopsy. Patients were treated with combined antiretroviral therapy and enalapril. They were followed at 3 months interval for one year. Short term outcome was assessed using changes in serum creatinine and proteinuria. Long term outcome assessments were done using progression to end stage renal disease and patients survival.

Result: Ten (Male=7; Female=3) HIV patients with clinical renal disease were included in this study. Their age ranged between 26-55 (Mean=40.5±8.8) years. The mean serum creatinine at the baseline, three, six, nine and twelve months was 2.46, 2.09, 2.43, 2.46 and 2.58 mg/dl respectively. The mean e-GFR by MDRD equation at 0, 3, 6, 9 and 12 months was 40.9, 45.5, 48.2, 51.1 and 52.5 ml/min/1.73m² respectively. The mean twenty four hour urinary protein excretion at 0, 3, 6, 9 and 12 months was 3.01, 2.82, 2.22, 2.02 and 1.79 grams respectively. Six patients showed improvement in creatinine and e-GFR, whereas worsening of renal function was seen in four patients. Proteinuria decreased in seven patients, whereas it remained unchanged in three patients. There was no mortality at the end of one year of follow up.

Conclusion: Treatment with combined ART and ACEIs slows the progression of HIV-associated kidney disease, decreases proteinuria and improves the GFR.
meticulous history and physical examination. The laboratory investigations included urine analysis, 24 hour urinary protein estimation, serum creatinine, electrolytes, calcium, phosphates, alkaline phosphatase, SGOT, SGPT, HBsAg, Anti HCV, CD4 count and ultrasound scan of the kidneys. Serum ANA, anti-dsDNA antibodies, and complement levels were done in selected cases. Renal biopsy was done in eight patients. One patient refused biopsy whereas another one had contracted kidneys. The samples were preserved in 10% buffered aqueous formaldehyde solution for light microscopy and sent immediately for histopathologic examination. The tissue sections were cut at 2 micrometer thickness and were studied under light microscopy using hematoxylin and eosin stain, periodic acid–schiff stain, acid fuchsin orange G and periodic acid silver methamine stains. Congo red stain was used in selected patients where amyloid was suspected based on the presence of organized extracellular deposits in the glomeruli. Electron microscopy and immunofluorescence studies were not done due to lack of facility at our centre. Patients received either a combination of tenofovir 300 mg, lamivudine 300mg and efavirenz 600 mg per day or abacavir 600 mg, lamivudine 300mg and efavirenz 600 mg per day. Tenofovir based regimen was given to the patients having serum creatinine less than 1.5 mg/dl whereas abacavir based regimen was given to the patients with serum creatinine more than 1.5 mg/dl. Dose adjustment for GFR level was done for lamivudine. All patients received ACEI (enalapril 5 to 10 mg per day).

### Table 1: Clinical renal syndrome at presentation (n=10)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Number</th>
<th>%age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subnephrotic Proteinuria</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Nephrotic Syndrome</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Acute kidney injury (AKI)</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Chronic kidney disease (CKD)</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Acute Glomerulonephritis</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>100</td>
</tr>
</tbody>
</table>

Immunosuppressive agents were not used. Renal function test, twentyfour hour urinary protein excretion CBC and CD4 count were measured at every three months. The data was systematically collected, coded and analyzed using SPSS 20 software and the results were recorded as mean, median and standard deviation. Short term outcome were assessed using changes in serum creatinine and proteinuria. Long term outcome assessment were done using progression to ESRD and patients survival.

### Observations and Result

Ten (male =7, females = 3) patients with age range of 26 to 55 (mean = 40.5±8.8) years were included in the study.80% of the patients had acquired the infection through heterosexual contact. Physical examination revealed edema (60%), pallor (40%) and hypertension (20%). Oliguria was noted in 20% of the patients. CKD (30%), AKI (20%), subnephrotic proteinuria (20%), nephrotic syndrome (20%) and acute glomerulonephritis (10%) were the presenting renal syndromes (Table 1). Markers of hepatitis B and C infection were negative in all patients. C3 and C4 were low in three and one patient respectively. ANA and anti-
Baseline 40.9 ± 27.50
3 Months 2.09 ± 1.16
6 Months 2.43 ± 1.82
9 Months 2.46 ± 1.83
12 Months 2.58 ± 2.25

eGFR (ml/min/1.73 m²)
Baseline 40.9 ± 27.50 12 83
3 Months 45.5 ± 26.78 12 88
6 Months 48.2 ± 34.07 10 101
9 Months 51.1 ± 39.90 10 124
12 Months 52.5 ± 38.08 9 107

24 HUP, g/day
Baseline 3.01 ± 2.55 1 9
3 Months 2.82 ± 2.86 1 10
6 Months 2.22 ± 2.03 0 7
9 Months 2.02 ± 1.83 1 6
12 Months 1.79 ± 1.48 0 5

CD4/µL
Baseline 292.4 ± 24.82 250 334
3 Months 323.1 ± 28.49 288 360
6 Months 339.1 ± 22.68 307 365
9 Months 371.1 ± 32.71 316 411
12 Months 387.7 ± 35.94 300 415

Hb (g/dl)
Baseline 11.86 ± 2.62 9 16
3 Months 11.32 ± 1.79 9 14

Patient outcome
Survived 10 100

Discussion

Human immunodeficiency virus infection/AIDS is a major global health problem and HIV associated kidney diseases further increases the mortality and morbidity in the HIV infected patients.6,12 HIV associated nephropathy (HIVAN), a peculiar collapsing variant of FSGS was the first reported renal lesion in HIV positive patients.8 Since then, a wide spectrum of renal diseases have been reported in HIV positive patients. After the introduction of cART this spectrum has changed. There is a reduction in the incidence of HIVAN, whereas immune complex kidney diseases and comorbidity associated kidney diseases have emerged as important causes of renal dysfunction.6

The mean age of the subjects in our study was 40.5 ± 8.89 years with a range of 26 to 54 years which is similar to the age reported in other studies.5-13 Majority of the patients in our study were males. The male to female ratio was 2:3:1. The male predominance has also been reported in other studies from India,5,10 Africa,14,15 Brazil and United States.15 The higher number of males in our study may be a reflection of higher mobility of this age group in search of livelihood, high sexual activity phase, and to some extent highly emotional and stressful life which usually prevails in this age and sex group. Heterosexual contact was the probable mode of transmission of HIV in majority (80%) of our patients. Two patients had history of blood transfusion and use of injectable medications from quakes in the past. Similar mode of transmission was reported in other studies.6,10,17

Edema and Pallor were present in six (60%) and four (40%) patients respectively. Hypertension and oliguria were present in two patients (20%) each. None of the patients had gross hematuria at the time of presentation. Gupta V16 et al. reported that fever (35%), edema (27%), asymptomatic (27%), oliguria (19%), weight loss (15%), gastroenteritis (7%), and altered sensorium (4%)
were the clinical manifestation at the time of presentation. Prakash J et al. reported edema, oliguria and gross hematuria in 8.1 %, 6.4 % and 1.6% of a total of 393 HIV positive patients of which only 136 patients had renal involvement. Vali PS et al. reported hypertension in 40% of the patients. We excluded the patients with kidney dysfunction attributable to causes other than HIV infection. This may explain the different clinical features at the time of presentation in our study.

CKD was the presenting renal syndrome in three (30%) patients. Subnephrotic proteinuria, nephrotic syndrome and AKI were present in two patients (20%) each. One patient (10%) presented with features of acute glomerulonephritis. Another study from India reported that AKI, nephrotic syndrome, rapidly proliferative renal failure, CKD, accelerated hypertension and acute nephritic syndrome were the presenting renal syndromes.17 This study included all HIV patients with kidney disease irrespective of etiology. In our study the mean serum creatinine, estimated GFR and twenty four hour urinary protein at the time of presentation were 2.46 mg/dl, 40.09 ml/min/1.73 m² and 3.01 grams respectively. The mean serum albumin, total proteins and CD4 count were 3.7 g/dl, 6.4 g/dl and 292 per microl. respectively. In a study by Atta MG et al. the baseline mean serum creatinine, estimated GFR, proteinuria (g/day) and CD4 count respectively were 4.7 mg/dl, 20 ml/min/1.73 m², 7.2 grams/day and 160/ microL. This cohort had a more severe disease compared to our patients. This may be because this cohort included only biopsy proven HIVAN, a more severe form of HIV associated kidney disease which occurs more commonly in advanced HIV infection and was not seen in our patients. Booth JW et al. reported 56 cases of HIV associated immune complex disease. The mean estimated GFR and proteinuria at the time of presentation were 49 ml/min/1.73m² and 2.4 g/d respectively. The base line parameters in this study are comparable to our study which may be because majority of our patients also had histologic features of HIV associated immune complex disease.

ANA and anti-dsDNA were negative in all patients. C3 was low in three patients; two of them had diffuse endocapillary proliferative glomerulonephritis. Another patient who presented with acute glomerulonephritis (biopsy not done) had low C3 and C4. Vali PS et al. reported 27 cases of kidney disease in HIV patients, of which two patients had a low serum C3 level. All patients in our study were negative for hepatitis B and hepatitis C infections. Booth JW et al. reported 18.5% and 7.6% prevalence of hepatitis B and hepatitis C infection respectively in HIV associated immune complex kidney diseases.

Mesangio proliferative glomerulonephritis (Figure 1) and Diffuse endo-capillary proliferative glomerulonephritis was present in three (37.5%) and 2 (25%) patients respectively. Amyloid nephropathy (Figure 2), membranous nephropathy and acute interstitial nephritis were present in one (12.5%) patient each. Other studies from India,14,16 Thailand18 and Italy19 have also reported Mesangio proliferative Glomerulonephritis as the most common histologic renal lesion in HIV infection. However, in contrast to our study, mesangio proliferative GN has been reported infrequently from the western world.20 HIVAN has been consistently reported to be the most common glomerular lesion in HIV-seropositive patients from the US, Brazil, African countries, and Western Europe.21 Classic HIVAN histopathology can be seen in adults and children at any stage of HIV infection but is most common in the advanced diseases, including AIDS.22 West African descent is highly susceptible to classic HIVAN.23 HIVAN has been reported to a lesser degree in Hispanic population and variably in Asian Indian cohort.23,24 However, the disease is notably absent in Swiss–European and Thai population.19 The current prevalence of HIVAN is declining as result of the widespread use of cART.25

During the follow up period serum creatinine / eGFR and proteinuria improved in 60% and 70% of the patients respectively. Other studies have also reported improvement in HIVAN23,26 and HIVICD16,17 with the use of combined ART. Atta MG et al. and Nicholas Weaner et al. reported stabilization or increase in GFR and decrease in proteinuria in biopsy proven HIVAN patients treated with combined ART. June Fabian et al. reported that the use of ART was associated with rapid and sustained improvement in GFR and a decrease in proteinuria irrespective of the histological class but the histological improvement was inconsistent and lagged behind the clinical response. Robert C. Kalayjian28 noted an improvement in renal function and patient survival in HIV positive CKD patients treated with c-ART. Thus, the results of our study are consistent with these studies.14,27 The consistent improvement in proteinuria in our study may be attributed to both c-ART and use of ACEI in all patients.

The one year patient survival in the present study was 100%. Gupta V et al. reported two deaths in 26 HIV associated kidney disease patients over a mean follow up of eight months. Both patients had received immunosuppression with low dose steroids. Bige N et al. reported that 71% of HIVAN patients treated with ACEI and c-ART either developed ESRD or died within two years.29 Post FA et al. reported that 48% of HIVAN patients treated with c-ART and ACEI developed ESRD with in four years.30 Patients with HIVICD had a lower cumulative progression to ESRD compared to patients with HIVAN.31

Conclusion

This study describes the clinico-histopathologic profile of HIV related kidney disease and the effect of combined antiretroviral therapy on its outcome. Treatment with combined ART and ACEIs slows the progression of kidney disease, decreases proteinuria and improves the GFR. Further well designed and adequately powered studies are needed in Indian patients to classify the histologic patterns of HIV associated kidney diseases, explore the treatment option and to document long term patient and renal outcomes on combined antiretroviral therapy.

References

When it comes to Protection Quality makes the Difference

According to the WHO, each year hundreds of millions of patients are affected by healthcare associated infections (HAIs) around the world. When it comes to infection control, the practice of appropriate hand hygiene and the proper use of medical gloves as a standard precaution are important measures in minimizing and preventing HAIs.
A Clinical Study of Prevalence of Microalbuminuria in Patients of Primary Hypertension and its Correlation with Left Ventricular Mass Index

Suresh Kumar Sharma¹, Anurag Aggarwal², Varsha Shirish Dabadghao¹*, Vikrant B Khese³, Satbir K Malik³, Sonal Agarwal⁴

Abstract

Introduction: Hypertension is one of the most challenging health problems in the world. Hypertension is closely related to kidney diseases. Microalbuminuria is a reflection of early kidney dysfunction and a marker of asymptomatic preclinical disease which precedes and predicts the occurrence of major morbid events.

Aims and objectives: To investigate the relationship between microalbuminuria and LVH in patients with primary hypertension. To establish microalbuminuria as an independent risk factor for increased Left Ventricular Mass Index in patients with Primary Hypertension.

Methods: This was a cross-sectional prevalence, analytical study conducted for a period of two years in a tertiary care teaching hospital in Western India. 126 patients diagnosed as primary hypertension, according to JNC 7 criteria were included in the study. Left ventricular Mass Index was measured using 2D Echo Machine using the formula of Left ventricular mass. Multiple logistic regression was conducted to find out independent correlation of Left Ventricular Hypertrophy.

Results: Mean age was 64.32 years in patients without LVH while it was 63.85 years in patients with LVH. Serum creatinine, albumin-creatinine ration and Microalbuminuria were independently correlated with the Left Ventricular hypertrophy. Multiple logistic regression concluded that presence of microalbuminuria increases risk of LVH 2.04 times more as compared to absence of microalbuminuria. Serum creatinine level was higher in patients with LVH compare to patients without LVH. patients with Microalbuminuria were higher in LVH group compare to non LVH group and this difference was statistically significant.

Conclusion: This study demonstrates that microalbuminuria has an independent correlation with Left Ventricular Mass Index and hence an independent risk factor for increased cardiovascular morbidity and mortality.

Introduction

Hypertension is one of the most challenging health problems in the world. It has been estimated that, globally, almost one billion individuals have hypertension.¹Latest WHO statistics show that hypertension is the leading cause of mortality worldwide (responsible for 13% of global deaths).²

Hypertension is closely related to kidney diseases.³Primary hypertension is considered to be strongly associated with end-stage renal disease (ESRD). Using longitudinal data from the Glasgow Blood Pressure Clinic (GBPC), it has been found that progression to ESRD in subjects attending this tertiary/secondary clinic is uncommon (only 1% of the population).⁴

The relationship between albuminuria and cardiovascular outcomes seems to exhibit a continuous relationship with no clear threshold for such association. The conventional threshold that is used currently for the definition of microalbuminuria is arbitrary and was chosen more than 25 years ago based on data of diabetic patients.⁵ Microalbuminuria is defined as 24-hour urinary albumin in the range of 30-299mcg is often found in primary hypertension and represents a sign of renal and cardiovascular damage.⁶ It has been proposed that microalbuminuria is a reflection of early kidney dysfunction and a marker of asymptomatic preclinical disease which precedes and predicts the occurrence of major morbid events.⁷ Although several studies have attempted to define the prevalence of microalbuminuria in primary hypertension, the exact figure is still unclear. The published prevalence of microalbuminuria in hypertensive subjects ranges from 4.7% to 58.4%.⁸ The present study aimed to investigate the relationship between microalbuminuria and LVH in patients with primary hypertension. The aim of this study was to establish Microalbuminuria as an independent risk factor for increased Left Ventricular Mass Index in patients with Primary Hypertension.

Materials and Methods

This was a cross-sectional prevalence, analytical study conducted for a period of two years in a tertiary care teaching hospital in Western India. Institutional ethics committee approval was obtained before the start of study. Informed consent was taken from each patient. 126 patients diagnosed as primary hypertension according to JNC 7 criteria, admitted to medicine ward were included in the study. Institutional ethics committee approval was obtained before the start of study. Informed consent was taken from each patient. 126 patients diagnosed as primary hypertension according to JNC 7 criteria, admitted to medicine ward were included in the study.
study. Secondary hypertension was ruled out by an elaborate questionnaire. Patients were asked the history of breathlessness, cough, expectoration, chest pain and palpitations, swelling over feet, syncope. A thorough physical examination was conducted and vital signs, pallor, edema, icterus, cyanosis and lymphadenopathy were recorded. All patients included in the study then underwent routine blood investigations such as hemogram, erythrocyte sedimentation rate, blood sugars, renal function tests, liver function tests, electrocardiograph and 2D echocardiography. Left ventricular Mass Index was measured using measurements taken from 2 D Echo Machine using the formula Left ventricular mass = 0.80 x 1.04 [(VSTD x LVIDD x PWTd) 3 — (LVIDd) 3] +0.6 where VST is ventricular septal thickness, LVID is left ventricular internal dimension, and PWT is posterior wall thickness. Prognostic value of LVH, defined as a binary variable, after correction for body surface area (a left ventricular mass 125 g/m² in men and 110 g/m² in women). Body surface area (in square meters) was estimated according to the Briars equation. Multiple logistic regression was conducted to find out independent correlation of Left Ventricular Hypertrophy. All significant variables in bi-variate analysis like Smoking, Diastolic blood pressure, Serum creatinine, Albumin-creatinine ratio and Microalbuminuria were taken. Apart from this some non significant variables in bi-variate analysis like Systolic blood pressure, Serum cholesterol, High-density lipoprotein and Low-density lipoprotein were also taken to remove their probable confounding effect.

**Results**

The present study was conducted among 126 patients of hypertension. Mean age of the patients were 64.41 years with standard deviation of 11.65 years. Females were 58 (46.03%) while males were 68 (53.97%). All patients were categorized based on presence of Left Ventricular Hypertrophy (LVH). LVH was present in 49 (38.89%). All other variables were compared with presence of LVH. Tables 1, 2 and 3 show comparison of these variables.

Table 1: Comparison between age and Left Ventricular Hypertrophy (LVH)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age, years Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No LVH</td>
<td>77 64.32</td>
<td>11.14</td>
</tr>
<tr>
<td>LVH</td>
<td>49 63.85</td>
<td>12.01</td>
</tr>
</tbody>
</table>

Table 2: Comparison between microalbuminuria and Left Ventricular Hypertrophy (LVH)

<table>
<thead>
<tr>
<th>Microalbuminuria</th>
<th>No LVH (n=77)</th>
<th>LVH Present (n=49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>25 (32.5)</td>
<td>30 (61.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Absent</td>
<td>52 (67.5)</td>
<td>19 (38.8)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Comparison between left ventricular mass index, and Left Ventricular Hypertrophy (LVH)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Left ventricular mass index, g/m² Mean</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No LVH</td>
<td>77 102.32</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LVH</td>
<td>49 188.78</td>
<td></td>
</tr>
</tbody>
</table>

Mean age was 64.32 years in patients without LVH while it was 63.85 years in patients with LVH. This difference was statistically non significant (p value >0.05).

In LVH group proportion of patients with Microalbuminuria was 61.22% while in non LVH group proportion of patients with Microalbuminuria was 32.47%. Thus patients with Microalbuminuria were higher in LVH group compare to non LVH group and this difference was statistically significant p value (p <0.05). Mean Left ventricular mass index was 102.32 gms/m² in patients without LVH while it was 188.78 gms/m² in patients with LVH. This difference was statistically significant (p-value <0.05) indicating that LVH was 2.04 times more compared to its absence.

**Discussion**

Primary hypertension (PH) is one of the most common medical problems in the general population and is one of the most important modifiable cardiovascular risk factors. Left ventricular hypertrophy (LVH) has also a prognostic value in patients with PH that strongly correlates with adverse cardiovascular outcome. It is identified that presence of LVH is
associated with an increased risk of sudden cardiac death, myocardial infarction, arrhythmia, progression of congestive heart failure, stroke, and abdominal aorta enlargement.\textsuperscript{5,10} Primary hypertension (PH) is one of the most common medical problems in the general population and is one of the most important modifiable cardiovascular risk factors. Left ventricular hypertrophy (LVH) has also a prognostic value in patients with PH that strongly correlates with adverse cardiovascular outcome. Microalbuminuria is often found in primary hypertension and represents a sign of renal and cardiovascular damage.\textsuperscript{6} In a study by Monfared et al\textsuperscript{11} also demonstrated that microalbuminuria levels were higher in patients with LVH compared with patients without LVH. The study also documents that the microalbuminuria levels were increased in patients with hypertension and correlated with LVH.

The study also documents that the microalbuminuria levels were increased in patients with hypertension and correlated with LVH. In present study, it was found that only serum creatinine, albumin-creatinine ratio and Microalbuminuria were independently correlated with the Left Ventricular hypertrophy. Presence of microalbuminuria increases risk of LVH 2.04 times more compared to its absence. In present study mean Serum Creatinine was 0.76 mg/dL in patients without LVH while it was 0.84 mg/dL in patients with LVH. This difference was statistically significant (p value <0.05) indicating that serum creatinine level was higher in patients with LVH compared to patients without LVH. Monfared et al\textsuperscript{11} found that patients with LVH compared with those without LVH had significantly higher serum creatinine levels (P = .02). Smilde and co-workers reported that kidney dysfunction was independently related to a 1.47-fold increased risk of LVH (95% CI, 1.15 to 1.88, P = .009). In addition, both creatinine clearance (OR, 1.56; 95% CI, 1.07 to 2.2; P = .04) and microalbuminuria (OR, 1.37, 95% CI, 1.04 to 1.80; P = .02) were independently associated with the presence of LVH.\textsuperscript{12}

Finally overall epidemiological and experimental data show that microalbuminuria is associated with an increased risk for all-cause and cardiovascular mortality, cardiac abnormalities, cerebrovascular disease, and, possibly, peripheral arterial disease.\textsuperscript{13} In hypertensive children and adolescents, microalbuminuria also is a predictor of LVH, and microalbuminuria lowering may stop the progression and even persuades the regression of LVH.\textsuperscript{14}

**Conclusion**

This study demonstrates that microalbuminuria has an independent correlation with Left Ventricular Mass Index and hence an independent risk factor for increased cardiovascular morbidity and mortality.

**Ethical approval**

The study was approved by the Institutional Ethics Committee.

**References**

Seroprevalence and Co-infection of Hepatitis B and Hepatitis C among Patients in a Tertiary Care Hospital in Eastern India

Julius Rahaman1, Mallika Sengupta2*, Gautam Barik3, Soma Sarkar4, Riya Sarkar5, Manideepa Sengupta6

Abstract

Introduction: Hepatitis B (HBV) and Hepatitis C (HCV) are two common viral infections causing cirrhosis.

Aim: The aim of this study was to find the seroprevalence of HBV and HCV along with occurrence of co-infection of HBV and HCV in patients attending a tertiary care hospital.

Materials and Methods: The study was done for a period of one year (January to December 2016) in the Department of Microbiology, Medical College, Kolkata. After obtaining ethical clearance and informed consent from the patients, serum samples were collected from all patients referred to Department of Microbiology for antibody to HCV and Hepatitis B surface antigen (HBsAg) screening. ELISA was performed for anti HCV antibody and HBsAg. The results and relevant clinical information were noted and analysis was done.

Results: A total of 10802 samples were received, of which 316 (2.92 %) were HBsAg positive, 115 (1.06%) were HCV antibody positive and a total of 7 (0.07%) patients were positive both for HBsAg and Anti HCV antibody. There was male preponderance. Anti HCV antibody was more common in age below 10 years and in thalassemia patients. Out of 7 patients positive for both, 5 patients were on regular blood transfusion due to beta thalassemia and 2 patients had history of chronic liver disease.

Conclusion: In this study, it was found that there was seroprevalence of 2.92 % of HBsAg, 1.06% of HCV antibody and 0.07% positive both for HBsAg and HCV antibody among the patients of a tertiary care centre in Eastern India.

Introduction

Hepatitis B virus infection is a major public health problem worldwide, around 30% of the world’s population show serological evidence of current or past infection. Hepatitis B virus is a partly double-stranded DNA virus with several serological markers like HBsAg, anti-HBsAb, HBeAg, anti-HBeAb, and anti-HBc IgM and IgG. It is transmitted through contact with infected blood and semen. A safe and effective vaccine has been available since 1981, and the implementation of universal vaccination in infants has resulted in a sharp decline in prevalence. Hepatitis B infection may lead to liver cirrhosis or hepatocellular carcinoma.1

Hepatitis C is a major cause of acute hepatitis and a common aetiological agent for cirrhosis of liver. It is the leading cause of liver transplantation and the most common chronic blood borne infection.2 Hepatitis C virus (HCV) is a hepatotropic RNA virus that causes progressive liver damage, which might result in liver cirrhosis and hepatocellular carcinoma. Globally, between 64 and 103 million people are chronically infected. Major risk factors for this blood-borne virus infection are unsafe injection drug use and unsterile medical procedures (iatrogenic infections) in countries with high HCV prevalence. Diagnostic procedures include serum HCV antibody testing, HCV RNA measurement, viral genotype and subtype determination and, lately, assessment of resistance-associated substitutions. As long as a prophylactic vaccine is not available, the HCV pandemic has to be controlled by treatment and prevention strategies, effective screening programmes and global access to treatment.3

Single infection with either hepatitis B or hepatitis C virus represents one of the major causes of chronic liver disease globally. However, in endemic areas a substantial number of patients are infected with both viruses mainly due to the common routes of transmission. There are studies which have shown that dually infected patients carry a greater risk of advanced liver disease, cirrhosis and hepatocellular carcinoma compared with infection in patients by one virus. Due to lack of large scale population based studies the exact number of HBV/HCV co-infected patients is unknown. Moreover, the true number of patients with HBV/HCV co-infection is further underestimated due to the unknown prevalence of occult HBV infection in patients with chronic HCV infection. The reported prevalence of HBV/HCV infection in different studies reveals wide differences depending on the geographical region, the study population, the selection criteria of the patients’ and the study design.4

There is paucity of studies regarding the co-infection of Hepatitis B and Hepatitis C in India and few studies that are available are mostly from North India. Hence, this study was designed to find the serological prevalence of...
Hepatitis B and Hepatitis C infection along with the occurrence of co-infection of HBV and HCV, risk factors and epidemiological features in patients attending a tertiary care hospital in Eastern India.

Materials and Methods

The study was done for a period of one year (January to December 2016) in the Department of Microbiology, Medical College, Kolkata. After obtaining ethical clearance from the institutional review board and informed consent from the patients, 4ml of blood in a clotted tube and relevant clinical information was collected from all patients referred to Department of Microbiology for antibody to Hepatitis C virus (HCV) and Hepatitis B surface antigen (HBsAg) screening. Serum was separated by centrifugation at 1500 rpm for 5 minutes.

The serum sample was used for performing Enzyme Linked Immunosorbent Assay (ELISA) for detection of anti HCV antibody by Hepa-Scan (Bhat Biotech, Bangalore, India) and HBsAg by Hepa-Scan (Bhat Biotech, Bangalore, India). The test was performed according to the manufacturer’s instructions, optical density (OD) was noted and positive was taken above the cut-off value. The relevant clinical information was also noted in the study proforma. All data were entered in Excel spreadsheet (Microsoft, USA) and analysis was done using SPSS version 16.

Results

A total of 10802 patients, who were referred to the Department of Microbiology, Medical College, Kolkata for anti HCV and HBsAg screening during the period of one year (January to December 2016) were included in the study.

Out of 10802 samples 316 (2.92 %) were HBsAg positive, 115 (1.06%) were HCV antibody positive. Among these patients, a total of 7 (0.07%) patients were positive both for HBsAg and anti HCV antibody. There was male preponderance seen in all groups (Table 1).

Anti HCV antibody was more common in age below 10 years (45.2%) whereas HBsAg was more positive in 21 to 40 years of age (Table 2). 5 patients positive for both HBsAg and HCV were less than 10 years age. Anti HCV antibody was significantly positive (P value is less than 0.0001 and Chi squared equals 157.734). There was a prevalence of 92/ 2974 (3.1%) of HCV among thalassemia patients. Out of 7 patients positive for both HBsAg and HCV antibody, 5 (71.4%) patients were on regular blood transfusion due to beta thalassemia and 2 (28.6%) patients had history of chronic liver disease (CLD).

Discussion

Total global HCV prevalence is estimated at 2.5% (177.5 million of HCV infected adults), ranging from 2.9% in Africa to 1.3% in Americas. The estimated prevalence of HCV in the whole Asian continent is 2.8%, accounting over 60% of the cases worldwide. The prevalence of anti-HCV in the general population of South Asia including Afghanistan, Bangladesh, India and Pakistan is 2.5%, being 6.7% in Pakistan and 0.8% in India. There is paucity of large-scale prevalence studies on Hepatitis C in the general population of India. The reported prevalence rates vary (range 0.09% – 2.02%) as shown by the large population based studies. This study showed a prevalence of 1.06% of anti HCV antibody among the patients of a tertiary care centre in Eastern India. In a community based study done in 1999 in West Bengal, among 2973 subjects, 0.87% were HCV antibody positive.

The overall rate of HBsAg positivity has been reported to range between 2% and 8% in most studies. Based on the prevalence of Hepatitis B surface Antigen (HBsAg), different areas of the world are classified as having high (28%), intermediate (2–7%) or low (<2%)
HBV endemicity. Countries which have high endemicity include South-East Asia, China, most of Africa, most of Pacific Islands, the Amazon basin and parts of the Middle East. Countries with intermediate endemicity include South Asia, Eastern and Southern Europe, Russia and Central and South America. The areas with low endemicity include United States, Western Europe and Australia. In the present study there is a prevalence of 2.92 % HBsAg positive cases. In a similar study done in Morocco, out of 503 HIV-infected patients there was a prevalence of 3.1% of HCV antibody among thalassemia patients undergoing haemodialysis and renal transplant is 5.2–18.7%.

