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Systemic Lupus Erythematosus and Antiphospholipid Syndrome-The Double Trouble

Vikram Londhey

Systemic lupus erythematosus is a chronic autoimmune multisystem disorder more commonly seen in females of the reproductive age group, diagnosed by ACR criteria. Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia, characterized by vascular thrombosis, recurrent pregnancy losses and thrombocytopenia; supported by lab evidence for circulating antibodies against phospholipids or phospholipid binding protein co factors in blood. APS can be primary or secondary. The revised Sapporo Classification criteria are used for the diagnosis of APS. The term APLA (antiphospholipid antibody) is not synonymous with the antiphospholipid syndrome (APS). There are patients who may harbour these antibodies but never develop the clinical symptoms of APS. There is a well-known link between SLE and APS; 40% of SLE patients have aPL, and, in turn, some, but only a minority of patients with APS, eventually will develop features of SLE.

In a Spanish Study of 1000 patients of APS reported by Cervera et al, 36.2 % had APS in association with SLE. Earlier studies from India have reported young stroke (by Makhija et al), recurrent pregnancy loss (Vora et al and Ghosh et al), cortical sinus thrombosis, deep vein thrombosis and myocardial infarction (Chandrashekhara et al) as the common clinical presentations of APS. In a study by Singh NK et al published in JAPI 2013, prevalence of APS in SLE was 25.38%; foetal loss contributing to 26.5% and deep vein thrombosis 16.32%.

In SLE patients, nephritis is a common clinical manifestation and hence the patients are usually divided into subgroups as lupus nephritis and non-nephritis. The pathogenesis of lupus nephritis includes the deposition of antigen antibody complexes in the glomeruli and glomerular thrombosis. Glomerular thrombosis is more common in patients of SLE with APS. However, there are conflicting reports in the published literature. In a study by Iaoniss Parodis et al, the authors have found no association between the association of either aPL positivity or levels with the occurrence of lupus nephritis. In patients with LN, IgG aPL may contribute to a short-term impairment of the renal function, but no effect on the long-term renal outcome was observed in this study. Furthermore, reductions of IgG and IgM aPL levels were noted in LN patients who responded to induction treatment, but not in non-responders, indicating that aPL levels are affected by immunosuppressive drugs in a response-dependent manner. The authors have recommended further investigation of aPL in LN, in order to determine their expression and functional role on a tissue level.

In a study reported by Gao R et al, 31 renal biopsy specimen were retrospectively evaluated and investigated for the β2 GPI expression. It was detected in 38.1% of patients of SLE with aPL associated nephropathy. Coexistence of aPL with intrarenal vascular lesions such as thrombotic microangiopathy, fibrous intimal hyperplasia and focal cortical atrophy constitute a condition called aPL associated nephropathy.

Just as our country has geographical differences, there are variations in the clinical manifestations of the same disease from the different geographic regions of the country. This is so true for a multisystem disease like SLE. Hence, in this issue of JAPI, Doley et al have tried to compare the Indian scenario of SLE with APS patients from Eastern and Western India. It is intriguing to read that there are similarities in the clinical features like rash, arthritis and renal involvement but gross differences in the manifestations like photosensitivity, autoimmune hemolytic anaemia and serositis. There is female preponderance of the disease at both the centres with most of the patients in the third decade of life. The authors are complimented for carrying out such a comparative study to...
correlate the presence of APLA in SLE patients.

The drawbacks of this study are the patient population selected from Eastern India is from 2013-14 and that from Western India is 2008 to 2010. The authors have mentioned that IgG and IgM β2 GPI have been done by ELISA in methodology, but it has not been mentioned in the results or discussion. Also, lupus anticoagulant has not been checked in these patients. In discussion, the authors have mentioned a higher incidence of systemic vascular thrombosis, but there is no mention about what were the thrombotic events and its description would have been interesting to read whether there were more arterial or venous events. Also the number of patients having systemic vascular thrombosis is only 5. There is no mention about the pregnancy losses or bad obstetric history in the study population which is quiet surprising. Pregnancy loss which is very common in SLE with APS has not been discussed in this study.

Every woman has a desire to become a mother and is her birthright. But these females who are suffering from SLE with APS may not always be lucky enough to fulfill the desire of becoming a mother. In the natural course of the disease, poor pregnancy outcome and recurrent pregnancy losses are known to occur. However, with the advances in the management of pregnant patients suffering from SLE with APS, there is an improvement in the pregnancy outcome as compared to the outcome before 2 decades. Planning of pregnancy when the lupus is fairly controlled results in a favourable outcome of the pregnancy. Primary prophylaxis with aspirin and hydroxychloroquine in SLE patients gives beneficial effects in controlling the disease. In patients with history of prior thrombosis or fetal loss, heparin is indicated throughout pregnancy and in the post partum period. Thus, the earlier concept of avoiding pregnancy in these patients is no longer advocated. The presence of all 3 antibodies namely anticardiolipin antibody, anti β2 glycoprotein I antibodies and lupus anticoagulant increases the risk of bad pregnancy outcome. However, a recent study published by Lockshin et al, it is reported that LAC positivity is the only predictor of adverse pregnancy outcome and not affected by presence or absence of anticardiolipin antibody and anti β2 glycoprotein I antibodies. It is controversial whether specific serological findings (i.e presence of autoantibodies) or clinical association with SLE and other connective tissue disorders will predict a bad pregnancy outcome.

More multicentric prospective observational studies should be done from India to have a strong evidence in understanding the interesting association and relationship in these two Double Trouble disorders.

References
A Comparative Study of Anticardiolipin Antibodies among Systemic Lupus Erythematosus Patients from Western and Eastern India

D Doley¹, S Kakati¹, L Saikia², A Rajadhyaksha³, Milind Nadkar³, P Khadilkar⁴, M Patwardhan⁴, V Pradhan⁴

Abstract

Introduction: Anti-phospholipid antibodies (APA) like anticardiolipin antibodies (ACA) are important cause of venous and arterial thrombosis and other occlusive vascular diseases. Prevalence of these antibodies in SLE patients at the time of diagnosis is not known in Indian SLE patients. This study was conducted to evaluate the prevalence of ACA in SLE patients from Eastern and Western India and to correlate them with disease activity.

Material and Methods: Seventy SLE patients from Assam Medical College, Dibrugarh, Assam and 85 SLE patients from Rheumatology Department, KEM Hospital, Mumbai were studied. SLE disease activity was evaluated by SLE Disease Activity Index (SLEDAI) score at the time of evaluation. All patients studied were in an active stage of disease.

Results: Demographic data showed significant variations in the clinical manifestations of SLE between two regions. Renal manifestations were higher (42.9%) among SLE patients from Eastern region as compared with 37.6% patients from Western region. These patients were categorized as Lupus Nephritis (LN) and patients that did not show any renal manifestations were categories as non-LN. ACA to IgG and IgM subclasses were tested by ELISA. IgGACA positivity was 20%, 12.9% and IgM-ACA positivity was 18.6%, 12.9% whereas IgG + IgM ACA positivity as found in 12.9%, 3.5% patients respectively among SLE patients from Eastern and Western India.

Conclusion: ACA positivity was higher among LN patients from Eastern India whereas the same was higher among non-LN patients from Western India. Hence detection of ACA along with associated clinical manifestations were helpful to evaluate their possible association with disease severity in SLE patients. A long term follow up of patients having ACA antibodies without thrombotic event is needed to detect their possible thrombotic event in future along with their clinical presentation from these two different geographic regions from India.

Editorial Viewpoint

- Prevalence of anti-phospholipid antibodies in Indian SLE patients at the time of diagnosis is not known.
- This study found higher anticardiolipin antibody positivity in lupus nephritis patients from Eastern India and higher in non-lupus nephritis patients from Western India.

Introduction

Anti-phospholipid antibody syndrome (APS) is perhaps one of the most confounding immunologic disorders. It’s an acquired autoimmune disorder defined by the presence of antibodies against phospholipids. Anti-phospholipid antibodies (APA), namely the lupus anticoagulant (LAC) and the anti-cardiolipin antibodies (ACA) are a group of antibodies directed against negatively-charged phospholipid antigens (phosphatidylserine), on endothelial cell membranes and platelets. Previously these

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antibodies were thought to be recognizing epitopes on anionic phospholipids and a complex of lipid-bound human prothrombin.¹

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem, inflammatory disorder of autoimmune etiology, occurring predominantly in young women in their child-bearing age. Common manifestations may include arthralgias and arthritis, malar and other skin rashes, pleuritis or pericarditis, renal and/or CNS involvement and hematologic cytopenias. SLE may be precipitated by currently unknown environmental triggers that cause autoimmune reactions in genetically predisposed people.²,³ Lupus Nephritis (LN) is histologically evident in most patients with SLE with the involvement of varying degree of renal disease. Autoimmunity plays a major role in the pathogenesis of LN where autoantibodies form pathogenic immune complexes that deposit in kidneys. Glomerular thrombosis is another mechanism that may play a role in pathogenesis of LN, mainly in patients with APS and is believed to be the result of antibodies directed against negatively charged phospholipid-protein complexes.⁴,⁵ APS is classified as primary or secondary depending on its association with other autoimmune disorders. Primary APS is diagnosed in patients demonstrating the clinical and laboratory criteria without other recognized autoimmune disease. Secondary APS is diagnosed in patients with other autoimmune disorders such as SLE. One-third of patients with SLE also have antiphospholipid antibodies, and approximately one-third of those with antibodies have clinical signs of antiphospholipid antibody syndrome.⁶

Phospholipids such as cardiolipin, b2 glycoprotein and LAC are responsible for prevention of blood clotting. In patients with SLE who have bad obstetric history (BOH) or recurrent pregnancy loss (RPL), both cardiolipin and lupus anticoagulant antibodies are often present in high titre.⁷ ACA may belong to both IgG and IgM subtypes. The IgG antibodies seem to be better predictors of fetal outcome. More recent studies suggest that the antibodies that really matter are those to b2GP, the cofactor by which ACA binds to phospholipid and usually are present with ACA.⁸ Earlier studies have confirmed that patients positive for ACA are at risk of repeated episodes of thrombosis, fetal loss and thrombocytopenia. APA occur in up to 60% of patients with SLE and may be of pathogenic significance in LN where the presence of intraglomerular capillary thrombosis has also been described.⁹,¹² There is a wide difference in the clinical presentation of SLE reported from different geographical regions.¹³ Though there are a few reports on clinical manifestations of SLE and autoantibody profile from different regions in India, the absolute geoepidemiological picture of SLE is still unclear. Present study was designed to evaluate the prevalence of ACA autoantibodies in SLE patients from Eastern and Western India to correlate them with disease activity to know the variation in ACA development among SLE patients from these two heterogenous populations.

Material and Methods

In this study 70 patients from Department of Medicine, Assam Medical College and Hospital, Dibrugarh were included over a period of one year (2013-2014). It was a hospital based cross-sectional study. These patients were further divided into four linguistic ethnic groups found in India i.e. Indo-European, Tibeto-Burman, Austro-Asiatic and Dravidian.¹⁴-¹⁶ The Tubero-Burman group included the indigenous Assamese tribal people including Ahom, Mising etc., and also the people of Mongoloid origin those from other North-Eastern states Arunachal Pradesh, Nagaland, Meghalaya, Manipur, Mizoram etc. Austro-Asiatic group included mostly the tea tribes like Mundari, the Khasi-Khuic, and the Mon-Khmer. The Dravidian group included SLE patients of South Indian origin and some from central Indian origin. Remaining like Brahmins, the Muslims, Bengalis, and other indigenous people were included in Indo-European group.

Along with this 85 SLE patients from Rheumatology department of KEM hospital, Mumbai, India over the period of 2 years (2008-2010) were also studied. All SLE patients from both the geographical regions were diagnosed according to the American College of Rheumatology (ACR) criteria.¹⁷ This study was carried out after obtaining the requisite Ethics Committee approval from each hospital and a written consent from all the patients were obtained. The disease activity was assessed at the time of evaluation using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).¹⁸ Pregnant and post-menopausal women, smokers, patients with diabetes and patients with significant hyperlipemia were excluded. After blood collection, sera were stored in aliquots at -80°C until tested. Renal biopsies of Lupus Nephritis (LN) cases were examined by light microscopy using hematoxylin, eosin, periodic Schiff (PAS) staining. Immunofluorescence microscopy was done using anti-IgG, anti-IgM, anti-IgA, anti-C3, anti-C4 and anti-fibrinogen fluorescein isothiocyanate conjugate (FITC). In LN patients the renal histology was classified according to WHO criteria.¹⁹ Anti-Cardiolipin antibodies (ACA) to IgG and IgM isotypes and anti-b2GP autoantibodies to IgG as well as IgM isotypes were detected by ELISA using commercially available kits (Euroimmune, Lubeck). The Laboratory at each
Results

A total of 155 SLE patients including 70 patients from Eastern India and 85 SLE patients from Western India were included in the study. This was a retrospective study conducted over a period of eighteen months at the two centres. Table 1 gives the baseline characteristics of patients included in the study from these two geographical regions. When the clinical manifestations based on ACR criteria were noted at the time of presentation, there was a statistically significant difference noted for photosensitivity, serositis and haematological manifestations like photosensitivity, renal disorders, arthritis and hematological manifestations when patients from both the regions were compared. Table 2 gives detailed distribution of ACA positivity when patients were categorized further into LN and non-LN groups, ACA positivity was slightly higher in LN group in Eastern Indian SLE patients.

Table 3 gives the correlation of ACA positivity among Eastern and Western Indian SLE patients. It was observed that ACA positivity for IgG, IgM and and IgG+IgM autoantibodies was higher (20%.18.6%, 12.9%) among Eastern Indian patients as compared to Western Indian patients (12.9%,12.9%,3.5%). There was no statistically significant difference for ACA positivity when two regions were compared. When these patients were categorized into mild (SLEDAI <8), moderate (SLEDAI 8-18) and severe (SLEDAI >18) based on the SLEDAI scores, there was no statistically significant difference among ACA positive patients for clinical manifestations like photosensitivity, oral ulcers, arthritis and hematological manifestations when patients from both the regions were compared. Table 5 shows detailed distribution of ACA positivity with clinical severity categorized into mild (SLEDAI <8), moderate (SLEDAI 8-18) and severe (SLEDAI >18) based on the SLEDAI scores among SLE patients from Eastern and Western regions.

Discussion

Antiphospholipid antibodies are commonly encountered in SLE patients and are associated with increased risk for thrombo-occlusive incidents. In such patients, primary or secondary prevention of thrombosis is warranted. SLE patients also are at risk for various adverse pregnancy outcomes, including miscarriage, stillbirth, and premature delivery. This risk is even higher for patients with antiphospholipid antibodies, as suggested by several prospective and retrospective studies. Diagnosis of the antiphospholipid syndrome (APS) requires that a patient have both a clinical
event (thrombosis or pregnancy morbidity) and the persistent presence of antiphospholipid antibody (aPL), (anticardiolipin or anti–β2-glycoprotein I [anti–β2GPI] immunoglobulin [Ig] G or M), the lupus anticoagulant, or both.20

Because high-level aPLs may persist for years in asymptomatic persons, it is likely that vascular injury, endothelial cell activation, or both immediately precede the occurrence of thrombosis in those bearing the antibody (second-hit hypothesis). Of note, at least 50% of APS patients with vascular factors possess other acquired thrombosis risk factors at the time of their events.21,22 Positive aPL results require a repeat test after 12 or more weeks to exclude a transient, clinically unimportant antibody. The diagnosis of APS should be questioned if less than 12 weeks or more than 5 years separate the positive aPL test from the clinical manifestation. The lupus anticoagulant test is a more specific but less sensitive predictor of thromboses than is anticardiolipin; it correlates better with aPL-related clinical events.23

Mostafa et al, 2010 had reported an incidence of 16.7% for ACA among SLE patients.24 Similar incidence was found in our study where IgG-ACA and IgM-ACA positivity was 12.9% each. Other studies such as Petri et al, 2010 reported 47% ACA autoantibodies in SLE, Biggioggero et al, 2010 had reported 16.5% IgG-ACA and 9.4% of IgM-ACA, Jallouli et al, 2008 had reported 71.6% for ACA and Descloux et al, 2008 had reported an incidence of 49% ACA.25-28 In a study on South African SLE patients, Gould et al, 2006 had reported a very high incidence of 53% for ACA antibodies where as Al Arfaj et al, 2009 had reported an incidence of 49.7% and 33.5% for IgG-ACA and IgM-ACA respectively among Saudi Arabian SLE patients.29,30 Woo et al., 2010 had reported an incidence of 18.2% and 31.8% for IgG-ACA and IgM-ACA respectively in Korean SLE patients. Shrivastav et al., 2001 had reported 51% IgG-ACA autoantibodies.31,32

Thrombosis varies in SLE patients from 7.2% to 12%. Sarabi et al, 2005 reported that the most frequent causes of death in active SLE are infection and thrombosis.33 The risk of thrombosis for SLE patients reported to be significantly higher and due to the increased incidence of traditional cardiovascular and nontraditional lupus-related thrombosis risk factors, SLE patients are at significantly increased risk of premature atherosclerosis and/or thrombosis. The prevalence of vascular events in SLE patients ranges between 10% and 30%, for symptomatic coronary artery disease 6–20%, stroke 2–15%, and subclinical coronary artery disease

Table 3: Correlation of ACA levels with SLEDAI scores in LN and non-LN groups

<table>
<thead>
<tr>
<th>SLE type and SLEDAI</th>
<th>Eastern India (n=70)</th>
<th>Western India (n=85)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgM</td>
<td>IgG</td>
<td>IgM</td>
</tr>
<tr>
<td>Total SLE</td>
<td>14</td>
<td>13</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Range</td>
<td>9–26</td>
<td>8–26</td>
<td>4–43</td>
<td>4–24</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>16.93 ± 4.97</td>
<td>16.00 ± 5.37</td>
<td>14.6 ± 11.1</td>
<td>12.1 ± 5.9</td>
</tr>
<tr>
<td>LN</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Range</td>
<td>14–26</td>
<td>14–26</td>
<td>4–19</td>
<td>4–15</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>19.26 ± 4.96</td>
<td>19.50 ± 5.39</td>
<td>11.3 ± 7.3</td>
<td>10.8 ± 5.0</td>
</tr>
<tr>
<td>Non-LN</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Range</td>
<td>9–22</td>
<td>8–16</td>
<td>4–43</td>
<td>4–24</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>14.57 ± 3.99</td>
<td>13.00 ± 3.27</td>
<td>16.6 ± 12.9</td>
<td>12.9 ± 6.6</td>
</tr>
</tbody>
</table>

Table 4: Distribution of clinical manifestations according to ACR criteria among ACA positive patients from Eastern and Western India (n=155)

<table>
<thead>
<tr>
<th>Geographical Regions</th>
<th>Eastern India (n=27)</th>
<th>Western India (n=22)</th>
<th>p value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgM</td>
<td>IgG</td>
<td>IgM</td>
<td></td>
</tr>
<tr>
<td>Malar / discoid rash</td>
<td>7</td>
<td>25.9%</td>
<td>9</td>
<td>40.9%</td>
<td>0.3612</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>15</td>
<td>55.5%</td>
<td>4</td>
<td>18.2%</td>
<td>0.0095</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>2</td>
<td>7.4%</td>
<td>7</td>
<td>31.8%</td>
<td>0.0293</td>
</tr>
<tr>
<td>Arthritis</td>
<td>7</td>
<td>25.9%</td>
<td>14</td>
<td>63.6%</td>
<td>0.0105</td>
</tr>
<tr>
<td>Serositis</td>
<td>5</td>
<td>18.5%</td>
<td>6</td>
<td>27.3%</td>
<td>0.5905</td>
</tr>
<tr>
<td>Renal disorders</td>
<td>7</td>
<td>25.9%</td>
<td>3</td>
<td>13.6%</td>
<td>0.4478</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>0</td>
<td>0%</td>
<td>2</td>
<td>19.1%</td>
<td>----</td>
</tr>
<tr>
<td>Hematological disorders</td>
<td>13</td>
<td>48.1%</td>
<td>1</td>
<td>4.5%</td>
<td>0.001</td>
</tr>
<tr>
<td>Systemic vascular thrombosis</td>
<td>1</td>
<td>3.7%</td>
<td>4</td>
<td>18.2%</td>
<td>0.1597</td>
</tr>
<tr>
<td>Myositis</td>
<td>7</td>
<td>25.9%</td>
<td>7</td>
<td>31.8%</td>
<td>0.7597</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15</td>
<td>55.5%</td>
<td>8</td>
<td>36.4%</td>
<td>0.252</td>
</tr>
<tr>
<td>Fever</td>
<td>6</td>
<td>22.2%</td>
<td>4</td>
<td>18.2%</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table 5: Distribution of ACA positivity with clinical severity based on the SLEDAI scores among SLE patients from Eastern and Western India

<table>
<thead>
<tr>
<th>SLE type (SLEDAI)</th>
<th>Eastern India (n=70)</th>
<th>Western India (n=85)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgM</td>
<td>IgG</td>
<td>IgM</td>
</tr>
<tr>
<td>Mild (&lt;8)</td>
<td>0</td>
<td>0</td>
<td>(4)</td>
<td>(3)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>–</td>
<td>–</td>
<td>5 ± 1.1</td>
<td>5 ± 2.3</td>
</tr>
<tr>
<td>Range</td>
<td>–</td>
<td>–</td>
<td>4 - 6</td>
<td>4 - 8</td>
</tr>
<tr>
<td>Moderate (8 - 18)</td>
<td>10</td>
<td>(10)</td>
<td>(4)</td>
<td>(7)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>14.20 ± 2.39</td>
<td>13.50 ± 2.80</td>
<td>15 ± 2.6</td>
<td>13.3 ± 2.9</td>
</tr>
<tr>
<td>Range</td>
<td>9–18</td>
<td>8–16</td>
<td>12 - 18</td>
<td>10 - 18</td>
</tr>
<tr>
<td>Severe (&gt;18)</td>
<td>4</td>
<td>(3)</td>
<td>(3)</td>
<td>(2)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>23.75 ± 1.71</td>
<td>24.33 ± 1.53</td>
<td>27 ± 13.8</td>
<td>22 ± 2.8</td>
</tr>
<tr>
<td>Range</td>
<td>22–26</td>
<td>23–26</td>
<td>19 - 43</td>
<td>20 - 24</td>
</tr>
</tbody>
</table>
Our study showed a higher incidence of systemic vascular thrombosis in anti-ACA positive patients from Eastern India as compared to ACA positive patients from Western India where an equal distribution was noted for venous and arterial thrombosis.

Shrivastav et al, 2001 reported that incidence of neurological disorders such as seizures were noted in 9.4% SLE patients which was significantly associated with ACA. In our study, neurological disorders such as seizures were noted in 9.4% SLE patients which incidence of neurological disorders were seen more in ACA positive patients from Western India and none of the ACA positive patients from Eastern India as compared to ACA positive patients from Eastern Indian SLE patients and Indian Council of Medical Research, New Delhi, India for financial support to conduct study conducted on Dibrugarh, Assam for financial support to conduct on future along with their clinical manifestations were found to be helpful parameters to evaluate their possible association with disease severity in SLE patients. A long term follow up of patients having ACA without thrombotic event is also required to detect their possible thrombotic event in future along with their clinical presentation.

Acknowledgement

We are grateful AMC, Dibrugarh, Assam for financial support for study conducted on Eastern Indian SLE patients and to Director, National Institute of Immunohaematology, Mumbai and Indian Council of Medical Research, New Delhi, India for the financial support to conduct this work in Western Indian SLE patients.

References

8:195-201.


Correlation of Functional Ability of the Hand with Upper Limb Function and Quality of Life in Patients with Rheumatoid Arthritis

Chhaya Verma¹, Ruchita Parikh¹, Milind Nadkar², Amita Mehta¹

Abstract

Background/ Objectives: Rheumatoid arthritis (RA) is associated with significant pain and deformities, where individuals continue to perform activities with reduced abilities. Fatigue and functional disability ensues with the progressive nature of the disease. The study was designed to observe the correlation between the Functional Ability of the Hand with Upper Limb function and Quality of Life in patients with Rheumatoid Arthritis.

Methods: 75 patients diagnosed with RA who were classified in Class I, II, III as per the revised criteria for Classification of Functional Status as given by the American College of Rheumatology were asked to perform the Grip Ability Test to calculate the Hand function. They were then asked to grade their Upper limb function on the Disabilities of Arm, Shoulder and Hand Questionnaire and Quality of Life on the Health Assessment Questionnaire- Disability Index. The scores were analyzed and statistical analysis was done using the Spearmann Rho Correlation.

Results: A total of 75 patients (68 females, 7 males) were included. The mean age of the patients was 41.10 years, with the range being from 19 to 55 years. The Hand function, upper limb function and Quality of life was affected in varying degrees amongst the patients.

Conclusion: We concluded that, there is a moderate positive correlation between the functional ability of the hand and upper limb function, a moderate positive correlation between the functional ability of the hand and quality of life and a strong positive correlation between the upper limb function and quality of life. Thus we need to incorporate newer techniques and approaches to assessment and treatment for enhancing functioning of the upper extremity, thus reducing disability.

Introduction

Rheumatoid Arthritis (RA) is the most common chronic autoimmune systemic inflammatory arthritis, characterized by symmetrical joint synovitis and pain, commonly affecting the wrists and smaller joints of the hand, in about 0.5- 1% of the general population.¹,²

The hand is the principle means by which an individual interacts with people and objects in the external environment. The Grip Ability Test (GAT) is an Activity of Daily Living (ADL) specific tool to evaluate hand function in patients with RA.³ The GAT hand function test has three tasks which evaluate 4 grips: lateral pinch, 5 finger pinch, pulp pinch and transverse volar grip.³

The International Classification of Functioning, Disability and Health (ICF) gives a classification of health and health related domains, describing changes in body function and structure.⁴ It gives a Biopsychosocial model which is an interaction of the medical and social models (Figure 1).

The WHO defines ‘disability’ as an “umbrella term covering...
impairments, activity limitations and participation restrictions.” Disability is a consequence of pain, active synovitis and joint damage and ultimately affects the Quality of life (QoL) which can be assessed by self-reported questionnaire; the Health Assessment Questionnaire-Disability Index (HAQ-DI).5

Functionally, patients with RA can also be categorized as per the revised criteria for Classification of Functional Status as given by the American College of Rheumatology.6 The 30 item Disabilities of Arm, Shoulder and Hand questionnaire (DASH) Outcome Measure is a self-reported questionnaire designed to measure physical function and symptoms in patients with musculoskeletal disorders of the upper limb.

Despite pain and deformities, individuals with RA continue to function, causing secondary consequences on the overall functioning of the individual. Hence, we need to evaluate the correlation between a bimanual dexterity hand function task and upper limb function, and to find the association between hand function and disability. This can provide valuable insight on the impact of hand dysfunction on disability in RA. Hence, there is a need for exploring the relationship between hand function and Quality of life in an Indian population diagnosed with Rheumatoid Arthritis.

Aims and Objectives

The aim of the study was to observe the correlation between the Functional Ability of the Hand with Upper Limb function and Quality of Life in patients with Rheumatoid Arthritis.

The objectives of the study were to assess and correlate the functional ability of the hand with upper limb function, the functional ability of the hand with quality of life and upper limb function with quality of life in patients with Rheumatoid Arthritis.

Methodology

Study Design: Observational Correlational Study

Setting: Physiotherapy Rheumatology OPD of Seth GS Medical College and KEM Hospital, Mumbai.

Inclusion Criteria

Patients of either sex in the age group of 18-55 years diagnosed with Rheumatoid Arthritis as per the 1987 revised criteria of the American College of Rheumatology, who were under DMARDs as prescribed by the rheumatologist and who were categorized as Class I, II and III as per the revised criteria for Classification of Functional Status in RA by American College of Rheumatology (ACR).

Exclusion Criteria

Patients with any recent history of trauma and surgery, any neurological involvement, visual and hearing deficit and significant secondary cardiovascular and respiratory involvement.

Study Procedure

A total of 75 patients were included as calculated by the census method. The study was approved by the Institutional ethics committee and a written informed consent was taken from each patient. After taking a brief history and a routine physiotherapy examination, the patients were asked to:

- Perform the Grip Ability Test (GAT), which was subsequently timed.
- Fill the Disabilities of Arm, Shoulder and Hand (DASH) Questionnaire to grade their upper limb functional ability.
- Fill the Health Assessment Questionnaire-Disability Index (HAQ-DI) for grading overall quality of life.

The above three scores were calculated and the data collected was statistically analyzed using appropriate tests. Using SPSS software version 16.0, Spearman’s rho correlation coefficient (two tailed) was used to find out the association between the variables.

Results

A total of 75 patients were included. The mean age of the patients was 41.10 years, with the range being from 19 to 55 years. Out of 75, 68 were females and 7 were males.

Amongst them, 35 patients (46.66%) were in Class I (Completely able to perform usual activities of daily living: self care, vocational and avocational), 26 patients (34.66%) in Class II (Able to perform usual self care and vocational activities, but limited in avocational activities) and 14
patients (18.66%) in Class III (Able to perform usual self care activities, but limited in vocational and avocational activities) as per the revised Classification of Functional Status.

Overall, females were affected more than males.

GAT scores were seen affected in 95% of the patients studied. Amongst these, 8% showed severely affected scores.