There was a prevalence of 3.1% of HCV antibody among thalassemia patients. In a study done in Pakistan, it was seen that out of 845 patients 1.3% were seropositive for both HBsAg and anti-HCV co-infection. However, though there are quite a number of studies regarding co-infection of HBV or HCV in HIV patients, there are few studies regarding the co-infection of HBV and HCV and the rates are vastly variable. In a study done in Pakistan, 1.06% of HCV antibody and 0.07% positive for both for HBsAg and anti-HCV antibody showing co-infection or dual infection among the patients of a tertiary care centre in Eastern India. Anti HCV antibody was more common in age below 10 years and thalassemia patients. Out of 7 patients positive for both, 5 (71.4%) patients were on regular blood transfusion due to beta thalassemia and 2 (28.6%) patients had history of chronic liver disease (CLD).

In this study, it was found that there is seroprevalence of 2.92% of HBsAg, 1.06% of HCV antibody and 0.07% positive for both for HBsAg and anti-HCV antibody having co-infection or dual infection among the patients of a tertiary care centre in Eastern India. Anti HCV antibody was more common in age below 10 years and thalassemia patients. Out of 7 patients positive for both, 5 patients were on regular blood transfusion due to beta thalassemia and 2 patients had history of chronic liver disease. However, larger field studies are required to corroborate these findings.

References

15. Chowdhury A. Epidemiology of Hepatitis B virus infection in India. Hepat B Annu 2004; 117.
Clinical Profile, Severity and Outcome of Acute Upper Gastrointestinal Bleeding in Elderly Patients Compared to Non-elderly Patients: A Prospective Observational Study

Sumit Sourabh 1 , Neetu Sharma 2 , Rajesh Sharma 3 , Ramesh Kumar 4 , Surinder Thakur 5 , Vishal Bodh 6 , Brij Sharma 5*

Abstract
Aim: To determine the clinical profile, severity and outcome of acute upper gastrointestinal bleeding (UGIB) in elderly subjects (>60 years) compared to the non elderly ones (<60 years).

Methods: In a prospective observational study, 380 consecutive adult patients presenting with acute UGIB were enrolled. Patients were divided into two groups: elderly (≥60 years) and non-elderly (<60 years).

Results: Out of 380 patients, 254(66.84%) patients were non-elderly and 126(33.15%) patients were elderly. The proportion of patients with co-morbidity and consumption of non-steroidal anti-inflammatory drugs was higher among elderly patients. The commonest mode of presentation was hematemesis and melena in the both groups, while isolated hematochezia (29% vs. 1.9%, p<0.01) was more common in elderly group. The variceal bleeding was significantly higher among non-elderly group (38.1% vs. 18.2%, p<0.01) and bleeding from gastric or duodenal ulcer was the predominant cause of bleeding among elderly group (65% vs. 43% p<0.01). The proportion of patients with tachycardia (68.2% vs. 20%, p<0.01), postural hypotension (29.3% vs. 14.9%, p<0.01) and blood transfusion requirement of 4 units or more (20.2% vs. 10.1%, p<0.01) was significantly higher among elderly group than in non-elderly group. Despite similar re-bleeding rates, mortality rate was significantly higher in elderly patients compared to the non-elderly patients (10.32% vs. 1.94%, p<0.01).

Conclusions: Nearly 33% of the patients with acute UGIB are over 60 years old. The severity of bleeding and mortality rates was higher in elderly in comparison to non-elderly patients.

Introduction

Acute upper bleeding (UGIB) remains a common emergency and a potentially serious condition that generally requires hospitalization. UGIB occurs more commonly in men and older subjects. 1,2 It is estimated that 35-45% of all patients presenting with upper GI bleed are over the age of 60. 3,4 Age and co morbidities are the most important factors for high mortality in patients with UGIB. GI bleeding in elderly is associated with increased mortality and morbidity than in young, which is in part attributable to increased co morbid illness and greater use of medication such as aspirin, non-steroidal anti-inflammatory drugs, warfarin. 5,6 The profile of UGIB varies in different age groups. While duodenal ulcer bleeding is more common in younger age group, bleeding from gastric ulcer or esophageal varices are commonly seen in middle age group and from gastro-esophageal malignancy in elderly. 7-9 Furthermore, the pain sensitivity decreases with age. This along with frequent use of analgesic drugs cause suppression of gastroduodenal ulcer pain in up to 50% of elderly leading to delay in the diagnosis and development of complications such as perforation and hemorrhage. 10-11 The epidemiological spectrum of UGIB in terms of magnitude, etiology, gender distribution and severity may vary in different geographical regions. Such data, though scant in India, are important in making strategies to combat morbidity and mortality. The current study was aimed to determine the clinical profile, severity and outcome of UGIB in elderly subjects (>60 years) compared to the non elderly ones (<60 years).

Methods

This was a prospective observational study was conducted at Indira Gandhi Medical College, Shimla, India between July 2014 to June 2015. The study was approved by the Institute Ethics Committee. A diagnosis of acute UGIB was based on the history of hematemesis and/or melena. Consecutive adult patients presenting with UGIB in the department of Medicine and gastroenterology were included. Patients below 18 years and In-patients developing UGIB during hospitalization were excluded from the study. After initial resuscitation, a detailed history was obtained from each patient. Clinical examination was done to look for tachycardia, postural hypotension, pallor, and stigmata of chronic liver disease. Relevant blood radiological investigations were done in all patients. All patients were managed individually with standard medical therapy. Transfusion of blood and blood products were done whenever necessary. Upper GI
Table 1: The demographic, clinical and laboratory parameters of elderly and non-elderly patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>&lt;60 Years</th>
<th>≥60 years</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=254</td>
<td>N=126</td>
<td></td>
</tr>
<tr>
<td>Demographic Profiles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>42.1 (15.6)</td>
<td>67.3 (5.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>197 (77.5%)</td>
<td>101 (80.1%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>12 (04.7%)</td>
<td>30 (23.8%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>06 (02.3%)</td>
<td>31 (24.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>COPD, n(%)</td>
<td>03 (01.8%)</td>
<td>07 (05.5%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiovascular Diseases, n (%)</td>
<td>08 (03.1%)</td>
<td>26 (20.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chronic Kidney Disease, n (%)</td>
<td>03 (01.8%)</td>
<td>07 (05.5%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Chronic Liver Disease</td>
<td>90 (35.4%)</td>
<td>23 (18.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of alcohol and drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption, n(%)</td>
<td>90 (35.4%)</td>
<td>30 (23.8%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NSAID</td>
<td>80 (31.4%)</td>
<td>62 (49.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>06(2.3%)</td>
<td>22 (17.4%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematemesis+Malena, n(%)</td>
<td>134 (552.7%)</td>
<td>79 (62.6%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Isolated Malena, n(%)</td>
<td>47 (18.1%)</td>
<td>29 (23.0%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Hematochezia, n(%)</td>
<td>05 (1.9%)</td>
<td>08 (29.3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tachycardia, n(%)</td>
<td>51 (20.0%)</td>
<td>86 (68.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Postural hypotension, n(%)</td>
<td>38 (14.9%)</td>
<td>37 (29.3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pallor, n (%)</td>
<td>131 (51.5%)</td>
<td>88 (69.8%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Splenomegaly, n (%)</td>
<td>24 (9.4%)</td>
<td>13 (10.3)</td>
<td>0.78</td>
</tr>
<tr>
<td>Laboratory Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, n(SD) g/dL</td>
<td>9.2 (2.4)</td>
<td>8.2 (2.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum Creatinine, n(SD) mg/dL</td>
<td>0.9 (0.5)</td>
<td>1.03 (0.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>Total Bilirubin, n(SD) mg/dL</td>
<td>2.1 (1.02)</td>
<td>1.05 (0.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ALT, n (SD) IU/L</td>
<td>35.3 (23.6)</td>
<td>29.1 (21.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>AST, n(SD) IU/L</td>
<td>61.4 (53.0)</td>
<td>49.2 (38.0%)</td>
<td>0.01</td>
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<tr>
<td>Serum Albumin, n(SD) gm%</td>
<td>3.1 (0.5)</td>
<td>3.2 (0.5)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Statistical Analysis

Normally distributed continuous variables were expressed as mean (SD) and the continuous variables with skewed distribution were expressed as median (range). Categorical data was presented as proportions. Comparisons were done using t test for continuous variables and the chi square test or Fishers test for discrete variables, wherever applicable. Data were analyzed by using SPSS software version 23.0 (SPSS, Chicago, IL, USA). A p value of <0.05 was taken as significant.

Results

During study period, 380 adult patients were presented with UGIB. The mean age (SD) of the patients was 50.03 (15.5) years and the majority (78.4%) were male. Out of 380 patients, 254 (66.84%) patients were of less than 60 years of age and 126 (33.15%) patients were 60 years or more of age. The demographic, clinical and laboratory parameters of elderly and non-elderly patients are depicted in Table 1. As expected, the proportion of patients with co-morbidity and consumption of non-steroidal anti-inflammatory drugs or oral anti-coagulants were higher among elderly group of patients.

The commonest mode of presentation was hematemesis and melena in the both groups, while the presentation as isolated hematochezia (29% vs. 1.9%, p<0.05) were more common in elderly group than in non-elderly group. The proportion of patients with tachycardia (68.2% vs. 20%, p<0.05) and postural hypotension (29.3% vs. 14.9%, p<0.05) was significantly higher among elderly group as compared to non-elderly group.

All patients underwent endoscopy out of which, among elderly group, 23 (18.2%) patients had variceal bleeding and 123 (81.8%) patients had non-variceal bleeding. The corresponding proportions were 97 (38.1%) and 157 (61.9%) patients among non-elderly group. Thus, variceal bleeding was significantly higher among non-elderly group (38.1% vs. 18.2%, p<0.05). The proportion of patients with large (grade III-IV) esophageal varices (91% vs. 88%) and gastric varices (6.5% vs. 5.1%) were similar between elderly and non-elderly group. Successful initial hemostasis was achieved in all patients both group using endotherapy along with medical management. Rebleeding occurred in 8.8% and 10% of patients in elderly and non-elderly group (Table 2), respectively, the difference was statistically insignificant. None of the patients with variceal bleeding required surgical therapy. Bleeding from gastric or duodenal ulcer was the predominant cause of bleeding among elderly group of patients (65% vs. 43%, p<0.05). Nine patients from elderly and 12 patients from non-elderly group developed rebleeding from duodenal or pre-pyloric ulcer, and one patient from each group required surgical therapy after failed repeat endotherapy.

Rockall score >2 was present in 29.3% patients of elderly group than 14.9% patients of non-elderly group (p<0.05). The requirement of blood transfusion 4 or more units was higher among patients of elderly group than in non-elderly group (20.2% vs. 10.1%, p<0.05). In this study, the mortality rate was 4.73% (n=18) patients, of which 10.32% (n=13) patients were over the age of 60 years and 1.94% (n=05) patients were less than 60 years (p<0.05).

Discussion

The approach towards managing acute UGIB in elderly patients needs special consideration because these patients may have atypical presentation and high mortality rates. In elderly patients, the history of UGIB may be clouded or complicated by presence of cognitive, auditory and visual, impairment. The presences of co-morbidities and medications that may aggravate bleeding tendency further complicate the problems. Our study unequivocally found that the severity and overall mortality rate of UGIB in elderly subjects were significantly higher than that in non-elderly ones.
In our study, patients over 60 years of age constituted around 33% of the total population with acute UGIB. In previous studies too, about 35% to 45% of all patients presented with acute UGIB were over 60 years old.\(^4,12,13\) The prevalence of peptic ulcer related bleeding was higher among elderly population compared to the younger ones. This may be due to less frequent use of NSAID and frequent eradication of H. pylori infection in young patients.\(^14\) Half of our elderly patients had history of NSAID consumption. Notably, the risk of NSAID induced peptic ulcer bleeding is nearly 4 times higher in older patients compared to young patients.\(^15\) The variceal bleeding was less common in elderly group. The severity of UGIB in terms of tachycardia, postural hypotension, units of blood transfusion requirement was significantly higher among elderly group in comparison to non-elderly group. Rebleeding rate in our study was around 18% and it was similar between two groups. Most of recurrent bleeders were having high-risk gastric or duodenal ulcer (Forrest Class 1a/1b) or large esophageal varices. In the literature, rebleeding rates have been reported to occur in 20-30% of patients.\(^16,17\)

Age has been found to be an independent risk factor for poor clinical outcome in patients with acute UGIB. The Mortality rates among patients aged over 60 years vary from 12% to 35%, while the corresponding rate for patients younger than 60 years of age is <10%.\(^16,20\) In our study, mortality rate among elderly patients was 10.32% patients and in those with age <60 years was 1.94% (p<0.05). The majority of elderly patients who died had co-morbid illness. It appears that co-morbid illness, and not the bleeding per se, is directly related to increased mortality among elderly patients.

In conclusion, nearly 33% of the patients with acute UGIB were over 60 years old. Bleeding from gastric or duodenal ulcer was the predominant cause of bleeding among elderly group. Severity of bleeding in elderly was higher than in younger patients. The majority of these patients could be treated medically by a combination of drugs and endoscopic therapy. Despite similar re-bleeding rates, mortality rate was significantly higher in elderly patients compared to the non-elderly patients.

### References

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Quantitative Analysis of Competency Levels in Medical Interns of a Tertiary Care Hospital in India – A Questionnaire Based Cross Sectional Study

Deidre L Dias¹*, Amey S Kamat², Sam S Gomes³, Edwin J Gomes⁴, Sushama A Bhounsule⁵

Abstract

Context: The MCI has laid down a basic framework for interns, which it expects all prospective doctors to be well versed in. Asking students to demonstrate their understanding of the subject, ability to think critically, analyze, infer and act accordingly is imperative to the learning process.

Aims: To assess competency levels in medical interns post internship via a questionnaire developed based on MCI framework and departmental expectations of clinical capabilities.

Settings and Design: This descriptive cross-sectional study was done in a tertiary care hospital involving 74 interns nearing end of internship in the year 2017.

Methods and Material: A questionnaire consisting of core competencies such as professionalism, communication skills, learning competency, clinical problem solving amongst others was provided to each and competency levels were assessed against a pre-defined scale. Answers were graded as Poor, Average, Good and Excellent with corresponding numerical equivalents 0, 1, 2 and 3 respectively.

Statistical analysis used: The values obtained were analysed using Weighted Sum technique through Microsoft Excel tool.

Results: An ideal average competency score was initially established and overall competency of each intern was adjudged against the same. Out of 74 candidates that answered the questionnaire, a vast majority of 50 were found at below average competency. Cardio pulmonary resuscitation was known only to 13 students. Around 50 students were severely lacking with regards to knowledge about the use of preferred antibiotic in sepsis and seizures.

Conclusions: There seems to exist significant disconnect in the expectations of MCI on one hand and actual knowledge and skill acquisition of the doctors on other. A departmental wise curriculum and exams at the end of each departmental posting which is more skill based will enable a well-trained doctor with reasonable skills and knowledge to obtain his license to practice.

Subjects and Methods

Ethical approval

Approval from the Institutional Ethics Committee was obtained prior to commencement of this study.

Subjects

95 interns who completed their internship in February 2017 (regular batch) and those in August 2017 (casual batch) were chosen as candidates for this study, excluding one intern who completed four years of MBBS outside India. Out of the 95 subjects, 75 consented and answered the questionnaire. One incomplete questionnaire was discarded amongst the submitted answers. Thus, 74 anonymous complete questionnaires were considered for evaluation. Interns were chosen as sample population as they not only reflect the entire undergraduate training program but also represent the future practicing doctors, considering not all may pursue further education in different specialties.

Questionnaire

A questionnaire consisting of 45 questions was developed as per the following framework depicted in Figure 1.

Grading of the questions

- Q1- Q15 (Except Q14): Graded as per self-evaluated ratings of each individual subject
- Q14: Grading of Q14 is as shown in table 2 below.
- Q16 to Q45: These questions have multiple choice options. Each question could have multiple right choices. The highest attainable

Introduction

Approximately 6000 MBBS doctors pass out each year out of the MCI approved medical colleges in India.¹ MCI has laid down general guidelines for colleges to train their doctors.² Though all colleges follow these guidelines, there exists a deficit in the fundamental knowledge of students across the country, exposing their practical inadequacies. This study aims to assess competency levels of medical interns post internship. Objectives were to develop a questionnaire based on MCI framework and departmental expectations of clinical capabilities and then use it to gauge the ability of the interns with respect to its knowledge-based application, required for a clinical establishment. Thus, quantitatively estimating competency levels against a pre-defined scale.

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score per question is 3. These were graded as follows:

- Each correct choice equaled 3 divided by the number of correct options. The total value for each question was then sum of all the correct choices marked by the subject.

- Each incorrect choice equaled deduction amounting to 1/3rd of the corresponding value of the chosen option.

- A positive final score was rounded off to the nearest grade, while a negative final score was considered as zero to match the grading system of 0 to 3.

### Statistical analysis

Specific competencies in each of the categories tested and a few highly weighted questions were assessed and evaluated. The final competency score for each individual was determined via a Weighted Sum Technique, amalgamating all the questions. An Analytical Hierarchy Process matrix was developed to assess the weight of each question and the specific category of questions relative to other questions and categories. This was undertaken by two senior doctors, experts in the field of Medicine and Pharmacology respectively. A baseline AHP matrix was thus developed based on the experience and knowledge of the faculty. An iterative approach using eigen vectors was adopted to derive consistent weight values.

Weights for each question obtained through the AHP matrix were entered in the Pugh matrix and the grades obtained by each intern were noted against them. A sum-product of the grades and the weights resulted in each subject’s overall competency score. Similarly, category wise competency was calculated considering only those questions specific to each category. The AHP and Pugh matrices were developed in Microsoft Excel.

### Results

#### Overall competence

An ideal average score of 153.41 was calculated that separated the average competent interns from the below average ones. This was done by assigning a score of 1 to those questions that weighed less than 2.5% and a score of 2 for those that weighed 2.5% and above. The results are as shown below in Figure 2.

#### Category wise competency

All 74 interns seemed confident about possessing the requisite general skills including history taking to application of undergraduate content for a holistic treatment approach. They also claimed to possess important interpersonal qualities such as professionalism, personal effectiveness and communication skills. However, only 13 interns performed average to above average when objectively measured.

#### Specific competencies

Assessment of those questions that weighed more than 2.5% was conducted
with a view to highlight necessary frontages and are elaborated below in descending order.

**CPR**

The technique of Cardio Pulmonary Resuscitation (CPR) was known perfectly to only 13 out of the 74 as shown below.

**Situational management**

Figure 5 shows the competency of interns in different health settings. Here a case of poisoning that reported to Emergency Room (ER) was diagnosed appropriately as caused due to organophosphorus compound by 57 subjects (Q31). Subjects were assessed with respect to the management of Myocardial Infarction (MI) at a Peripheral Health Centre (PHC) and Intensive Care Unit (ICU) of a tertiary hospital. Only 1 subject was capable of timely referral from PHC to a tertiary care after rendering first level of treatment (Q44).14 subjects did select the appropriate treatment plan for MI in ICU (Q45).

**Basic knowledge**

It is imperative to have adequate knowledge of common as well as essential drugs. However, barring paracetamol (Q34, Q42) and treatment of Bronchial Asthma (Q39) in which majority performed exceptionally well, knowledge of most subjects seemed poor to average regarding drugs for common chronic disorders like diabetes (Q21, Q24), hypertension (Q33, Q41, Q22) and drugs requiring gradual withdrawal (Q40) amongst others. This is depicted in figure 6.

**Selection of antibiotics**

Subjects were also tested on their knowledge of choice of antibiotics preferred in sepsis (Q38), urinary tract infection in pregnant mothers (UTI+P) (Q35) and antimicrobials to be avoided in seizures (Q20). It was observed that only a minority performed above average in all 3 cases.

**Problem Based Learning (PBL)**

- Case based scenarios: Subjects were tested not just with direct questions but also scenarios where they would have to make a diagnosis and/or give adequate treatment. A casualty scenario was presented where a patient indicated severe spasm of the neck. This was to be diagnosed and treated (Q37). 49 subjects did poorly at this, while 22 did excellent. Questions 16 and 17 were cases diagnostic of meningitis and fever with rash and majority performed in the average range.

- Interpretation of tests: Although most subjects rated their clinical skills based on history, physical examination and relevant investigations to be assessed as above average to excellent, it was not translated in this section of the questionnaire. Correct interpretation of tests such as Complete hemogram, electrocardiogram and liver function tests (LFT) seemed to range mostly between poor to average as shown in figure 9.

**Discussion**

Internship is an essential rite of passage in an environment that facilitates active learning and reinforces the theoretical knowledge obtained in classrooms and books by executing it in actual bedside situations. This aids in re-encoding the afore mentioned information to last a long time, thereby preparing a medical graduate to assess, control and treat patients independently. It was thus decided upon to evaluate the competency of interns.

These 45 questions when evaluated, revealed that though every intern felt efficacious in performing the duties of a doctor at personal and professional
level, the same did not hold true when knowledge and clinical problem solvers were measured. Studies done in few countries of Africa and USA showed a drop, although minor, in objectively measured versus self-perceived competency. The reason claiming to be either lack of exposure to clinical practice or the apprehension of committing a mistake. In contrast, the institution where the study was performed revealed a much larger drop. Accordingly, implementation of serious measures to bridge this gap considerably is the need of the hour.

Specifically, common consensus is that CPR is an indispensable technique to all doctors. This is re-established in this study owing to the high weight values associated with the CPR question. Therefore, knowing its fundamentals is crucial and allows the right execution. In Delhi and this study, less than a quarter of the subjects tested as part of the study sample knew CPR techniques, which is quite alarming. Kumar et al. found medical graduates themselves lack this knowledge; hence to rectify it, proposed the curriculum to incorporate frequent training sessions. This was reiterated by Zaheer and Haque.

Similarly, another case study-based question about Organophosphorus is important. This compound is an easily available, highly efficacious and equally cheap insecticide available in India. Acute poisoning cases have been reported quite frequently in hospitals of India. For suicidal purposes alone in 2007, a rate of 19.7% was noted in National Crime Bureau of India reports with mortality rates reaching limits of 70% as well. However early diagnosis and effective management improves survival outcomes. It was for this reason that the interns’ ability to detect such a case was tested upon. The results were a pleasing 77%.

The next two scenarios were to test treatment of AWMI (Anterior wall Myocardial Infarction) in two different settings. One in ICU of a tertiary care hospital where the best modalities are available and the other in a peripheral health centre where one must provide best care possible within limited resources, whilst deciding upon timely referral in case of intervention. Given that only less than 20 subjects performed above average in each setting, this raised concerns as prompt treatment can improve prognosis of the most serious MI of them all.

From what appears to be a poor performance by the subjects in almost all PBL questions, modification of the existing internship and general undergraduate curriculum seems necessary for a more practice-oriented learning approach. A study conducted amidst first year foundation students from three different types of medical schools (traditional, reformed and PBL), showed that PBL model along with Objective Structured Clinical Examination (OSCE) for evaluation, enhanced their practical as well as learning skills, imbibed professionalism and personal effectiveness in them and also allowed scope for improvement, as those areas needing focus emerged clearly.

In order to be able to act effectively, knowledge is essential, but in its entirety. Misdiagnosis or incorrectly prescribed medicines, especially with regards to antibiotic usage can not only result in no alleviation of condition but instead worsen the ever-growing resistance. Even in the field of common chronic disorders like diabetes and hypertension, the questionnaire results were less than satisfactory. This throws light on the need to master basic prerequisites for common disorders before diving into the complex medical conditions of the human anatomy.

**Strength**

It is the first study ever to be conducted that objectively assessed competency amongst medical interns in this state. Secondly, the use of AHP matrix had a two-fold benefit. In this study, it helped rank each question as per importance by assigning definite quantitative values to various intangible attributes such as professionalism and interpersonal skills. It also helped affinitize the qualitative questions with the relatively objective type questions. Lastly, being the major teaching hospital in the state, any intervention brought about here affects all its medical graduates directly.

**Limitation**

Intellectual background and difficulty level of questions were not accounted for while determining overall competency. Lastly, error states or margins due to the above-mentioned factors were not accounted for.

**Conclusion and future work**

Having understood that the knowledge and skills acquired by the individuals during internship are far from the expectations of MCI and the institution, conducting skill-based exams like supervising during patient history taking and examination seems like a logical step. Further, even OSCE along with oral exams or written multiple choice questions which are a mix of factual as well clinical scenarios like in the questionnaire itself, on pertinent topics at the end of each departmental posting will ensure a standard and acceptable level of expertise in each intern. Also, inculcating this along with a professional and personal values code as part of the medical undergraduate curriculum will help concrete the learned practice, behavior and knowledge. The programme needs to be structured meticulously and modified as per the ever-evolving needs.
of the population and the perceptions of the medical fraternity as internship is a crucial process in producing complete, competent and confident future doctors.

Acknowledgement

The authors would like to thank the Institutional Ethics committee, the Dean, Head and professor of department of Pharmacology, Head and professor of department of Medicine, and the batch of 2011 that took part in this study willingly.

References


Association of Maternal Risk Factors to Congenital Anomalies among Infants: A Community Based Study in Rural Areas of Haryana, India

Manisha Malik1, Pardeep Khanna2, Ramesh Verma3

Abstract

Objectives: The present study was aimed at assessing Association of Maternal Risk Factors to congenital anomalies of infants.

Material and Methods: This community based retrospective and cross-sectional study was carried out in 23 rural sub-centres of block Beri, district Jhajjar (Haryana, India) among 920 mothers. A pre-designed pretested semistructured questionnaire was used to collect information. Univariate analysis along with logistic regression analysis was performed.

Results: The prevalence of congenitally malformations was 1.2%. Most common congenital malformations were cleft lip/palate (18.18%) and hydrocephalus (18.18%). Mothers with < 3 years gap between pregnancies had higher prevalence (1.7%) of congenital malformations in live births. Mothers with previous history of congenital malformation (8.3%) and abortions (13.6%) had higher prevalence of congenitally malformed babies with 2.6 and 4 times higher odds of having a malformed baby.

Conclusions: The study concluded that mothers with risk factors like extreme of ages, illiteracy, bad obstetric history, history of previous congenitally malformed baby are at increased risk of fetal congenital malformation.

Introduction

Congenital anomalies (also referred as birth defects) affect an estimated 1 in 33 infants and an estimated 303 000 newborns die within 4 weeks of birth every year, worldwide, due to congenital anomalies.1 It accounts for 8-15% of perinatal deaths and 13-16% of neonatal deaths in India.2 The true magnitude of birth defects in India is not known, though research on congenital malformations has reported varied prevalence 0.8% to 3.7%.3-5

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The present study was carried out in the study area which covered 40 sub-centres- serve the urban population and the rest 23 subcentres cater services to rural population.

According to the annual report of Indian Council of Medical Research (2002-03) cardiovascular, musculoskeletal and genitourinary were the most commonly affected systems in a descending order of frequency.6 The congenital anomalies are not only a leading cause of foetal loss, but also contribute significantly to preterm birth, childhood and adult morbidity along with considerable repercussion on the mothers and their families. The maternal factors like mother’s age, educational level, occupation, socioeconomic status, maternal height, parity, birth spacing, bad obstetric history, diseases during pregnancy like anemia, hypertension, diabetes and health care services utilization by mothers bear significant associations with outcome of pregnancy. The present study was carried out to know the pattern of congenital malformations and their relationship with socio-demographic and above mentioned maternal risk factors as it is important to study this on regional basis.

Material and Methods

This community based retrospective and cross-sectional study was carried out in Community Development Block, Beri (District Jhajjar) after approval from institutional ethics committee from September 2012 to August 2013. Beri block serves as the field practice area of Department of Community Medicine, Pt. B. D. Sharma Post Graduate Institute of Medical Sciences, Rohtak. Out of the 25 subcentres, two subcentres- serve the urban population and the rest 23 subcentres cater services to rural population.

Considering the prevalence of high risk pregnancy as approximately 10% and allowable error of 20% at 95% level of significance and 90% power, the sample size was calculated using the formula (n) = Z2α/2+β p (1-p)/d2, where Z = Value of area under the normal curve (1.96 for 2-sided test; 5% significance level), α = Level of significance (0.05), β = Power of the study, p = Prevalence (proportion-10%), d = Relative Allowable error (20%) and n= Sample Size. The calculated sample size came out to be 900. Mothers who delivered in the last one year were included in the study fulfilled the inclusion criteria of permanent residents of the area for at least last one year, had ANC records at subcentres and who had given informed written consent with a literate witness thereof. Women who could not be contacted even after two home visits, women who did not give consent, multiple births like twins and Maternal death were excluded from study.