The DASH scores were affected in 83% of the patients. Amongst these, 33% were moderately and 49% were severely affected.

The HAQ-DI scores were varyingly affected. 32% showed mild affection, 53% showed moderate affection and 14% showed severely affected HAQ-DI scores.

Of the 75 patients studied, we observed

- A moderate positive correlation between the functional ability of the hand (using GAT) and upper limb function (using DASH). (Figure 2) The Spearman’s rho correlation coefficient was 0.530 with the correlation being significant at 0.01.
- A moderate positive correlation between the functional ability of the hand (using GAT) and quality of Life (using HAQ-DI). (Figure 3) The Spearman’s rho correlation coefficient was 0.531 with the correlation being significant at 0.01.
- A strong positive correlation between the upper limb function (using DASH) and quality of Life (using HAQ-DI). (Figure 4) The Spearman’s rho correlation coefficient was 0.801 with the correlation being significant at 0.01.

Discussion

Rheumatoid Arthritis is a disease associated with considerable impairments, activity limitations and participation restrictions which cause disability and affect
the individual’s Quality of life.

Figure 2 shows the correlation between functional ability of the hand (using GAT) and upper limb function (using DASH) with the two variables showing a moderate positive correlation.

In a study by Vliet Vlieland and Van der Wijck TP in 1996, 78% of the variance of the combined hand function factor could be explained by pinch strength, stiffness of the hands, and the presence of Z deformity and ulnar deviation. We observed the GAT scores to be delayed in patients with RA. The reasons for it could be the associated hand deformities. Studies have shown reduced motor performance function with an increase in the reaction time, speed of movement and reduction in co-ordination in individuals diagnosed with RA. Also, muscle wasting is seen in RA, which reduces grip and pinch strength. In a study by Kristina Calder et al, they concluded that women with hand RA have axonal loss of sensory fibers in the median, ulnar and radial nerves. All these along with pain could contribute to reduced hand functioning and increase in GAT scores in patients with RA.

Shoulder function is typically affected in RA. Gleno-humeral (GH) joint synovitis, tendinitis involving the rotator cuff and tendon tears in the rotator cuff are common. Muscle strength weakness especially the gleno-humeral rotators contribute to upper limb limitations in ADLs. Radiologically, joint space narrowing and destruction is seen, and pain ensues from upward migration and medialisation of humeral head which reduces subacromial space. In our study, patients reported reduced capability to use their shoulder in functional activities, which increased their overall DASH scores.

Slungaard B et al in 2013 in a study concluded that active motion deficit along with reduced passive ROM, poor muscle strength and pain, explained about one-third of the limitations in shoulder function in daily life.

At least 70-75% of individuals diagnosed with RA have wrist and hand symptoms, 67–91% individuals have shoulder pain, and more than one in five present moderate or severe glenohumeral (GH) joint destruction during the first 15 years from the disease onset. These values are consistent with the results of our study. Along with this, the RA elbow presents with pain, swelling, flexion and valgus deformity.

Thus it can be undoubtedly said that hand dysfunction can hugely impact upper limb function in this population.

These results concur with a study done in 2004 by J Adams and J Burridge in UK on 36 RA patients. A study in 2007 concluded that RA patients were weaker, had poorer upper limb functional performance, hand grip strength and proprioceptive acuity than the healthy subjects.

Thus, the correlation can be justified.

Figure 3 shows the correlation between the functional ability of the hand (GAT) and the QoL (HAQ-DI) and the two variables show a moderate positive correlation.

Disability is a complex phenomenon reflecting the interaction between features of a person’s body and features of the society in which they live. Overcoming the difficulties faced by people with disability requires intervention to remove the environmental and social barriers. Disability related to RA can be described in terms of impairment, activity limitation and participation restriction. The WHO ICF component assessed with the HAQ-DI is activity limitation.

A number of factors affect the HAQ-DI like age and sex. Joint damage, disease duration, serum rheumatoid factor, disease activity (ESR, CRP levels) and bodily fatigue are directly related to the scores on the HAQ-DI, whereas education and socioeconomic status are indirectly related.

HAQ-DI is a patient perceived quality of life measure which assesses the individual’s performance and disability over the past one week. As hand function deteriorates, the individual dependence on aids and help by another person increases. These directly contribute to increased HAQ-DI scores.

The common factors affecting GAT and HAQ-DI are disease duration, joint damage, disease activity, fatigue along with pain and poor muscle strength. A study by Berit Dellehag and Anders Bjelle mentions that the development of dependence in ADL was explained by reduction in hand function. Also a study by Eva Hallert et al in 2012 concluded that HAQ-DI values could significantly be predicted by GAT values. Thus, the correlation between hand function and QoL and can be justified.

The results explained in Figure 3 are supported by two studies, by Berit Dellehag et al in 1999 and by Mathilda A. Bjork et al in 2007.

Figure 4 shows the correlation between the upper limb function (DASH) and QoL (HAQ-DI) and the two variables show a strong positive correlation.

RA has an important impact on health that can be related to the WHO’s International ICF framework. The physical consequences of RA for the individual relate to body functions and structures in the ICF framework. The functional consequences of RA are related to activity in the ICF framework, and the impact of RA on society relates to participation in the ICF framework. Despite conventional treatment, early RA continues
to result in significant physical consequences for most patients. From the patient’s perspective this primarily results from persistent pain, although symptoms such as fatigue and depression are also relevant.

In the thirty item DASH Outcome Measure, which is concerned with upper limb disability and symptom, twenty one items reflect the degree of difficulty in performing various physical activities due to arm, shoulder or hand problems, 5 items represent the severity of each symptom of pain, activity-related pain, tingling, weakness and stiffness and 4 items reflect the effect on social activities, work and sleep. The HAQ Disability Index measures the QoL by assessing difficulties in performing activities of daily living.

The upper extremity is central to performing most skilled tasks, used principally for reaching, grasping and manipulation, sometimes for lifting the body mass as well as other weights, and at periods of postural stability for preserving balance. Effective functional use of the upper limb is absolutely dependent on functional hand grasp and release. Motor impairment of the upper extremity has a considerable impact on an individual’s ability to complete activities of daily living, hobbies and work which affects the quality of life and is associated with a low level of subjective well being.

Both the DASH and the HAQ-DI target the psychosocial element and are patient perceived scores grading their performance in their daily environment. The HAQ-DI has more items involving the use of upper extremity as compared to lower extremity. Also, both the scales measure the subjective scores of the individual in ADLs in the same time frame. Thus, the correlation between upper limb function and quality of life can be justified. These results are supported by studies done by Annelie Bilberg and Tomas Bremell17 and Aktekin et al.18.

Thus, in an Indian population diagnosed with RA, the functional ability of the hand correlates positively with upper limb function and quality of life. The limitation of the study was not having included the disease activity as one of the indices. Further research involving the disease duration, deformities, disease activity and functional outcome measures in relation to upper limb can be carried out.

**Conclusion**

In our study, we conclude that, in patients with RA, there is a moderate positive correlation between the functional ability of the hand and upper limb function, a moderate positive correlation between the functional ability of the hand and quality of life and a strong positive correlation between the upper limb function and quality of life.

The impact of hand dysfunction on the functioning of an RA patient can lead to grave disabilities. Hand function disability poses as one of the greatest obstacles to independent living, thus leading to the need of incorporating newer techniques and approaches to assessment and treatment for enhancing functioning of the upper extremity. Assessment using the GAT, DASH and HAQ-DI can provide us a quick and early insight on the debilitating effects of RA on functioning and disability. Early intervention can then be initiated which will help limit joint damage and thereby improve functional outcomes.

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Knowledge, Attitudes and Practices Relating to Vertigo among Newly Diagnosed Patients: Findings of a Prospective, Observational Registry in India


Abstract

Objective: Vertigo is a common complaint in clinical practice, with multi-causative etiology, substantially impacting individual's overall lifestyle and behavior. However, so far no much data is available to understand the knowledge, attitude and practices (KAP) about vertigo in newly diagnosed Indian patients. Hence, the objective of this prospective, non-interventional, observational registry was to evaluate KAP towards vertigo and assessment of their awareness through a questionnaire-based survey.

Methods: Newly diagnosed patients with vertigo (aged ≥18 years), visiting the physicians, were provided with a self-administered validated questionnaire with domains namely knowledge (18 questions), attitude (7 questions), and practices (8 questions). Primary objective was to analyze the percentage of patients with high, average and low level of knowledge; percentage of patients who were little, quiet and extremely concerned about vertigo and its treatment; percentage of patients taking high, moderate and poor level of precaution towards vertigo. All variables were subjected to statistical analysis.

Results: Overall, 1167 (76.8%) patients completed the KAP questionnaire (women: 52.9%; men: 47.1%). A total of 17.3% patients had low level of knowledge, 73.9% had average and 8.74% patients had high level of knowledge regarding vertigo. Attitude domain revealed that majority of the patients (86.20%) had little concerned attitude towards vertigo; 9.85% patients were extremely concerned and 3.94% patients were not concerned regarding vertigo. Practice domain revealed that none of the patients took high level of precautions, 79.8% patients took moderate precautions and 20.2% took less precaution for disease prevention.

Conclusion: This study revealed that the knowledge, attitude and practice patterns amongst Indian vertigo patients are inadequate, highlighting the need for awareness and scientific education amongst these patients in India. Moreover, health care providers should be trained to provide counseling to these patients effectively.

Editorial Viewpoint

• Vertigo substantially impacts lifestyle and behaviour.
• The study reveals that knowledge, attitude and practice patterns amongst Indian vertigo patients are inadequate emphasizing need for awareness and education.

Introduction

Vertigo, a common complaint in clinical practice, is characterized by dizziness and illusion or hallucination of movement, usually rotation, either of oneself or the surroundings or both. Secondary symptoms include postural instability, cold sweating, nausea and vomiting. Vertigo is about two to three times more common in women than in men and its incidence increases with age. A survey in Germany reported prevalence of vertigo to be 22.9% and an incidence of 3.1%. The 1-year prevalence for vertigo was reported to be 48.3% according to an epidemiological study conducted in France.

The most common causes of vertigo are vestibular disorders including benign paroxysmal positional vertigo (BBPV), Meniere’s disease (MD), vestibular neuritis, and labyrinthitis. The
improving the health-related quality of life.

**Methodology**

**Study Design**

This multicentre, prospective, non-interventional, observational registry enrolled patients visiting physicians, from 37 sites (17 ENTs, 10 Neurologists and 10 Consulting Physicians), across four different geographical zones (North, South, West and East) of India, between June 2015 and May 2016. Data regarding the KAP amongst these enrolled patients are included in this publication. A validated questionnaire was used to assess the KAP in these patients.

This study was conducted in accordance with the protocol, International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines, the Declaration of Helsinki, Indian Council of Medical Research (ICMR), and Indian GCP guidelines. Independent Ethics Committee (IEC) approved the study protocol, questionnaire and participant authorization form (PAF) used in this study.

**Selection Criteria**

Patients (aged ≥18 years) visiting physicians, diagnosed with new onset vertigo, able to read/write English for administrating KAP questionnaire and willing to provide a written authorization to participate were included in the KAP study. Patients newly diagnosed with vertigo requiring hospitalization for any cause, patients already on vertigo treatment and/or pregnant women were excluded from the study.

**Study Assessments**

A self-administered study questionnaire with three domains namely knowledge, attitude and practice (KAP) patterns amongst Indian patients with new onset vertigo. Understanding the KAP responses will enable the health authorities/policy makers to implement feasible evidence based health policies to enhance awareness level, eventually improving the health-related quality of life.
### Appendix 1: Validated Vertigo KAP Questionnaire

#### SECTION I: KNOWLEDGE

Please indicate whether you agree or disagree with the following statements by marking ‘True’ or ‘False’. In case you are not sure of your response please tick ‘Don’t know’

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Statements</th>
<th>True</th>
<th>False</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vertigo is a feeling of fainting due to fear of height.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2</td>
<td>Vertigo is a feeling of nausea and vomiting while in motion.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3</td>
<td>Vertigo is a feeling of moving or spinning when not in motion or that the world is spinning around you.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>4</td>
<td>Vertigo is a feeling of drifting to one side while walking.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>5</td>
<td>Vertigo is a disease transferred from parents to children.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>6</td>
<td>If you have vertigo, you may feel worse when you move your head or change positions (stand up, roll over).</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>7</td>
<td>If you have vertigo, you may feel worse when you cough or sneeze.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>8</td>
<td>Vertigo may last for seconds, hours or days.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>9</td>
<td>Vertigo may be accompanied by nausea and vomiting.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>10</td>
<td>Vertigo may be accompanied by loss of hearing and ringing sensation in the ears.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>11</td>
<td>Vertigo may be accompanied by mood swings.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>12</td>
<td>Vertigo may be accompanied by seeing double, having trouble speaking or swallowing, or feeling weak.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>13</td>
<td>Vertigo may be accompanied by a headache or sensitivity to light and noise.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>14</td>
<td>Vertigo may occur due to a viral or bacterial infection of the inner ear (after cold or flu).</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>15</td>
<td>Vertigo may be associated with migraine.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>16</td>
<td>Head injury may cause vertigo.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>17</td>
<td>Vertigo may occur due to use of certain medications.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>18</td>
<td>Vertigo can be treated with physiotherapy.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

#### SECTION II: ATTITUDE

(Please tick the most appropriate option for the below statements)

| 1      | Medication for treatment of vertigo should be taken in consultation with physicians only. | ☐ Strongly agree | ☐ Agree | ☐ Neutral | ☐ Disagree | ☐ Strongly disagree |
| 2      | If suffering from vertigo, one should keep still and rest when symptoms occur. | ☐ Strongly agree | ☐ Agree | ☐ Neutral | ☐ Disagree | ☐ Strongly disagree |
| 3      | One should restrict social activities with friends and family, if suffering from vertigo. | ☐ Strongly agree | ☐ Agree | ☐ Neutral | ☐ Disagree | ☐ Strongly disagree |
| 4      | If suffering from vertigo, one should inform his/her employer if his/her job involves operating machinery or climbing ladders. | ☐ Strongly agree | ☐ Agree | ☐ Neutral | ☐ Disagree | ☐ Strongly disagree |
| 5      | Physiotherapy exercises to treat vertigo advised by the physician/physiotherapist can be done once in a while. | ☐ Strongly agree | ☐ Agree | ☐ Neutral | ☐ Disagree | ☐ Strongly disagree |

Contd...
**Appendix 1: Validated Vertigo KAP Questionnaire (Contd...)**

**SECTION III: PRACTICE**

(Please indicate whether you practice the following or not by marking ‘Yes’ or ‘No’ for the below-mentioned statements)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Practice Measures</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you keep still and rest when you feel the symptoms of vertigo?</td>
<td>□ □</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Do you get up slowly when getting out of bed and sit on the edge of the bed for a minute or so before standing?</td>
<td>□ □</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Do you avoid sudden bending down to pick things or looking for something on a high shelf?</td>
<td>□ □</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Do you exercise regularly as advised by physicians to prevent vertigo?</td>
<td>□ □</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Do you move your head carefully and slowly during daily activities?</td>
<td>□ □</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Do you avoid activities such as driving, operating heavy machinery, and climbing until 1 week after your symptoms disappear?</td>
<td>□ □</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Do you avoid bright lights, TV, and reading during a vertigo attacks?</td>
<td>□ □</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Do you use a cane or other help for walking if you have a loss of balance during a vertigo attack?</td>
<td>□ □</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1: Baseline characteristics of the study population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (N=1520)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50.0 (18.88)</td>
</tr>
<tr>
<td>Age groups, n (%)</td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>191 (12.6)</td>
</tr>
<tr>
<td>31-40</td>
<td>268 (17.6)</td>
</tr>
<tr>
<td>41-50</td>
<td>308 (20.3)</td>
</tr>
<tr>
<td>≥51</td>
<td>753 (49.5)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>712 (46.8)</td>
</tr>
<tr>
<td>Female</td>
<td>808 (53.2)</td>
</tr>
<tr>
<td>Educational Qualification*, n (%)</td>
<td></td>
</tr>
<tr>
<td>Undergraduates</td>
<td>235 (20.1)</td>
</tr>
<tr>
<td>Graduates</td>
<td>660 (56.6)</td>
</tr>
<tr>
<td>Post-graduates</td>
<td>231 (19.8)</td>
</tr>
<tr>
<td>Others</td>
<td>41 (3.51)</td>
</tr>
</tbody>
</table>

*The data is calculated for 1167 patients who completed the KAP questionnaire.

The primary variables of the study were percentage of patients with high, average and low level of knowledge regarding vertigo; percentage of patients who were not concerned, little, quite and extremely concerned about vertigo and its treatment; and the percentage of patients taking high, moderate and poor level of precaution towards vertigo.

**Statistical Analysis**

All variables were subjected to statistical analysis. All continuous and semi-quantitative variables were described in terms of a number of observations (n), mean, standard deviation (SD), median, minimum and maximum. The summary of categorical data was presented in terms of frequency count (n) and percentages (%). Further, pair wise association between the three endpoints, namely knowledge, attitude and practice domain was analyzed using Pearson chi-square test at 5% level of significance. Statistical analyses were performed using SAS® Version 9.2 (SAS Institute Inc., USA).

**Results**

**Patients**

A total of 1520 patients were enrolled in the vertigo registry. Out of this, 1167 (76.8%) patients who fulfilled the inclusion criteria and consented, participated and completed the KAP questionnaire (women: 52.9% [n=617]; men: 47.1% [n=550]). The mean (± SD) age of the population was 50.2±15.37 years (min: 18; max: 88). Out of 1167 patients, about 20.1% patients were undergraduates; 56.6% of the patients were graduates; and 19.8% patients were post graduates. The baseline characteristics of the patients are presented in Table 1.

A total of 202 (13.3%) out of 1520 patients had history of at least one significant medical condition at baseline. Among these patients, 55.5% had history of cardiovascular disease and 38.6% had diabetes mellitus. Other medical conditions reported by the patients included neurological disorder (7.4%), hormonal dysfunction (5.9%), recent infections (3.5%), head and neck trauma (1.0%), psychological disorder (0.5%) and others (6.9%). Surgical history was reported in 24 (1.6%) patients.

**Knowledge Domain**

The results revealed that majority of the patients (73.9%) had moderate level knowledge, as indicated by score of 8-13 points. About 17.3% patients had low level of knowledge regarding vertigo (score ≤7 points). Only 8.7% patients had high level knowledge (Figure 1). Majority of the patients were aware of the signs such as that vertigo is a feeling of moving or spinning when not in motion or that the world is spinning around you (86.7%); feeling worse when the patient move head/change positions (74.0%) or when the patient cough or sneeze (65.6%). More than half of the patients were also aware that vertigo may last for seconds, hours or days (69.0%) and may be accompanied by nausea and vomiting (68.2%), loss of hearing...
and ringing sensation in the ears (63.8%), seeing double, having trouble speaking, swallowing, feeling weak (69.7%) or by a headache or sensitivity to light and noise (71.4%). Patients were also aware that vertigo may occur due to a viral or bacterial infection of the inner ear after cold or flu (59.3%), could be associated with migraine (64.7%) and/or may result due to head injury (61.7%), use of certain medications (61.3%) and can be treated with physiotherapy (69.3%).

However, a significant proportion of patients had misconceptions that vertigo is the feeling of fainting due to height (76.2%); feeling of nausea and vomiting while in motion (75.7%) or the feeling of drifting to one side while walking (76.3%). About 54.3% of the populations believed that vertigo is transmitted from parents to children and is often associated with mood swings (60.2%) (Table 2).

### Attitude Domain

The attitude of the patients towards vertigo showed that majority of the patients (86.2%) was little concerned about vertigo as interpreted by their agreement to 4-6 statements. About 3.9% patients were not concerned regarding vertigo (agreed for ≤3 statements). A total of 9.9% patients showed extremely concerned attitude (agreement to all 7 statements on attitude scale) (Figure 1). Most of the patients agreed that medication for treatment of vertigo should be taken in consultation with physicians only (93.8%) and if suffering from vertigo, one should keep still and rest when symptoms occur (88.9%). However, 65.7% patients had misconception that social activities with friends and family should be restricted if suffering from vertigo (strongly agree: 37.8%; agree: 27.9%; strongly disagree: 2.5%) and that physiotherapy exercises advised by the physician/physiotherapist can be done once in a while.

### Table 2: Awareness in patients with respect to knowledge domain

<table>
<thead>
<tr>
<th>Statement</th>
<th>Total (N=1167)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>True</td>
</tr>
<tr>
<td>Vertigo is a feeling of fainting due to fear of height</td>
<td>76.2%</td>
</tr>
<tr>
<td>Vertigo is a feeling of nausea and vomiting while motion</td>
<td>75.7%</td>
</tr>
<tr>
<td>Vertigo is a feeling of moving or spinning when not in motion or that the word is spinning around you</td>
<td>86.7%</td>
</tr>
<tr>
<td>Vertigo is feeling of drifting to one side while walking</td>
<td>76.3%</td>
</tr>
<tr>
<td>Vertigo is a disease transferred from parents to children</td>
<td>54.3%</td>
</tr>
<tr>
<td>If you have vertigo, you may feel worse when you move your head or change positions (stand up, roll over)</td>
<td>74.0%</td>
</tr>
<tr>
<td>If you have vertigo, you may feel worse when you move you cough or sneeze</td>
<td>65.6%</td>
</tr>
<tr>
<td>Vertigo may last for seconds, hours or days</td>
<td>69.0%</td>
</tr>
<tr>
<td>Vertigo may be accompanied by nausea and vomiting</td>
<td>68.2%</td>
</tr>
<tr>
<td>Vertigo may be accompanied by loss of hearing and ringing sensation in the ears</td>
<td>69.3%</td>
</tr>
<tr>
<td>Vertigo may be accompanied by mood swings</td>
<td>63.8%</td>
</tr>
<tr>
<td>Vertigo may be accompanied by seeing double, having trouble speaking or swallowing or feeling weak</td>
<td>59.3%</td>
</tr>
<tr>
<td>Vertigo may be accompanied by headache or sensitivity to light and noise</td>
<td>71.4%</td>
</tr>
<tr>
<td>Vertigo may occur due to a viral or bacterial infection of the inner ear (after cold or flu)</td>
<td>59.3%</td>
</tr>
<tr>
<td>Vertigo may be associated with migraine</td>
<td>64.7%</td>
</tr>
<tr>
<td>Head injury may cause vertigo</td>
<td>61.7%</td>
</tr>
<tr>
<td>Vertigo may occur due to use of certain medications</td>
<td>61.3%</td>
</tr>
<tr>
<td>Vertigo can be treated with physiotherapy</td>
<td>69.3%</td>
</tr>
</tbody>
</table>

* N = total number of subjects who had completed KAP questionnaire

### Table 3: Awareness in patients with respect to attitude domain

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication for treatment of vertigo should be taken in consultation with physicians only</td>
<td>58.3%</td>
<td>35.5%</td>
<td>6.1%</td>
<td>0.2%</td>
<td>0</td>
</tr>
<tr>
<td>If suffering from vertigo, one should keep still and rest when symptoms occur</td>
<td>47.8%</td>
<td>41.1%</td>
<td>10.4%</td>
<td>0.7%</td>
<td>0</td>
</tr>
<tr>
<td>One should restrict social activities with friends and family, if suffering from vertigo</td>
<td>37.8%</td>
<td>27.9%</td>
<td>21.4%</td>
<td>10.4%</td>
<td>2.5%</td>
</tr>
<tr>
<td>If suffering from vertigo, one should inform his/her employer if his/her job involves operating machinery or climbing ladders</td>
<td>36.6%</td>
<td>40.6%</td>
<td>19.3%</td>
<td>3.4%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Physiotherapy exercises to treat vertigo advised by the physician/physiotherapist can be done once in a while</td>
<td>40.5%</td>
<td>31.0%</td>
<td>17.1%</td>
<td>9.9%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

* N = total number of subjects who had completed KAP questionnaire
About 79.8% patients took moderate level of precautions and 20.2% patients took poor level of precautions (Figure 1). Most of the patients kept still and rested when they felt the symptoms of vertigo (86.5%) or got up slowly out of bed and sat on the edge of the bed for a minute before standing (79.6%). Other precautions taken by the patients included avoiding sudden bending down to pick things or looking for something on a high shelf (76.0%); exercising regularly as advised by physicians to prevent vertigo (66.2%); moving their head carefully and slowly during daily activities (68.0%); avoiding activities such as driving, operating heavy machinery, and climbing until one week after symptoms disappear (72.4%); avoiding bright lights, TV, and reading during a vertigo attacks (66.6%); and using a cane or other help for walking if experiencing a loss of balance during a vertigo attack (55.6%) (Table 4).

**Association of Gender and Age with KAP**

The KAP was independent of gender of the patients (Table 5). Higher proportion of patients in younger age groups (≤30 years) had high knowledge regarding vertigo; majority of patients from older age groups (>40 years) had average knowledge. Further, patients in younger age group (≤30 years) showed extremely concerned attitude towards disease and treatment. However, poor level of precaution was shown by more patients in ≤ 50 years’ group. Majority of the patients in >50 age group showed moderate level of precaution (Table 6).

**Discussion**

The number of vertigo patients are definitely rising both in rural and urban India. Despite its frequent occurrence and effective treatment options, vertigo still remains under-estimated because of lack of awareness among the patients.
and clinicians. Spontaneous remission, atypical presentations and benign course of the disease may be other contributory factors. Studies have shown that about 20% of an unselected Scottish population have restricted daily life activities due to dizziness. However, only 23% of those people visit their doctor because of their suffering, and dizziness seems to be an underestimated reason for handicap. This point towards a lack of awareness among the patients regarding the condition. Better understanding about cause of the disease, signs and symptoms, and necessary lifestyle modifications would be helpful in adapting preventive measures, improving therapeutic outcomes and the overall quality of life. Patient’s knowledge, attitude and practices also have an effect on medication compliance.

To the best of our knowledge, this is the first study evaluating the level of knowledge, attitude, and practice patterns among the newly diagnosed vertigo patients in India. The results of the knowledge domain of our study revealed that only 8.7% patients had high level of knowledge about the disease whereas 17.3% patients demonstrated low level of knowledge. Even though majority of the patients were aware that vertigo is a feeling of moving or spinning when not in motion, about three-fourth of the population had misapprehensions about the associated signs and symptoms related to the disease (76%). Furthermore, more than half of the patients (60.2%) even believed that vertigo is transmitted from parents to children and is often associated with mood swings.

The attitude domain of the study revealed that majority of the patients (86.2%) were little concerned while 3.9% patients had ‘not concerned’ attitude towards vertigo. Only about 9.9% patients exhibited extremely concerned attitude. When questioned regarding the attitude of the patients towards medication, 93.8% patients agreed that medication for treatment of vertigo should be taken in consultation with physicians only. However, more than half of the patients (65.7%) had misconception that social activities with friends and family should be restricted if suffering from vertigo and that physiotherapy exercises advised by the physician/physiotherapist for vertigo treatment can be done once in a while, if suffering from vertigo (71.5%).

Understanding the cause and taking necessary precautionary measures form the important priorities of patients suffering from vertigo. Surprisingly, none of the patients took high level of precautions towards the disease; about 79.8% patients took moderate level of precautions and 20.2% patients took poor level of precautions. More than half of the population took precautionary measures such as avoiding sudden bending down to pick things or looking for something on a high shelf (76.0%), exercising regularly (66.2%), avoiding activities such as driving, operating heavy machinery, and climbing until one week after symptoms disappear (72.4%), avoiding bright lights, TV, and reading during a vertigo attacks (66.6%) and using a cane or other help for walking if experiencing a loss of balance during a vertigo attack (55.6%).

No association between KAP patterns and gender of the patient was noted in this study. Higher proportion of patients from younger age groups had high knowledge and showed extremely concerned attitude towards vertigo but took poor level of precautions. However, older patients (>50 years) took good precautions but had average level of knowledge. These findings suggest the need for an age dependent counselling of patients with vertigo.

Being the first of its kind KAP study among the newly diagnosed vertigo patients in India, may be considered as strength of the study. Our study was performed in over 37 centres across four different geographical zones of India, involving 1520 patients ranging between 18 and 88 years of age. To the best of our knowledge, this is the largest sample size for the study of vertigo in India, in a diverse population. The participants were representative of different gender, age groups and economic conditions. More than half of the study population were graduates/post graduates.

The participating investigators included ENT specialists, Neurologists, and MD Medicine. However, data regarding the educational qualification were not captured, which would have been in turn helpful in understanding the response appropriately based on their educational qualification.

The finding of this study revealed that the knowledge, attitude and practice patterns amongst Indian vertigo patients is inadequate, highlighting the need for awareness and scientific education amongst these patients in India. The gaps between the knowledge and the prevailing practices were obvious in this study. This data will be helpful for the clinicians to comprehend the real-world picture of disease, practices followed, misconceptions and treatment outcomes. India being a developing country requires targeted awareness campaigns to make its people well-informed and well-resourced with the disease condition. These awareness campaigns need to be organized at physician level and also at the doorstep of general people. Furthermore, health care providers should be trained to provide counseling to these patients effectively.

Acknowledgements

The authors thank the study participants without whom this study would not have been accomplished, as well as the
investigators, for their participation in this study. Dr. Shalini Nair (Abbott India Ltd) provided writing support during the development of this manuscript.

**Funding/Support**

This study was funded by Abbott.