A list of all the 23 rural sub-centers in the study area was obtained from the concerned Community Health Centres. All mothers who delivered in the last one year and had antenatal records were enlisted from the ANC, Birth and immunization register from subcenter. Out of enlisted mothers, 40 mothers were selected by simple random sampling from each subcenter. Though the calculated sample size was 900, a total of 920 (40X23) mothers were included in the study to make the sampling procedure more convenient. The investigator herself contacted these selected mothers at their home. All the subjects were fully informed about the purpose of the study. A written informed consent was obtained from the individual before conducting the interview. A pre-tested semi-structured interview schedule was used which included information on socio-demographic profile, past obstetrical, medical and contraceptive history, details of latest pregnancy like antenatal care visits, Iron Folic Acid tablets consumption, time of pregnancy registration and complications during pregnancy like anemia, hypertension, diabetes, etc. The detailed obstetric history, along with presence of any congenital malformation in live single births were recorded. The health records available with the mother were also reviewed. Socioeconomic status of study population was assessed using Modified Udai Parikh scale for rural areas.8

Data analysis was done in SPSS
Table 4: Logistic regression analysis of variables with congenital malformations in live births (stepwise method) (N=900)

<table>
<thead>
<tr>
<th>Variable</th>
<th>aOR</th>
<th>Confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous history of ≥ 3 abortions</td>
<td>4.15</td>
<td>3.32-10.29</td>
<td>0.000</td>
</tr>
<tr>
<td>Previous history of congenital malformation</td>
<td>2.61</td>
<td>1.06-17.28</td>
<td>0.044</td>
</tr>
<tr>
<td>IFA tablets intake during pregnancy</td>
<td>0.78</td>
<td>0.03-0.99</td>
<td>0.046</td>
</tr>
</tbody>
</table>

The present study revealed that nearly half of the mothers were anemic during pregnancy (52.0%). Similarly, NFHS-3 data revealed that 57.9% pregnant women in India and 56% in Haryana were anemic.9 Singh et al reported the overall prevalence of anemia as 42%.10 The prevalence of diabetes during pregnancy was 6.8% in our study. The prevalence of gestational diabetes has been reported to be in the range of 6.9 to 13.9%.11-13 Hypertension was found out to be 5.0% among pregnant women in the present study. Almost, similar observation (6.9%) was quoted by Bharti et al while Sachdeva et al and Zareen et al had reported it as 15% and 14.8% respectively among rural women in hospital based studies.14-16

The present study found that mothers aged more than 35 years had higher prevalence of congenitally malformed babies when compared to mothers below 35 years of age. This association was found to be statistically significant. Sarkar et al, Taksande et al and Sheridan et al also concluded that prevalence of congenitally anomalous babies born was higher for mothers with advanced age and this association had statistical significance.17,25,26 Increase in age brings with it lot many other chronic diseases in the mother which affect her state of immunity and impair her withstanding abilities. Moreover, non-disjunction and mutations increase with advanced age. In our study, congenital anomalies among live births were seen more commonly (3.3%) among multiparas in comparison to primiparas (1.8%). Similarly, Taksande et al4 and Sarkar et al17 reported an increase in occurrence of congenital malformations with increasing parity i.e. congenital malformations were more common in multipara mothers as compared to primipara. In the present study, another significant finding surfaced out that women with a gap of <3 years between pregnancies had significantly higher prevalence (1.7%) of congenital malformations in live births than those with a gap of ≥3 years (p=0.04). Chen et al studied the relationship between inter-pregnancy interval and congenital anomalies’ and reported the same sort of observation i.e association of inter-pregnancy interval with congenital anomalies was found to be statistically significant.18 Although nearly half of the mothers were anemic during pregnancy in...
the present study, the prevalence of congenital anomalies was equal in both in anemic and non-anemic mothers. This association was found to be non-significant statistically as well (p=0.219). It was also observed that prevalence of congenital malformation was a bit higher among hypertensive mothers (2.6%) and diabetic mothers (3.4%) as compared to non-hypertensive (1.2%) and non-diabetic mothers (1.1%). However, when subjected to analysis with chi square test, the associations of hypertension and diabetes during pregnancy with congenital malformations were found to be non-significant. Wahi et al in their study reported 1.6% congenital anomalies in babies of mothers with GDM while no congenital anomaly was reported among controls. Agarwal et al (1991) in their study observed that pre-eclamptic toxemia was significantly associated with occurrence of congenital malformations.

Conclusions

Though the present study has limitation that it was retrospective and only the women who registered at the sub-centres were enrolled for the study, still it was an attempt to throw light on the pattern of congenital malformations and their associations with different risk factors in mothers. In order to improve the general health of the newborn and to reduce the cases of congenital malformations, it seems imperative to plan and make a policy for adoption of family planning methods by the most vulnerable. Apart from this, there is a need to render proper counseling, recognize dangerous pregnancies, ensure prompt management of mothers’ diseases, and improve pregnancy care and mothers’ health status and of course enhance all round efforts on women empowerment.

References

Abstract

Introduction: The incidence of the urinary tract infections caused by Candida species, are becoming more common. Recently, an increase in the incidence of infection caused by fungi especially non albicans candida species (NAC) has been reported. Several virulence factors like biofilm formation, toxin production and presence of adhesins contribute to its pathogenesis.

Objectives: This study was undertaken to determine species distribution, biofilm formation and in-vitro antifungal susceptibility of candida isolated in our tertiary care hospital.

Method: Eighty seven clinical isolates obtained from urine specimens were subjected to wet mount, Gram’s stain and cultured on Sabouraud’s Dextrose agar (SDA) medium. Conventional method for yeast identification was done. Biofilm forming ability of each isolate was detected using microtitre plate method. Antifungal susceptibility against posaconazole, amphotericin-B, fluconazole, itraconazole, ketoconazole, 5-flucytosine, voriconazole, and caspofungin was tested using Sensititre® Yeastone ® (Trek diagnostic systems).

Results & Discussion: Out of 87 candida isolates, 31.03% (n=27) were C. albicans and 68.97% (n=60) were non albicans candida species (NAC). Among 60 NAC, C. kruseii 29.89% (n=26), C. glabrata 24.14% (n=21), C. tropicalis 14.94% (n=13). Among all isolates, 36.78% (n=32) were biofilm producers and biofilm positivity more among C. albicans 55.56% (n=15) as compared to NAC 28.33% (n=17) (P-value<0.002). The maximum positivity was observed with isolates from plastic devices (61.8%). The minimum inhibitory concentrations of all antifungal drugs against all isolates were within susceptible range except for fluconazole which was resistant to C. kruseii.

Conclusion: C. albicans remains the major isolate from urine samples and also biofilm formation as a virulence factor might have a higher significance for C. albicans than for NAC and its ability to form biofilm is intricately linked with ability of organisms to adhere, colonize and subsequently cause infection.

Introduction

Candida species are ubiquitous yeast found on many plants and are members of the normal flora of alimentary tract of mammals and mucocutaneous membranes of humans. They exist predominantly in the unicellular form with both sexual and asexual forms and show thin walled ovoid cells (blastospores) that reproduce by budding. Out of more than 150 species of candida, only nine species are regarded as frequent pathogens for humans. 1 Candida is the sixth most common isolated nosocomial pathogen, especially from urinary tract.2

The finding of candiduria in a patient with or without symptoms should be requires a careful evaluation, which should proceed in a logical fashion.3 Candida UTI are increasingly common due to prolonged antibiotic use, indwelling urinary catheters and immunocompromised individuals.4 Moreover drug resistance is a major cause of treatment failure in these patients. Among the different antifungal agents, resistance to the polyene compounds has remained an uncommon problem. But resistance to flucytosine and azoles now appears to be increasingly important in some group of patients, especially after the widespread use of fluconazole for extended periods.5

Several virulence factors like biofilm formation and presence of adhesins contribute to its pathogenesis. Biofilms are universal, complex, interdependent communities of surface-associated microorganisms, enclosed in an exopolysaccharide matrix occurring on any surface, including medical devices. Since biofilms are notoriously difficult to eliminate and serve as a source of recalcitrant infections, their study is highly relevant for public health.6 Biofilm drug resistance is a phenomenon of great clinical relevance explaining persistence of infection even in the face of an appropriate antifungal therapy.7, 8

In view of the above observations, this study was carried out with an aim to study species distribution of Candida isolates among UTI patients, biofilm formation as a virulence factor and their antifungal susceptibility pattern.

Material and Methods

The prospective cross sectional study was conducted, after obtaining approval from institutional ethical committee and fully informed and voluntary consent were obtained from the patient and / or their attendants,
in the Mycology section of Department of Microbiology, G.R. Medical College, Gwalior, Madhya Pradesh during the period of one year from Jan, 2015 to Dec, 2015.

All urine specimens of suspected case of UTI patients attending OPD, or admitted in various wards and ICU, among them which are culture positive for fungal growth (Yeast only) were included in the study. And those specimens which are culture negative (No growth) or culture positive for bacterial growth were excluded.

Clean catch mid-stream urine samples were collected in a sterile wide mouth leak-proof container. In catheterized patients’ catheter clamp technique were used for sample collection. Samples were transported to the laboratory as soon as possible with mean transport time of one hour, if delay of 2 to 4 hours samples were refrigerated and if more than 4 hour then samples were discarded and fresh sample were collected. Samples were processed as shown in Flow Chart 1 with their proper requisition form including age, sex, past medical and surgical history, presence of an indwelling urinary catheter, patient on antibiotics and duration of stay in ICU etc.

A total of 87 Candida isolates were recovered from 3381 urine specimens as a part of routine diagnostic procedures (Figure 1). These patients had no history of antifungal drug exposure prior to the collection.

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**Flow chart 1: Isolation and Identification**

1. **Sample processing**
2. **Inoculated & incubated at 37°C for 24 hours**
3. **Look for colony morphology**
4. **Microscopy look for budding yeast cells**
5. **Subculture on**
   - **SDA**
   - **CMA**
    - **Subculture for viability of isolate**
    - **Look for chlamydospore formation**
6. **Serum Germtube test**
7. **Carbohydrate assimilation test**
8. **Biofilm formation**
9. **Antifungal susceptibility**
10. **Growth at 45°C**
11. **Microtitre Plate method**
12. **Sensititre® Yeastone**
These candida isolates were subcultured on Sabouraud’s Dextrose Agar (HiMedia Laboratories Pvt. Ltd. Mumbai, India) for study (Figure 2). Identification was carried out by performing Gram’s stain, Germ tube test, Chlamydospore production test (Figure 3), Growth at 45°C and Carbohydrate assimilation test as per the CLSI guidelines. Antifungal susceptibility against posaconazole, amphotericin-B, fluconazole, itraconazole, ketoconazole, 5-flucytosine, voriconazole, and caspofungin was tested using Sensititre® fluconazole, voriconazole, and itraconazole, ketoconazole, 5-flucytosine, voriconazole and, except for all C. tropicalis and all C. krusei, to fluconazole antifungal agents as shown in Table 3.

Biofilm production (Microtiter plate method) 24 hour old isolates on Sabouraud dextrose agar (SDA) were washed and suspended in sterile saline equivalent to 0.5 McFarland standards. 20 μl of isolate suspension and 180 μl of Sabouraud dextrose broth (SDB) with 8% glucose were inoculated in each well of flat bottom polystyrene micro-titer plate (Figure 4) and incubated at 37°C for 24 hours without agitation. Then wells were washed twice with 0.15 M phosphate buffer saline (PBS) by Thermo Scientific Well wash machine. And 200 μL of PBS was added to each well and spectrophotometric readings were performed twice at 405 nm with SkanIt Software (version 4.1) for Microplate Reader (Thermo Fisher Scientific). The percent transmittance (%T) was calculated by subtracting the %T value for each test sample from the %T value for the reagent blank to obtain a measure of the amount of light blocked passing through the wells (%T_block). Biofilm production by each isolate was scored as given below in the Table 1.

- Mean percent transmittance (%T) of test = (%T1 + %T2)/2
- Mean %T of test = mean %T value of Blank well = %T_block of that test.

**Result and Discussion**

A total of 87 patients with candida UTI were evaluated during the study period. Organism causing infection included Candida albicans (31.03%; 27 patients), C. krusei (29.89%; 26 patients), C. glabrata (24.14%; 21 patients) and C. tropicalis (14.94%; 13 patients). Graph 1

![Graph 1: Bar diagram of distribution of Candida species among UTI cases](image)

Thirty two (36.78%) of 87 patients were infected by biofilm forming isolates, as assessed by the %T method. Biofilm production by C. albicans was significantly more frequent (55.56%) than that by all other NAC (28.33%; P-value < 0.002). Among the species, most commonly isolated from candida UTI patients (C. albicans, C. krusei, C. tropicalis and C. glabrata), biofilm production was most frequently observed for isolates of C. tropicalis (69.23% [9 of 13]), followed by C. albicans (55.56% [15 of 27]), C. glabrata (19.04% [4 of 21]) and C. krusei (15.38% [4 of 26]) Graph 2 and Table 2.

Isolates of Candida species were all found susceptible in vitro to amphotericin B, caspofungin, posaconazole, fluconazole, itraconazole, ketoconazole, 5 flucytosine, voriconazole and, except for all C. tropicalis and all C. krusei, to fluconazole antifungal agents as shown in Table 3.

**Patient demographic and clinical characteristics**

Of 87 patients with candida UTI having age of 42.9 ± 13.2 (mean ± standard deviation), male to female ratio of 1:2 as shown in Tables 4 and 5.

**Discussion**

Candida species are now the sixth most common cause of nosocomial urinary tract infection worldwide. Variables, such as patient age, underlying disease, location in hospital (ICU or non- ICU), indwelling urinary catheter and higher antibiotic exposure may influence the frequency and rank order of Candida species causing urinary tract infections. In this study, the distribution of Candida species was similar to reports from other countries, with C. albicans being the fungal species most frequently isolated from urine but there were significant increases found in the prevalence of non-C. albicans Candida species causing urinary tract infection. In this study, among the non- C. albicans Candida, C.krusei (n=26, 29.89%) was predominating isolated species followed by C. Glabrata (n=21, 24.14%), and C. tropicalis (n=13, 14.94%). In the
present study, biofilm production was found to occur most frequently among C. albicans (55.56%) than in NAC (28.33%). This finding is in concordance to an earlier report that suggested that pathogenic C. albicans were more likely to produce biofilms than among NAC. The explanation for this observation is not clear and warrants further study, but it is possible that some medical procedures might consistently impact the risk of developing urinary tract infection, caused by a fungal isolate capable of forming biofilm over the years. In this study, we used polystyrene plates to grow biofilms. Although a valid assay for biofilm formation in C. albicans based on polystyrene microfilter plates has now been established and standardized, it is possible that use of other materials, such as silicone catheters (e.g., silicone elastomer), may give results different from those we obtained here, perhaps because the polystyrene may not reflect exactly the ability to form a biofilm in vivo. In addition to the substrate material, it is important to note that other environmental parameters, such as substrate preconditioning solutions (i.e., those mimicking physiologic conditions, such as the presence of serum or saliva) and growth media can affect biofilm production. Antifungal resistance was rarely found in our study and was restricted to fluconazole resistance for all isolates of C. krusei and C. tropicalis only. In the present study it was observed that incidence of Candiduria was reported higher among the females (66.67%) than males (33.33%). Mahajan A. et al. reported 74 females and 26 males had Candiduria. In a study, N. Safdar et al. found that 77% females had candiduria. N. Jain et al. observed that 77.4% females had candiduria. However Kobayashi et al. reported female incidence to be 57.8%. Kauffman CA et al. reported 59.9% females with candiduria. Hence, all studies done in different parts of the world, show that females have more predilections towards candiduria, most probably due to short urethra in females.

In the present study common predisposing condition included urinary catheter 61.8%, patients using antibiotics 54.4%, diabetes in 44.5%, ICU stay in 26.4%, age between 31 to 60 year and sex that was affected more is female that is 66.67%. According to Navin Paul et al. incidence of various predisposing factors was catheterization 66.6%, intake of antibiotics 47.6%, diabetes 38.09% and surgery in 38.09%. That is in accordance to the present study. Kobayashi et al. reported incidence of various predisposing factors was: intake of antibiotics 100%, urinary catheter was present in 84.4%, surgical procedure in 66.7%.

**Conclusion**

C. albicans remains the major isolate from urine samples and also biofilm formation as a virulence factor might have a higher significance for C. albicans than for NAC and its ability to form biofilm is intricately linked with ability of organisms to adhere, colonize and subsequently cause infection.

**Acknowledgments**

We thank “Acer Pathology Lab, Gwalior” for granting us Sensititre Yeastone® (Trek diagnostic systems)

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**References**

Endoscopic Findings in Persistent Dyspepsia in Secondary Care Hospital Setting in North Kashmir

Riyaz U Saif Andrabi1*, Wani Abdul Ahad2, Mohammed Yousuff3, Banday Dawood4, Muzamil Mudasir5, Syed Mushtaq6

Abstract

Background: Dyspepsia is a common clinical problem and has a great impact on the patient’s quality of life. More than half of patients presenting with dyspepsia have no detectable lesion for their symptoms. The common organic causes of dyspepsia include peptic ulcer, esophagitis and cancer. The diagnostic test of choice is endoscopy. Age specific thresholds to trigger endoscopic evaluation may differ by gender, availability of resources and regional disease specific risks.

Aim: The aim of the study was to determine the prevalence of significant endoscopic lesions in patients presenting with dyspepsia.

Materials and Methods: This was a retrospective study. Data on patients presenting with dyspepsia and scheduled for upper gastrointestinal (UGI) endoscopy between January 2011 and December 2016 was collected.

Results: Nine thousand five hundred and twenty five patients with persistent dyspepsia were assessed by Upper Gastrointestinal (UGI) endoscopy. 58.8% were male. The mean age was 41 years. Endoscopy revealed normal findings or miscellaneous irrelevant findings in 6967 patients (73.1%). Significant endoscopic findings were diagnosed in 2558 (26.9%). These included peptic ulcers in 493 patients (5.1%), esophagitis in 560 (5.9%), erosive gastroduodenitis in 1069 (11.2%), Varices in 40 patients (0.4%) and UGI malignancy in 279 (2.9%).

Conclusions: The endoscopic diagnosis of persistent dyspepsia in our setting showed a predominance of functional disease. Every 4th person (26.7%) with persistent dyspepsia had organic lesions whereas UGI malignancy was an uncommon finding. The most frequent significant pathologies included erosive gastroduodenitis, esophagitis and peptic ulcer disease. Patients with recent onset of dyspepsia who are in the age group at risk of gastric malignancy should undergo early endoscopy. UGI endoscopy is simple procedure that can be undertaken for early diagnosis of benign as well as malignant lesions in patient presenting with dyspepsia.

Introduction

Dyspepsia is defined as pain or discomfort in the upper abdomen. Dyspepsia is a prevalent complaint in general practice and gastrointestinal clinics, with a prevalence of around 30% among adults in India. Dyspepsia represents up to 8.3% of all primary care physician visits and causes huge economic costs to patients and the economy. Only 75% of the dyspepsia experts, 73% of gastroenterologists and 59% of primary care providers adhere to dyspepsia best practices; so “dyspepsia” means different things to different providers. Without a common diagnostic language, general practitioners may be unable to provide adequate treatment following common dyspepsia guidelines. Rome definitions have been helpful in better-standardizing patients that are included in studies of dyspepsia but are less relevant to clinical practice as there is considerable overlap in symptom presentation making classification difficult in many patients presenting in primary and secondary care. For this reason, a clinically relevant definition of dyspepsia as predominant epigastric pain lasting at least 1 month is preferred. This can be associated with any other upper gastrointestinal symptom such as epigastric fullness, nausea, vomiting, or heartburn, provided epigastric pain is the patient’s primary concern. The rapid introduction of new diagnostic criteria for dyspepsia has made very difficult or virtually impossible to compare prevalence rates from different periods or geographic regions. Because structural UGI tract diseases, such as peptic ulcer, erosive esophagitis, luminal strictures and malignancy can course with dyspepsia, esophagogastroduodenoscopy (EGD) is the diagnostic procedure of choice to differentiate patients with organic from those with functional dyspepsia. Although it is possible to propose endoscopy as the initial strategy for dyspepsia, the establishment of this procedure for every dyspeptic patient may not be practical approach, as the high prevalence of the syndrome will result in very high costs to any health system. Moreover, the diagnostic procedure and its cost effectiveness must be considering that a large number of uninvestigated dyspepsia are functional cases. More than half of the patients presenting with dyspepsia have no detectable cause for their symptoms. Once the decision has been made to investigate, the diagnostic
Cancer of the UGI tract is usually advanced at the time of diagnosis but a low threshold of suspicion for gastric malignancy in dyspeptic patients may result in earlier diagnosis and improved survival. However cancer accounts for only 1–2% of diagnoses at UGI tract and less in patients under the age of 50 years.

This study was undertaken to determine the prevalence of significant endoscopic lesions in patients presenting with persistent dyspepsia (> 8 weeks proton pump inhibitors [PPI] trial).

Material and Methods

This was a retrospective study carried out at Government District Hospital, Baramulla in North Kashmir over a period of six years from January 2011 to December 2016. Government District Hospital, Baramulla is a secondary-care Governmental hospital in North Kashmir. The hospital serves a population of nearly two million people. The endoscopy unit provides an open-access service and receives patients from outpatient clinics and other hospitals in the area. Patients are from a lower socioeconomic background. All patients presenting with persistent dyspepsia were included in the study. Endoscopic biopsy was done at the discretion of an endoscopist. Pathological examination was performed by expert pathologists.

Definitions

Dyspepsia is defined as predominant epigastric pain lasting at least 1 month. This can be associated with any other upper gastrointestinal symptom such as epigastric fullness, nausea, vomiting, or heartburn, provided epigastric pain is the patient’s primary concern. Persistent dyspepsia is defined as symptoms of dyspepsia persisting after two months of adequate PPI trial. Heartburn is not included in the diagnostic symptom criteria for dyspepsia. Significant endoscopic findings in the UGI tract were defined as those benefiting from specific treatment or those that are life threatening. The presence of any of the following lesions was considered as a significant finding in UGI endoscopy: peptic ulcer, esophagitis (with or without hiatal hernia), erosive gastritis or duodenitis, stricture, Barrett’s esophagus, esophageal candidiasis, neoplasm, mass and polyps. The presence of any of the following lesions was considered as an irrelevant endoscopic finding: erythematous gastritis, atrophic gastritis and incidental miscellaneous abnormalities (portal hypertensive gastropathy, hiatal hernia without esophagitis and vascular ectasia).

Patients and exclusions

A total of 9525 patients underwent UGI endoscopy between January 2011 and December 2016. Data on patients presenting with persistent dyspepsia and scheduled for UGI endoscopy were collected. Patients who underwent UGI endoscopy for reasons other than dyspepsia such as dysphagia, UGI bleeding, or strong suspicion of cancer were excluded from the study. Patients with prior peptic ulcer were also excluded. Presence of systemic decompensated diseases (congestive heart failure, coronary heart disease, liver failure, diabetes mellitus, thyroid disease, acute or chronic respiratory failure, hematological diseases), presence of major psychiatric disorders, impediment to endoscopy and difficulty for the patient to understand the aims and procedures of the study were also excluded from the study. Those whose procedures were not completed were excluded subsequently.

Data recording and statistics

A standardized data collection form (sheet) was completed for each patient. Recorded information included demographic data (age and gender) and endoscopic findings. Data were analyzed to assess presence of significant gastrointestinal lesions. The data from the patients were registered, and tabulated.

Results

Patients’ characteristics

9525 patients with persistent dyspepsia were assessed by EGD. 5603 (58.8%) patients were male and 3922 (41.2%) were female. Ages ranged from 18 to 88 years with a mean age of 41 years.

Endoscopic findings

Endoscopy revealed normal findings or miscellaneous irrelevant findings in 6967 patients (73.1%). Endoscopy revealed significant pathology in 2558 patients (26.9%). Peptic ulcer was diagnosed in 493 patients (5.2%), duodenal ulcers in 403 (4.2%) and gastric ulcers in 90 (1%). Esophagitis was diagnosed in 560 patients (5.9%). Erosive gastritis was diagnosed in 760 (8.0%) patients and duodenitis was diagnosed in 309 patients (3.2%). Gastric malignancy was diagnosed in 40 patients (0.4%) and esophageal cancer in 239 (2.5%).

Discussion

Dyspepsia is a common clinical problem seen by both primary care physicians and gastroenterologists. Dyspepsia accounts for about 4–5% of all the general practitioner consultations and 20–40% of all gastroenterological consultations. Initial evaluation should focus on the identification and treatment of potential causes of symptoms such as gastro-esophageal reflux disease, peptic ulcer disease,
and medication side effects but also on recognizing those at risk for more serious conditions such as gastric cancer. Endoscopy is recommended as the first investigation in the work up of a patient with dyspeptic symptoms aged 60 years or more and is essential in the classification of the patient’s condition as organic or functional dyspepsia and patients under 60 years EGD is done on case to case basis. Approximately 40% of dyspeptic patients have an organic cause, and only 20% of patients have significant gastroduodenal lesions, such as peptic ulcer. The most commonly reported major endoscopic abnormalities are: gastric ulcer (1.6–8.2%), duodenal ulcer (2.3–12.7%), esophagitis (0–23.0%), and gastric malignancy (0–3.4%). Only in a few cases are dyspeptic symptoms caused by gastro-esophageal malignancy. While gastric or esophageal cancer is an unusual finding in patients with dyspepsia, excluding malignancy is a common reason given for performing endoscopy. Once an organic cause for symptoms has been excluded, a diagnosis of functional dyspepsia can be made.

In the present study Nine thousand five hundred and twenty five patients presenting with persistent dyspepsia at a secondary care hospital over a 6-year period were assessed. Our goal was to describe significant endoscopic findings among patients with persistent dyspepsia. In our study male (58.8%) to female (41.2%) ratio was 1.4:1. Gado A et al reported an incidence of 51% in males and 49% in females. Thomson A. B.R et al reported a male to female ratio of 1:1. In India Sumathi B et al reported a male to female ratio of 1.5:1 and Sunil Kumar et al (24) reported a ratio of 1.05:1.

Our observation shows a male preponderance most probably attributed to the increased smoking and tobacco which play a key role in pathogenesis of dyspepsia. It may also be attributed to the fact that in our society women’s health problems are not given priority and fewer symptomatic women than men present to health facilities. Gado A et al reported normal findings in 65% patients presenting with dyspepsia and 82% of patients younger than 30 years (average of 73.5%). Our study is almost in concordance with other studies.

Among the benign lesions, most common was gastritis (8.0%), followed by esophagitis 5.9%. Also peptic ulcer was seen in 5.1% patients. In the present study, we observed UGI Malignancy in 279 (2.9%) patients of dyspepsia. Gado A et al reported 16 (1%) patients with UGI malignancy among patients with dyspepsia. Ages ranged from 37 to 75 years. UGI malignancy was diagnosed in 1% of patients aged 30–50 years and 2% of patients more than 50 years (P = 0.003). UGI malignancy was not found in dyspeptic patients younger than 30 years old. Sumathi B et al reported a total of 282 patients (8.27%) of UGI malignancy, among these 125 (4.5%) were reported in patients of dyspepsia without alarm symptoms and 48 (21.6%) were reported in patients of dyspepsia with alarm symptoms. Sunil Kumar et al reported gastric cancer in 2.8% patients and Manes et al reported 6 (0.86%) patients of gastric cancer out of 706 patients studied. Thomson A.B.R et al reported malignancy in less than 2% of the patients.

The results in our study are consistent with most other studies. Gado et al and Sunil Kumar et al reported Oesophagitis in 0–23.0% and 15.6% respectively. The discrepancy in the studies can be attributed to the differences in socio-cultural factors, absence of alcohol use in the study population and different food habits and the lack of proper defining landmark for differentiating heart burn and epigastric pain or burning.

The findings of the present study confirmed that the majority of patients with dyspepsia had no important endoscopic lesions. Further, unmeasured benefits could include improvement in quality of life, if anxiety is reduced, and reduction in subsequent health care utilization.

Conclusion

The endoscopic diagnosis of persistent dyspepsia in our setting showed a predominance of functional disease. Every 4th person (26.7%) with persistent dyspepsia had organic lesions whereas UGI malignancy was an uncommon finding. The most frequent significant pathologies included erosive gastroduodenitis, esophagitis and peptic ulcer disease. Patients with recent onset of dyspepsia who are in the age group at risk of gastric malignancy should undergo early endoscopy. UGI endoscopy is simple procedure that can be undertaken for early diagnosis of benign as well as malignant lesions in patient presenting with dyspepsia.

References

6. Udai C. Ghoshal Functional dyspepsia: The Indian Scenario, supplement to JAPI march 2012 vol 60 page 6
Clinical Profile, Risk Factors and Outcomes in Patients with Cerebral Venous Sinus Thrombosis: A Study from Western India

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Abstract

Aim: Study of cause and clinical profile of venous sinus thrombosis in Western India

Settings and Design: A retrospective study was conducted to ascertain the clinical profile, etiology, and follow up of patients with venous sinus thrombosis.

Methods and Material: Hospital database of patients suffering from venous sinus thrombosis from two tertiary care hospitals in West India were studied. A telephonic follow up was taken for assessment of outcome.

Inclusion criteria were a) Age more than 15 years of age b) clinically symptomatic patients c) Diagnosis confirmed by Magnetic resonance Venography (MRV) or CT Venography (CT Venography)

Exclusion criteria: Patients with infarct in arterial territory, hypertensive hemorrhage, metabolic encephalopathy and eclampsia were excluded from the study.

Statistical analysis used: Descriptive statistic was performed as frequency, mean and standard deviation or percentages. Difference in continuous variables was evaluated by using independent t-test while chi-square test was performed in categorical variables. Statistical P<0.05 was considered statistically significant.

Results: We conducted a retrospective study of patients with venous sinus thrombosis in Rajasthan in western India. Out of 71 patients in our study group the mean age of presentation was 36.64 years. 42 patients were male (59.2%) and 29 were female (40.8%). Only 9 patients (12.6%) had pregnancy or puerperium related venous sinus thrombosis. The most common presenting feature was headache 47/71(66.2), followed by seizures 33 (46.5%), paresis 20/71 (28.16%) and coma 15/71(21.1%).

5/27 patients, Protein S in 6/27 patients and Anti thrombin III in 1/23 patient studied respectively. History of oral contraceptive was present in 33/71(46.5%), 23/71 (32.4%) had anemia, 21/71 (29.5%) had hyperhomocysteinemia and 18/71 (25.3%) had a history of pregnancy or puerperium. Raised homocysteine level was found in 26/35 (74.3%) patients in whom they were measured. 9 patients had moderately elevated homocysteine levels (15-30), another 9 had intermediate values (31-64) and 5 patients had elevated homocysteine level >65. Hyperhomocysteinemia was the commonest causative factor and was far more common in men (21/25) than in women (5/10). (p value 0.019). 24 out of 71 patients were found to be anemic (33.8%). Anemia was far more common in women than in men. (p value .002). Protein C level was found abnormal in 5/27 patients, Protein S in 6/27 patients and Anti thrombin III in 1/23 patient studied respectively. History of oral contraceptive intake was recorded in only a minority of women with venous sinus thrombosis (7/24.1%) compared to the western data where most of the venous sinus thrombosis are related to the contraceptive pills.

Conclusions: The clinical presentation of venous sinus thrombosis in tertiary care centers is changing outside the traditional puerperium / pregnancy related venous sinus thrombosis. Common risk factors include hyperhomocysteinemia, anemia, coagulopathy, pregnancy related, vasculitis, malignancy and oral contraceptive usage. Male involvement was far more common than females and was usually associated with a higher level of homocysteine.
Introduction

Cerebral vein and dural sinus thrombosis are an uncommon cause of stroke and is often more difficult to diagnose than usual causes of stroke. In the era of magnetic resonance imaging (MRI) and increased awareness of disease, more individual are being diagnosed with this condition. This study was carried out in Rajasthan, India which has a fairly hot and dry climate. There is a change in profile and presentation of this condition. This study was carried in department of neurology with one or more features of venous sinus thrombosis like seizures, headache, papilledema, focal neurological deficit, long term outcome was not available.

Material and Methods

A retrospective study was conducted from hospital database of patients suffering from venous sinus thrombosis. Two sites were included both of which were tertiary care hospitals in West India. A computerized data base was accessed for discharge summaries and original files were then retrieved from Medical Research Department.

Inclusion criteria

Clinical symptoms consistent with diagnosis of venous sinus thrombosis, age >15 years and cerebral venous thrombosis proven, either with CT venography or MRI venography.

Exclusion criteria

Patients with infarct in arterial territory, hypertensive hemorrhage, metabolic encephalopathy and eclampsia were excluded from the study.

A telephonic follow up was taken for assessment of outcome where long term outcome was not available. 58 patients were selected out of 3295 neurology admissions from the first center between January 2012 to Jan 2017 and 13 patients were selected from the second center for same duration. All patients were admitted in department of neurology with one or more features of venous sinus thrombosis like seizures, headache, papilledema, focal neurological deficit.

Fig. 1: The age band with gender distribution

Table 1: Common presenting symptom with CVST

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertigo</td>
<td>8(11.3%)</td>
<td>2(4.8%)</td>
<td>6(20.7%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Numbness</td>
<td>11(15.5%)</td>
<td>9(21.4%)</td>
<td>2(6.9%)</td>
<td>0.096</td>
</tr>
<tr>
<td>Headache</td>
<td>47(66.2%)</td>
<td>29(69.0%)</td>
<td>18(62.1%)</td>
<td>0.541</td>
</tr>
<tr>
<td>Fever</td>
<td>11(15.5%)</td>
<td>6(14.3%)</td>
<td>5(17.2%)</td>
<td>0.735</td>
</tr>
<tr>
<td>Visual loss</td>
<td>4(5.6%)</td>
<td>1(2.4%)</td>
<td>3(10.3%)</td>
<td>0.153</td>
</tr>
<tr>
<td>Diplopia</td>
<td>13(18.3%)</td>
<td>6(14.3%)</td>
<td>7(24.1%)</td>
<td>0.291</td>
</tr>
<tr>
<td>Papilledema</td>
<td>9(12.7%)</td>
<td>4(6.5%)</td>
<td>5(17.2%)</td>
<td>0.337</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>10(14.1%)</td>
<td>6(14.3%)</td>
<td>4(13.8%)</td>
<td>0.953</td>
</tr>
<tr>
<td>Coma</td>
<td>15(21.1%)</td>
<td>11(26.2%)</td>
<td>4(13.8%)</td>
<td>0.291</td>
</tr>
<tr>
<td>Seizure</td>
<td>33(46.5%)</td>
<td>23(54.8%)</td>
<td>10(34.5%)</td>
<td>0.092</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26(36.6%)</td>
<td>15(35.7%)</td>
<td>11(37.9%)</td>
<td>0.849</td>
</tr>
<tr>
<td>Mental Disorder</td>
<td>6(8.5%)</td>
<td>1(2.4%)</td>
<td>5(17.2%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Paresis</td>
<td>20(28.1%)</td>
<td>15(35.7%)</td>
<td>5(17.2%)</td>
<td>0.363</td>
</tr>
</tbody>
</table>

Table 3: Distribution of Thrombosis in MRV/CTV

<table>
<thead>
<tr>
<th>Sinus</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior sagittal sinus</td>
<td>51(70.8%)</td>
<td>28(66.7%)</td>
<td>23(79.3%)</td>
<td>0.244</td>
</tr>
<tr>
<td>Transverse sinus left</td>
<td>28(34.4%)</td>
<td>15(35.7%)</td>
<td>13(44.8%)</td>
<td>0.440</td>
</tr>
<tr>
<td>Transverse sinus right</td>
<td>24(33.8%)</td>
<td>15(35.7%)</td>
<td>9(31.0%)</td>
<td>0.682</td>
</tr>
<tr>
<td>Sigmoid sinus left</td>
<td>28(39.4%)</td>
<td>16(38.1%)</td>
<td>12(41.4%)</td>
<td>0.268</td>
</tr>
<tr>
<td>Sigmoid sinus right</td>
<td>3(4.2%)</td>
<td>2(4.8%)</td>
<td>1(3.4%)</td>
<td>0.848</td>
</tr>
<tr>
<td>Both sigmoid sinus</td>
<td>1(1.4%)</td>
<td>1(2.4%)</td>
<td>-</td>
<td>0.403</td>
</tr>
<tr>
<td>Straight sinus</td>
<td>15(21.4%)</td>
<td>9(21.4%)</td>
<td>6(20.7%)</td>
<td>0.940</td>
</tr>
<tr>
<td>Internal cerebral vein of galen</td>
<td>9(12.7%)</td>
<td>5(11.9%)</td>
<td>4(13.8%)</td>
<td>0.544</td>
</tr>
<tr>
<td>Cortical veins</td>
<td>16(22.5%)</td>
<td>12(28.6%)</td>
<td>4(13.8%)</td>
<td>0.143</td>
</tr>
<tr>
<td>Jugal veins</td>
<td>13(18.3%)</td>
<td>7(16.7%)</td>
<td>6(20.7%)</td>
<td>0.667</td>
</tr>
<tr>
<td>Cerebellar veins</td>
<td>4(4.6%)</td>
<td>2(4.8%)</td>
<td>2(6.9%)</td>
<td>0.701</td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>1(1.4%)</td>
<td>1(2.8%)</td>
<td>-</td>
<td>0.403</td>
</tr>
</tbody>
</table>

Table 2: Risk factor for CVT in included patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>26(36.6%)</td>
<td>21(50%)</td>
<td>5(17.2%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
<td>26(36.6%)</td>
<td>19(45.2%)</td>
<td>7(24.1%)</td>
<td>0.189</td>
</tr>
<tr>
<td>Anemia</td>
<td>24(33.8%)</td>
<td>8(19%)</td>
<td>16(55.2%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lupus anticoagulant plant</td>
<td>5(7%)</td>
<td>5(11.9%)</td>
<td>0(0.0%)</td>
<td>0.132</td>
</tr>
<tr>
<td>Thrombophilia genetic</td>
<td>17(30.4%)</td>
<td>8(24.2%)</td>
<td>9(31.9%)</td>
<td>0.384</td>
</tr>
<tr>
<td>Thrombophilia acquired</td>
<td>8(14.3%)</td>
<td>6(18.2%)</td>
<td>2(8.7%)</td>
<td>0.057</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>1(1.4%)</td>
<td>1(2.4%)</td>
<td>0(0.0%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Outside CNS</td>
<td>1(2.4%)</td>
<td>1(2.4%)</td>
<td>0(0.0%)</td>
<td>0.688</td>
</tr>
<tr>
<td>Hematological</td>
<td>2(2.8%)</td>
<td>1(2.4%)</td>
<td>1(3.4%)</td>
<td>0.560</td>
</tr>
<tr>
<td>CNS disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dural fistulae</td>
<td>4(5.6%)</td>
<td>3(7.1%)</td>
<td>1(3.4%)</td>
<td>0.560</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>2(2.8%)</td>
<td>2(4.8%)</td>
<td>0(0.0%)</td>
<td>0.560</td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behcet's disease</td>
<td>1(1.4%)</td>
<td>1(2.4%)</td>
<td>0(0.0%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>2(2.8%)</td>
<td>2(4.8%)</td>
<td>0(0.0%)</td>
<td>0.932</td>
</tr>
<tr>
<td>Mixed connective tissue disorder</td>
<td>2(2.8%)</td>
<td>2(4.8%)</td>
<td>0(0.0%)</td>
<td>0.932</td>
</tr>
<tr>
<td>Family History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>3(4.2%)</td>
<td>3(7.1%)</td>
<td>0(0.0%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2(2.8%)</td>
<td>2(4.8%)</td>
<td>0(0.0%)</td>
<td>0.146</td>
</tr>
<tr>
<td>Artery embolism</td>
<td>4(5.6%)</td>
<td>4(9.5%)</td>
<td>0(0.0%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Drugs used in last six months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>7(9.9%)</td>
<td>0(0.0%)</td>
<td>7(24.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Steroids</td>
<td>6(8.5%)</td>
<td>3(7.1%)</td>
<td>3(10.3%)</td>
<td>0.634</td>
</tr>
<tr>
<td>Hormone Replacement Therapy</td>
<td>5(7%)</td>
<td>0(0.0%)</td>
<td>5(17.2%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>2(2.8%)</td>
<td>0(0.0%)</td>
<td>2(6.9%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Puerperium</td>
<td>7(23.3%)</td>
<td>0(0.0%)</td>
<td>7(24.1%)</td>
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<tr>
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<tr>
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<td>6(14.3%)</td>
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<td>2(4.8%)</td>
<td>0(0.0%)</td>
<td>0.062</td>
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<td>4(5.6%)</td>
<td>0(0.0%)</td>
<td>4(13.8%)</td>
<td>0.138</td>
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<tr>
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<td>9(21.4%)</td>
<td>5(17.2%)</td>
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<td>6(14.3%)</td>
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<td>9(7%)</td>
<td>1(2.4%)</td>
<td>8(27.6%)</td>
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<tr>
<td>Surgery</td>
<td>14(19.7%)</td>
<td>8(19%)</td>
<td>6(20.7%)</td>
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<td>Dehydration</td>
<td>18(25.4%)</td>
<td>11(26.2%)</td>
<td>7(24.1%)</td>
<td>0.845</td>
</tr>
<tr>
<td>Others</td>
<td></td>
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<td>Alcoholism</td>
<td>10(14.1%)</td>
<td>9(21.4%)</td>
<td>1(3.4%)</td>
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<tr>
<td>Smoking</td>
<td>15(21.1%)</td>
<td>15(35.7%)</td>
<td>0(0.0%)</td>
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</table>
altered sensorium and evidence of venous sinus thrombosis on magnetic resonance venography (MRV) or computerized tomography venous study (CTV). Presenting features, detailed demographic profile, evaluation of risk factors including genetic and acquired procoagulant states and infections, malignancy (central nervous system, outside CNS and hematological), vasculitis, anemia, hyperhomocysteinemia, vitamin B 12 levels, drug usage including hormone replacement therapy, oral contraception, steroid usage, thyroid disorder, smoking, alcoholism, surgery, pregnancy and puerperium were recorded. Physical parameters at time of presentation including systolic and diastolic blood pressures heart rate were recorded on admission with level of consciousness, papilledema and focal neurological deficits. On radiology presence or absence of infarct and/or hemorrhage and the site of venous sinus occlusion was recorded. Treatment during hospital stay was recorded in form of use of unfractionated heparin, low molecular weight heparin, mannitol, antiepileptic medications, oral anticoagulants and decompressive craniotomy. Outcomes were recorded in form of complete recovery, dependency and death/brainstem death. Descriptive statistic was performed as mean and standard deviation or percentages. Difference in continuous variables was evaluated by using independent t-test while chi-square test was performed in categorical variables. For the establishing the differences in clinical observations between male and female, data were analyses as male vs. female and p value < 0.05 was considered as statistically significant.

Results

Out of 71 patients in our study group the mean age of presentation was 36.64 years with minimum age of 17 years and maximum age of 79 years. 42 patients were male (59.2%) and 29 were female (40.8%). The age band of presentation with respect to number of cases is indicated in figure 1 with the gender distribution. Maximum numbers of patients were in 20 to 30 years age group and in almost all subgroups the number of men exceeded than women.

The most common presenting feature was headache 47/71(66.2%), followed by seizures 33(46.5%), paresis 20/71 (28.16) and coma 15/71(21.1%). Vertigo was present in 8 patients (11.3) out of which 2 were men (4.8) and 6 were women (20.7) with a p value of 0.037. Fever at time of presentation was recorded in 11/71 patients. 6 patients, one male
and 5 females presented with dullness, depression like picture preceded by headache and one had psychosis like presentation. This presentation was far more common in women than men. (P value 0.027). Diplopia was present in 13/71 patients and vomiting was present in 26(36.6%) patients (Table 1).

Among the women only 2 patients had venous sinus thrombosis during pregnancy and seven during puerperium. 20(28.18%) patient had limb paresis out of which 12 had left sided and 7 had right sided weakness and one patient had quadriparesis. Family history of DVT and pulmonary embolism was recorded in 5 patients and arterial embolism was recorded in 4 patients. MRI Brain recorded infarcts in 32/71 patients and predominant hemorrhage was recorded in 34/71 (Figure -2f). 4 cases were associated with malignancy (one CNS, one outside CNS and 2 hematological). One case had Behcet’s syndrome, two had sarcoidosis, 2 patients had mixed connective tissue disorder and 2 had nonspecific vasculitis, difference between sexes in these patients was not significant. Raised homocysteine level was found in 26/35 (74.3%) patients in whom they were measured. 9 patients had moderately elevated homocysteine levels (15 - 30 μmol/L), another 9 had intermediate values (31 - 64 μmol/L) and 5 patients had elevated homocysteine level >65 μmol/L. Hyperhomocysteinaemia was the commonest risk factor and was far more common in men (21/25) than in women (5/10) (P value 0.019). B12 deficiency was found in 26/41 patients where it was checked, again more common in men than in women. This however did not reach statistical significance. 24 out of 71 patients were found to be anemic (33.8%). Anemia was far more common in women than in men. (P value .002). Protein C level was assessed in 27 patients and found to be low in 6 patients (3 males and 3 females). Factor V Leiden mutation was not found in any of the patient studied (total no 16). Abnormal anti thrombin III levels were found in one patient (1/23). One patient had associated nephrotic syndrome with steroid intake. 16 patients had associated infections (Table 2). History of oral contraceptive intake was recorded in only a minority of women with venous sinus thrombosis 7(24.1%) compared to the western data where most of the venous sinus thrombosis are related to the contraceptive pills.

Maximal number of patients had sagittal sinus involvement, followed by transverse sinus and sigmoid sinus (Table 3). In majority of patients more than one venous sinus was affected. No gender difference was found in site of involvement between male and females. As far as treatment was concerned most of the patients received low molecular weight heparin / unfractionated heparin, number of patients receiving low molecular weight heparin were more than those receiving unfractionated heparin possibly due to the ease of administration. Only a small fraction received additional antiplatelet medication. 73.2 % patients were on antiepileptic medication. Three patients underwent decompressive hemicraniectomy. Most patients were treated with low molecular weight heparin followed by oral anticoagulants. Mannitol was used in 17/42 patients (Table 4). No difference was observed between groups receiving mannitol and otherwise in terms of recovery, dependency or death. A longer hospital stay was observed in the group receiving mannitol 9.5±6.3 days compared to the group not receiving same 5.2±4.3 (P 0.014). Average duration of hospital stay was 7.4 days. Most patients survived with good recovery 43.7%, complete recovery were observed in 18(25.4%) patients and death was an outcome in 4(5.6%) of total patients (Table 5). Dependency was present in 25.4 % patients.

### Discussion

Venous sinus thrombosis has been traditionally considered a disease of women in the postpartum period in tropical countries. Most of the Indian studies done earlier have shown a female predisposition with a few international studies also showing the same pattern. With time the clinical profile of disease is evolving and atypical presentation in men are now fairly common. A study from south India also revealed a male predominance in a large cohort of patients with predominant risk factors of anemia, hyperhomocysteinemia, and alcoholism. Similarly, in other studies from Chennai and Mumbai showed venous sinus thrombosis in younger patients and male female ratio of 1.5:1 and 1.6:1. Our study also revealed a male preponderance with 59.2% male patients and 40.8% female patients.

Anemia also was fairly common and was seen more frequently in women than in men. Most patients were seen in the younger age group for stroke between 21 to 40 years of age. In a study by Saroja et al in women with CVT anemia was found in 76.64% of women. History of alcoholism was far less in our study 10(14.1%) in comparison to study by Narayan et al, out of which 9 were men and one was of female gender.

In the ISCVT study hyperhomocysteinemia was found in just 4.5 % of cases (28/624) compare to our study where hyperhomocysteinemia was found in 36.6% cases. The raised homocysteine level in men reached statistical significance in our study (0.019). Vitamin B 12 deficiency was also more common in men compared to females although it did not reach statistical significance. In the study from Narayan et al 18.2% of patients had raised homocysteine levels. In a study from south India hyperhomocysteinemia was found in 17/40 (42.5%). A study conducted in Karnataka, women of South India with CVT by Saroja et al found more patients with non-pregnancy related
venous sinus thrombosis (81/150-54%) among which hyperhomocysteinemia was found in 11/48 (22.9%). Another study Martinelli et al 2003 conducted in Italy which specifically evaluated the role between raised homocysteine level and cerebral venous thrombosis found hyperhomocysteinemia in 27% patients with CVT compared to control where it was found in only 8% patients and concluded that it is associated with 4-fold increased risk of CVT. In a Japanese study by Takemaru M 2004 for patients of hyperhomocysteinemia and CVT found a strong association between elderly males. Their population was found to have a different demographic distribution compared to western literature. Very few studies have been done in our region where incidence of venous stroke appears fairly high. In a study by Pangariya et al 1997 on CVT in pregnancy and puerperium, CVT was associated with half of young stroke and 40% of stroke in women. A comprehensive review by Dash et al 2012 also eluted the unique Indian pattern of venous sinus thrombosis. Whether hot dry climate, with increased homocysteine level predisposes these individuals to venous sinus thrombosis is debatable. While most women with hyperhomocysteinemia had only mildly elevated levels, most men with same had moderate to severe elevation in these levels. Most of the Indian population in this part of India follows a vegetarian diet and low vitamin B12 levels are fairly common. Low Vitamin B12 level is associated with a raised homocysteine level. Another patient in this study had stopped vitamin B12 and folate being used for treatment of increased homocysteine level and developed recurrence of thrombosis along with elevated homocysteine level without any trigger and in absence of any other hypercoagulable factors suggesting possible pathogenesis. We had a few interesting presentations which were worth a mention. 16 patients had associated infections out of which 10 (14.1) were in central nervous system (CNS) infections and the rest were outside nervous system 02 (ENT / Neck) and four elsewhere. What was interesting about these infections was the fact that these patients often deteriorated after showing some improvement on treatment for these infections. One patient who was a diagnosed case of progressive supra nuclear palsy suffered with chikungunya. After a period of improvement secondary deterioration was observed due to CVT possibly as a result of immobility. Another patient had herpes encephalitis following which secondary deterioration was observed. A third patient had concurrent tubercular granulomas brain/cold abscess (positive for Acid fast bacillus) with inferior vena cava and sagittal sinus thrombosis. There were a few cases of vasculitis / connective tissue disorder among these patients including Bechet’s syndrome and mixed connective tissue disorder (MCTD).

Whether to use mannitol or not in patients with venous sinus thrombosis is debatable. In our study the mannitol group had a longer hospital stay compared to the group where it was not used. Most of the patients had a good outcome.

**Conclusion**

The clinical presentation of venous sinus thrombosis to tertiary care centers is changing outside the traditional puerperal / pregnancy related venous sinus thrombosis. Common risk factors include hyperhomocysteinemia, anemia, coagulopathy, pregnancy related, vasculitis, malignancy and oral contraceptive usage. Male involvement was far more common in our study than females and was usually associated with a higher level of homocysteine.

**References**

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Neuropathy in Prediabetics: Is Oxidative Stress to Contribute?

Amrinder Singh¹, Ajay Chauhan²*, Parul Goyal³, Priyamvadha Ramesh¹

Abstract

Objective: To assess the association of oxidative stress and serum vitamin D levels in sensory neuropathy in prediabetes.

Method: Serum and urine levels of 8-OHdG (a marker of oxidative stress) and serum levels of vitamin D were compared in prediabetic patient having sensory neuropathy to those who did not have sensory neuropathy as determined by VPTs measured by Digital Biothesiometer and MNSI (Michigan Neuropathy Screening Instrument).

Result: A total of 60 prediabetic cases between 35 years to 60 years were included in this study. Among all the prediabetic subjects, 43.3 % subjects had neuropathy according to VPTs measured by Biothesiometer. T-test analysis suggested that serum levels of 8-OHdG were significantly higher in subjects with neuropathy than subjects without neuropathy (1006.58 ± 511.8 vs 688.6 ± 607.3, p value = 0.035). Urinary levels of 8-OHdG were also significantly higher in subjects with neuropathy than subjects without neuropathy (699.35 ± 419.5 vs 474.57 ± 402.5, p value = 0.04). No such significant difference however was present in serum levels of vitamin D between neuropathic and non-neuropathic prediabetics (20.13 ± 18.44 vs 16.96 ± 11.72, p value = 0.419). VPTs were found to have statistically significant positive correlation with serum 8-OHdG (Pearson Correlation Coefficient = 0.317(R), 0.307(L); p-value=0.014(R),0.017(L)) and urine 8-OHdG levels (Pearson Correlation Coefficient= 0.288(R), 0.255(L); p-value=0.026(R), 0.049(L)). According to MNSI physical assessment score (> or = 2), 38.3 % subjects (23 subjects) had neuropathy. MNSI score is positively correlated with serum 8-OHdG (Pearson Correlation Coefficient = 0.308; p-value = 0.017). Correlation with urine 8-OHdG was not statistically significant (Pearson Correlation Coefficient = 0.687; p value = 0.06). Correlations of MNSI scores (Pearson Correlation Coefficient=0.14, p-value=0.287) and VPTs(Pearson Correlation Coefficient=0.058(R), 0.189(L); p-value=0.660(R), 0.148(L)) with serum vitamin D levels were not statistically significant.

Conclusion: Oxidative stress, as confirmed by the biomarker, 8-OHdG, has an important role in the development of this sensory neuropathy.

Introduction

Type 2 DM is characterized by a long asymptomatic phase (ranging from 4 to 7 years) between the genuine onset of hyperglycemia and clinical diagnosis which may explain the relatively high prevalence of microvascular complications in newly diagnosed patients of type 2 DM.¹

Emerging body of evidence suggests that the pathophysiological process of these microvascular and even macrovascular complications, to some extent, starts as early as in prediabetic stage.² Impaired glucose tolerance (IGT)/ prediabetes is a marker of insulin resistance and is predictive of microvascular and macrovascular complications, irrespective of progression to diabetes.³

In a study done in India in 2014, neuropathy was detected in 32.8% subjects with IGT (prediabetes). Thus, the peripheral neuropathy may be much more common in prediabetics than previously thought.⁴ In another study done in 2015, the prevalence of peripheral neuropathy was 50%, 49%, and 29% for new-onset diabetes, prediabetes, and normal glycemia, respectively.⁵ Going by all the above information and data, it’s very likely that the process of microvascular complications like neuropathy starts well before the onset of overt diabetes. Conventional wisdom of diabetic peripheral neuropathy being caused by advanced glycation end products is giving way to newer emerging knowledge which lays great emphasis on the role of oxidative stress in the pathogenesis of diabetic neuropathy. This has even led to clinical trials of antioxidants such as α-lipoic acid, (a powerful antioxidant that scavenges hydroxyl, superoxide and peroxyl radicals and regenerates glutathione) in the treatment of diabetic neuropathy.⁶ 8-OHdG (8-Hydroxy-2′-deoxyguanosine) is one of the major by-products of DNA oxidation.⁷ Serum and urinary 8-OHdG are being used as a novel biochemical marker of oxidative damage in various newer studies in many diseases including atherosclerosis, diabetes, prediabetes, colorectal cancers etc. Other factors like vitamin D deficiency have also been implicated in pathogenesis of diabetic peripheral neuropathy in various studies. The aim of the present study is to assess serum and urine levels of 8-OHdG, and serum vitamin D levels as predictors of occurrence of sensory neuropathy in prediabetes.

Materials and methods

Place of study

The study was conducted in the Departments of Medicine and Biochemistry at PGIMER and Dr. Ram Manohar Lohia hospital, New Delhi

¹Postgraduate Resident of Medicine, ²Professor of Medicine, ³Professor of Biochemistry, PGIMER, Dr. RML Hospital, New Delhi
*Corresponding Author

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during the study period between November 2016 and March 2018.

**Study Design**

A cross sectional observational study was performed.

**Sample size**

A total of 60 prediabetic (as defined by American Diabetes Association) subjects were evaluated.

**Selection of study population**

The target population consisted of patients of prediabetes either admitted as In-patient (IPD) or visiting the Outpatient Department (OPD) between November 2016 and March 2018. 60 consecutive patients fulfilling all inclusion and exclusion criteria were included in the study.

**Inclusion criteria** considered were:
- Age of 30-60 years
- Fasting plasma glucose between 100 to 125 mg/dL or
- 2-hour postprandial plasma glucose between 140 to 199 mg/dL [were included in the study only after reconfirming with standard 2-hour OGTT (after 75 gm of glucose solution ingestion)] or
- HbA1c =5.7-6.4%

**Exclusion criteria** were cases of:
- Cerebrovascular accidents
- Hypothyroidism
- Chronic alcoholics
- Patients on anti-tubercular treatment and other drugs known to cause neuropathy
- Smokers
- Patients on chemotherapy and/or Radiotherapy

**Laboratory tests** and **Neurological Examination**

- Serum vitamin D levels
- Spot Urinary 8-Hydroxy-2′-deoxyguanosine (8-OHdG)
- Serum 8-Hydroxy-2′-deoxyguanosine (8-OHdG)
- MNSI (Michigan Neuropathy Screening Instrument)
- VPTs

**Algorithm 1: Statistical analysis and correlation**

- SLE
- Leprosy
- Vasculitis
- Malignancy
- Neurological disorders like Guillain-Barré syndrome, Multiple Sclerosis
- HIV +ve patients
- Chronic glucocorticoid therapy
- Vitamin B12 deficiency.

Levels of Serum 8-OHdG, urine 8-OHdG serum vitamin D, and vibration perception thresholds (VPT) were measured along with calculation of MNSI physical assessment score in all the subjects.

The spot urine samples and fasting serum samples for 8-Hydroxy-2′-deoxyguanosine (8-OHdG) and Vitamin D were collected and centrifuged at 3000rpm for 10 minutes. For estimation of urine and serum 8-OHdG, the supernatant was immediately aliquoted and stored at –20°C till batch analysed by ELISA on EVOLIS Twin Plus by Biorad. Serum Vitamin D levels were measured by Enhanced Chemiluminescence on ECIQ, by Orthoclinical Diagnostics.

VPTs were measured by Digital Biothesiometer (Vibrotest) using PLANTAR method (Figure 1) and average value was calculated in both feet. Biothesiometer is a useful diagnostic tool for quantitatively grading the neuropathy, manufactured by Diabetik Foot Care India Pvt Ltd. Subjects with average VPT of >15 V on either side were considered to have neuropathy.

MNSI (Michigan Neuropathy Screening Instrument)’ local extremity examination was also performed in this study and score >2 was considered as peripheral sensory neuropathy.

Data were analysed for statistical correlation of serum Vitamin D levels, serum 8-OHdG levels, urine 8-OHdG with both the neuropathy parameters. A brief summary of methodology is given in algorithm 1.

**Data analysis**

The Data obtained were entered in Microsoft Excel Worksheet. Statistical analysis was done using statistical software package SPSS v22.0. Data is represented as means SD. Mean value of continuous variable was compared using t-test and nominal variables were compared using chi square test. Pearson’s correlation coefficient was calculated to assess the correlation between two continuous variables.
P-value <0.05 was taken as statistically significant.

**Results**

A total of 60 prediabetic cases were included in this study. Among study population, the age distribution ranged from 35 years to 60 years with the mean age of 48.68 years. Male and female formed 65% and 35% of study population respectively. The maximum serum Vitamin D levels were 95.3 ng/ml and the minimum were 8.0 ng/ml with the mean value being 18.3 ± 14.9 ng/ml. The maximum Serum 8-OHdG levels were 2882.4 pg/ml and the minimum were 105 pg/ml with the mean value being 826.4 ± 583 pg/ml. The maximum Urine 8-OHdG levels were 1974.9 pg/ml and the minimum were 82.0 pg/ml with the mean value being 571.975 ± 421.7 pg/ml (Table 1). Among all the prediabetic subjects, 43.3 % subjects had neuropathy according to VPTs measured by Biothesiometer. T-test analysis suggested that serum levels of 8-OHdG were significantly higher in subjects with neuropathy than subjects without neuropathy (1006.58 ± 511.8 vs 474.57 ± 402.5, p-value = 0.04) (Graph 1). No such significant difference however was present in serum levels of vitamin D between neuropathic and non-neuropathic prediabetics (20.13 ± 18.44 vs 16.96 ± 11.72, p-value = 0.419 (Table 2). VPTs were found to have statistically significant positive correlation with serum 8-OHdG (Pearson Correlation Coefficient= 0.317 (R), p-value=0.017) and VPTs|Pearson Correlation Coefficient= 0.288(R), p-value=0.049| (Graphs 2, 3, 4, 5). According to MNSI physical assessment score (> or = 2), 38.3 % subjects (23 subjects) had neuropathy. MNSI score is positively correlated with serum 8-OHdG (Pearson Correlation Coefficient= 0.308; p-value = 0.017) (Graph 6). Correlation with urine 8-OHdG was not statistically significant (Pearson Correlation Coefficient= 0.687; p value = 0.06) (Graph 7). Correlations of MNSI scores {Pearson Correlation Coefficient=0.14, p-value=0.287} and VPTs|Pearson Correlation Coefficient= 0.058(R), 0.189(L); p-value=0.660(R), 0.148(L)} with serum Vitamin D levels were not statistically significant.