**Author Contributions**

All authors contributed to study design, data interpretation, development of this manuscript and approved the final manuscript for submission. All authors met the ICMJE criteria for authorship and all those who met those criteria are listed as authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Conflict of Interest**

Dr. Kameswaran, Dr. Pujari, Dr. Basumatary and Dr. Singh has received research funding from Abbott as a consultant. Dr. Sarda is an employee of Abbott India Ltd.

**References**

Association of Serum Prolactin Level with Impaired Glucose Regulation and Diabetes

Chitresh Chahar¹, Kapil Chahar², BS Ankit¹, Ajeet Gadhwal¹, RP Agrawal³

Abstract

Background: Increase in prolactin during pregnancy has been identified as a major stimulus for β cells. These effects have been demonstrated in both in-vitro and in-vivo non-pregnant animal models. Recently, bromocriptine has also been approved for the therapy of type 2 diabetes, regardless of the baseline prolactin level, with its mechanism of action poorly understood. Hence, this study was planned to assess whether prolactin levels within normal range associates with prediabetes and diabetes.

Methods: A total of 300 participants, 180 males and 120 females, with equal number of subjects in the prediabetes, diabetes and normal group were analyzed. The participants were categorized into sex-specific quartiles of serum prolactin, with the first quartile representing subjects with the lowest prolactin levels and the fourth quartile having the highest levels. In addition, multinomial logit analyses were performed to evaluate the odds ratio and 95% confidence interval of having prediabetes & diabetes for each quartile.

Results: Prolactin levels in the normal group were 10.99 ± 3.65 ng/ml for the males and 12.25 ± 3.67 ng/ml for the post-menopausal females. The prolactin levels for the males in prediabetes group were 9.46 ± 3.43 ng/ml and for diabetes group were 8.98 ± 3.43 ng/ml (p value = 0.005). In females, the prolactin levels were 10.20 ± 3.99 ng/ml for the prediabetes group and 9.60 ± 3.85 ng/ml for the diabetes group (p value = 0.007). The mean fasting plasma glucose for the four male quartiles in their numerical order were 135 mg/dl, 128 mg/dl, 120 mg/dl and 110 mg/dl (p value = 0.04) and the mean HbA1c in the same order for the quartiles were 7%, 6.4%, 6.1% and 5.9% (p value = 0.01). Similarly, the mean fasting plasma glucose for the four female quartiles in their numerical order were 138 mg/dl, 124 mg/dl, 107 mg/dl and 110 mg/dl (p value = 0.03) and the mean HbA1c in the same order for the quartiles were 7.2%, 6.7%, 6.3% and 5.8% (p value = 0.01). The age adjusted odds ratio for 2nd, 3rd and 4th quartiles as compared to the 1st quartile for prediabetes in men were 0.82, 0.72 and 0.61 and for diabetes were 0.84, 0.65 and 0.55, respectively. Risk for diabetes in females ranged from 0.04 to 0.72 for the 3rd quartile and 0.03 to 0.56 for the 4th quartile as compared to 1st quartile. The risk for prediabetes in females ranged from 0.06 to 0.95 for 3rd quartile and 0.04 to 0.74 for the 4th quartile as compared to 1st quartile.

Editorial Viewpoint

• Increased prolactin level during pregnancy is a stimulus for β cells.
• The study assesses relationship between prolactin levels and prediabetes and diabetes.
• Prolactin levels were lower in prediabetes and lowest in diabetes.
• Prolactin level did not correlate with obesity and dyslipidemia.

Introduction

Prolactin hormone is named after its primary physiological role in preparing the breast for lactation in the postpartum period. Also, in normal physiologic concentrations, it is trophic to corpus luteum function, giving rise to the name luteotrophic hormone. However, prolactin receptor is also expressed in other tissues and cells such as lymphoid cells, adipocytes and pancreatic β cells¹. Physiologic increase in prolactin levels during pregnancy has been identified as major stimulus for β cells to adapt towards increased metabolic demands.² The most important changes are enhanced glucose mediated insulin secretion and enhanced β-cell mass. Failure for this reprogramming to occur.
in response to the increased metabolic demands leads to gestational diabetes. Moreover, this glucose metabolic regulation effect of prolactin is recognized not to be confined to the period of pregnancy as these effects have been demonstrated in both in-vitro cell cultures and in-vivo non-pregnant rodent models. On the other end of the spectrum, high levels of prolactin such as those seen in patients with prolactinoma and patients with different prolactin levels.\(^6\) On the other side, the drugs that block dopamine D2 receptors such as antipsychotics increase appetite and result in significant weight gain. Bromocriptine has been approved for the therapy of type 2 diabetes.\(^7\) Timed short acting bromocriptine administration within 2 h of awakening is believed to exert its beneficial metabolic effects exclusively through the central nervous system. Causes for improved glycaemia under bromocriptine are not fully understood, but there is evidence for improved insulin sensitivity. Interestingly, potency of bromocriptine to decrease prolactin levels seems to be a surrogate marker for its effectiveness to improve glycaemia in patients with diabetes, suggesting common underlying mechanism.\(^5\)

Although previous investigations about the potential effects of prolactin within normal range on glucose and fat metabolism are scarce, existing studies suggest an influence of prolactin on these processes. In this study, we tried to explore this association.

**Aims and Objectives**

1. To determine whether the variation of circulating prolactin concentration in normal range associates with prediabetes and diabetes.
2. To ascertain whether BMI differs in subgroups of patients with different prolactin levels.
3. To study variation in lipid profile parameters in patient’s groups with differing prolactin levels.

**Material and Methods**

It was a single centered cross sectional study carried out between the period of July 2014 to June 2015. 300 Subjects were selected from the people presenting for check-up at medicine outpatient facility in the PBM hospital, either previously aware of their glycemic status or newly diagnosed with prediabetes (IGT, IGF) and diabetes. Participants were recruited to represent three groups of glycemic status in equal numbers namely:

- Diabetes.
- Prediabetes i.e. Subjects with impaired fasting glucose and impaired glucose tolerance.
- Normal glycemic status.

Patients with type 1 diabetes, premenopausal women and individuals with elevated prolactin levels (outside the normal range) such as prolactinoma patients were excluded, as also, subjects with thyroid disorders and/or on thyroid related medications and patients on any medication known to affect serum prolactin levels. Subjects with chronic medical illnesses were also excluded.

All the patients attending the medicine outpatient facility fulfilling the inclusion criteria underwent detailed history, clinical examination and laboratory testing. The data were collected on a specially designed proforma. Post-menopausal status was defined as: all women ≥60 years of age and all women between 40–60 years who reported no menstrual cycle for consecutive 12 months.

Weight was measured with an analog portable weighing scale to the nearest 0.5 kg. Height was measured to the nearest 0.1 cm. WHO Asia Pacific guidelines\(^8\) were used to define overweight and obesity.

Plasma glucose in the venous samples were measured using the hexokinase method. HbA1c testing was done by ion exchange chromatography, with reporting done in percentage values. Prediabetes and diabetes were defined according to the American Diabetes Association standards\(^10\) as follows:

1. **Prediabetes:**
   - Impaired fasting glucose: Fasting plasma glucose: 100–125 mg/dl.
   - Impaired glucose tolerance: 2–h plasma glucose in the 75-g OGTT 140 mg/dl to 199 mg/dl
2. **Diabetes:**
   - Based on self-reported physician’s diagnosis; use of antidiabetic medication.
   - Fasting (>8 hrs) plasma glucose ≥126 mg/dl
   - 2–h plasma glucose ≥200 mg/dl
   - HbA1c concentrations > 6.5%
3. **Normal / Control:** absence of both above.

Lipid profile was done by autoanalyzer (Chemwell® 2910 Automated EIA and Chemistry Analyzer – Ark Diagnostics).
Table 1: Comparison of subjects in three groups based on glucose regulation status

<table>
<thead>
<tr>
<th></th>
<th>Males (n=180; 60 each)</th>
<th>Females (n=120; 40 each)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Prediabetic</td>
</tr>
<tr>
<td>Age (yrs.)</td>
<td>52.3 ± 6.4</td>
<td>52.7 ± 5.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.76 ± 2.44</td>
<td>24.43 ± 2.26</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>39 ± 6</td>
<td>36 ± 5</td>
</tr>
<tr>
<td>TGL* (mg/dl)</td>
<td>116</td>
<td>136</td>
</tr>
<tr>
<td>T. Chol. (mg/dl)</td>
<td>162 ± 18</td>
<td>173 ± 16</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>10.99 ± 3.65</td>
<td>9.46 ± 3.43</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>9.81 ± 3.59</td>
<td></td>
</tr>
</tbody>
</table>

*Reported as geometric mean.

Observations and Results

A total of 300 participants, 180 males and 120 females were enrolled, with equal number of subjects in the prediabetes, diabetes and normal group. As a result, the final cohort comprised of 60 males and 40 postmenopausal females in each group. The three study groups based on glycemic status have been compared in Table 1. They were comparable with respect to the mean age, with age ranging from 39-65 yrs. for males and 47-68 yrs. for females. The differences with regard to mean BMI and lipid profile parameters were statistically significant.

The mean serum prolactin levels for the male and female participants were 9.81 ± 3.59 ng/ml and 10.68 ± 3.98 ng/ml respectively. Prolactin levels in the normal group were 10.99 ± 3.65 ng/ml for the males and 12.25 ± 3.67 ng/ml for the females. The prolactin levels for the males in prediabetes group were 9.46 ± 3.43 ng/ml and for diabetes group were 8.98 ± 3.43 ng/ml. In females, the prolactin levels were 10.20 ± 3.99 ng/ml for the prediabetes group and 9.60 ± 3.85 ng/ml for the diabetes group. Post-hoc analysis of the mean prolactin levels for the three groups by Tukey test revealed the differences to be significant between the normal and the prediabetes group, and the normal and the diabetes group. The differences observed between the prediabetes and diabetes group were not significant.

The subjects were reclassified on the basis of serum prolactin concentrations into four quartiles, with 1st quartile containing subjects with lowest serum prolactin concentrations and 4th quartile subjects’ having the highest concentrations. The four quartiles therefore generated for males were prolactin ≤7.20ng/ml, between 7.2-9.80, between 9.8-12.60 and ≥12.60, with 45 subjects in each. Similarly, for the post-menopausal females the four prolactin quartiles were ≤7.60ng/ml, between7.6-10.60ng/ml, 10.6-13.4ng/ml and ≥13.40ng/ml, with 30 subjects in each quartile. The four quartiles in both males and females were analyzed for differences pertaining to age, BMI, FPG, HbA1c and lipid profile parameters (Table 2). A trend of decrease in age with increasing prolactin quartile was noted which however was not statistically significant. The mean fasting plasma glucose and average HbA1c levels of the subjects in the four quartiles differed significantly. The mean fasting plasma glucose for the four male quartiles in their numerical order were 135 mg/dl, 128 mg/dl, 120 mg/dl and 110 mg/dl and the mean HbA1c in the same order for the quartiles were 7%, 6.4%, 6.1% and 5.9%. Similarly, the mean fasting plasma glucose for the four female quartiles in their numerical order were 138 mg/dl, 131 mg/dl, 124 mg/dl and 107 mg/dl and the mean HbA1c in the same order for the quartiles were 7.2%, 6.7%, 6.3% and 5.8%. The differences in BMI and lipid profile parameters between the four quartiles were not statistically significant in either males or females.
Multinomial logit regression analysis was performed to calculate the age-adjusted odds ratio of prediabetes and diabetes across the prolactin quartiles for both males and females (Figure 1). A trend for decreasing risk for prediabetes and diabetes was observed with increasing prolactin quartiles for both males and females. The age-adjusted odds ratio for 2nd, 3rd, and 4th quartiles as compared to the 1st quartile for prediabetes in men were 0.82, 0.72 and 0.61 and for diabetes were 0.84, 0.65 and 0.55 (Table 3). However, the 95% confidence intervals were quite wide. In the females, the decreasing trend of adjusted odds ratio with 95% confidence intervals for the prediabetes and diabetes were significant for 3rd and 4th quartiles as compared to 1st quartile. Risk for diabetes ranged from 0.04 to 0.72 for the 3rd quartile and 0.03 to 0.56 for the 4th quartile as compared to 1st quartile. Similarly, the risk for prediabetes ranged from 0.06 to 0.95 for 3rd quartile and 0.04 to 0.74 for the 4th quartile as compared to 1st quartile.

**Discussion**

The role prolactin might be playing in regulating metabolic homeostasis, in particular glycemic status, under non-lactating conditions has not received much attention. Most of the knowledge on prolactin in this area comes from studies conducted in-vitro and on rodents. Except for the research conducted in prolactinoma patients, limited information is available in this aspect in humans. Bromocriptine, a dopamine agonist, has been approved for diabetes mellitus type 27. The efficacy of bromocriptine has been shown to correlate with its potency to decrease prolactin levels, but in few epidemiological studies it has been observed that increased prolactin levels are associated with lower fasting plasma glucose and HbA1c. The present study was carried out to investigate this discrepancy.

The mean serum prolactin concentrations between the three groups in both male and female sex turned out to be significantly

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**Table 2: Comparison of the subjects in the four quartiles based on the serum prolactin levels**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male (n=45 each quartile)</th>
<th>Female (n=30 each quartile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>≤7.20</td>
<td>7.2-9.80</td>
</tr>
<tr>
<td>Age (yrs.)</td>
<td>54.4±5.9</td>
<td>53.0±6.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9±2.5</td>
<td>24.4±2.6</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>135±4</td>
<td>128±4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.0±1.8</td>
<td>6.4±1.8</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>35±4</td>
<td>36±4</td>
</tr>
<tr>
<td>TGL* (mg/dl)</td>
<td>138</td>
<td>136</td>
</tr>
</tbody>
</table>

*Reported as geometric mean.