**Discussion**

Prediabetes is considered to be a precursor phase of diabetes mellitus in which blood sugar levels are higher than normal but not high enough to meet the criteria of diabetes mellitus. Thus, this intermediate stage is often referred to as the grey area or grey zone between normoglycemia and overt diabetes. Prediabetic neuropathy is a new emerging entity. There is paucity of literature pertaining to diabetic peripheral neuropathy (87%). The sensitivity of VPT to predict definite clinical neuropathy and abnormal nerve conduction was 80 and 75%, respectively. P. Jayaprakash et al quoted that Vibration perception threshold (VPT) is considered as a gold standard for diagnosis of diabetic peripheral neuropathy. Hence, VPTs can reliably detect sensory neuropathy and serve as a useful, less time-consuming and less painful alternative to nerve conduction studies.

8-Hydroxydeoxyguanosine (8-OHdG) is a novel biochemical marker of oxidative stress which is formed by oxidative DNA damage following oxidant stress.

**Table 1: Baseline characteristics**

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<th>Minimum</th>
<th>Maximum</th>
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<td>Age (years)</td>
<td>60</td>
<td>35</td>
<td>60</td>
<td>48.68±7.782</td>
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<tr>
<td>Serum Vit. D levels (ng/ml)</td>
<td>60</td>
<td>8</td>
<td>95.3</td>
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<tr>
<td>Serum 8-OHdG (pg/ml)</td>
<td>60</td>
<td>105.0</td>
<td>2882.4</td>
<td>826.405±583.0078</td>
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<tr>
<td>Urine 8-OHdG (pg/ml)</td>
<td>60</td>
<td>82.0</td>
<td>1974.9</td>
<td>571.975±421.7249</td>
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**Table 2: Comparison of biochemical parameters in subjects with or without neuropathy**

<table>
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<th>N</th>
<th>Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin-D</td>
<td></td>
<td>16.9±11.72</td>
<td>0.419</td>
</tr>
<tr>
<td>Serum 8-OHdG</td>
<td>34</td>
<td>688.6±607.3</td>
<td>0.035</td>
</tr>
<tr>
<td>Urine 8-OHdG</td>
<td>34</td>
<td>474.57±402.5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Graph 1:** Bar diagram showing comparison between 8-OHdG levels in subjects with or without neuropathy.
specific enzymatic cleavage after ROS induced 8-hydroxylation of the guanine base in mitochondria and nuclear DNA. Leinonen J et al found presence of elevated levels of 8-OHdG in urine in NIDDM patients, especially in patients with poor blood glucose control.\textsuperscript{13} This reflects the ongoing DNA damage in uncontrolled hyperglycaemia. In another article, by Valavanidis A et al, 8-OHdG was described as a critical marker of oxidative stress as well as carcinogenesis.\textsuperscript{14}

There is growing evidence to suggest that the role of vitamin D is not confined to calcium and phosphate homeostasis. In recent years, there has been interest among researchers to identify other target organs affected by vitamin D. Hypovitaminosis D is highly prevalent in patients with Type 2 diabetes and could be a prelude to the development of diabetic neuropathy as deficiency of vitamin D contributes to the development of neurotrophic deficits. There was no statistically significant correlation between serum vitamin D levels and sensory neuropathy in prediabetic subjects in our study. However, in contrast to this finding, Shehab D et al, in a study done in 2012, found that Vitamin D deficiency is an independent risk factor for diabetic peripheral neuropathy.\textsuperscript{15} On reviewing previous literature, we found that relationship between this variable and sensory neuropathy has not been studied previously in prediabetic cases.
As per our knowledge, this is the first study to investigate the role of serum vitamin D levels in pathogenesis of sensory neuropathy in prediabetes. Serum and urine 8-OHdG levels were found to be significantly higher in prediabetics with neuropathy (p-value < 0.05). Their levels also significantly correlated with sensory neuropathy in prediabetic subjects (p-value < 0.05). This is well supported in a study by Chan Soo Shin et al who found that Diabetic patients, especially those with advanced microvascular complications, had significantly higher serum 8-OHG levels; suggesting that oxidative damage plays a vital role in the development of microvascular complications of diabetes like neuropathy, nephropathy and retinopathy. We already know that microvascular complications like neuropathy are caused by direct endothelial injury, production of advanced glycation end products and oxidative stress. With the help of the novel biomarker 8-OHdG, our study further consolidated the role of oxidative stress in peripheral neuropathy in prediabetes. This biomarker has not been previously studied for its role in sensory neuropathy in prediabetes and our study is first to underscore the significance of this marker and consequently the role of oxidative damage in neuropathy in prediabetes. Though the occurrence of neuropathy in prediabetes has been studied, but as per our knowledge, there are no published studies, in Indian medical literature dwelling upon the roles of the probable causative factors of sensory neuropathy in prediabetes.

**Conclusion**

To sum it all up, sensory neuropathy, like in diabetes, also occurs in prediabetic stage. Oxidative stress, as confirmed by the biomarker, 8-OHdG, has a role to play in the development of this sensory neuropathy. Further larger studies are required to elaborate upon this further.

**Glossary of abbreviations**


**References**

Evaluation of Clinical Acceptability of Perindopril / Indapamide Single-pill Combination in Moderate to Severe Hypertension

Sanjay Kalra1, Aravind Sosale2, Siddharth N Shah3, Georges Jabre4, Sofi Joseph5*, Manjusha Rajarshi4

Abstract

Background: Current European hypertension guidelines recommend to initiate the treatment of patients with moderate to severe hypertension with a Single Pill Combination (SPC) containing two drugs, as SPC use leads to more effective and faster blood pressure control. The guidelines also recommend tighter blood pressure control in hypertensive patients with cardiovascular risk factors such as diabetes mellitus.

Objective: To evaluate efficacy on blood pressure reduction and acceptability of the single pill combination of Perindopril/Indapamide in patients with moderate to severe hypertension.

Methods: In this multicentre, prospective, observational study, patients with moderate to severe hypertension were prescribed Perindopril 4mg/Indapamide 1.25 mg for 90 days. The primary outcomes were blood pressure decrease and achievement of BP control. Patients were up-titrated to Perindopril 8 mg/Indapamide 2.5 mg SPC, if target BP control (≤140/90 mm Hg) could not be achieved by day 30.

Results: In this study, 173 hypertensive patients, with a mean age of 51 years were enrolled at 3 centres from different geographic areas within India. Mean SBP/DBP decreased significantly from baseline (155.70 ±10.39) / 95.72 (±6.99) mmHg) over 90 days (30.31 (±14.15) / 17.14 (±9.33) mmHg; p < 0.0000). Few side effects were reported during the 90-day period.

Conclusion: Perindopril/Indapamide given as a SPC was found to be an effective and well-tolerated antihypertensive combination resulting in rapid blood pressure control in patients with moderate to severe hypertension.

Introduction

Hypertension plays a major role in the development of cerebrovascular disease, ischemic heart disease, cardiac and renal failure. Treating hypertension has been linked with about 40% reduction in the risk of stroke and about 15% reduction the risk of myocardial infarction. Although the treatment for hypertension has been shown to prevent cardiovascular disease and to increase life expectancy, hypertension remains inadequately controlled.1,2

Based on the available clinical evidence today the algorithm of hypertension treatment pertains to age and ethnic background. The ESC/ESH 2013 as well as 2018 guidelines recommend to commence the two drugs therapy in patients with moderate to severe hypertension (Systolic BP above 160 mmHg and/ or Diastolic BP above 100 mmHg). The guidelines suggests tighter blood pressure control in patients with cardiovascular risk factors such as patients with diabetes mellitus.3-5

This study examines the efficacy, in terms of blood pressure control, and acceptability of Perindopril/Indapamide SPC in moderate to severe hypertensive patients.

Materials and Methods

Study Design

This study was an open-label, Multicentric, Non-comparative Phase IV study in patients with moderate to severe hypertension. The study protocol was approved by the Indian regulatory authorities and registered on the clinical trial registry of India (CTRI/2017/07/009160). The study was conducted in accordance with the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. Written informed consent was obtained from all patients before participation in the study.

The study aimed to evaluate the clinical efficacy and acceptability of the Perindopril/Indapamide SPC. The recommended initiation dose of Perindopril 4 mg /Indapamide 1.25 mg) was administered to all eligible subjects in the morning for 90 days. The study protocol included an up-titration step to Perindopril 8 mg/Indapamide 2.5 mg at visit 3 (Day 30) when the blood pressure response achieved was inadequate with the initiation dose of a Perindopril 4 mg + Indapamide 1.25 mg. The target for BP control was set by Principal investigator based on patient’s health profile, co-morbid health issues and risk factors however control rate of the BP was considered as ≤140/90 mm Hg.

Selection of patients

To be enrolled in the study, patients had to be diagnosed with hypertension (grade II or above) and aged between 18 and 65 years, either newly diagnosed patients with baseline blood pressure...
Table 1: Baseline characteristics (ITT)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. Total number of patient population</td>
<td>N= 173</td>
</tr>
<tr>
<td>ii. Age, years ± SD</td>
<td>50.96 ± 9.22</td>
</tr>
<tr>
<td>iii. Men, n (%)</td>
<td>96 (55.5%)</td>
</tr>
<tr>
<td>iv. Cardiovascular risk:</td>
<td></td>
</tr>
<tr>
<td>a. Current smokers</td>
<td>05</td>
</tr>
<tr>
<td>b. Current alcohol consumption</td>
<td>11</td>
</tr>
<tr>
<td>c. Weight, kg ± SD</td>
<td>72.42 ± 12.10</td>
</tr>
<tr>
<td>d. BMI, kg/m² ± SD</td>
<td>26.6 ± 4.16</td>
</tr>
<tr>
<td>e. Diabetes, n (%)</td>
<td>106 (61.27%)</td>
</tr>
<tr>
<td>f. Dyslipidaemia, n (%)</td>
<td>66 (38.15%)</td>
</tr>
<tr>
<td>g. Hypothyroidism, n (%)</td>
<td>17 (9.82%)</td>
</tr>
<tr>
<td>h. HLD, n (%)</td>
<td>2 (1.15%)</td>
</tr>
<tr>
<td>i. Other, n (%)</td>
<td>11 (6.35%)</td>
</tr>
<tr>
<td>v. Systolic blood pressure, mmHg</td>
<td>95.72 ± 6.99</td>
</tr>
<tr>
<td>vi. Diastolic blood pressure, mmHg ± SD</td>
<td>131.65 ±10.53</td>
</tr>
<tr>
<td>vii. Heart rate, bpm ± SD</td>
<td>81.84 ±7.93</td>
</tr>
</tbody>
</table>

Results

Patient population
A total of 181 patients were screened out of which 173 patients were enrolled in the study, across 3 study centers in India. 133 patients completed the study as per the protocol. Baseline characteristics of study population are shown in Table 1. At baseline, mean age was 50.96 years (±9.22), 55.5% of patients were male, with 61% had diabetes mellitus and 38% had dyslipidemia as a co-morbid condition.

Primary efficacy analysis: Blood pressure response to treatment
Treatment with Perindopril/Indapamide SPC led to a reduction in SBP by 15.11 mmHg and in DBP by 8.35 mmHg at Day 15 compared to baseline. At Day 30, further significant reduction was observed in SBP by 8.96 mmHg and in DBP by 5.50 mmHg compared to day 15. At the final study visit (Day 90), statistically highly significant (p value: 0.000 student t-test) reduction in blood pressure from baseline SBP 30.31 (14.151) / DBP 17.14 (9.336) mmHg was observed. Mean SBP/DBP values decreased from 155.7 ± 10.39 / 95.72 ± 6.99 mmHg at baseline to 131.65 ±10.53 / 81.82 ±7.79 mmHg at day 30 and to 125.4 ± 9.072 /78.5 ± 7.713 mmHg at day 90 (Figure 1). Mean heart rate decreased from 81.57 ± 7.93 at baseline to 79.45±6.61 bpm at day 30 and to 78.90 ± 7.83 at day 90. The SPC of Perindopril/Indapamide was found to be effective in more than 90% of the patients recruited in the study. 127patients achieved blood pressure control (SBP less than 140 mmHg and DBP less than 90 mmHg, including those with diabetes) after 90 days.

Withdrawals and up-titration
Out of 181 screened patients, 173 were enrolled and 133 patients completed the study being adherent to protocol schedule and treatment.

The up-titration of the study medication was required in 14 patients; they were up-titrated to the SPC of Perindopril 8 mg/Indapamide 2.5 mg at Visit 3. All these patients achieved target blood pressure control following the up-titration (reviewed at day 5 following the ingestion of higher dose)
without any further change in treatment line and the same treatment was continued. Seven patients discontinued the study for various reasons such as difficulties to follow up and personal decision. None of the patients were withdrawn due to adverse events. The global assessment by the investigators rated the efficacy of the treatment as very good (73%) and tolerance (95%) at the end of the study (Figures 2 and 3).

**Safety analysis**

During the entire study period, a total of nine adverse events were reported such as dry cough, headache, high fever, gastroesophageal reflux disease, giddiness, and paronychia. Adverse events were mild in severity and not related to SPC (perindopril + indapamide) and all resolved during the study period. The laboratory parameters remained within the normal range and the study treatment had no impact on the laboratory parameters particularly the electrolytes. None of the patients had any signs and symptoms of hyponatremia and/or hypokalemia and any other electrolyte imbalances and as confirmed by the lab investigations.

**Discussion**

It is usual practice to add 1-2 sentences at the beginning of discussion, summarising the main findings of the study.

Recent epidemiological data reveals prevalence of hypertension in 25–30% urban and 10–20% rural subjects in India. This translates into 100–110 million persons with this condition in the country. Hypertension is classified as Category 3 (specific factors) risk factors for disease burden (disability adjusted life years) and mortality in India as per the Global Burden of Disease Study 2015. It is well understood that hypertension management and control is crucial to prevent its vascular complications. There is strong evidence from clinical trials and meta-analyses of systolic blood pressure > 140 mmHg being harmful and prompt initiation and titration of therapy to achieve and maintain systolic blood pressure < 140 mmHg is recommended. A meta-analysis reported that each 10 mmHg reduction of systolic blood pressure was associated with significantly lower risk of mortality, cardiovascular events, coronary heart disease, stroke, albuminuria and retinopathy in patients with hypertension. Strong evidence also exists from randomised clinical trials that systolic blood pressure < 130 mmHg and diastolic blood pressure < 90 mmHg is associated with decreased adverse vascular complications.

Using two-drug SPCs is one of the key recommendations of latest guidelines on hypertension ESC/ESH 2018 especially when the monotherapy is inadequate to achieve target range of BP control in moderate to severe hypertensive patients as well as grade I patients with risk factors. The exceptions to these recommendations are frail older patients and those at low risk and with grade I hypertension (particularly if SBP is <150 mmHg). This strategy also enhances adherence to BP-lowering medication contributing to higher rates of reduction in blood pressure.

The present phase IV study considered a wide spectrum of hypertensive patient population ranging from grade II to grade III hypertensive patients who were inadequately managed on monotherapy or any other two drug combinations. Few of the included patients presented some other comorbid conditions. The target BP for patients receiving treatment was <140/90 mmHg for patients with hypertension alone whereas a tighter BP control (<140/85 mm of Hg) was expected in hypertensive patients with history of diabetes mellitus. Approximately, 60% of study population had co-morbid conditions like diabetes mellitus (60%) and dyslipidaemia (38%).

While planning a treatment algorithm for such wide range of hypertensive population, a single pill combination of an ACE inhibitor (Perindopril) and thiazide like diuretic (Indapamide) should be considered as first line treatment in clinical practice. The single-pill combination of Perindopril/Indapamide leads to additive synergistic action on vascular endothelium, arteriocapillary microcirculation and the target organs of hypertension and thus helps in gradual but definite achievement of target BP control. The clinical assessments of present study confirmed efficacy of Perindopril + Indapamide in more than 90% of study population with lower dose of SPC after 90 days. Less than 10% of the study population (n=14) required an up-titration to Perindopril 8 mg/Indapamide 2.5 mg during the study period and all these patients achieved target blood pressure without addition of any other new drug. Reduction in the heart rate in consequence to the reduction in blood pressure was also observed. The study medications demonstrated satisfactory safety profile.

The study treatment was rated by investigators for global evaluation parameters like Treatment efficacy, Treatment compliance, Treatment tolerance, Treatment satisfaction with treatment. The study results demonstrated coherent acceptance of this SPC by investigators as well as the patients.

The beneficial effects of combination of Perindopril and Indapamide in
Reducing blood pressure have been demonstrated in many trials and meta-analysis. A meta-analysis involving 3 large randomized controlled trials conducted with fixed combination of Perindopril 4 mg and Indapamide 1.5 mg concludes significant reduction of vascular death and major cardiovascular events.

**Recommendation of fixed combination of Perindopril + Indapamide has been confirmed in Diabetic hypertensive patients through a detailed meta-analysis.** Perindopril being an ACE inhibitor class of drug imparts cardioprotective and nephroprotective effects in hypertensive patients. The study results with this SPC are similar to the reported data in the literature. The available clinical literature and recommendations from all the guidelines support use of Perindopril and Indapamide as the drugs for the treatment of hypertension. This recommendation is based on the established clinical efficacy and safety of these two drugs in monotherapy as well as in combination treatment. Although the number of patients requiring higher dose has been limited, the clinical efficacy and acceptability is well demonstrated and reconfirmed among the Indian patients.

**Conclusion**

This observational study showed that treatment with Perindopril/Indapamide SPC reduced BP rapid and significantly, resulting in high rates of BP control, and was well tolerated in patients with moderate to severe hypertension, newly diagnosed or uncontrolled on monotherapy or combination therapy, in daily clinical practice.

**Acknowledgement**

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**Conflicts of Interest**

The study was sponsored by Serdia Pharmaceuticals (India) Pvt. Ltd. Mumbai. Dr. G. Jabre, S. Joseph and Dr. M. Rajarshi are employees of Serdia Pharmaceuticals. All other authors have no conflicts of interest to declare. Editorial assistance and article processing charges were funded by Serdia Pharmaceuticals (India) Pvt. Ltd. Mumbai.

**References**

Management of Diabetes during Fasting and Feasting in India

Banshi Saboo1, Shashank Joshi2, Siddharth N Shah3, Mangesh Tiwaskar4, Vijay Vishwanathan5, Sudhir Bhandari6, Sujit Jha7, Tirthankar Chaudhary8, SR Arvind9, Rajeev Chawla10, Sanjay Kalra11, Dhruvi Hasnani12

Abstract
Fasting and feasting are integral part of many religions and cultures. As the amount of food and fluid intake are markedly altered during these phases, patients with diabetes are prone to higher risk of complications. Even though several guidelines for fasting and feasting are available; Indian specific recommendations are the need of the hour, because of the distinct dietary habits and the diet content (high carbohydrate) of Indians. To fill this void, the current guidelines have been developed by experts from India who extensively reviewed the literature, shared their practical knowledge and ultimately arrived at a consensus.

Introduction
Fasting and feasting are the common practices observed by people as a regimen for traditional or cultural reasons.1-3 People observe fasting or feasting depending on the religion and festival in context.4-7 Literature suggests that medically supervised fasting for 7-21 days is efficacious in treatment of several diseases; however, erratic eating pattern and disrupted daily fasting and feasting cycle may have an impact on the progression of metabolic diseases in India.9

The International Diabetes Federation (IDF) in their current report states that approximately 73 million people with diabetes are living in India.10 Data from multi-country studies, including India, report that around 79-94% of Muslims with type 2 diabetes mellitus (T2DM) undergo fasting during Ramadan for at least 15 days. It is evident that many people with diabetes observe fasting or feasting during various festivals in India, hence management of diabetes during these phases becomes extremely important.11-14 Important to the best of our knowledge there is no consensus statement available on the management of diabetes during fasting and feasting in Indian population. This consensus will highlight the evidence-based management strategies for control of diabetes and its associated complications during fasting and feasting in Indian population.

Methodology
An extensive systematic review of literature has been initiated in several search engines including PubMed, Google Scholar, and Cochrane library databases in order to find out the best possible evidence and quality studies for management of diabetes during fasting and feasting. In the process of literature search, various MeSH keywords including fasting, feasting, hypoglycaemia, hyperglycaemia, Ramadan, diabetes, etc. have been used. Existing guidelines, meta-analyses, systematic reviews, randomized controlled trials (RCTs), non-RCTs, and key articles related to diabetes management were reviewed.

Types of fasting
Hindu fasts and feasts
There are several types of fasting observed by the Hindu religion; for example women observe day-long fast during annual Karva Chauth and Guru Purnima to pray for long life for their husbands, monthly fasts during Ekadashi, Purnima, and Pradosha, and longer fasts during the Navratri (9 days) twice a year etc.2 Moreover, fasting may be “mirahara” – without food; “phalahara” – where fruit and milk are allowed and “alpahara” – when broken rice and the likes are allowed.3 Alike fasting, feasting is also marked by the Hindu religion where during various festivals including Diwali, Pongal, Dussehra, Holi etc.; people consume high amount of carbohydrates from sweets prepared from sugar, jaggery, rice flour and ghee.3

Islamic fasts and feasts
Islamic fast, also known as Sawn, is abstaining from eating and drinking during daylight hours. During Ramadan, all Muslims desist from both eating and drinking from dawn to sunset and refrain from smoking, taking oral medications, and sexual activities.14 Followers consume a high calorie food at iftar (evening meal after breaking the fast), and at suhur (meal consumed before the fast), and at suhur (meal consumed early in the morning). Similarly, during Eid-ul-Fitr, the festival of breaking the fast after Ramadan, Muslims celebrate with eating and drinking.15

Jain fasts and feasts
Jain people do fast at special times during festivals and on holy days.1 In Jainism, “Paryushan” is the most observed festival during monsoon, which lasts eight days in Svetambara Jains and ten days in Digambar Jains.

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Table 1: Risk Stratification of patients with diabetes during fasting

<table>
<thead>
<tr>
<th>Very high risk</th>
<th>High risk</th>
<th>Moderate risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Severe hypoglycemia / ketoacidosis / hyperosmolar hyperglycaemic coma within 3 months prior to Ramadan</td>
<td>o Moderate hypoglycemia (Average blood glucose 150-300mg/dL)</td>
<td>o Well controlled patients (HbA1c &lt;7.5%) treated with short-acting insulin secretagogues and modern sulphonylureas</td>
<td>o Well controlled patients (HbA1c &lt;7%) treated with diet alone, metformin, or a thiazolidinedione who are otherwise healthy</td>
</tr>
<tr>
<td>o History of recurrent hypoglycemia</td>
<td>o Renal insufficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Hypoglycemia unawareness</td>
<td>o People living alone that are treated with multiple insulin injections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Sustained poor glycemic control</td>
<td>o Old age with ill health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Patients on dialysis</td>
<td>o Patients with macro and microvascular complications that present additional risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Patients who perform intense physical labor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Acute illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Gestational diabetes mellitus treated with insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Type 1 diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients with the following conditions should refrain from fasting:  
- Pregnant and lactating women;  
- Type 1 diabetes;  
- Acute peptic ulcer;  
- Cancer;  
- Severe bronchial asthma, pulmonary tuberculosis;  
- Overt cardiovascular diseases- recent MI, sustained angina;  
- Hepatic dysfunction

Adapted from: South Asian Consensus Guideline, ADA 2005, IDF 2016, and IGDR 2015

Furthermore, Digambar Jains do not take food and/or water (boiled) more than once in a day, and Shwetambar Jains take only boiled water during their fast days. In addition, most Jains observe “Ratri Bhojan Tyag,” where they abstain from food and water after sunset. During Diwali, New Year day, Mahavir Jayanti, and other festivals they offer Prasad made from ghee, sugar, jaggery, and mark their feasting.

Buddhist fasts and feasts

Many people follow Buddhism in China and India. Vassa or Buddhist Lent is the fast and feast observed by Buddhists for three lunar months every year in the rainy season. During this time they follow fast for 12 hour period (from noon to midnight) and a feast for 12 hours period (from midnight to noon).

Fasts and feasts in other religions

Apart from discussed religions, India is the home for several other religious people including Christians, Sikhs, Parsis etc. They also celebrate various festivals and observe fasting and feasting. Literature advocates that Greek Orthodox Christians undergo a fast for a total of 180 to 200 days in each year. Nativity Fast (40 days before Christmas), Lent (48 days before Easter), and the Assumption (15 days in August) are the main fasting periods. However, Parsis don’t have fasts on their calendar but, have feasts and most of their diet is rich in non-vegetarian food.

Diabetes, fasting and feasting

Risk population

It is important to stratify patients into different risk categories according to their comorbid status, continued medication, health status etc. (Table 1, Figure 1). Hyperglycaemia, hypoglycaemia, dehydration, diabetic ketoacidosis (DKA), microvascular and macrovascular problems may create challenges.

Challenges

- Hyperglycaemia, hypoglycaemia, dehydration, diabetic ketoacidosis (DKA), microvascular and macrovascular problems may create challenges.
- Taking insulin and other OADs without any dose adjustment during fasting periods increases the risk of complications.
- In spite of ill health, some people do fast.
- During fasting, alteration of physical and mental health, especially in elder and comorbid patients with diabetes, places them at great risk of complications.
- Due to irregular food habit some patients may miss their usual medication dose.
- Poor monitoring of diabetes complications, and blood sugar, specifically in rural areas pose a significant risk.
The risk of severe hypoglycaemia increases in people with diabetes. A study reports that fasting increases the risk of diabetes associated complications, particularly for patients with type 1 diabetes (T1DM) or type 2 diabetes (T2DM) who are uncontrolled or poorly managed. Patients with uncontrolled diabetes are at a higher risk of hypoglycaemia and should be closely monitored. Patients taking insulin or sulfonylureas should be monitored for hypoglycaemia, especially if they are prone to fasting like Ramadan, Navratri, and Vaasa.

### Management of T1DM

Patients with T1DM have been considered as a very high-risk group for fasting in various guidelines and literature. This risk increases in patients with uncontrolled/poorly-controlled diabetes and having no access to medical care or being unwilling to monitor blood glucose level, uneducated and unaware of hypoglycaemic events that require recurrent hospitalizations. The evidence suggests that fasting for 25 hours is safe and can be observed by patients with T1DM. This group of patients should be made aware of the associated potential risks and be monitored closely.

The South Asian Consensus Guideline on insulin use during Ramadan advocates that once-or-twice daily injections of intermediate or long-acting insulin along with pre-meal rapid-acting insulin can be safely used in patients during fasting.

### Management of T2DM

#### Non-pharmacological management

Fasting is considered as an element of lifestyle modification (LSM), and LSM itself is a management strategy for T2DM patients. Physical activity and Yoga can be performed to lose body weight and to control the emotions; however, excessive and aggressive physical activity should be avoided during prolonged fasting periods.

#### Nutrition plan

A food-plate comprising all foods for diabetes individuals during fasting is depicted in Figure 4. The pre-fast meal should be composed of complex carbohydrates with low glycaemic index and proteins. In contrast, post-fast meal should be composed of simple carbohydrates like bread, cereals, rice,
Adequate water and fluids must be taken prior to the fast especially in cases where fluid intake will be restricted throughout the day.