**Table 3: Association of circulating prolactin level with diabetes and prediabetes**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Male (n=45 each quartile)</th>
<th>Female (n=30 each quartile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediabetes</td>
<td>1</td>
<td>0.82 (.29-2.35)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>0.84 (.30-2.36)</td>
</tr>
</tbody>
</table>

*Age-adjusted Odds Ratios with 95% Confidence Intervals.
differences with average prolactin values being lower in prediabetes group and lowest in diabetic group. This was surprisingly opposite to what was expected from the observation that bromocriptine, a potent inhibitor of prolactin, improves glycaemia and has been approved recently by FDA for use in patients with diabetes. In addition, bromocriptine has been observed to be therapeutic in all the patients of diabetes irrespective of whether their serum prolactin concentrations were elevated or in normal range. Also, it goes against the observation that antipsychotics, with their anti-dopaminergic activity leading to elevated prolactin levels, have been traditionally associated with increased risk of diabetes. Although, most evidence suggesting an association between antipsychotic medications and diabetes have been based on retrospective studies not controlled for important confounders and a review of prospective data by the expert group presented in the consensus meeting on “Schizophrenia and diabetes 2003” failed to show any difference in the incidence of glycemic related abnormalities. However, the present study findings are in line with the ones previously observed by Wang et al (2013). They too observed the mean prolactin levels to be significantly lower in patients with prediabetes and diabetes while comparing prediabetic and diabetic Chinese adults with their normal counterparts. In addition, the mean fasting plasma glucose and HbA1c values in their study decreased with increasing serum prolactin quartiles. Moreover, Wagner et al (2013), while analysing the data from subjects without diabetes in the German region of Tubingen, too observed a similar trend in HbA1c between the four prolactin quartiles. Moreover, they even conducted hyperinsulinaemic-euglycemic clamp test in a subgroup of patients, the result of which demonstrated statistically significant positive association between prolactin levels and insulin sensitivity. In our study, on multinomial logistic regression analysis, a trend of decreasing relative risk for prediabetes and diabetes was found in both males and females with increasing concentrations of serum prolactin. Balbach et al (2013), carrying out population based study in Pomrenia region of Germany too observed risk for diabetes to be higher in individuals with lower prolactin levels. They observed the relative risk for diabetes to be 1.55 in subjects in the lowest prolactin quartile as compared to those in the highest quartile for males with confidence intervals ranging from 1.13 to 2.14. Similarly, they reported relative risk for females in lowest quartile to be 1.70 times in comparison to those in highest quartiles, with 95% confidence intervals ranging from 1.10 to 2.62.

It has been observed that prolactin increases the levels and activity of glucose sensors in β-cells i.e. glucokinase, hexokinase, and glucose transporter 2 thereby reducing the threshold of glucose-stimulated insulin release, in addition to inducing insulin gene transcription. Prolactin up-regulates a cluster of genes associated with cell-cycle regulation while down-regulating apoptosis-related genes. The best characterized molecular pathway through which prolactin brings into motion these effects has been the activation of JAK2/STAT5 (Signal Transducer and Activator of Transcription). However, it has been shown in subsequent research that STAT5 is not essential for prolactin to act. Prolactin also regulates islet structure and function by inducing phosphorylation of insulin receptor kinase substrate-1 and -2 via PI3K activation, and it also activates the MAPK pathway.

BMI did not correlate with varying prolactin levels in this study, with all the four quartile having no statistically significant difference between them. Whereas prolactin has well-established weight promoting/orexigenic roles in fish and birds, it has moderate, inconsistent, or no effects on body weight in most mammals.

Similar to the findings with BMI, the differences in lipid profile parameters between the four quartiles were not statistically significant. There have been very few studies directly investigating the association between lipid profile parameters and prolactin, with all of them being in patients with prolactinoma. As discussed below, prolactin exerts several specific effects on the adipocytes, although they have yet not translated into global changes in body weight and lipid profile in the studies performed till date.

Studies have discovered that human adipose tissue produces prolactin and also expresses prolactin receptors. Prolactin down regulates lipoprotein lipase and fatty acid synthase. It has been demonstrated to increase leptin synthesis and secretion. On the other end, chronically high prolactin levels induce central leptin resistance and inhibit adiponectin production. Collectively, these studies raise the prospect that prolactin affects lipid metabolism and insulin sensitivity through its action as an adipokine.

**Limitations**

The study is limited by it being based on single centre, small sample size and cross-sectional in nature, therefore the observed associations do not allow us to deduce any causality. Also, as the single most important regulator of prolactin secretion is the inhibitory dopamine, prolactin could represent a surrogate parameter of dopaminergic tone within the CNS. In fact, it has been recently demonstrated that by simultaneously enhancing the discharge and spike duration of tuberoinfundibular dopamine cells,
serum prolactin can promote or inhibit dopamine release depending on its level\textsuperscript{27}. It is well known that the brain can influence peripheral insulin sensitivity through several pathways\textsuperscript{28}. Especially, hepatic glucose fluxes seem to be under tight CNS regulation\textsuperscript{29}, which therefore could very well be also reflected by prolactin levels, similar to the fact that prolactin levels have never been directly associated with insulin secretion. In addition, to performing such a study in pre-menopausal females, prospective studies will be needed to provide further insight into this relationship. The other limitation was due to the fact that a diurnally changing parameter was quantified at only one point of time.

Conclusion

- Lower prolactin levels were associated with prediabetes and diabetes as compared to control group.

- On quartile based analysis higher prolactin levels were found to associate with lower HbA1c and fasting plasma glucose.

- Decreasing relative risk trend for both prediabetes and diabetes were found in males and females with increasing prolactin levels.

- No significant differences were observed between various quartile with respect to BMI and various lipid profile parameters.

References

Clinical Profile and Outcome of Progressive Multifocal Leukoencephalopathy in HIV Infected Indian Patients

Vipul Shah¹, Harsh Toshniwal², Manoj Shevkani²

Abstract

Background and objectives: Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease of the Central nervous system (CNS) caused by the human polyoma virus JC (JCV). Human Immunodeficiency Virus (HIV) infection predisposes to PML. Very sparse data is available regarding the effect of Highly Active Anti Retroviral Therapy (HAART) on clinical outcome of PML in Indian settings. This study was carried out to look into clinical profile, survival and neurological outcome of HIV infected PML patients in HAART era.

Methods: We looked in our cohort of HIV-1-infected individuals retrospectively. Diagnosis of PML was done on basis of clinical and radiological abnormalities highly suggestive of the condition, with or without confirmation of JCV DNA in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR).

Results: Out of 892 HIV infected patients, 31 met the criteria for the diagnosis of PML. The median CD4⁺ cell count was 73 cells/µL (Interquartile range (IQR), 43-160 cells/µL) at the presentation of PML. Median duration of PML symptoms were 30 days (IQR, 15-60 days) before diagnosis of PML could be made. The median survival was 538 days. In those patients who survived more than one year, the median survival time was 1095 days (95% confidence interval (CI), 1090.35 –1099.64 days). Those who survived more than one year (n=13), Neurologic function were categorized as cure or improvement in 8, same status in 3 or progression in 2 patients.

Conclusion: In the pre-HAART era, PML patients had very poor prognosis with median survival of 4-6 months after diagnosis. Till date HAART is the only way for reversal of immune system in HIV infected patients and its prompt institution is the most effective therapeutic approach in increasing survival in this group. In this study, 46.4% patients survived after 1 year on HAART. Amongst them, 69% patients completed 3 years. There is strong need of research for the development of pharmacotherapy against JC virus to increase the survival.

Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by the human polyomavirus JC (JCV).¹

The number of PML cases has increased rapidly with the spread of human immunodeficiency virus type 1 (HIV-1) infection.² PML was an AIDS defining condition usually occurs in advanced disease with CD4⁺ cell count <100/µL.³ PML occurs in 1 to 10% of AIDS cases.⁴ Fifty five to eighty five percent of all PML cases are seen in HIV infected individuals.⁵ Clinically, PML was characterized by progressive neurologic deficits leading almost invariably to death with a median survival of few months after diagnosis in pre HAART era.⁶ Complaints of limb weakness, gait disturbances and speech disorders are the most common symptoms reported by patients with PML.⁷⁸ Radiologically, the brain lesion in PML is classically a white matter lesion, hypointense in T1 weighted images and hyperintense on T2 weighted images, without contrast enhancement and mass lesion. In most cases, PML is fatal, usually within few months from onset. Since there is no specific therapy, reversion of the immune suppression, when feasible, remains the only proven approach for management of this disease.
Material and Methods

In this retrospective study we looked into the outcome of PML in HIV infected patients across the globe. However, solid data about the effect of HAART on the outcome of AIDS-associated PML is lacking from India. The objectives of our study were to analyze clinical profile, patient survival, the neurologic function of patients of PML in a cohort of patients treated with HAART.

There are very few studies which looked into the outcome of PML in HIV infected patients across the globe. However, solid data about the effect of HAART on the outcome of AIDS-associated PML is lacking from India. The objectives of our study were to analyze clinical profile, patient survival, the neurologic function of patients of PML in a cohort of patients treated with HAART.

**Table 1: Presenting symptoms in patients with PML (N=31)**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb paresis</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Difficulty in speech</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Difficulty in walking</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>Cognitive defects</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

During the study period that is from 1st June 2007 to 31st May 2011, out of 892 HIV positive individuals, 31 patients met the criteria for the diagnosis of PML. Over all incidence was 3.5%. The median age of patient was 40 years (Interquartile range (IQR): 35-47 years); 64.5% (n=20) of the patients were male. In 77% (n=24) of patients, CD4 count at the time of diagnosis of PML was less than 200 cells/µL. The median CD4+ cell count was 73 cells/µL (IQR, 43-160 cells/µL) at presentation of PML. Those who had PML as index diagnosis had median CD4 cell count of 68/µL while those who developed PML later on had median CD4 cell count 153/µL (Figure 1). Almost one third (64.5%, n=20) patients had acquired HIV infection through heterosexual route, while 19.4% (n=6) had transmission through blood. In 5 (16.1%), the mode of HIV transmission was unknown.

In 55% (n=17) of patients PML was the index diagnosis (Presenting manifestation). Median days of duration of PML symptoms were 30 days (IQR, 15-60 days) before diagnosis of PML. The predominant neurological symptoms of PML at presentation were limb paresis (39%, n=12), speech disturbances (39%, n=12), coordination disturbance (29%, n=9), cognitive defects (23%, n=7), visual disturbance (10%, n=3) and seizure (10%, n=3) as shown in Table 1. Most common signs were limb weakness (48%, n=15), alterations of speech (39%, n=12) and lack of coordination, (45%, n=14) as shown in Table 2. On MRI examination, Supratentorial lesions were found in nearly 90% (n=28) of the patients, and infratentorial lesions were found in 52% (n=16).

After diagnosis of PML, all except two patients received antiretroviral therapy (ART). Out of 29 patients on ART, 24 (82.8%) patients were on non-nucleoside reverse transcriptase inhibitor (NNRTI) based therapy while 5 (17.2%) were on protease inhibitor
Three patients were lost to follow up. Total 15 patients died within 1 year after diagnosis of PML. Seventeen (60.7%), fifteen (53.6%) and thirteen patients (46.4%) remained alive after 3 months, 6 months and 1 year respectively. Those who survived till one year, all remained alive till censored date, 9 patients completed three years and another 3 completed two years. For those 28 patients who remained on follow up, the median survival was 538 days. We estimated the cumulative probability of survival after the diagnosis of PML using the Kaplan-Meier method. The follow up was censored at 31st December, 2011. Kaplan-Meier survival curve for the patients with a diagnosis of PML is shown in Figure 2. In those patients who developed symptoms of PML after initiation of ART, two out of these three patients shown contrast enhancing lesions in MRI. Out of these three patients, 2 survived and both had stable neurologic functions. Two patients who developed PML lesions on MRI after two years of starting ART, however plasma viral load was undetectable in both. Both patients survived, however one improved on same ART while other patient had shown progressive neurological dysfunction. In our cohort, 5 patients developed symptoms of PML after initiation of ART. Three patients were considered as Immune reconstitution inflammatory syndrome (IRIS) as they presented within 3 months of starting ART. Two out of these three patients showed contrast enhancing lesions in MRI. Out of these three patients, 2 survived and both had stable neurologic functions. Two patients who developed PML lesions on MRI after two years of starting ART, however plasma viral load was undetectable in both. Both patients survived, however one improved on same ART while other patient had shown progressive neurological dysfunction.

**Discussion**

Fifty three point six (53.6%) percent of patients with PML died despite receiving antiretroviral therapy in our study. All these patients died within one year and majority of them within 6 months. Those who remained alive after one year are all surviving till the end of study.

The most common predisposing cause for PML is Acquired immunodeficiency syndrome (AIDS) in comparison to other immunosuppressive conditions like malignancy, transplantation, autoimmune disorders, etc. The incidence of PML in HIV infected patient from developed countries has declined after the introduction of HAART. Most of the PML patients from India have been reported as case reports or case series. Recently two studies, one from North India and another from South India, reported PML as 1.2% and 2.8% respectively in their HIV cohort. In our cohort 3.5% of HIV patients developed PML. It is comparable to developed countries, where it has been reported in up to 5% of patients.

In our study, more than half (55%) of patients had PML as index diagnosis or presenting manifestation of HIV. Similar results have been documented in study from India and western countries. In remaining 45% of patients, 16% has developed PML after starting HAART and rest...
(29%) of had some other presenting disease as index diagnosis. Majority of patients had advance HIV/AIDS with CD4 count less than 200/µL (median CD4+ cell count-73 cells/µL) at the time of diagnosis of PML. Those patients who presented with PML as index diagnosis had significantly low CD4 count as compared to the remaining patients (mean CD4 count 68 v/s 153; p <0.000). Similar to other study,7 in our cohort, PML occurred in patients who presented late or as result of failure of HAART. This shows that PML as disease of advanced immunosuppression.

There are no significant differences between clinical, radiological, and pathological picture of PML between India and Western countries.12 In this study also, presenting symptoms in descending order were limb paresis, speech disturbances, coordination disturbance, cognitive defects, visual disturbance, seizure and headache. Gait abnormality, limb weakness, alterations of speech and lack of coordination were common examination findings while cranial nerve involvement and involuntary movement were found in very small number of patients. Exclusive infratentorial PML lesions were found only in 10 percent of patients while majority of patients had either supratentorial alone or both region lesions on MRI findings. Similar findings were found in European studies.7,8

In the pre-HAART era, PML patients had very poor prognosis. Most of them had fatal course and died in a median period of 4-6 months after diagnosis.1,13,14 There is no specific antiviral therapy for JC virus causing PML. The only way to improve prognosis is reversal of immunosuppression.15 The HAART is the only way for reversal of immune system in HIV infected patients and the prompt institution of it is the most effective therapeutic approach in increasing survival in this group.16 Probability of survival at one year was documented to be 50% on HAART as compared to 5% in patients not receiving HAART.17,18 Similarly significant reduction in PML-attributable one year mortality has been documented in Swiss HIV Cohort Study.3 Subsequently in one large study of 118 consecutive PML patients with HIV infection, (63.6%) remained alive for a median of 114 weeks (2.2 years) after diagnosis of PML.9 Long-term survival is now observed.10 In our study, 46.4% patients remained alive after 1 year. Amongst them, 69% patients completed 3 year till censored date. The median survival was 538 days for patients except loss to follow up. In those patients who survived more than one year, the median survival time was 1095 days (95% confidence intervals (CI), 1090.35 –1099.64 days) which was higher than that documented from North India.11 Antiretroviral therapy that especially included protease inhibitor (PI) was once shown to be reducing risk of death significantly in PML patients.15 Subsequently no advantage of PI based treatment over NNRTI based regimen has been found.19 In our study all patients got NNRTI based regimen except those who developed PML on failing first line ART.

We were not able to identify any baseline variable with prognostic significance like age, gender, duration of PML symptoms before starting HAART, PML as index diagnosis, CD4 cell count <100/µL or site of PML lesion in Brain. A western study has shown similar result except CD4 cell count <100/µL as risk factor of prognostic significance for mortality.6 However, subsequently in another study19 CD4 cell count <100 or <200/µL were not associated with mortality.

Earlier study had shown either no clinical improvement or marginal improvement that to in fewer number of patients who received HAART.20 Later on, in GESIDA 11/99 Study Group, there was improvement in neurologic status in almost 50% of survivors.6 In Recent study, there was marked improvement or stabilization of neurologic deficit (in 66 to 83%) in survivors of more than 3 years.7,16 In our study, 84% of the survivors after one year have shown either improvement or stabilization.

In our cohort, 16% (n=5) of patients developed PML after successful HAART. Three out of five patients presented within 3 months were considered as true IRIS. Amongst these, two patients had shown contrast enhancement of lesions on MRI findings. For the remaining 2 patients, we may call them late IRIS as both had undetectable virus in blood and developed PML lesion after 2 years of starting HAART. Delay in restoration of immune function may be the explanation as suggested in previous study.8 Rate of PML IRIS found to be the lowest in Swiss HIV Cohort Study (2.5%)9 while highest rate found to be 23%.17 Eighty percent of our PML IRIS patients survived as against all patients in western study.19

However, this retrospective study has some limitations. Majority of patients are diagnosed as PML by clinical and typical radiological findings. None of the patient was subjected for any histological evidence and only limited patients had been evaluated for JC virus PCR in CSF. However, there was no difference found in the prognosis of patients in both groups whether confirmed diagnosis or probable diagnosis of PML.7

In conclusion, HAART has changed the prognosis of PML with 46.4% survival at one year (median survival 1095 days), in compare to fewer months (median survival 4 to 6 months) in pre HAART era. However still there is strong need of research for the development of pharmacotherapy against JC virus to increase the survival and quality of life.

Acknowledgement

The author would like to thank
and acknowledge Dr. Hemant Tiwari, Assistant Professor (Biostatistics), Smt. NHL municipal medical college for carrying out statistical analysis.

References

Assessment of Diabetes Risk in an Adult Population Using Indian Diabetes Risk Score in an Urban Resettlement Colony of Delhi

Anita Shankar Acharya¹, Anshu Singh², Balraj Dhiman¹

Abstract

Background: Diabetes mellitus is one of the non-communicable diseases which has become a major global health problem whose prevalence is increasing worldwide and is expected to reach 4.4% by 2030. The risk of diabetes escalates with increase in the number of risk factors and their duration as well. The Indian Diabetic Risk Score (IDRS) is a simple, low cost, feasible tool for mass screening programme at the community level.

Objective: To assess the risk score of diabetes among the study subjects using IDRS.

Materials and Methods: A cross sectional survey was conducted on adults >30 years (n=580) on both gender in an urban resettlement colony of Delhi during December 2013 to March 2015. A Semi-structured interview schedule consisting of Socio-demographic characteristics, risk factor profile and Indian Diabetes Risk Score was used. Data was entered and analyzed in SPSS.

Results: Out of 580 subjects, 31 (5.3%) study subjects were not at risk of having diabetes, rest 94.5% were at moderate or high risk of diabetes. A statistically significant association of diabetes risk with marital status (p=0.0001), education (p=0.005), body mass index (p=0.049) and systolic blood pressure was seen (p=0.006).

Conclusion: More than 90% of the study subjects were at risk of having diabetes, hence screening is of utmost importance so that interventions can be initiated at an early stage.

Introduction

Diabetes is an insidious public health problem. The International Diabetes Federation (IDF) indicates that the number of people living with diabetes globally is expected to rise from 366 million in 2011 to 552 million by 2030, if no urgent action is taken. Presently, more than three-quarters of the estimated 179 million people with diabetes are in the 40-59 years age range, hence it is important to screen individuals early to increase the quality of life and delay complications.¹

India has the dubious distinction of being the diabetes capital just next to China having 62.4 million diabetics which is expected to rise to 100 million by 2030.¹ Every fifth diabetic in the world is an Indian. The problem is further compounded by the fact that 66% of Indian diabetics are not diagnosed as compared to 50% in Europe and 33% in USA.¹ The diagnosis, treatment and management of complications pose a considerable burden on individual and country as well.

The Indian Diabetes Risk Score (IDRS) is a simple, low cost, feasible tool for mass screening programme at the community level developed by V Mohan et al² and has been validated by other researchers.³⁻⁷ The IDRS has a sensitivity of 72.5% and specificity of 60.1% which takes into account two non-modifiable risk factors (age and family history of diabetes) and two modifiable risk factors (waist circumference and physical inactivity) which may be amenable to intervention and easy to measure at a very low cost. In a country like India, it can prove to be a cost effective tool for screening of diabetes at the community level.

The purpose of community-based screening for diabetes is to differentiate asymptomatic individuals who are at high risk

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of Diabetes from individuals at lower risk, so that appropriate preventive strategies can be initiated early. Ideally, screening tests should be rapid, simple, and safe. Since diabetes is an ice-berg disease, most of the subjects remain asymptomatic. Screening for diabetes can identify patients at an early stage of the disease, and identify those who will derive benefit from prevention and early treatment methods. Very limited studies on diabetes screening have been conducted in resettlement colonies in India. Hence this study was planned to screen the adult population above 30 years in an urban resettlement colony of Delhi.

**Objectives**

1. To assess diabetes risk in the study subjects using Indian diabetes risk score (IDRS).
2. To study the association of Diabetes risk with other risk factors

**Material and Methods**

The present community based cross-sectional study was conducted in an urban resettlement colony of East Delhi to assess the risk of diabetes in an adult population (>30 years) during January 2014 to December 2014. Both government and private health care agencies cater to the health care needs of the residents. There are 11 blocks in the urban resettlement colony. Out of these, 5 blocks were selected using simple random sampling. Proportionate numbers of houses were identified using Population proportional to size sampling in each block. Systematic random sampling was used to recruit individuals from each block. The sample size was calculated using the formula: N = 4pq/d², where p= 23% (prevalence of obesity as a risk factor of T2DM as conducted in similar type of study), q= (1-p) and permissible error=20% of p. Hence with design effect of 1.5 the sample size was 577.

Permanent residents of the resettlement colony (residing >1 year) were included as per inclusion criteria and 586 subjects gave consent to participate in the study. Six subjects were excluded as they were pregnant. Thereby, the final sample size was 580.

Information regarding diabetes was obtained from study subjects using a Semi-structured interview schedule consisting of;

a. **Socio-demographic characteristics:** age, gender, marital status, education, occupation, religion, family type and total family income. Socio economic status was calculated by modified Kuppuswamy scale.

b. **Risk factor profile:** A detailed interview was taken to assess the various life style related risk factors for Diabetes. Physical activity was assessed using GPAQ (Global Physical Activity Questionnaire) by WHO Dietary assessment: information regarding intake of fruits and vegetables and fats/oil intake was enquired. Addiction habits regarding smoking, alcohol, substance use were asked. Stress was assessed using General Health Questionnaire 12 (GHQ 12).

c. **Anthropometry:** The waist circumference was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, using a stretch-resistant tape that provides a constant 100 g tension. Digital weighing scale was used to measure weight. The weighing scale was adjusted to 0.0 and the study subject was asked to remove his/her footwear and stand in the middle of the scale with feet slightly apart, hands at sides, and ahead looking straight. Participants were weighed with minimal clothing and weight was noted down. Standing height was measured using a portable stadiometer with a fixed vertical backboard and an adjustable head piece. The study subject was told to stand up straight with the body weight evenly distributed and both feet flat on the platform and look straight. The height was recorded. The weight and height were then used to calculate body mass index (BMI).

d. **Indian Diabetes Risk Score (IDRS)** (Table 1): This includes four parameters: age, waist circumference, physical activity and family history. Each parameter has assigned score ranging from 0 to 60 and accordingly the subject was graded as having No risk, High risk or Moderate risk.

**Data Analysis**

Data was entered and analyzed in SPSS version 12. Continuous data was expressed as mean, median, standard deviation, and 95% CI was used. The categorical data was expressed as percentage/proportions and where ever applicable χ² test was used. P value < 0.05 was considered to be statistically significant.

**Ethical Issues**

**Approval** was taken from Institutional Ethical Committee. A written consent was taken from each study subject. Those who were illiterate, thumb impression were taken in front of a witness. All information collected was kept confidential. All the study subjects who had a diabetic risk score >30 (moderate and high risk) were referred to a secondary level/tertiary level hospital for getting their blood sugar levels checked and further workup.

**Results**

The present study was conducted in an urban resettlement colony of Delhi. A total of 580 study subjects were recruited. Out of the total 580 subjects 53.96% were women and 46.03% were men and nearly
three-fourths of the study subjects belonged to 30-49 age group. The overall mean age was 43.38 (±11.26) years with range: 30-75 years.

Figure 1 shows the distribution of study subjects according to IDRS score, only 31 (5.3%) study subjects were not at risk of having diabetes, rest 549 (94.5%) were at moderate or high risk of diabetes.

There was a statistically significant association of diabetes risk with marital status (p=0.00). Widowed were at higher risk of Diabetes. Poor educational status was also statistically significant as seen in table 2. Unemployed/homemakers/Unskilled workers were at higher risk (78.8%), although it was not found to be statistically significant (p=0.98). As socio economic status improved, the risk of having a high diabetes score was also found to increase though it was not found to be statistically significant (p=0.81).

Table 3 shows that there was a statistically significant association of diabetes risk with BMI and Systolic Blood Pressure. In the Overweight and Obese group the risk of having diabetes is increasing as BMI is increasing. Same as with Diastolic Blood Pressure where nearly 6.7 % subjects having (DBP >90 mmHg) were in the high risk category, though it was not found to be statistically significant (p=0.63). Inadequate consumption of fruits and vegetables was not found to be
BMI (kg / m²)

Discussion

smoking, tobacco and alcohol use. and behavioural risk factors like diabetes risk and stress (p=0.32) significant association between Similarly, there was no statistically with the risk of diabetes (p=0.49). statistically significantly associated with the risk of diabetes (p=0.49). Similarly, there was no statistically significant association between diabetes risk and stress (p=0.32) and behavioural risk factors like smoking, tobacco and alcohol use.

Table 3: Association of Diabetes Risk (IDRS) with BMI and blood pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No risk N=31</th>
<th>Moderate risk N=251</th>
<th>High risk N=298</th>
<th>χ²</th>
<th>df, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg / m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>0(0.0)</td>
<td>02(0.7)</td>
<td>02(0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (18.5-24.9)</td>
<td>27(87.0)</td>
<td>210(83.6)</td>
<td>231(77.7)</td>
<td>3.88</td>
<td>1</td>
</tr>
<tr>
<td>Overweight (25-29.9)</td>
<td>03(9.6)</td>
<td>29(11.5)</td>
<td>44(14.8)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Obese (&gt;30)</td>
<td>01(3.2)</td>
<td>10(3.9)</td>
<td>20(6.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120</td>
<td>19(61.3)</td>
<td>138(54.7)</td>
<td>177(59.4)</td>
<td>14.46</td>
<td></td>
</tr>
<tr>
<td>120-139</td>
<td>11(35.4)</td>
<td>105(41.8)</td>
<td>92(30.8)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>140-159</td>
<td>1(3.2)</td>
<td>8(3.1)</td>
<td>29(9.7)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>21(67.7)</td>
<td>152(60.5)</td>
<td>176(59.0)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>80-89</td>
<td>10(32.3)</td>
<td>90(35.8)</td>
<td>102(34.2)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>90-99</td>
<td>0(0.0)</td>
<td>7(2.7)</td>
<td>17(5.7)</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>≥100</td>
<td>0(0.0)</td>
<td>2(0.8)</td>
<td>3(1.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Association of Diabetes Risk (IDRS) with behavioural risk factors

<table>
<thead>
<tr>
<th>Behavioural risk factors</th>
<th>No risk N=31 Number (%)</th>
<th>Moderate risk N=251 Number (%)</th>
<th>High risk N=298 Number (%)</th>
<th>χ²</th>
<th>df, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>2(6.4)</td>
<td>29(11.6)</td>
<td>35(11.7)</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>03(9.6)</td>
<td>31(12.3)</td>
<td>38(12.7)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>26(83.8)</td>
<td>191(78.9)</td>
<td>225(75.5)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Smokeless tobacco</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-tobacco chewer</td>
<td>2(6.4)</td>
<td>10(3.9)</td>
<td>08(2.7)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Current tobacco chewer</td>
<td>02(6.4)</td>
<td>23(9.1)</td>
<td>29(9.7)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Non-tobacco chewer</td>
<td>27(87.1)</td>
<td>218(86.8)</td>
<td>261(87.5)</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use of alcohol</td>
<td>01(3.2)</td>
<td>17(6.7)</td>
<td>15(5.0)</td>
<td>.78</td>
<td></td>
</tr>
<tr>
<td>Past use of alcohol</td>
<td>0(0.0)</td>
<td>12(4.7)</td>
<td>26(8.7)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Non-alcoholic</td>
<td>30(96.8)</td>
<td>222(88.4)</td>
<td>257(86.2)</td>
<td>0.68</td>
<td></td>
</tr>
</tbody>
</table>

This difference may be due to the study area being rural where less proportion of study subjects had high risk.

IDRS comprises of four risk factors viz. age, family history of diabetes, physical activity and waist circumference. We studied the association of socio-demographic characteristics, BMI, Blood pressure, dietary and other factors with IDRS in the study subjects. In our study, both men and women had higher risk of diabetes, and there was no statistically significant difference among gender. These findings were similar to that of Levitt. However, some researchers found difference in gender. The majority of study subjects were Hindus. There was no significant association between diabetes risk and religion which suggest that diabetes risk is similar across all religions. Though home makers, unemployed or unskilled workers were at higher risk (78.8%), but there was no significant association between diabetes risk and occupation. Similar results were found by other authors suggesting that occupation has no role in developing diabetes risk.

In our study it was seen that as socio-economic status increased, the risk of having diabetes also increased. However it was not found to be statistically significant.

The Indian diabetes risk score developed by Mohan V et al is a simple, fast, inexpensive, non-invasive, and reliable tool to identify individuals at high risk of type 2 diabetes which has been previously validated by other researchers in India.

In this study screening for diabetes was conducted for 580 subjects >30 years in the community. Out of these only 31(5.3%) were in low risk category, 251 (43.2%) were in moderate risk category and more than half 298 (51.3%) were in high risk group as per the IDRS. These observations made in our study were very close to that made by other authors. This shows that a large number (moderate and high risk) of the study subjects had some kind of risk of developing diabetes in future. This is the group where active interventions in the form of health education, counselling and further work up is urgently required. The earlier the interventions are started the later will be the onset of disease and its subsequent complications.