**Pharmacological management**

The details of dose adjustment of medications are provided in Table 3.14,20

### Metformin

Metformin can be safely used during fasting periods due to minimal chances of hypoglycaemia.14 However, patients who are taking metformin during lunch time should omit the dose during day fasting;37 morning dose can be taken as usual but, a larger dose should be taken after breaking the fast to avoid hyperglycaemia.2,14,37

### Sulfonylureas

Sulfonylureas (SUs), are widely used after metformin in patients with T2DM in India.14 The main concern with their use is hypoglycaemia and this might be due to their glucose-independent insulin secretory action. However, this is not the class effect and differs with agents due to variations in their individual pharmacokinetic and pharmacodynamic properties.38 Glibenclamide, gliclazide, glipizide, and glimepiride are the various SUs used in India for the management of T2DM. Evidence advocates that gliclazide, among all the SUs, is associated with good glycaemic control with lesser hypoglycaemia.39 This might be due to its lesser pancreatic overstimulation action and restoration of the early insulin peak in response to glucose stimulation and higher reversibility of binding with receptors present in beta-cell.38 Moreover, a meta-analysis of RCTs did not find any significant difference in the incidence of symptomatic hypoglycaemic events between DPP-4 inhibitor and gliclazide (5.6% versus 7.2%, risk ratio 1.12, 95% CI 0.73-1.73, p=0.61) in patients during fasting.40 A systematic review and network meta-analysis of RCTs reports that gliclazide compared to other SUs is associated with lower risk of all-cause and cardiovascular-related mortality in patients with T2DM (Table 4).41-51 Thus, gliclazide pertaining to its efficacy in glycaemic control, lower risk of hypoglycaemia, less risk of CV complication and death, along with lower cost might be an suitable alternative and can be used
Table 3: Approach to adjustment or modification of continued antidiabetic medications in patients with diabetes during fasting period (IDF 2016, Sadikot S 2017, Kalra S 2015, Jhulka S 2017, and Latt TS & Kalra S 2012)

<table>
<thead>
<tr>
<th>Anti-diabetic agents</th>
<th>Muslim fast</th>
<th>Hindu fast</th>
<th>Infrequent but brief</th>
<th>Infrequent but prolonged</th>
<th>Frequent</th>
<th>Jain fast</th>
<th>Low-risk</th>
<th>Buddhist fast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ramadan</td>
<td>Karva chauth</td>
<td>Navratri</td>
<td>Somvaaar, Mangalvaar</td>
<td>Tiwihar upavas, Upavas, Bela (Chhath), Tela (Asthitham)</td>
<td>Byasana, Ekasana, Ratri Bhojan Tyag</td>
<td>Vaasa</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>• Once daily: take at iftar</td>
<td>• Once daily: take at iftar</td>
<td>• Once daily: take at night</td>
<td>• Once daily: take at night</td>
<td>• Once daily: take at night</td>
<td>• Ommit the therapy on the day of fast</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>• Twice daily: take at iftar &amp; suhar</td>
<td>• Twice daily: take at morning and night</td>
<td>• Twice daily: take at morning and night</td>
<td>• Twice daily: take at morning and night</td>
<td>• Twice daily: take at morning and night</td>
<td>• Ommit the therapy on the day of fast</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>• Thrice daily: take 2/3rd of the total daily dose at the iftar and 1/3rd at the suhar</td>
<td>• Thrice daily: omit the lunch dose and follow above</td>
<td>• Thrice daily: omit the lunch dose and follow above</td>
<td>• Thrice daily: take 2/3rd of the total daily dose at night and 1/3rd at the morning</td>
<td>• Thrice daily: omit the lunch dose and follow above</td>
<td>• Ommit the therapy on the day of fast</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Sulfonylureas*</td>
<td>• Once daily: take at iftar</td>
<td>• Once daily: take at dinner</td>
<td>• Once daily: take at dinner</td>
<td>• Once daily: take at dinner</td>
<td>• Once daily: take at dinner</td>
<td>• Ommit the therapy on the day of fast</td>
<td>Avoided, or taken in half dose at night</td>
<td>Full dose at morning and half dose at night</td>
</tr>
<tr>
<td></td>
<td>• Twice daily: take 1/2 of usual evening dose with the suhar and the usual morning dose with the iftar</td>
<td>• Twice daily: omit the morning dose in absence of breakfast</td>
<td>• Twice daily: omit the morning dose</td>
<td>• Ommit the therapy on the day of fast</td>
<td></td>
<td></td>
<td>Taken at night</td>
<td>No change</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>• No dose adjustments is required</td>
<td>• No change, take at dinner</td>
<td>• No change, take at dinner</td>
<td>• No change, take at dinner</td>
<td>• No change</td>
<td>• Ommit the therapy on the day of fast</td>
<td>Evening dose avoided, or taken in half dose</td>
<td>No change</td>
</tr>
<tr>
<td>SGLT-2 inhibitors†</td>
<td>• No dose adjustment is required and the dose be taken with iftar</td>
<td>• No change, take at dinner</td>
<td>• No change, take at dinner</td>
<td>• No change, take at dinner</td>
<td>• No change</td>
<td>• Ommit the therapy on the day of fast</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>• No dose adjustments is required</td>
<td>• No change</td>
<td>• No change, or 2/3rd take at dinner</td>
<td>• No change</td>
<td>• No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>AGIs</td>
<td>• No dose adjustments is required</td>
<td>• No change</td>
<td>• No change</td>
<td>• No change</td>
<td>• No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>GLP-1 analogues</td>
<td>• The dose should be titrated 6 weeks prior to Ramadan and no dose adjustment is required</td>
<td>• Reduce the dose to 1/2nd and take at dinner</td>
<td>• The dose should be titrated prior to Navratri</td>
<td>• No change or reduce the dose to 1/2</td>
<td>• No change</td>
<td>Ommit the therapy on the day of fast</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Long-acting insulin</td>
<td>• Once-daily: i dose by 15–30% and take at iftar</td>
<td>• Need no change or may reduce the dose to 2/3rd</td>
<td>• Need no change or may reduce the dose to 2/3rd</td>
<td>• No change</td>
<td>25% reduction in dose</td>
<td>10-20% reduction in dose</td>
<td>Once daily, before the main meal of the 24 hour period</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Twice daily: Take usual morning dose at iftar &amp; i evening dose by 50% and take at suhar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting insulin</td>
<td>• Take normal dose at iftar and lunch dose at dinner</td>
<td>Reduce the dose to 1/2nd</td>
<td>Reduce the dose to 1/2nd</td>
<td>Reduce the dose to 1/2nd</td>
<td>1 bolus</td>
<td>2 bolus</td>
<td>Reduce the dose to 1/2nd</td>
<td></td>
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<tr>
<td></td>
<td>• suhar dose by 50%</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Premixed insulin</td>
<td>• Once-daily: Take usual morning dose at iftar &amp; i evening dose by 50% and take at suhar</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Twice daily: Take 1/2 of evening dose with suhar and the usual morning dose with the iftar</td>
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<tr>
<td></td>
<td>• Thrice Daily: Omit afternoon dose and adjust iftar and suhar doses</td>
<td></td>
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</tr>
</tbody>
</table>

AGIs, alpha-glucosidase inhibitors; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium-glucose co-transporter-2; † Gliclazide and glibenpiride should be preferred among all other sulphonylureas † Elderly patients, patients with renal impairment, hypotensive individuals, those at risk of dehydration or those taking diuretics should not be treated with SGLT2 inhibitors.

safely during fasting periods in Indian patients. Moreover, glibenclamide should be avoided and other SUs can be used with caution during the fasting period. They can be safely used during fasting period due to the reduced risk of hypoglycaemia, as they work by increasing insulin secretion in a glucose-dependent manner. However,
Table 4: Studies investigating efficacy and safety of antidiabetic agents during fasting

<table>
<thead>
<tr>
<th>Author et al.</th>
<th>N</th>
<th>Intervention</th>
<th>Outcomes/Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized clinical trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azar S T et al. 2016</td>
<td>343</td>
<td>Liraglutide vs sulphonylureas (gliclazide, glimepiride, glipizide, glibenclamide): outcomes</td>
<td>Similar i in fructosamine levels were observed for both groups during Ramadan: (liraglutide, −12.8 μmol/L; sulphonylurea, −16.4 μmol/L; p = 0.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No severe hypoglycemic episodes were reported by either group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More subjects in the glibenclamide stratum (14.8%) experienced hypoglycemic episodes than in the glimepiride/gliclazide/glipizide stratum (9.8%)</td>
</tr>
<tr>
<td>Hassanein M 2014</td>
<td>557</td>
<td>Vildagliptin (A) vs gliclazide (B) + metformin: Hypoglycemic events</td>
<td>Confirmed hypoglycemia (A vs B): 3.0% vs 7.0% (p=0.039)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adjusted mean change pre- to post-Ramadan in HbA1c (A vs B): 0.05%±0.04% vs −0.03%±0.04% (p =0.165)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adjusted mean i weight: −1.1±0.2 kg (p =0.987) for both group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No significant change in any parameter found in either group</td>
</tr>
<tr>
<td>Malha LP 2014</td>
<td>69</td>
<td>Vildagliptin vs sulphonylureas (Glimepiride/gliclazide): hypoglycemia event</td>
<td></td>
</tr>
<tr>
<td>Brady EM et al. 2014</td>
<td>99</td>
<td>Liraglutide (A) vs sulphonylureas (b) (glimepiride, gliclazide, or glibenclamide):</td>
<td></td>
</tr>
<tr>
<td>Aravind SR 2012</td>
<td>870</td>
<td>Sitagliptin (A) vs sulfonylureas (B) (Glimepiride/gliclazide/glipizide/glibenclamide): metformin: overall incidence of symptomatic hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Al Sifri S 2011</td>
<td>1066</td>
<td>Sitagliptin vs sulphonylureas (Glimepiride/gliclazide/glibenclamide): overall incidence of symptomatic hypoglycemia</td>
<td></td>
</tr>
<tr>
<td><strong>Observational studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shete A et al. 2013</td>
<td>97</td>
<td>Vildagliptin vs sulphonylureas (Glimepiride/gliclazide/glibenclamide/glipizide)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypoglycemic episodes were reported in low frequencies in both the vildagliptin and the sulfonylurea groups (0 vs 2 patients, respectively)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HbA1c Iby−0.43% in the vildagliptin group (P = 0.009) while 10.01% in the sulfonylurea group (P = 0.958)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Both treatment groups were well tolerated during Ramadan</td>
</tr>
<tr>
<td>Aravind SR 2011</td>
<td>1378</td>
<td>Glimepiride/gliclazide/glibenclamide ± metformin: overall incidence of symptomatic hypoglycaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Symptomatic hypoglycemia drug wise: glibenclamide, 25.6%; glimepiride, 16.8%; gliclazide, 14.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Symptomatic hypoglycemia country wise: Israel, 40%; Malaysia, 24%; UAE, 18%; India, 13%; Saudi Arabia, 10%</td>
</tr>
<tr>
<td>Zargar AH 2010</td>
<td>136</td>
<td>Gliclazide MR 60 mg monotherapy, switched to evening administration of the same dose during Ramadan</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean FPG by 0.01 mmol/l (p = 0.3) with evening medication by the end of the fast.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypoglycemic episodes: before Ramadan, 3.7%; during, 2.2%; after Ramadan, 1.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gliclazide evening administration safely maintains glycemic control during the fast</td>
</tr>
<tr>
<td>Sari et al, 2004</td>
<td>40</td>
<td>Repaglinide vs sulphonylureas (gliclazide &amp; glimepiride): outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Only 1 hypoglycemic event reported in glimepiride patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Triglyceride levels from BL: Repaglinide (p=0.024), SU (p=0.002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HDL-cholesterol from BL: Repaglinide (p=0.022)</td>
</tr>
</tbody>
</table>

1, decrease/reduction; ↑, increase/elevated; BL, baseline; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; UAE, United Arab Emirates

Precautions should be taken when they are used in combination with SU. Vildagliptin and sitagliptin are the mostly used DPP-4 inhibitors in the studies during the fasting period (Table 4). Alisher et al. compared the substitution of sitagliptin with SU with continuation of SUs during the Ramadan fasting and found that sitagliptin is associated with less hypoglycaemic episodes compared to SUs but similar hypoglycaemic episodes as gliclazide. The STEADFAST study compared vildagliptin and gliclazide treatment during Ramadan period and did not find any significant difference between two treatments in terms of hypoglycaemic episodes. The observational studies such as VECTOR, VERDI, and VIRTUE also reported higher efficacy and safety of vildagliptin during fasting period; however, gliclazide having similar efficacy and safety as vildagliptin might stand as an alternative option for Indian patients due to its lower cost.

### Thiazolidinedione

Thiazolidinedione (pioglitazone) may be used during fasting period due to the low risk of hypoglycaemia; however, weight gain is a concern in overweight and obese patients when it is used during fasting.

### Alpha-glucosidase inhibitors

There are no RCTs available...
which studied the outcomes of alpha-glucosidase inhibitors (AGIs) during the fasting period. Acarbose, miglitol, and voglibose can be safely used without any dose adjustment during the fasting period. However, ineffectiveness as monotherapy and concerns regarding the GI side effects reduces their applicability in T2DM patients during the fasting period.\(^{14}\)

**Glucagon-like peptide-1 receptor agonists**

Liraglutide, exenatide, albiglutide, lixisenatide, and dulaglutide constitute the family of glucagon-like peptide (GLP)-1 receptor agonists. The important association associated with these agents is weight loss and low risk of hypoglycaemia; thus, they are chosen over other agents especially in overweight and obese patients during the fasting period.\(^{21}\) Several trials (Table 4) have been published including the Treat 4 Ramadan trial and LIRA-Ramadan trial that investigated the efficacy and safety of liraglutide during fasting period,\(^{41,44}\) and did not found any significant difference between liraglutide and SU concluded that both agents can be safely used during fasting.\(^{41,44}\) GI upset was common with the usage of lixisludet.\(^{20}\) Furthermore, some patients don’t prefer these injectable agents due to their religious views.\(^{14}\)

**Insulins**

Many T2DM patients use insulin as a treatment option however the higher risk of hypoglycaemia and multiple injections reduces its usage in T2DM patients especially during the fasting period.\(^{14,21}\) Insulin analogues (basal, prandial and premix) are generally recommended over regular human insulin due to a number of advantages, including lower rates of hypoglycaemia.\(^{38}\) Studies related to the use of insulin are described in Table 4.\(^{39-62}\) Patients who are using insulin should practice SMBG monitoring system and communicate their readings to physicians regularly in order to reduce the risk of complications\(^{3}\) (Table 3).

**Post-fast debriefing**

Patient with diabetes and undergoing fasting should share their experience related to physical and mental health, symptoms, complications, steps taken to prevent complication, and about their quality of life during the fasting period.\(^{2}\)

### Special populations

Pregnant women, children, elderly, patients with comorbidities, and poorly controlled T1DM are group of patients requiring special attention during the fasting and feasting period. Unless stable disease, these people are categorized as high risk for fasting in various guidelines and need special precautions with strict monitoring (Table 1).\(^{13,20-24}\)

**Conclusion**

The panel concludes that appropriate lifestyle modifications including physical activity, nutrition plan, pre-fast counselling and structured diabetes education plan along with proper treatment dose adjustment or modification are important to ensure a safe fasting or feasting period.

### References


### Executive summary

- A structured diabetes education should be planned for patients with diabetes along with their family members in order to observe a safe fasting.
- Patient with diabetes should break their fast if the blood glucose level is <70 mg/dL (3.9 mmol/L) or >300 mg/dL (16.7 mmol/L) or when complications develop.
- Patients with stable T2DM can undergo fasting safely; however, their frequency and dose of medications need to be adjusted or modified.
- Metformin can be safely used during fasting, however, some dose modification might be required.
- Hypoglycaemia is the major concern associated with SU's. However, glitinide in this class has lowest risk of hypoglycaemia and CV complications with higher glycemic efficacy. Moreover, owing to its low cost, glitinide can be widely used in Indian population during the fasting period.
- DPP-4 inhibitors like vildagliptin and sitagliptin can be used during fasting; however higher cost might restrict their use in Indian population.
- The SGLT-2 inhibitors should be cautiously used in elderly and frail patients due to their weight loss effect and high risk of hypoglycaemia, however, high cost, GI side effects, and injectable nature reduces their applicability, especially during fasting.
- Insulin requires dose modification during the fasting period. Patients who are using insulin should be strictly monitored for hypoglycaemic complications.


From Individualized to Personalized Medicine in Diabetes: An Expert Overview

Viswanathan Mohan¹, Ashok Kumar Das², Jagat Jyoti Mukherjee³, Krishna Seshadri⁴, Sujeet Jha⁵, Sanjay Kalra⁶

Abstract
Personalized medicine is an individualized and stratified approach to the management of a disease. Personalized medicine can reform the prevention, prediction, and management of diabetes. Use of genetic information in polygenic and monogenic forms of diabetes can help to identify genetic variants and reclassify patients into pathophysiological subgroups. Targeted diagnostic, preventive, and therapeutic interventions can be defined for these groups for effective management of diabetes. Pharmacogenomics combines genotypic and phenotypic factors to develop personalized care in various pathophysiological subgroups of persons with diabetes. Personalized medicine finds wider utility in monogenic (especially Maturity Onset Diabetes of the Young (MODY) and Neonatal Diabetes Mellitus [NDM]) than in polygenic, diabetes. The most frequently mutated genes in MODY include HNF1A and HNF3A. The common genes responsible for NDM include KCNJ11 and ABCC8 (SUR) genes. These genes influence various aspects of glucose metabolism such as β-cell K-ATP channel modulation, production of insulin and development of pancreas. The Madras Diabetes Research Foundation has fostered research in personalized medicine for diabetes based upon genetic information and has developed a national registry for neonatal diabetes and other monogenic form of diabetes.

Personalized medicine, which refers to customization of management according to specific characteristics, including clinical phenotype, laboratory data or genetic constitution of an individual, can help to improve outcomes in various disease conditions. The objective of personalized medicine is to optimize treatment on an individualized, safe and efficient and which allows the clinician to select the most appropriate drug, at the right dose, for the right patient. The term ‘Pharmacogenetics’ refers to the effect of genetic variation among individual on their therapeutic or adverse the response to drug. Personalized medicine can help tailor strategies for detecting preventing, treating, or monitoring of diabetes.¹² The various derangements in diabetes, including pancreatic β cell dysfunction, abnormalities in glucose transporters and insulin resistance, arise out of a complex interplay between genetic and environmental factors.³ It is important to identify specific risk factors and describe populations at risk of development and progression of diabetes and its complications. Treatment should be tailored to meet individual requirements. The response to treatment is also influenced by the genetic constitution of a person with diabetes. This is leading to shift in the management of diabetes from protocol-driven algorithm to patient-centered approach.⁴

Personalized medicine in diabetes (PMID) involves four domains including risk identification, resource allocation, selection of individualized therapy, and measurement of circulating biomarkers for monitoring response to prevention or therapy.⁵ Single nucleotide polymorphisms (SNPs) in several genes, for example, ABCC8, SLC22A1, SLC22A2, and PPARG, modulate the response to oral anti-diabetic drugs (OADs)(6). Besides addressing clinical and laboratory abnormalities, personalized medicine in diabetes can also encompass the psychological and social state of person with diabetes. Moreover, the recent application of digital health initiatives and computational platforms together the omics data, genomics, proteomics, metabolomics, and transcriptomics, has transformed personalized medicine in diabetes care.¹ In this review, we shall limit ourselves to the common polygenic and monogenic forms of diabetes and their impact on personalized medicine in an individual with diabetes mellitus.

Personalized medicine in type 1 and type 2 diabetes
Genetic mutations and polymorphisms lead to heterogeneity in disease characteristics and response to treatment in both type 1 and type 2 diabetes. Candidate gene analysis and genome wide scanning have identified molecular markers for the risk, development, progression, and treatment response in diabetes. Type 1 diabetes is characterized by an autoimmune response-mediated loss of β cells in the pancreas. Individuals with glutamic acid decarboxylase or islet autoantibodies and those with a family history of type 1 diabetes are at a higher risk of developing type 1 diabetes. More than 40 genetic loci, linked to autoimmunity and β cell survival, have been described for type 1 diabetes. Variants in the HLA class II genes, carrying codes for polymorphic antigen-presenting proteins, account for almost 50% of

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the genetic risk of type 1 diabetes. Examples of other genes include INS, PTPN22, ERBB3, CCR5, IL7R, IL2RA, and PRKCQ.\textsuperscript{6,7} Specific HLA class II alleles and haplotypes are associated with progression of disease in type 1 diabetes and describe the acute-onset, fulminant, and slowly progressive variants of the disease.\textsuperscript{10} Genetic variants also explain the differential requirements of immuno-suppression in type 1 diabetes.

Insulin secretion and responsiveness in type 2 diabetes are influenced by genetic determinants. Variants in about 23 genes associated with type 2 diabetes can potentially impact diagnostics, therapeutics and prognostics, and treatment decisions. Genes have been identified for reduced \( \beta \) cell mass (HHIEX, CDKN2A/CDKN2B), \( \beta \) cell dysfunction (KCNJ11, TCF7L2), insulin resistance (PPARG, ADAMTS9), and altered body mass index (FTO).\textsuperscript{11,12} Polymorphisms in the transcription factor 7-like 2 (TCF7L2) gene are associated with an increased risk of type 2 diabetes.\textsuperscript{13,14}

Genetic predispositions might influence the development and progression of macrovascular and microvascular, in diabetes. These can guide personalized decisions in the management of both type 1 and type 2 diabetes.\textsuperscript{15}

Protein kinase C-\( \beta \)-1 (PRKCB1) gene has been associated with end-stage renal disease in type 2 diabetes.\textsuperscript{17} Polymorphisms in the angiotensin I converting enzyme (peptidyl-dipeptidase A) 1 (ACE) gene influence the incidence of diabetes nephropathy and response to ACE inhibitors in person with diabetes. Independent of glycemic control, the ACE II genotype is associated with a lower incidence and the I/D or DD genotypes with a higher incidence of nephropathy in patients with diabetes. When compared to the I/D and DD genotypes, the II genotype has a better antiproteinuric response to ACE inhibitors.\textsuperscript{18} While the population impact of genes on the phenotypic expression of diabetes is low, it is expected that at an individual level genetic polymorphism will impact the response to different therapies.

The focus of personalized medicine in type 2 diabetes has been gradually shifted from characterizing subgroups based on molecular architecture alone to subgroups based on differential treatment responses. Simple clinical information, such as age, gender, body mass index (BMI), and glomerular filtration rate, can be used to calculate the probability of glycemic response to anti diabetic medication. This may be supplemented with other biomarkers such as C-peptide) or the omics data such as pharmacogenomics to predict response to a particular class of antidiabetic medication or its safety profile. Gender and BMI have been used to stratify response to therapy with thiazolidinediones (obese females) and sulphonylureas (slim males).\textsuperscript{4} Novel subgroups of type 2 diabetes have been defined recently by a data-driven cluster analysis with newly diagnosed diabetes (n=8980) based on six variables: age at diagnosis, BMI, HbA1c, homoestatic model assessment 2 estimates of \( \beta \)-cell function, insulin resistance and glutamate decarboxylase antibodies. Five clusters were defined with different patient characteristics and risk of diabetic complications: Severe autoimmune diabetes (SAID), Severe insulin-deficient diabetes (SIDD), Severe insulin-resistant diabetes (SIRD), Mild obesity-related diabetes (MOD), and Mild age-related diabetes (MARD). These clusters included 65, 18%, 15%, 22%, and 39% patients, respectively in white Caucasians (Europeans). One interesting observation is the identification of lower risk clusters MOD and MARD. It is possible that a less aggressive approach may be warranted in this group if these results are applicable to the general population. However, Personalized medicine in type 1 and type 2 diabetes is still in its infancy and is mostly limited to monogenic forms of diabetes.

**Personalized medicine in monogenic diabetes**

 Genetic architecture defines specific subgroups with typical phenotypes and treatment response in monogenic diabetes.\textsuperscript{4}

**Neonatal diabetes**

Neonatal diabetes mellitus (NDM) has been defined as antibody negative, insulin-sensitive hyperglycemia that is diagnosed within the first six months of life. NDM is predominantly monogenic and is of two types: Transient neonatal diabetes (TNDM) and permanent neonatal diabetes (PNDM). TNDM is characterized with remittance before one-year of age followed by relapse in adolescence and persistence throughout life, whereas PNDM is permanent. About 10% patients with NDM have syndromes and pancreatic aplasia (PTF1A, FOXP3, EIF2AK3, HNF1B, and IPF1).\textsuperscript{19} Genes responsible for the development of NDM include KCNJ11 (30%), ABCC8 (20%), IDDM2 (20%), PTF1A, and FOXP3. These genes influence various aspects of glucose metabolism such as \( \beta \)-cell K-ATP channel modulation, production of insulin, pancreatic development, and control of immune response. Genes like GATA4, RFX6 and IER3IP1 are associated with heart defect, gall bladder atresia and microcephaly in NDM. In the experience of the Madras Diabetes Research Foundation (MDRF), the commonest mutations in NDM are, sulphonylureas receptor (SUR or ABCC8) and KCNJ11 genes while rarely they could be in INS genes or other rare mutations.\textsuperscript{20-23}

Patients of NDM with mutations in genes KCNJ11 and ABCC8 show excellent glucose control with high-dose sulfonylureas. These patients have no additional risks of hypoglycemia and may also show an improvement in neurological functions with sulfonylureas therapy. Patients with TNDM with 6q24 methylation defect respond to low- dose sulfonylureas.\textsuperscript{4} In a study of genetic screening of NDM in India, carrying the KCNJ11 (Cys42Arg, Arg201Cys) and ABCC8 (Val86Ala, Asp212Tyr) mutations from India reported a fall in fasting plasma glucose and glycated hemoglobin (HbA1c) after switching over from insulin to oral sulfonylurea.\textsuperscript{20}

**Maturity onset diabetes in the young**

Maturity onset diabetes in the young (MODY) accounts for about 5% of all person with diabetes. MODY has an early age at onset (<25 years) and an autosomal dominant inheritance. MODY may be controllable without insulin for at least 5 years after which patients need insulin therapy. The major phenotype is impaired insulin secretion due to an autoimmune response to beta cells. Obesity and insulin resistance are usually not seen. MODY is predominantly monogenic.\textsuperscript{24} The most common MODY genes include those encoding glucokinase (GCK), hepatic nuclear factor 1 alpha (HNF1A) and hepatic nuclear factor 4 alpha (HNF4A). These genes explain the variations in clinical course of MODY. GCK-MODY is associated with a stable and high fasting glucose whereas the genes HNF1A, HNF4A and HNF1B show progressive deterioration of glucose over time.
but respond to low dose sulfonylurea agents. HNF1B-MODY is associated with β cell development defect, exocrine pancreatic insufficiency, and developmental defects in other organs especially in the kidney. Patients with this gene architecture require insulin for treatment. HNF1A-MODY and HNF4A-MODY are associated with glycosuria and neonatal hypoglycemia, respectively. GCCK-MODY could explain 5% of the gestational Diabetes Mellitus (GDM) cases in various population. It is imperative to identify pregnant female harboring GCCK mutation, since it has major clinical implication and its management is different. The Madras Diabetes Research Foundation has been leading the research in MODY in India and has been reporting on the genetics of all forms of MODY for 20 years including HNF1A (MODY 3), HNF4A (MODY 1), GCK-MODY (MODY 2), HNF1B (MODY 5). Recently, the group has reported the largest and the most comprehensive report on all the 14 MODY subtypes and has shown that except MODY 10 (INS Gene) all other MODY subtypes are present among Indians. They have also reported on a possible novel MODY subtype with a mutation in the NKX6-1 gene in addition to possible other novel MODY genes.

The Christian Medical College, Vellore has also studied patients with MODY in India and have reported NEUROD1, PDX1, PAX4, INS and BLK mutations along with the common mutations identified among early onset diabetes patients and pregnant women.

In a genomic analysis of 152 clinically diagnosed cases of MODY at the Madras Diabetes Research Foundation, HNF1A (7.2%) and ABCC8 (3.3%) were the most frequently mutated MODY genes. In addition, variants were identified in RFX6, WFS1, AKT2, NKX6–1. The Christian Medical College, Vellore has developed a cost-effective and accurate Next-Generation Sequencing (NGS)-based strategy to screen for MODY mutations. Specifically studying GCK gene in women diagnosed with GDM, at Max Healthcare reported a novel pathogenic variant. In collaboration with Madras Diabetes Research Foundation, this group further compared GCK variants in women affected with GDM with the healthy controls and found no association.

The MDRF has developed a national registry for neonatal diabetes and other monogenic form of diabetes (www.neonataldiabetes.in).

**Personalized medicine in blood glucose management**

Response to treatment in diabetes is determined by the genetic architecture of patients. Pharmacogenetic studies aim to define biomarkers for predicting response to treatment in diabetes. Genetic variants with single nucleotide polymorphisms (SNPs) can explain the variations in the pharmacokinetics and pharmacodynamics of various drugs in different patient populations.

Variants of genes that code the drug targets, transporters, and metabolizing enzymes for various oral hypoglycemic agents can influence the response to these therapies (Table 1). An understanding of these genetic compositions and their impact on the drug metabolism can help to tailor treatment for high efficacy and safety. Better response to sulfonylureas is seen in patients who are K-allele carriers. Similarly, the carriers of CC genotype of ABCC8 show better response to sulfonylureas when compared to CT and TT genotype patients. Metformin dose needs to be increased in people with diabetes with SLC22A1 gene and decreased in those with SLC22A2 gene. Diabetic patients with SLC47A1 gene may have decreased glucose lowering effect of metformin. DPP4 inhibitors are more effective in patients with KCNJ11 gene polymorphisms and less effective in patients with TCF7L2 gene polymorphisms. The CTRB1 and CTRB2 genes produce chymotrypsin gene polymorphisms. The CTRB1 and CTRB2 genes produce chymotrypsin that reduces the efficacy of incretin therapy. Glucose-lowering effect of pioglitazone is partly ascribed to the polymorphisms associated with PPARG gene. Rosiglitazone shows a markedly increased effect in patients with the AA genotype of leptin G-2548A.

**Personalized medicine in glucose monitoring and follow-up**

Continuous glucose monitoring (CGM) for glucose values, glycated hemoglobin (HbA1c), and hypoglycemic episode can provide a more personalized approach towards the management of diabetes. Small, accurate, easy to use systems, for example, the flash glucose monitoring system, Free Style Libre™ (Abbott Diabetes Care, Alameda, CA), allow real-time monitoring of blood glucose values. It has become easier to identify glucose variability.

**Personalized medicine in the management of complications**

Diabetes management includes the management of its complications as well. One such chronic complication is painful neuropathy. Carabamazepine, commonly used for the relief of painful sensory neuropathic symptoms, is associated with hypersensitivity reaction including Steven-Johnson syndrome and toxic epidermal necrolysis. Both carry a mortality risk as high as 30%. It has been found that the risk of these life threatening complications is limited to individuals with HLA allele B*1502. Thus, precision medicine can help in identifying persons at high risk of adverse events, and in matching therapy to patient.

Another example of patient-centric precision medicine relates to the choice of an anti-platelet medication after acute coronary syndromes. Based upon the function of CYP2C19*2 and PYR1 gene variants, all individuals can be classified as ultrafast, fast, intermediate or slow metabolizers of clopidogrel. Slow and intermediate metabolizers respond well to this drug, and benefit from its use after acute coronary syndromes. Fast and ultrafast metabolizers, however, do not respond to clopidogrel, and are better treated with newer platelet aggregation inhibitors like prasugrel. Precision medicine not only allows appropriate choice of therapy but also, optimization of outcomes.

After 40 years of research, MDRF has brought Precision Diabetes to India. Mohan and colleagues have summarized the current role and place of precision diabetes (Table 2).

**Barriers to Personalized Medicine in Diabetes**

Despite all the potential advantages of personalized medicine (precision diabetes), there are several challenges that need to be addressed.

1. A lot remains unknown in the field of type 1 and type 2 diabetes regarding pathophysiology, genetic variation and pharmacogenetics. As such personalized medicine in diabetes is still in its infancy.

2. The cost of genetic analysis for currently known variants is high. Unless this cost comes down, it
### Table 1: Anti-diabetic agents, associated genes, and variant characteristics

<table>
<thead>
<tr>
<th>Anti-diabetic drug class</th>
<th>Gene and SNPs</th>
<th>Action</th>
<th>Variant characteristics</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>KCNJ1 Glu23Lys (rs5219)</td>
<td>Subunits of the KATP channel. Metabolism of glucose can affect ATP levels and thereby function of KATP channel.</td>
<td>K-allele carriers show higher decrease in HbA1c compared with EE homozygotes. Significantly associated with decrease in FPG</td>
<td>(43)</td>
</tr>
<tr>
<td></td>
<td>ABC28 Ser1369Ala (rs757110) Exon 163G&gt;T (rs1799854) rg1273Arg (rs1799859)</td>
<td>Potentiation activity of the KATP channel</td>
<td>Lower FPG Wild-type CC genotype shows significantly lower HbA1c levels compared to TT genotype</td>
<td>(34)</td>
</tr>
<tr>
<td></td>
<td>TCF7L2 rs7903146 C&gt;T rs12253372 C&gt;C</td>
<td>Potentiation activity of the KATP channel</td>
<td>Significant reduction in HbA1c and FPG in CC genotype compared to the CT and TT genotype</td>
<td>(34)</td>
</tr>
<tr>
<td></td>
<td>CYP2C9 *3(Ile359Leu) (rs1057910) *2 (Arg144Cys) (rs1799853) *3 (Ile359Leu) (rs1057910)</td>
<td>Oral clearance of tolbutamide</td>
<td>Carriers of *3 allele required lower doses of tolbutamide</td>
<td>(44)</td>
</tr>
<tr>
<td>Metformin</td>
<td>SLC22A1 gene coding the OCT1 protein transporter Site: Hepatocytes, Enterocytes</td>
<td>Mediates metformin uptake, accumulation and pharmacological action in the liver (AMPK activation)</td>
<td>Decreased hepatic and intestinal metformin uptake Decreased AMPK activation</td>
<td>(35)</td>
</tr>
<tr>
<td></td>
<td>SLC22A2 gene coding the OCT2 protein transporter Site: Renal distal tubule</td>
<td>Facilitate urinary elimination of metformin</td>
<td>Decreased metformin clearance Increased plasma concentration</td>
<td>(35)</td>
</tr>
<tr>
<td></td>
<td>SLC47A1 gene coding the MATE1 transporter sites: Bile canalicular, renal epithelium</td>
<td>Metformin secretion in bile and urine</td>
<td>May effect glucose lowering effect of metformin</td>
<td>(35)</td>
</tr>
<tr>
<td></td>
<td>SLC47A2 gene coding the MATE2K transporter: Renal epithelium</td>
<td>Excretion of metformin</td>
<td>Metformin excretion in urine is decreased</td>
<td>(35)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>PPARγ gene Pro12Ala</td>
<td>Energy Intake/expenditure, lipid metabolism</td>
<td>Loss-of-function mutations in PPARγ are associated with severe IR and DM Polymorphism Pro12Ala Significantly greater decrease in FPG and HbA1c</td>
<td>(44)</td>
</tr>
<tr>
<td></td>
<td>Uncoupling protein 2 (UCP2)</td>
<td>Gene of metabolic disorders; it negatively regulates glucose-stimulated insulin secretion.</td>
<td>Strong association between rosiglitazone treatment success and UCP2-866 G&gt;A polymorphism</td>
<td>(45)</td>
</tr>
<tr>
<td></td>
<td>OATP1B1, CYP2C8</td>
<td>Hepatic uptake of TZDs is and metabolism</td>
<td>Homozygous carriers of the gain-of-function allele for CYP2C8, CYP2C8*5 coding for the Arg139Ile and Lys399Arg amino acid substitutions have lower rosiglitazone plasma concentrations Lower efficacy</td>
<td>(46)</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 (DPP-4) inhibitors</td>
<td>KCNJ11 gene</td>
<td>Regulates one of the pancreatic KATP</td>
<td>Subjects with KCNJ11 rs2285676 (genotype CC) are more likely to response to DPP-4 inhibitor treatment</td>
<td>(47)</td>
</tr>
<tr>
<td></td>
<td>TCF7L2 gene</td>
<td>Incretin secretion from intestinal endocrine L cells and the proliferation of pancreatic beta cells</td>
<td>TCF7L2 variants are associated with diminished pancreatic islet-cell responsiveness to incretins</td>
<td>(47)</td>
</tr>
<tr>
<td>Sodium-dependent glucose transporter-2 (SGLT2) inhibitors</td>
<td>CTRB1 and CTRB2</td>
<td>Both encode chymotrypsin, in the regulation of the incretin pathway</td>
<td>Reduced response to treatment with DPP-4 inhibitors</td>
<td>(48)</td>
</tr>
<tr>
<td></td>
<td>SGLT2 gene (SLC5)</td>
<td>Inhibits reabsorption of glucose in renal proximal tubule, increasing urinary glucose excretion and decreasing glucose levels</td>
<td>Nonsense and missense mutations in the SLC2A3 gene that result in the loss of SGLT-2 function cause familial renal glycosuria and are associated with the reduced circulating glucose levels</td>
<td>(49)</td>
</tr>
</tbody>
</table>

**Summary**

Personalized medicine is a revolutionary transformation in medicine with emphasis shifting from ‘one size fits all’ to personalized treatment. Advances in personalized medicine will help to predict susceptibility of the drug, improve disease detection, preempt disease progression and also preventing adverse effects of drugs which occur because of genetic variations. In the field of diabetes, currently personalized medicine is mainly applied in the treatment of monogenic forms of diabetes like MODY and neonatal diabetes. However, in the years to come, this may well extend to type 2 diabetes and type 1 diabetes as well.

It can help to reduce the time, cost, and failure rate of pharmaceutical trials in clinical research. The application of molecular genetic approaches to research in diabetes will provide new opportunities for progressively more targeted, and hopefully, more effective treatments. In routine clinical practice, application of personalized medicine can lead to effective drug therapy with better patient adherence.

**Acknowledgments**

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for
1. Prevention (in high risk groups)
   • Genetic studies of type 1 diabetes
   • Genetic studies of type 2 diabetes

2. Clinical Diagnosis
   • Currently, this is mainly restricted to monogenic forms of diabetes due to maturity onset of the diabetes of the young (MODY) and Neonatal Diabetes (NDM).

3. Treatment:
   • Mild nonprogressive fasting hyperglycaemia (GCK MODY) – Can stop all antidiabetic medications and treat with diet and exercise alone.
   • Familial diabetes with affected parent (HNF 1A or HNF 4B MODY) – Respond to low dose sulfonylurea
   • Neonatal diabetes (KCNJ11 or ABCC8 mutation) - Respond to high dose of sulfonylurea.

4. Monitoring:
   • Use of continuous glucose monitoring (CGMS) and ambulatory glucose profile (AGP) to study glycemic variability and response to therapy.

authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published.

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References

42. Sweed AE, Donnelly LA, Tavendale R, Carr F, Leese G, Palmer CN, Pearson ER, ZK. CYP2C8 and SLCO1B1 Variants and Therapeutic Response to Thiazolidinediones in Patients with Type 2 Diabetes Diabetes Care.
Imaging Appearances following Oral and Parenteral Mercury Poisoning

Deepashree T¹, Mayank Jain², Jayanthi V²

A 29 year old male patient presented with alleged history of taking intravenous mercury (75 to 100 mL on 2 occasions within a span of 24 hours) in right upper limb reported to our hospital. He had simultaneously also swallowed 75 mL mercury. CT of chest and abdomen (Figures 1 to 2) showed well defined hyperdense foci scattered throughout lung fields, right side of heart, liver, small and large bowel, pelvicalyceal system of kidneys, spinal canal, and soft tissue in gluteal region and upper thighs. Ingested mercury was seen delineating both small and large bowel. On follow up after a month, there was clearance of mercury from the gut lumen but it was retained in lung parenchyma, liver and kidney. He was managed conservatively as the chelating agents were not available. He developed acute tubular necrosis and is being closely monitored on follow up.

Mercury is a toxic heavy metal which is widely dispersed in nature. Human mercury exposures occur chiefly¹,² through inhalation of elemental mercury vapour via occupational or dental amalgam exposure or through ingestion of mercury bonded to organic moieties (methyl, dimethyl, or ethyl mercury), primarily from seafood.

Exposure to mercury vapour is associated with erosive bronchitis and bronchiolitis potentially leading to respiratory failure and CNS symptoms such as tremor or erethism.³ Chronic exposure causes symptoms like weakness, fatigue, anorexia, weight loss, neurological deficits and gastrointestinal disturbance.⁴ Acute poisoning with mercuric salts (typically HgCl₂) generally targets the gastrointestinal tract and the kidneys. Extensive precipitation of enterocyte proteins occurs, with abdominal pain, vomiting, and bloody diarrhea with potential necrosis of the gut mucosa. Surviving patients commonly develop renal tubular necrosis with anuria.⁵ Chronic poisoning with mercury salts is rare. Brain dysfunction is less evident than with other forms of mercury.

Organic mercury poisoning damages many parts of the brain and peripheral nervous system.⁶ Mercury toxicity should be included in differential diagnosis of common subjective complaints such as fatigue, anxiety, depression, odd paresthesias, weight loss, memory loss, and difficulty concentrating, as these symptoms have been described in low-grade chronic mercury exposure. Given the ability of the various forms of mercury to deposit in most parts of the human body, the range of symptoms potentially caused by mercury is quite large.⁷

Diagnosis of mercury overload is difficult. The commonly used modalities (blood, urine, and/or hair levels) do not correlate with total body burden and offer little diagnostically useful information. Provocation with DMPS (2,3 Dimercapto-1-Propanesulfonate) appears to offer a more accurate assessment of body burden.⁸

References

Terry’s nails

Rakesh Agarwal¹, Rashmi Baid²

Fig. 1: Terry’s nails in fingers

Fig. 2: Terry’s nails in toes

A 45 year old non diabetic, alcoholic male patient presented with gradual distention of abdomen and melena for one week. He had a past history of cholecystectomy 10 years back. He had marked ascites, splenomegaly and oesophageal varices. His nails revealed diffuse dull whitening of the proximal nails beds with distal reddish brown bands parallel to the free edge of the nail plates, in all four extremities (Figures 1 and 2). He was managed with endoscopic variceal ligation and therapeutic paracentesis. Conservative management was given for his portal hypertension and he is being followed up on an outpatient basis.

Terry’s nails, named for Dr. Richard Terry, refer to nails with a characteristic “ground glass appearance” and no lunula.¹ They are bilaterally symmetrical and usually more marked in the thumb and forefinger. They were later redefined as nails with distal brown or pink band up 3 mm wide and caused by telangiectasia in the nail bed.² The proximal pallor may develop gradually. They are known to be associated with cirrhosis, chronic congestive heart failure, diabetes mellitus, and with age.³ Some have reported them to be present without any disease.⁴ They have been said to be due to abnormal steroid metabolism. A close differential is Lindsay’s nails which are usually associated with kidney disease.

References


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Received: 21-02-2017, Accepted: 25.07.2018
Multi-drug Resistant Tuberculous Osteomyelitis of the First Carpometacarpal Joint Presenting as Unmasking Immune Reconstitution Inflammatory Syndrome

Rohit Kumar1, Nitin Gupta1, Sundeep Malla2, Sanjay Ranjan3, Neeraj Nischal4, Naveet Wig5

Abstract
Tuberculosis (TB) is an important cause of significant morbidity and mortality, particularly in patients living with human immunodeficiency virus (HIV) infections. The co-infection of TB and HIV coinfection is further complicated by a relatively higher frequency of extra-pulmonary TB and upsurge of drug resistance. Musculoskeletal TB is a relatively less common form of extrapulmonary TB; involvement of carpometacarpal joint as an initial manifestation is even rarer. We herein present a retro positive patient who presented with low-grade fever, constitutional features and swelling of the base of the left thumb. On evaluation, he was found to have axillary and inguinal lymphadenopathy with lytic destruction of carpometacarpal joint as well as D10-D11 vertebrae. Fine needle aspiration (FNA) of synovial fluid was negative for tuberculosis but geneXpert from FNA of axillary node revealed Mycobacterium tuberculosis with rifampicin resistance. This case highlights the rarity of carpometacarpal joint involvement in TB as the initial manifestation and the importance of meticulous search of alternative sites for sampling in difficult situations such as osteoarticular TB. It also highlights the rising prevalence of drug-resistant TB and a definitive need for microbiological diagnosis wherever feasible.

Case Report
A 50-years old male patient, without any previous comorbidities, presented to an outside hospital with complaints of intermittent low grade fever for one year associated with loss of appetite and weight. There was no history of cough, hemoptysis, respiratory distress, abdominal complaints, headache or any bowel/ bladder disturbances. On evaluation, he was found to be positive for HIV-1 antibodies. He was started on zidovudine, lamivudine and nevirapine on which he showed initial improvement. Three months into the treatment, he started complaining of fever and noticed a gradually progressive painful inflammatory swelling in his left thumb (1st carpometacarpal joint). He took symptomatic treatment for these complaints but did not show any improvement. He presented to our clinic with non-resolving symptoms.

On general physical examination, lymphadenopathy was noted in the left axillary and bilateral inguinal region. The nodes were discrete, firm in consistency, and were not attached to underlying or overlying structures. Local examination of left hand showed soft, fluctuant and tender swelling at the base of the thumb. There was restricted range of motion in the affected joint. On systemic examination, mild spinal tenderness was noted at lower thoracic spine. Rest of the systemic examination was normal. His routine laboratory hematological and biochemistry were normal (Table 1). CD4 count was 392 cells/ul. Chest X-ray was normal.

Plain radiograph of right-hand (Figure 1) showed lytic destruction of carpal bone and base of 1st metacarpal. MRI dorso-lumbar spine revealed contiguous vertebral body destruction in D10-D11 with destruction of intervening disc along with an epidural abscess. Aspirate of joint fluid (metacarpal joint) was negative but fine needle aspiration cytology from the left axillary node was positive for Mycobacterium tuberculosis and resistant to rifampicin on GeneXpert (Cepheid). The patient was started on Category IV antitubercular therapy (ATT) according to the national program i.e. kanamycin, levofloxacin, cycloserine, ethionamide, pyrazinamide and ethambutol. Nevirapine was changed to efavirenz to avoid hepatotoxicity due to concurrent administration of nevirapine and ATT. On follow up after one year of initiation of ATT, he had no fever, his appetite was normal, and there was almost complete resolution of joint and lymph node swelling.

Table 1: Laboratory parameters of the patient with reference values

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>At admission</th>
<th>Ref. values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>12</td>
<td>12-15</td>
</tr>
<tr>
<td>Total leucocyte count (×10^3)</td>
<td>7700 (Neutrophil 66%, Lymphocyte 25%, Monocyte 8%)</td>
<td>4000 - 11000</td>
</tr>
<tr>
<td>Platelet count (×10^3)</td>
<td>2,54,000</td>
<td>150000 - 400000</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.8</td>
<td>0.8-1</td>
</tr>
<tr>
<td>Aspartate transaminase/Alanine transaminase (IU/l)</td>
<td>32/24</td>
<td>Up to 50</td>
</tr>
<tr>
<td>Urea/Creatinine (mg/dl)</td>
<td>32/0.7</td>
<td>0-40/0-1</td>
</tr>
</tbody>
</table>

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§Assistant Professor, Department of Medicine, ¶Professor, Department of Medicine, AIIMS, New Delhi
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Discussion

Tuberculosis (TB) is one of the commonest illness in patients living with Human immunodeficiency virus (HIV). HIV infection is associated with increased risk of re-activation of TB. Also, initiation of anti-retroviral drugs (ART) may lead to reactivation of underlying latent infection (usually within three months), a phenomenon called as unmasking Immune reconstitution inflammatory syndrome (IRIS). In HIV positive patients, incidence of both extra-pulmonary (EPTB) and multi-drug resistant tuberculosis (MDR-TB) is increased. In those with EPTB, musculoskeletal involvement is a less common presentation. We report a rare case of TB involving the first carpometacarpal (CMC) joint.

IRIS is a condition associated with initiation of antiretroviral therapy (ART) leading to a state of overwhelming inflammatory response due to immune recovery. 1 IRIS may lead to reactivation of underlying latent infection i.e. unmasking infection, which occurs within few months after ART initiation or paradoxical infection, which occurs when patient is already on ATT and is started on ART leading to flare up. As per International Network for the Study of HIV-associated IRIS (INSI) consensus definition, unmasking TB IRIS usually occurs within three months of ART initiation. 1 We considered the possibility of unmasking TB IRIS in our case, as he developed symptoms within 3 months of ART initiation. On further evaluation, he was found to have involvement of 1st CMC joint, lumbar spine and peripheral lymph nodes.

Musculoskeletal system TB is an uncommon manifestation of extra-pulmonary TB (EPTB): it accounts for around 2.8% - 14% of EPTB cases. 2 Within the spectrum of skeletal TB, involvement of carpometacarpal joint (CMC) is very rare; there is scanty literature on CMC joint TB arthritis as initial manifestation. To the best of our knowledge, there is only one more case of TB of 1st carpometacarpal joint reported from India. 3

The diagnosis of musculo-skeletal TB is commonly based on clinical and radiological findings but with increased incidence of MDR-TB, especially in HIV positive patients, the role of microbiological diagnosis becomes very important. In our patient, although the diagnosis of TB was clear based on the radiological findings and it is a common practice to empirically start ATT in such situations, we went for invasive sampling. The aspiration of joint fluid was negative for tuberculosis but the lymph node FNAC yielded positive results and he was started on appropriate treatment. This emphasizes the importance of meticulous search for possibility of dissemination and involvement of other sites which can be sampled for diagnostic purpose and may provide information relevant to diagnosis and management. Another important lesson learnt from this case was the fact that the diagnostic accuracy of GeneXpert is variable in different samples. Its sensitivity is higher in tissue aspirates as compared to that in the body fluids like synovial fluid. 5-7 According to studies from India, prevalence of MDR-TB (newly diagnosed or previously treated for TB) in PLHIV varies from 12.5% to as high as 47% in a study in ART clinic attendees. 8-10 MDR TB is generally associated with poor outcomes unless diagnosed early and initiated on appropriate treatment. Therefore, high index of suspicion is extremely important.

This case also highlighted the fact that TB in endemic countries may present with unusual presentation or unusual sites like first carpometacarpal joint.

Conclusion

Extra-pulmonary involvement at unusual sites and multi-drug resistance is common in immunosuppressed patients living in endemic areas. Establishment of microbiological diagnosis by invasive sampling of appropriate site (with higher yield) is of utmost importance for adequate management.

References

Bisphosphonates use in Pachydermoperiostosis

Rakesh Kumar Jagdish¹, MK Bhatnagar², Ayush Malhotra³, Rajaram Aggarwal³, Shailly⁴

Abstract

Pachydermoperiostosis is a rare genetic disorder which commonly presents with clubbing, bone pains and skin changes. The treatment is mostly unsatisfactory. We tried bisphosphonates in our case with encouraging results. We suggest that parenteral bisphosphonates should be tried early in treatment of Pachydermoperiostosis.

Introduction

Pachydermoperiostosis is also known as Touraine-Solente-Golé syndrome, primary or idiopathic Hypertrophic osteoarthropathy (HOAP). It is a rare autosomal disorder with variable expression. Pachydermoperiostosis is characterised by bilateral symmetrical grade IV clubbing, periosteal new bone formation, thickening of skin (pachyderma), and excessive sweating (hyperhydrosis). No treatment is curative. Symptomatic treatment such as NSAIDS, steroids, Colchicine are used. There are case reports of bisphosphonate (Pamidronate) use with good results in secondary HOAP. The reports about use of bisphosphonates in primary HOAP/Pachydermoperiostosis are only few.

Case Report

A 31 years old, male patient, non smoker, non alcoholic, resident of Bihar, presented to us with history of pain and swelling in hands and feet, followed by involvement of ankle, knee and wrist joints, of 15 years duration. This was associated with hyperhydrosis of palms and soles. There was no history of fever, palpitation, bluish discolouration, backache, haemoptysis, haematemesis, hematuria, haematochezia, cough, expectorations, dyspnea, oral ulcers, weight loss or bleeding tendency. Family history of similar complains positive in paternal cousin brother.

On physical Examination, He was afebrile, pulse-70/min, respiratory rate-16/min, BP-122/80 mm Hg, SpO₂-98% at room air. There was no cyanosis, pallor, lymphadenopathy, oedema. On systemic examination, respiratory, cardiovascular, abdominal and neurological examination were normal. On skin examination, there was furrowing on the forehead, skin as oily and shiny in appearance (Figure 1) and hyperhydrosis of hands and feet. Musculoskeletal examination showed grade IV clubbing along with widening of wrist and ankle joint, swelling of both the knee joint (Figures 5a, 6a, 7a and 8a).

On investigation his haemoglobin, ESR, CRP, leukocyte counts and platelet counts were within normal limits. Peripheral blood film showed normocytic normochromic picture. Liver, kidney and thyroid function tests were normal. Blood sugar was within normal range. Urine examination was also within normal range. Stool for occult blood, chest X-ray PA view, Contrast enhanced CT chest, 2 D echocardiography, USG abdomen and pelvis were normal. Other radiological investigations, X-ray of ulna, radius, tibia and fibula showed wavy periosteal reaction along the distal meta-diaphyses (Figures 2, 3 and 4). On the basis of history, physical examination and investigations, we made diagnosis of Primary HOAP (Pachydermoperiostosis).

His main problem was of bony pains and swelling. We started him on NSAID, steroids, colchicine, added one after the other to relieve pain over six months without much relief. We gave bisphosphonates infusion (Pamidronate) 60 mg over 2 hours slowly, after hydration with 500 ml normal saline. Patient responded well in the form of pain relief in 3-4 days of treatment and decrease in swelling of hands, feet and knee in 7-10 days. Patient is still feeling better after 30 days of follow up. Oral glycopyrrolate was given for hyperhydrosis with good result.
Fig. 2, 3, 4: Periosteal reaction—wavy periosteal reaction along the distal meta-diaphyses of ulna, radius, tibia and fibula and around knee joint.
(image-2,3 and 4)

Fig. 5: Hands-Soft tissue swelling significantly reduced post treatment
(5a) Before Pamidronate injection (5b) After Pamidronate injection

Fig. 6: Feet and ankle swelling reduced significantly post treatment.
(6a) Before Pamidronate injection (6b) After Pamidronate injection

Fig. 7: Knee Effusion—decreased significantly post treatment
(7a) Before Pamidronate injection (7b) After Pamidronate injection

Disscussion

Primary HOAP / Pachydermoperiostosis is an autosomal dominant disease with incomplete penetrance and variable expression, in few cases autosomal recessive and X-linked inheritance can be there and family history is present in 1/3rd of cases only. The disease begins insidiously at puberty and is nine times more common in males. Symptoms usually disappear at adulthood but in our patient symptoms persisted and patient did not respond to usual treatment. Exact pathology is unclear but it is suggested that abnormal production of growth factors like VEGF (vascular endothelial growth factor) and PDGF (platelet derived growth factor) are playing central role. It is a rare disease and should be differentiated from other causes of clubbing like chronic suppurative pulmonary diseases, bronchogenic carcinoma and lung metastases, cystic fibrosis, and cyanotic congenital malformations of the heart, thyroid acropachy, acromegaly, and chronic inflammatory rheumatic diseases. Long term prognosis of Pachydermoperiostosis is generally non fatal. No treatment is curative. Various symptomatic treatment strategies are there for Pachydermoperiostosis, including NSAIDS, Steroids, colchicine, vagotomy for skeletal symptoms, botulinum toxin type A, Isotretinoin and plastic surgery for dermatological manifestation, Beta blockers, glycopyrolate or neurotoxins for hyperhydrosis. Newer therapies
Novel Technique of Transfemoral Venous Pacing in a Rare Case of Inferior Vena Cava Stenosis

Neeraj Varyani¹, Cinosh Mathew², Rajneesh Calton³

Abstract
Temporary transvenous pacing is a simple and routinely performed invasive procedure for treatment of life threatening bradyarrhythmias. We present a novel technique for transfemoral venous pacing in a patient with rare co-occurrence of inferior vena cava stenosis, rheumatic mitral stenosis, left ventricular dysfunction and digitoxicity.

Introduction
Cardiac bradyarrhythmias represent a heterogeneous group of rhythm disorders of impulse generation and conduction. Temporary cardiac pacing may be required to bridge patients through hemodynamic instability and recovery or to permanent pacemaker implantation. Transvenous cardiac pacing is a life saving and routinely performed invasive procedure for treatment of bradyarrhythmias.¹ Inferior vena cava (IVC) stenosis is a rare disorder that may be asymptomatic and detected incidentally during temporary transvenous pacing. We present a novel technique for transfemoral pacing in a patient with IVC stenosis and rheumatic mitral stenosis (MS).

Case Presentation
A 68-year old lady with a diagnosis of rheumatic valvular heart disease (RHD) with severe MS, moderate mitral regurgitation (MR), left ventricular (LV) dysfunction and atrial flutter had presented with complaints of syncopal episodes and worsening dyspnea for 7 days. On examination she was found to have bradycardia (heart rate of 30 / min) and hypotension (systolic blood pressure of 60 mm Hg). Her initial ECG showed junctional bradycardia and frequent ventricular premature complexes. Chest radiograph revealed cardiomegaly, left atrial enlargement and pulmonary edema. Transthoracic two-dimensional echocardiography confirmed severe MS with transvalvular mean gradient of 12 mmHg, a mitral valve area of 1.0 cm², moderate MR and LV dysfunction. Digoxin levels were found to be 3.4 ng/ml confirming digoxin toxicity as the cause for bradycardia. Emergency temporary transvenous pacing was planned for symptomatic bradycardia.

Right ventricular pacing was initially attempted through transfemoral route under fluoroscopic guidance using 6 French (F) lead but it was noted that

References
and treatment for mitral stenosis and

Patient was advised further workup

obstruction at drainage site into RA.

suggesting a membranous or a web like

ultrasonography revealed no evidence

pacing lead was in situ. Abdominal

heparin till the time the temporary

to sinus rhythm. Patient was given

after 4 days when rhythm had reverted

pacing lead and sheaths were removed

shaped into a more curved manner

wire (0.035 inch and 150 cm)

in the west, thrombotic and

as membrane occlusion or stricture

cause of acquired IVC obstruction is

membranous obstruction of the IVC

femoral vein as in our case. Congenital

transfusion and post IVC filter

be of help to interventionist to provide

stenosis is a safe alternative and could

over a terumo wire to cross the IVC

technique of using an armoured sheath

lack of diaphragmatic stimulation at

apex (Figure 2). Adequate pacing and

positioned into right ventricle (RV)

was used but it could be passed till D8

level only (drainage site of IVC into

right atrium). Repeated manipulations

were attempted but neither the pacing

lead nor a diagnostic 0.032 inch wire
could pass into the right atrium (RA).

Stenosis of the IVC at the D8 level was

confirmed by a contrast venogram. A

Terumo wire (0.035 inch and 150 cm)

was advanced into the IVC and then

negotiated past the stenosis through
gentle manipulation and passed into
the RA (Figure 1). A 6F armoured sheath (24 cm length) was advanced over the Terumo wire into the RA and then after removal of the wire, a 6F pacing lead with its proximal end shaped into a more curved manner was inserted through the armoured sheath and advanced into the RA. The armoured sheath was then pulled back into the IVC and the lead was positioned into right ventricle (RV) apex (Figure 2). Adequate pacing and sensing thresholds were obtained and lack of diaphragmatic stimulation at high output was noted. Armoured sheath and pacing lead were anchored to the thigh with sutures. Procedure was successful and uneventful and pacing lead and sheaths were removed after 4 days when rhythm had reverted to sinus rhythm. Patient was given heparin till the time the temporary pacing lead was in situ. Abdominal ultrasonography revealed no evidence of extrinsic compression on IVC suggesting a membranous or a web like obstruction at drainage site into RA. Patient was advised further workup and treatment for mitral stenosis and IVC stenosis but she declined for the same. Patient was discharged on 7th post procedure day in a stable condition.

Discussion

Intracardiac temporary pacing by placement of electrode catheter into RV for management of bradyarrhythmias was first described by Furman and Robinson in 1958. It can be attempted through femoral, jugular, subclavian or brachial vein. IVC obstruction occurs in 3% of congenital heart diseases, especially heterotaxy. Isolated obstruction of caval veins is rare, usually iatrogenic and may be detected during right heart catheterization, percutaneous balloon mitral valvotomy (PBVM) or temporary pacing through femoral vein as in our case. Congenital membranous obstruction of the IVC at junction with RA or a restrictive eustachian valve has been described. In Asian countries, the most common cause of acquired IVC obstruction is Budd-Chiari syndrome which presents as membrane occlusion or stricture of IVC. In the west, thrombotic and proliferative disorders, post hepatic transplantation and post IVC filter placement are the predominant causes of acquired IVC obstruction. External compression by a tumor, aneurysmal dilation of aorta, pseudoaneurysm of a venous coronary graft, goiter, mediastinal fibrosis, constrictive pericarditis, bile bladder distention, polycystic kidneys, hydatid cyst, and hematoma after blunt liver trauma have been reported. Vasculitis such as Behçet’s disease may lead to shrinkage and obstruction of caval veins. Our patient denied history of any surgical intervention or blunt trauma to the abdomen in past.

In presence of IVC obstruction, the conventional transfemoral approach may not be feasible. In such situations, options are to use a transjugular or subclavian approach. But these approaches can be time consuming and requires considerable instrumentation and surgical skills. Moreover, manipulation of pacing lead from this site into right atrium is not always easy, especially in older people and use of subclavian route compromises later plans for permanent pacemaker implantation.

A transfemoral approach has several advantages: it can be accomplished quickly in 3-13 minutes and is particularly valuable in management of patients with cardiogenic shock where expediency is of paramount importance. With the use of fluoroscope, placement of the pacing lead is precise, and the repositioning or replacement of lead can be done quickly. It does not compromise later plans for permanent pacemaker implantation. It is a simple and safe technique and has a short learning curve. A long armoured sheath is helpful in not only these situations but also in procedures attempted through femoral arterial route where the aorta might be tortuous.

Conclusion

Cost efficacy is a concern in developing countries. This novel technique of using an armoured sheath over a terumo wire to cross the IVC stenosis is a safe alternative and could be of help to interventionist to provide successful outcome when faced with similar difficult situation without significant increase in the procedural cost.

References

Pulmonary Vocal Syndrome

Suhas HS¹, Ketaki Utpat², Jyotsna M Joshi³

Abstract
Vocal cord paralysis is a common entity with diverse causes clinically manifesting as dysphonia. Vocal cord paralysis due to respiratory cause is due to involvement of left recurrent laryngeal nerve usually secondary to bronchogenic carcinoma. However, it can also be seen in association with other less well recognised causes such as pulmonary tuberculosis. We present to you a patient with hoarseness of voice due to left recurrent laryngeal nerve paralysis secondary to endobronchial tuberculosis.

Introduction
Hoarseness of voice can occur due to anatomical or functional abnormality of larynx. Common cause includes laryngeal infections, blunt trauma, iatrogenic affection of recurrent laryngeal nerve, malignancies of thyroid, oesophagus and lung and cardiovascular conditions such as mitral stenosis. Vocal cord paralysis due to respiratory cause is known as pulmonary vocal syndrome. We present a case of pulmonary vocal syndrome due to endobronchial tuberculosis.

Case Report
A 30-year-old lady presented with symptoms of three months duration of intermittent fever, cough and hoarseness of voice. There was no history of preceding viral illness, vocal cord abuse, paroxysmal nocturnal dyspnoea or rheumatic heart disease. Her general physical and systemic examination was within normal limits.

Chest radiograph showed left upper lobe fibrosis. Sputum examination did not reveal acid fast bacilli. High resolution computerised tomography of thorax showed fibrosis in left upper lobe and lingula with absence of any other intrathoracic lesion or enlarged mediastinal lymph nodes (Figure 1). Fibreoptic bronchoscopy revealed left vocal cord palsy along with an additional finding of scarring of trachea at the distal end with the stenosis of left main stem bronchus (Figure 2). Bronchial washing gene Xpert detected Mycobacterium Tuberculosis thus confirming the diagnosis of endobronchial tuberculosis.

Discussion
Hoarseness of voice is a frequently encountered symptom seen due to structural or functional involvement of larynx or secondary to involvement of recurrent laryngeal nerve. Common causes include iatrogenic such as following thyroid surgeries (41%), idiopathic causes (33%) and well defined causes (25%) such as lung malignancy, thyroid malignancy, oesophageal malignancy, cardiac causes such as Ornters syndrome and chronic benign inflammatory conditions such as tuberculosis.

Earlier hoarseness of voice after ruling out malignancy of the lung was largely attributed to cardiovascular causes such as mitral stenosis, left atrial enlargement or pulmonary hypertension. This entity was known as Ornters syndrome. Hoarseness of voice due to involvement of recurrent laryngeal nerve secondary to a respiratory cause is known as pulmonary vocal syndrome. The involvement of left recurrent laryngeal nerve is more common when compared to right as it arches around the arch of aorta and has a substantial intrathoracic course. Such an entity is more often encountered in association with

Fig. 1: HRCT axial and sagittal images showing upper lobe fibrosis and narrowing of left main bronchus (red arrow)

Fig. 2: Bronchoscopy images showing left main bronchus stenosis
bronchogenic carcinoma. However, it can also be seen in association with chronic benign inflammatory conditions such as tuberculosis. Later Radner quoted in his article about the possibility of tuberculosis leading to recurrent laryngeal nerve palsy. The various mechanisms responsible in tuberculosis that might lead to pulmonary vocal syndrome are:

1. The nerve passing through caesating lymph node.
2. The nerve might get stretched due to dense pleural thickening or fibrosing mediastinitis.
3. The nerve being stretched due to retraction of upper lobe bronchus towards apex as in endobronchial tuberculosis.
4. The nerve being compressed by enlarged pulmonary artery.

Cases of pulmonary tuberculosis associated with mediastinal lymphadenopathy or upper lobe fibrosis leading to pulmonary vocal syndrome have commonly been reported in literature. However, endobronchial tuberculosis leading to pulmonary vocal syndrome is rarely documented. Endobronchial tuberculosis is defined as tuberculous infection of the tracheobronchial tree. Clinically a case of endobronchial tuberculosis may present with cough with sputum production, fever, haemoptysis and rarely with hoarseness of voice as in our case. Endobronchial tuberculosis has been classified into seven subtypes as non-specific, granular, stenotic type with fibrosis, stenotic type without fibrosis, actively caseating type, ulceroproliferative and tumorous type. Establishing the diagnosis of endobronchial tuberculosis is often challenging as the lesion is usually not evident radiologically. Sputum examination is often unyielding and bronchial washings need to be obtained. The mainstay of therapy is eradication of tubercle bacilli with appropriate antituberculous regime followed by prevention of stenosis or fibrosis of endobronchial tree.

**Conclusion**

Our patient was a case of pulmonary vocal syndrome secondary to endobronchial tuberculosis. To the best of our knowledge pulmonary vocal syndrome attributable to primary endobronchial tuberculosis has not been reported earlier. Hence endobronchial tuberculosis should be considered as a differential diagnosis in cases presenting with vocal cord palsy after ruling out other etiologies in the correct clinical context.

**References**


**Gitelman’s Syndrome- A Rare Cause of Recurrent Syncope**

**DG Dastidar¹, Ashish Gupta², Dibyendu Das³, Byomesh Tripathi⁴**

**Abstract**

Gitelman’s syndrome, or congenital hypokalemic hypomagnesemic hypocalciuria with metabolic alkalosis, is widely described as a benign or milder variant of Barter’s syndrome. It presents with variable clinical symptoms including tachycardic episodes, muscle cramps, muscle paralysis, tingling numbness, perioral tingling sensation, salt craving and nocturia. This milder salt wasting syndrome can rarely cause significant ventricular arrhythmias and even death. Here, we report a case of 59 year old male who presented with history of recurrent syncope. He was found to have recurrent polymorphic VT with persistent hypokalemia and hypomagnesia. After extensive metabolic investigation, he was diagnosed as a case of Gitelman’s syndrome. We report this case because of this rare malignant presentation of a seemingly benign syndrome.

**Introduction**

Gitelman syndrome, is an autosomal recessive renal tubular disorder and is characterised by hypokalemic metabolic alkalosis, hypomagnesemia, hypocalciuria. It is milder than other sub- types of Barter’s syndrome. Patients with GS usually present with tachycardic episodes, muscle cramps, muscle paralysis, tingling numbness, perioral tingling sensation, salt craving and nocturia. Most cases of GS result from inactivating mutations to the SLC12A3 gene, which encodes the thiazide-sensitive Na-Cl cotransporter (NCC) on the apical membrane of distal convoluted tubule (DCT) cells. A minority of GS patients have mutations in the basolateral chloride channels (CLCNKB). The defect in thick ascending loop of Henle (TALH) or distal convoluted tubule (DCT) results in a failure to reabsorb chloride and sodium, that leads to excessive sodium and chloride delivery to the distal tubules, resulting in excessive salt and water loss from the body. The renin angiotensin-aldosterone system (RAAS) is a feedback system activated...
with volume depletion. Although Gitelman syndrome, presents with seemingly mild symptoms, rarely it may provoke cardiac arrhythmias.

Here we describe a 59 year old male who presented with recurrent syncope. During his stay in hospital, he was found to have recurrent polymorphic VT. Investigations in this patient revealed persistent hypokalemia, metabolic alkalosis, hypocalciuria, and hypomagnesemia, a tetrad diagnostic of Gitelman’s syndrome.

Case Report

A 59 year old male was referred from a peripheral hospital with history of recurrent syncope since last 2 years. Syncope occurred at rest with no precipitating factors. No history of associated chest pain, dyspnoea, polyuria or symptoms suggestive of seizures. He was not on any regular medications. No significant past history.

One year ago, he was admitted for similar episode at a peripheral hospital. He was treated conservatively at that time. ECG at that time was suggestive of NSVT. He was discharged with a advice to consult cardiologist. This time again he went with history of syncope and was transferred to our hospital.

On admission, the initial electrocardiogram (ECG) revealed nonsustained polymorphic ventricular tachycardia with intermittent sinus beats showing prolonged QT interval, features consistent with Torresades de Pointes. He was urgently put on temporary pacemaker support and intravenous calcium and magnesium were started.

Initial serum chemistries revealed a Potassium level of 2.6 mEq/L (normal range, 3.5 to 5.5 mEq/L) and a Magnesium level of 1.3 mEq/L (normal range, 1.2 to 2.1 mEq/L). Subsequent analysis of 24-hour urine chemistries revealed renal wasting of potassium, with a transtubular potassium gradient (TTKG) was approximately 12 (TTKG>7 indicates renal loss). The patient was also found to have persistently elevated serum bicarbonate of 28-30 mEq/L (normal, 22 to 32 mEq/L). The urinary calcium was subnormal at 1.2 mols/24 hour (2.5-7.5 mmols). A transthoracic echocardiogram done on admission revealed an ejection fraction of 55%. The renin and aldosterone levels were within normal on serum assays, essentially ruling out hyperaldosteronism. Given the combination of hypokalemia, hypomagnesemia, and metabolic alkalosis, the patient was given the diagnosis of acquired long QT syndrome secondary to a metabolic disorder, most likely Gitelman Syndrome. He was treated with intravenous/oral repletion of potassium and magnesium daily, the serum potassium and magnesium levels normalized after 5 days of treatment, temporary pacemaker was removed and patient was discharged with advise of regular potassium and magnesium supplements. He has been in 4 years of regular follow up with no recurrence of syncope since then.

Discussion

Gitelman Syndrome is a disorder that causes a defect in the sodium-chloride cotransporter in the renal distal convoluted tubule, causing hypokalemia, hypomagnesemia, and metabolic alkalosis. The prevalence of Gitelman Syndrome is estimated at approximately 1 per 40,000.3,4 It is an autosomal recessive disorder which may not be diagnosed until adulthood, with common complaints of cramps, fatigue, dizziness and polyuria.

It is caused by missense mutations in the SLC12A3 gene (located on chromosome 16q) that encodes the thiazide-sensitive sodium chloride co-transporter.3,4 In SLC12A3, 172 distinct mutations have been described, leading to extreme phenotype variability.5 Female patients with the same mutations are relatively asymptomatic compared with their male counterparts. The nature and position of the SLC12A3 mutation, combined with male gender, seem to be a determinant factor in the severity of GS.5

Diagnosis is often one of exclusion, ruling out other causes of hypokalemia and metabolic alkalosis, such as vomiting and diuretic use. However, diagnosis can also be made with the following laboratory findings: hypokalemia due to renal losses, metabolic alkalosis, hypomagnesemia due to renal losses, elevated urinary chloride excretion, and a decrease in urinary calcium excretion.7

The laboratory values in this patient explicitly satisfied all of the above criteria for the diagnosis of Gitelman Syndrome, except elevated urinary chloride excretion (which were not assayed for in the urine).

Hypokalemia and hypomagnesemia can prolong the QT interval and increase the susceptibility of the heart towards fatal ventricular arrhythmias. It has been demonstrated that there is a tendency for prolonged QT intervals in patients with Gitelman Syndrome, one study showing the prevalence of more than 40%.8 However, cardiac arrhythmias have been described in far fewer patients. Sudden cardiac death has been reported in a few cases.9

Gitelman Syndrome was the most likely predisposing condition that lead to the episodes of recurrent syncope and ventricular arrhythmias in this patient. Before starting patients on antiarrhythmic therapy for recurrent syncope due to arrhythmias, metabolic causes, such as hypokalemia and hypomagnesemia should be fully evaluated.

Treatment is directed at correcting potassium and magnesium depletion. It requires life-long supplementation and liberal salt intake. Potassium supplementation is with potassium chloride and potassium-sparing diuretics, including amiloride and spironolactone. However, in hypotensive patients, these drugs should be used with caution. Hypomagnesemia is corrected with magnesium chloride (magnesium sulfate or oxide are avoided to prevent diarrhea).10,11

References

Ovarian Teratoma presenting as Anti NMDAR Antibody Negative Limbic Encephalitis

Ancil George Thomas¹, Madhusudanan Mohan², Reji Thomas², Finu Mathew Baby³

Abstract

Anti NMDA receptor (NMDAR) antibody mediated limbic encephalitis is the most common type of autoimmune encephalitis. Nearly half of the females presenting with anti NMDAR encephalitis have associated ovarian teratoma. Almost all of them have positive anti NMDAR antibody. Here we present a case of ovarian teratoma associated limbic encephalitis, with clinical picture typical of anti NMDAR mediated encephalitis, who was found to be negative for the antiNMDAR antibody. Clinicians should not defer from investigating a case of suspected anti NMDAR encephalitis for ovarian teratoma, even if antibody is negative.

Introduction

The incidence of autoimmune encephalitis is increasing with improved recognition of clinical syndromes and diagnostic testing of various neuronal cell surface antibodies. Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common autoimmune encephalitis, which presents with classical clinical features. The classic presentation of this syndrome is a subacute encephalopathy with core clinical features of encephalopathy, psychiatric symptoms, cognitive symptoms, seizures and extrapyramidal movement disorder often associated with inflammatory CSF. About 43 % of Anti NMDA encephalitis women have associated ovarian teratoma.³

We report a case of clinically typical case of anti NMDAR encephalitis with negative antibody screening for NMDAR- ab, who was found to have associated ovarian teratoma and had remarkable clinical improvement with removal of the tumour.

Case Report

We report the case of a 24 year old unmarried female, studying for Chartered Accountancy who presented with altered behavior, irrelevant talk and fever for 10 days. To begin with, she spent one whole night scribbling in a diary and sending irrelevant messages to friends in the mobile phone. She was talking irrelevant things and was angry, restless and pacing about. Following this, the patient developed delusions and hallucinations. She claimed that she could see media personnel in her room with cameras. She tried to drive them away, saying they are there to harm her. She was scared and would shut herself in her room. She started repeating religious verses. Later on, her word output decreased progressing to mutism.

About a week later, patient developed orofacial dyskinesia in the form of jaw opening and closing, chewing, facial grimacing and lip pouting. Patient continued to be catatonic and mute. Meanwhile occasional fever spikes persisted.

On examination the patient was mute and there was no eye-to-eye contact during conversations. She kept her eyes tightly closed, was grimacing to pain but not obeying commands. The blood pressure recordings and pulse rate fluctuated over a wide range. She had orthostatic hypotension and was sweating profusely. She had generalized rigidity with exaggerated tendon reflexes and extensor plantar response.

She was started on acyclovir suspecting viral encephalitis. However cerebrospinal fluid showed no cells with normal protein and sugar. MRI brain didn’t reveal any abnormality. EEG showed generalized slowing. HSV polymerase chain reaction (PCR) was negative and acyclovir was discontinued. Serum and CSF samples were tested negative for antibodies against voltage-gated potassium channel and NMDARs. Serum paraneoplastic panel of neuronal antibodies were also negative. Ultrasonogram abdomen was essentially normal. A thorough work up for fever including vasculitic profile was normal. However in view of her neuropsychiatric symptoms, fever, catatonia, orofacial dyskinesia and autonomic instability, the possibility of autoimmune encephalitis was strongly considered. So methylprednisolone 1g intravenous for 5 days followed by intravenous immunoglobulins (0.4 g/kg/day) was started.

With a strong suspicion of autoimmune encephalitis, with a possible paraneoplastic association, her computerized tomography (CT) scan of the abdomen was done, even though ultrasonogram was normal. CT scan showed a cystic lesion arising from her left ovary suggestive of teratoma. In view of such strong clinical possibility and the paraneoplastic association, the cerebrospinal fluid study was repeated which showed nervous system specific autoimmunity in the form of an unclassified antibody, but anti NMDAR-ab was again negative. She underwent a left ovarian cystectomy and histopathology of the tumor specimen revealed benign mature cystic teratoma.

Her autonomic instability reduced over the next three days and rigidity and fever decreased by one week. By the end of the first week, she was able to talk with her family members and ask for food and water. By the 10th day, she was making eye-to-eye contact during conversations with good word output. By the 20th day, she was well oriented, had no rigidity and could walk normally. By the end of two months, she was performing her household chores and school work easily.

Discussion

Anti NMDAR encephalitis, a well-recognized autoimmune encephalitis

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with autoantibodies to the NRI subunit of NMDA receptor was first described by Dalmau et al. Clinicians should consider antibody testing in patients presenting with acute encephalitis. In a UK study of encephalitis presenting to district hospitals, of the patients (36%) without an identifiable infectious aetiology, had autoantibodies to either NMDAR (9 patients) or VGKC complexes (7 patients), making autoimmunity the third highest association with acute encephalitis. Furthermore, in a series of patients from the Queen Square intensive care unit, around a fifth of the patients with encephalopathies had NMDAR-abs.

About 43% of anti NMDA encephalitis women have associated ovarian teratoma. The frequency of ovarian teratomas was 56% in women >18 years old, but only 31% in women <18 years old. The pathogenesis involves autoimmunity over expression of NR2 subunits by nerve tissues in the teratomas that lead to a break in the immune tolerance. Associated factors such as a prodomal viral-like illness and genetic factors may play additional roles in the initiation of the immune response. Rarely, tumours such as testicular teratomas and small cell lung cancers have also been associated with this entity.

In those patients with ovarian or other tumours, the syndrome responds to immunotherapy once the tumour is removed; later removal can be associated with poor outcome.

Previous studies have shown a universal association of anti NMDAR-ab in all patients with ovarian teratoma associated with limbic encephalitis. Only very rarely, ovarian teratomas with autoimmune encephalitis have presented without anti NMDAR-ab. In our patient, even though the clinical picture was classical of the anti NMDAR encephalitis, antibody testing was negative on two occasions both in the serum and CSF. Sensitivity for NMDA receptor antibodies was higher for CSF (100%) than for serum (86%).

Rarely, AMPA receptor mediated encephalitis can be associated with ovarian teratoma.

Patients with AMPA receptor antibodies develop acute limbic dysfunction that can be associated with prominent psychiatric symptoms. The disorder most commonly affects middle-aged women. Most patients present with the subacute onset of confusion, disorientation and memory loss with or without seizures. About 70% of patients will have an underlying tumour in the lung, breast or thymus. Romana Höftberger, Agnes van Sonderen et al reported 22 patients with autoimmune encephalitis associated with AMPA receptor antibody, among which two patients had ovarian teratoma.

In our patient, even though the clinical presentation was different from that reported in literature, the possibility of AMPA receptor antibody mediated encephalitis cannot be ruled out. Unfortunately AMPA receptor antibody testing could not be done in our patient because of non-availability.

Sadahisa Okamoto, Teruyuki Hirano, Yukitoshi Takahashi reported a rare case of ovarian teratoma associated limbic encephalitis who had autoantibodies to glutamate receptor (GluR) in the CSF. This was a case of 35-year-old woman with altered consciousness and was initially diagnosed as non-herpetic encephalitis. Her signs and symptoms improved with acyclovir and steroid pulse therapy. However, after the treatment, an ovarian tumour was discovered, and autoantibodies to GluR were detected in the CSF.

Andrew D. Smith, Lawrence Samkoff et al reported a woman in her mid-20s who presented with fever, headache, encephalopathy and predominant ataxia and later found to have ovarian teratoma and antiNMDA antibody was negative in that patient. Marina Frasquet, Luis Bataller et al reported a patient with AQP4 antibody positive longitudinally extensive transverse myelitis (LETM) revealing ovarian teratoma. The teratoma expressed the AQP4 antigen, providing a possible paraneoplastic link between both diseases.

These case reports may suggest that ovarian teratoma can also present with cerebellar ataxia and longitudinally extensive transverse myelitis other than the picture of LE and those patients presenting with LE associated with ovarian teratoma need not always have anti NMDAR antibody as previously thought.

It is important to realize that there are patients whose syndromes appear to be identical to the established phenotypes, but who are negative on the tests currently available. Moreover, many autoantibodies to specific neuronal proteins are only beginning to be unravelled in patients with otherwise unexplained subacute onset of neurological symptoms, with or without MRI and CSF evidence of inflammation. In all of these patients, immunosuppressive treatments should be seriously considered, once the alternate possibilities are reliably ruled out.

Conclusion

The case is presented to highlight the fact that the neurophysicians should not defer from investigating for ovarian tumour in patients with strong clinical suspicion of autoimmune encephalitis, even if anti NMDAR antibody is negative.

References

Development of the polymerase chain reaction (PCR) has been a major breakthrough in the analysis of genetic information. Such analysis earlier required quite a large amount of DNA sample. In 1985, Kary Mullis (1944-) is credited for inventing the process known as PCR, in which a small amount of DNA can be copied in large quantities over a short period of time.

Mullis claims that concept came to him in a flash of inspiration and that he invented PCR by accident. Idea occurred to him while he was driving home to California redwood for the weekend in April 1983 and later worked out the process at Cetus Laboratory with some colleagues where he was working. Mullis described the detailed technique for the first time in December 1985 issue of Science and received a patent for it in 1987.

The process has multiple applications in medicine, genetics, and forensic medicine. PCR, because of its ability to extract DNA from fossils, has become the basis of a scientific discipline palaeobiology.

Forensic scientists use it to identify crime suspects or victims from traces of blood, and other biological material left at a crime scene via DNA comparison. In Medicine PCR makes it possible to identify the causative agent of a bacterial or viral infection directly from a very small sample of material. PCR is also used to screen for genetic disorders. It is an important tool in gene sequencing.

Union Cabinet has cleared a DNA profiling bill (July 2019), for establishing a regulatory board to control the use of DNA technology.

Kary Banks Mullis (b-1944) was born in Lenoir, North Carolina. After graduating from the Georgia Institute of Technology (1966), he earned a Ph.D. in biochemistry from the University of California, Berkeley, in 1972. Mullis pursued postdoctoral research in pediatric cardiology at the University of Kansas Medical School before turning his attention to pharmaceutical chemistry.

Mullis joined the Cetus Corporation at Emeryville, California (1979) as a DNA chemist. During the time he carried out research on the synthesis of oligonucleotides synthesis for use as probes and primers.

Mullis work was based on the work of 1968 Nobel Prize winner Hargobind Khorana (1922-2011) and associates Nirenberg and Holley, for their part in the genetic code discovery. Khorana was the first scientist to chemically synthesize oligonucleotides.

PCR uses three ingredients. 1-Sample of double stranded DNA segment to be copied (the template DNA), 2-oligonucleotide “primers” (short segments of single-stranded DNA, each of which is complementary to the template DNA nucleotides). 3-Key enzyme- thermo-resistant DNA polymerase (Taq) is then added. When these ingredients are heated, the template DNA separates into 2 strands. The mixture is then cooled, allowing the primers to attach themselves to the complementary sites on the template strands. Enzyme Taq DNA polymerase is able to begin copying the template strands by adding nucleotides onto the ends of the primers, producing two molecules of double-stranded DNA. Repeating this cycle increases the amount of DNA exponentially. Few cycles, yields large number of copies of original DNA. Repeated thermal cycling led to the automation with thermocycling machine (1984) of the initially slow and laborious PCR technique.

In 1993, Nobel Prize in chemistry was awarded jointly to Kary Banks Mullis (1944-) for his invention of the PCR and Michael Smith (1932-) for developing procedure of site-directed mutagenesis.

Kary Mullis received many other rewards and in 1998, was inducted into the US National Inventors Hall of Fame for his invention of PCR.
Renal Granulomas in Hansen’s Disease

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Sir,

Renal abnormalities in leprosy have been widely described in medical literature.¹ Kidney is one of the target organs during the splanchnic localization of leprosy without direct involvement of bacteria. Renal involvement is more often seen in lepromatous leprosy, especially with recurrent type II reaction as immune complexes deposits.² The histological renal spectrum includes glomerulonephritis, amyloidosis and interstitial nephritis. Leprous granulomas are known to occur frequently in liver, spleen, testes but rarely in kidneys. We present a case of Hansen’s disease with presence of specific leprous granulomas in renal interstitium.

A 47 yrs. old male patient presented to our hospital with 3 months history of generalized oedema initially noticed on hands and feet. He had no history of joint pain, hemoptysis, nasal bleeding or any chronic illness. His past history too was unremarkable. On examination, there was pitting acral oedema (Figure 1). Cutaneous examination revealed multiple asymptomatic well defined erythematous plaques of variable size all over body (Figure 2). There was hypoesthesia to touch, temperature and pain over the lesions along with glove and stocking hypoesthesia. Examination of peripheral nerves showed thickened and slightly tender bilateral ulnar, right radial cutaneous, right common peroneal and bilateral posterior tibial nerves. There was no motor deficit. He had proteinuria and altered renal functions. Laboratory investigations revealed Hb-6.9 gm/dl, ESR-75 mm in 1st hour, TLC-6600/mm³ and Platelet count-3.26 lac/mm³. Urine analysis revealed 2+albumin, however there was no hematuria or any type of cast. His blood urea level was 51.3 mg/dl; serum creatinine 3.5mg/dl and urinary total protein was 1.6gm/24hrs. Renal biopsy was performed and on light microscopy it showed normal looking glomeruli with diffuse mononuclear inflammatory infiltrate in the interstitium along with non-caseating granulomas with presence of giant cells (Figure 3). On immunofluorescence immune deposits were absent. Slit skin smear showed a Bacteriological Index of 2+ and skin biopsy showed band like granulomatous infiltrate of epitheloid granulomas in the upper dermis and small granulomas filling a follicle in the mid dermis (Figure 4). Fite stain for acid fast bacilli (AFB) was negative. On the basis on these findings, we made a diagnosis of Borderline tuberculoid (BT) Hansen’s disease with renal involvement in the form of minimal change disease and chronic interstitial nephritis along with chronic granulomatous inflammation. Patient was treated with conventional multi drug therapy (MDT) containing dapsone, clofazimine and rifampicin. Following MDT there was rapid improvement in both his skin lesions (Figure 5) as well as renal functions.
One month post-treatment, patient had no proteinuria and his blood urea and serum creatinine levels were 26.7 mg/dl and 1.6 mg/dl, respectively.

Most authors in their studies of renal changes in leprosy have reported acute and chronic glomerulonephritis, interstitial nephritis, secondary amyloidosis and pyelonephritis. Leprosy granulomas have rarely been reported. Nakayama et al reported one granuloma in two of their 199 necropsies, while Sainani and Rao reported only one granuloma in 60 cases. Gupta et al did not find a single case of leprosy granuloma in renal biopsies in 50 cases. In our case, even though no AFB could be demonstrated in skin or renal biopsy specimen, presence of well-defined epitheloid granulomas, absence of caseation, clinical picture and response to treatment suggests that granulomas observed in renal interstitium were of leprous origin. This case is reported because of rare findings of specific leprous granulomas in renal tissue.

References

Letter to the Editor in Response to Article “Severe Hyponatremia as an Uncommon Presenting Feature of Pituitary Macroadenoma”

Rajesh Aggarwal1, Blessy Sehgal1, Gaurav Bhalla2
1Senior Consultant, 2Consultant, Sribalaji Action Medical Institute, New Delhi; 3Consultant, Max Superspeciality Hospital, Delhi

Sir,

I came across an interesting case of severe hyponatremia as an uncommon presenting feature of pituitary macroadenoma published in JAPI August 2018. This was a case of a 60 years old gentleman who presented with vomiting, giddiness, blackout and fatigue. On examination patient was found to be hypotensive, tachycardia was present, he also had dry tongue and loss of skin turgor (all signs of hypovolemia). On investigating he was found to have hyponatremia with normal potassium, normal renal and liver function test. ABG showed respiratory and metabolic alkalosis. Investigating further the authors have reported low cortisol, aldosterone and testosterone with a low ACTH, and diagnosed it as secondary addisons due to pituitary tumor as the cause of hyponatremia.

Although a very well investigated and written case, we have a few queries and comments.

1. The patient had hyponatremia and all signs of hypovolemia. His serum osmolality has been reported as 288.5 mosm/l whereas the calculated osmolality is 231 mosm/l. If the reported osmolality is measured then the reason for this osmolar gap is not clear.

2. With this grade of hyponatremia and low osmolality, normal response of the kidney would be to produce a highly dilute urine with urine osmolality of < 100 mosm/l, but the authors have reported a urine osmolality of 373 mosm/l which is inappropriately high for this patient and indicate a state of excess of ADH. So this patient has a syndrome of excess of ADH.

This can very well be explained in this patient due to the following reasons:

a. presence of hypovolemia causes increase ADH release (normal osmotic response),
b. vomiting is a strong non - osmotic stimuli for ADH release,
c. presence of pituitary macroadenoma causes decrease ACTH which causes decrease cortisol release. Decrease cortisol release is a stimulus for release of ADH

Furthermore this patient is having as high urinary loss of sodium which is because of presence of excess of Atrial natriuretic peptide (ANP ) in SIADH. The estimation of urinary sodium was done over a period of 24 hours during which time the patient was on saline infusion and salt replacement, and it is well known that in SIADH the urinary sodium excretion depend s upon the salt intake of the patient. So this patient probably had an underlying SIADH, and developed vomiting which can explain the presence of hypovolemia in him.

3. The authors have reported that the aldosterone levels were low in this patient but ACTH stimulation test done showed a normal adrenal reserve and a suppressed pituitary adrenal axis. The secretion of aldosterone is not dependent on pituitary adrenal axis instead it is dependent on volume status and renin angiotensin aldosterone axis. In a patient who is hypovolemic has increased renin secretion which causes increased aldosterone secretion when the adrenal gland is normal. So in this patient we expected a high aldosterone levels. This is further supported by the fact the serum potassium is normal and not high, the Abg is showing metabolic alkalosis. The authors have not reported TTKG values which would have further supported the diagnosis. The diagnosis of secondary addisons as the cause of hyponatremia is not explainable.

So in our opinion this is a patient who developed symptomatic hyponatremia secondary to SIADH, which is secondary to pituitary macroadenoma and not due to secondary addisons.
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