However, in a study done by Gupta showed low risk category had a higher number of individuals.
There was no statistically significant association with consumption of fruits and vegetables with diabetes risk. It was in agreement with the findings by Agrawal. Major (69.8%) of the study subjects were taking inadequate fruits and vegetables (<5 times/day) which was almost similar for both men and women. The reported fat and oil consumption was less in the community as nearly 92% were taking <25 gm per day. The probable reason could be not taking into account the food consumed by the study subjects outside home specially the fried and junk food.

In the present study, there was no statistically significant association between diabetes risk and smoking. The findings were in agreement with the studies done in Puducherry, a nationwide cross-sectional survey and Bruneck study but differs from studies done in southern India where significant association was seen between smoking and diabetes.

There was no statistically significant association between tobacco intake and IDRS in our study which corroborate with findings of Bharath et al. However, tobacco use showed a statistically significant association with diabetes (p<0.00) in studies done by Valliyot B, Shrivastava, Ram S, Frank BH, and Muninarayana. In the overweight and obese group, the risk of diabetes is increasing as BMI increases being 14.8% of overweight and 6.7% of obese as high risk. There was statistically significant association of Diabetes risk with BMI (p=0.04). Many studies have showed quite identical results. As the BMI increases the risk of diabetes is found to increase. Few studies of Tamil Nadu and Kerela did not find any association of Diabetes risk with BMI. As BMI has been found to be an important predictor of risk, more emphasis needs to be given to increase the physical activity. Also, Waist circumference which is an important risk factor can be reduced both by dietary restrictions and increasing physical activity.

Majority, 89.4% of the study subjects had SBP of less than 140 mm Hg. Out of the 38 study subjects who had SBP of >140, majority 29 (9.7%) were in the high risk category which was highly statistically significant (p=0.00). Various studies including that of Ravikumar PS Valliyot B, Pan XR, Shrivastava reported similar findings. It was also seen that as the DBP increases the risk of having diabetes also increases, but it was not found to be statistically significant. Hence for reducing blood pressure, physical activity needs to be increased which would subsequently lower Diabetes risk.

Conclusion

The study used simplified Indian Diabetes Risk Score for assessing diabetic risk in an adult population. Mass screening can be done by using IDRS in developing country like India that is cost effective also. IDRS score involves collection of data for two non-modifiable risk factors such as age and family history of diabetes and two modifiable risk factors such as physical activity and waist circumference. Screening and early identification of high risk individuals would help to take appropriate intervention like lifestyle modification. It would also help in early diagnosis and treatment to prevent or to delay the onset of diabetes mellitus and its complications.

References

14. Pan XR, Yang W, Wei Li G. Prevalence of diabetes...


Oration – 2018

Recommendations are invited from members for the following assignment so as to reach, Hon. General Secretary – API, Dr. Mangesh Tiwaskar by 25th March 2017.

Category No. (iii): All lectureships viz

1. Sanofi Aventis Lectureship in Diabetes – 2018

The selected candidate has to deliver his/her lecture at the Annual Conference of API - 2018. The above lectureship will get the award money of Rs. 10000/- (Rupees ten thousand only) and TA by Economy Class airfare from API, Complimentary Registration and complimentary stay of one night in the designated conference hotel by the APICON Organizing Committee.

Persons are selected from the recommendations received from members of the API. The orator in the discipline of medicine should preferably be a member of API. The recommendations for the above assignments must be accompanied with reasons for recommending a particular person showing the value of his/her research and eight copies each of three of his/her best publications. All relevant papers in connection with the suggestions, such as the bio-data, list of publications etc., should be submitted in 8 sets by the proposer. The recipient of the above oration should deliver a lecture pertaining to his/her work at the Annual Conference in January, 2018.

For the above lectureship is open to eminent persons from the discipline of medicine and allied subjects such as Pharmacology, Biochemistry, Pathology and Physiology. All relevant papers in connection with the suggestions, such as the bio-data, list of publications etc., should be submitted in 8 sets by the proposer.

Those who have received Oration / Lectureship in a given category are eligible for application for the other two categories.

The members of the Governing Body of API and the Members of the Faculty Council of ICP are not eligible to receive any Oration, Lectureship or Award.

The prescribed nomination form for the above orations / Lectureship are on the API website “www.apiindia.org”

The completed application forms for the above Lectureship should reach to Dr. Mangesh Tiwaskar, Hon. General Secretary of API, Unit No. 6 & 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E. Moses Road, Near Mahalaxmi Station West, Mumbai – 400 011 not later than 25th March 2017. Tel. No. 022 66663224; 24912218 • Fax 24920263 • e-mail: api.hdo@gmail.com

Dr. Mangesh Tiwaskar
Hon. General Secretary
Efficacy of C.E.R.A. in Routine Clinical Practice for Correction of Anaemia and Maintenance of the Haemoglobin Levels in CKD Patients not on Dialysis

PJ Promod 1, R Deshpande 2, NK Mohanty 3, S Kulkarni 4, HA Shah, A Ganju 6, A Kukreja 7, S Joshi 7

Abstract
Introduction: C.E.R.A. reported effective correction of anaemia and was well tolerated in International studies on CKD patients not on dialysis.

Objective: The study aimed to describe the management of renal anaemia in CKD patients not on dialysis with C.E.R.A. in routine clinical practice in India.

Methods: This was a prospective, single-arm, open-label, multi-centre, non-interventional, Phase IV study which followed 108 CKD Stage III-IV patients, not on dialysis with Hb < 10 g/dL for correction of anaemia with C.E.R.A.

Results: Of the 108 patients with Hb < 10 g/dL at baseline, 83 (90.2%) patients achieved target Hb of 10-12 g/dL and the time taken to achieve correction of anaemia was 9.6 weeks ± 6.13 weeks in the Intent-to-treat population. Haemoglobin concentration increased from 8.59 ± 0.808 g/dL pre-therapy to 10.91 ± 0.634 g/dL post-therapy. The change in mean ± SD Hb value was 2.32 ± 0.174 g/dL. Maintenance of Hb levels within the target range of Hb 10 - 12 g/dL was observed in 78.2% of ITT and 80.8% of the PP population for mean duration of 16.69 weeks. Four patients (3.7%) experienced 5 AEs and 2 patients (1.9%) experienced 3 SAEs in the safety population. As per the treating physician none of the AEs or SAEs was considered related to study drug. There were no deaths reported.

Conclusions: This study demonstrated successful correction of anaemia in Indian patients with C.E.R.A. treatment as well as maintenance of Hb levels within the target range. C.E.R.A. was well tolerated with no new safety concerns specific to the Indian population. The less frequent up to monthly dosing schedule of C.E.R.A. may offer clinicians and patients a simplified regimen of anaemia management as compared to traditional frequently administered (thrice weekly to once weekly) ESAs.

Introduction

Anaemia is a common complication of chronic renal disease (CKD) that results primarily from inadequate erythropoietin production by damaged kidney. 1 Anaemia may develop in these patients early in the course of CKD and is often poorly controlled initially 1-3 It is associated with an increased risk of morbidity, mortality, hospitalisation and diminished physical wellbeing, quality of life. 5-7 The use of erythropoiesis-stimulating agents (ESAs) for management of renal anaemia relieves the symptoms of anaemia and is associated with improvements in quality of life. 8 It also has potential to slow the progression of renal dysfunction. 9 However, less than third of patients with CKD who have anaemia...
receive ESA treatment before they progress to end-stage renal disease (ESRD).

Anaemia management has improved with the introduction of clinical practice guidelines, nevertheless many patients fail to achieve target Hb levels and > 90% of those who do achieve target are unable to maintain stable Hb levels. Hb cycling is observed in > 90% of patients receiving epoetin and generally occurs three to four times a year.

Maintaining Hb levels within target ranges requires close monitoring of Hb and often requires frequent dosage adjustment. Hence, agents that provide predictable and stable Hb responses with minimal intervention from health care professionals have been gaining favour as the treatment option.

Methoxy poly-ethylene glycol epoetin beta (C.E.R.A.), a continuous erythropoietin receptor activator, is approved for the management of renal anaemia in CKD patients. C.E.R.A has been evaluated for the treatment of patients with CKD-related anaemia in numerous Phase II studies and Phase III studies. The Phase II studies were designed to establish dose and tolerability of C.E.R.A. The Phase III studies focused on the efficacy, safety, and tolerability of C.E.R.A. as compared to other ESAs.

The purpose of this Phase IV, non-interventional study was to describe the management of renal anaemia in CKD patients not on dialysis in routine clinical practice in India.

Subjects and Methods

Subjects

Adult dialysis patients between 18–65 years of age (both inclusive), with chronic renal anaemia not on dialysis and receiving therapy with C.E.R.A according to the routine clinical practice and/or in line with local labelling, were followed for the treatment duration of 6 months. Patients with Hb < 10 g/dL were followed for correction of anaemia. Patients with Hb 10-12 g/dL and receiving any other ESA were to be followed for maintenance of Hb. Adequate iron status was judged by the treating physician as in routine clinical practice.

Patients who were not eligible for being prescribed C.E.R.A as per updated local prescribing information or were not prescribed C.E.R.A by the treating physician were not observed as part of the study population.

Study Design

This prospective, single-arm, open-label, multi-centre, non-interventional, Phase IV study was conducted at six centres across India. Data was collected from patients who provided voluntary written informed consent and received intravenous or subcutaneous C.E.R.A. (Methoxy poly-ethylene glycol epoetin beta [MIRCERA®; F-Hoffman-LaRoche Ltd. Basel Switzerland]) in accordance with local clinical practice or prescribing information. The conduct of the study did not influence the treatment procedure of individual patients, and had no influence on medical decisions and procedures. The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, Good Pharmacoepidemiology Practices Guidelines, and local ethics committees.

Data Collection Overview

The patients’ medical history and demographics were recorded at screening. Clinical examination, blood pressure, heart rate, and Hb assessment were done at pretherapy and at every visit at week 0, 2, 4, 8, 12, 16, and 24. Concomitant medicines and adverse events (AEs) and serious adverse events (SAEs) were recorded at every visit post therapy. Iron parameters and haematological profile including laboratory assessments were performed in accordance with routine clinical practice and when performed during the data collection period, available results were documented in the case report form (CRF).

Efficacy and Safety Evaluation

Management of renal anaemia with C.E.R.A was assessed by determining the correction of anaemia and maintenance of Hb levels. Correction of anaemia was evaluated in patients with Hb < 10 g/dL at enrolment and determined by the percentage of these patients achieving and the time required to achieve target Hb range (10-12 g/dL). Maintenance of target Hb was evaluated by the mean time spent in target Hb range.

Route of administration of C.E.R.A, dose per injection, concomitant treatment for anaemia like iron and incidence of AEs during the study were also recorded and evaluated.

Statistical Analysis

All tables and listings were generated in Statistical Analysis Software (SAS®) Version 9.2. Demographics and baseline characteristics were summarised using descriptive statistics. Co-morbidities were summarised using counts and percentage. Summary tables (descriptive statistics and/or frequency tables) were provided for all baseline variables, efficacy variables, and safety variables, as appropriate.

Time to achieve target range was presented using descriptive statistics (n, mean, SD, median, range and 95% confidence interval for proportions calculated by exact method). Mean change in Hb concentration from baseline was described using descriptive statistics (n, mean, SD, median, range) and significance for subsequent visits was assessed using paired t-test at 5% level of significance.

Safety was assessed by summarising frequencies and relative frequencies of adverse events
Patient Characteristics

The study was carried out at six centres across India between August 2011 and November 2013. A total of 108 CKD Stage III-IV patients, not on dialysis were screened and enrolled for this study. Efficacy analysis was conducted on the intent-to-treat (ITT) and per protocol (PP) population. The ITT population consisted of 92 patients who received at least 1 dose of C.E.R.A. (Week 0) and had recorded at least one follow-up variable. The per protocol (PP) population included 89 patients who had at least 3 recorded Hb values and safety. The safety population comprised of all 108 patients (Figure 1).

The study population comprised of 72 males and 36 females with the mean age of $55.5 \pm 7.178$ years, the mean height of $163.15 \pm 7.366$ cm and mean weight of $60.23 \pm 9.618$ kg (Table 1).

Efficacy

All the enrolled patients had Hb < 10 g/dL at baseline and were considered for correction of anaemia. A total of 83 patients (90.2% in ITT and 93.2% in PP population) achieved target Hb of 10-12 g/dL during the study. The mean time taken to achieve the target range for correction of anaemia was $9.6 \pm 6.1$ weeks in both the ITT and PP populations (Table 2).

A statistically significant increase in Hb concentration from pre-therapy to Visit 2 onwards (Visit 2-7: $p < 0.001$) was observed during the study. The mean Hb concentration increased from $8.59 \pm 0.808$ g/dL pre-therapy to $10.91 \pm 0.634$ g/dL post-therapy at Visit 7 and the mean change in Hb concentration was $2.32 \pm 0.174$ g/dL from pre-therapy to Visit 7 in the ITT population (Table 4 and Figure 2).

Similarly in the PP population, the mean change in Hb was $2.28 \pm 0.029$ g/dL from pre-therapy to Visit 7.

None of the patients enrolled the study had pre-therapy Hb
Table 4: Summary of change in haemoglobin concentration at every visit (ITT population)

<table>
<thead>
<tr>
<th>Haemoglobin (g/dL) /Visit</th>
<th>Result</th>
<th>Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Therapy</td>
<td>92</td>
<td>-37</td>
<td>0.0120</td>
</tr>
<tr>
<td>n</td>
<td>55</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.42 (0.958)</td>
<td>-0.17 (0.150)</td>
<td></td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>8.60 (4.2,9.7)</td>
<td>-0.20 (0,0.0)</td>
<td></td>
</tr>
<tr>
<td>Visit 1</td>
<td>83</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>n</td>
<td>88</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9.58 (0.973)</td>
<td>0.99 (0.165)</td>
<td></td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>9.80 (7.0,13.1)</td>
<td>1.00 (2.8,3.4)</td>
<td></td>
</tr>
<tr>
<td>Visit 4</td>
<td>88</td>
<td>-4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>n</td>
<td>88</td>
<td>-4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.25 (0.969)</td>
<td>1.65 (0.161)</td>
<td></td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>10.40 (6.9,12.8)</td>
<td>1.60 (2.7,3.1)</td>
<td></td>
</tr>
<tr>
<td>Visit 5</td>
<td>85</td>
<td>-7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>n</td>
<td>82</td>
<td>-10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.91 (0.634)</td>
<td>2.32 (-0.174)</td>
<td></td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>11.00 (7.6,12.1)</td>
<td>2.20 (3.4,2.4)</td>
<td></td>
</tr>
</tbody>
</table>

Note: p-values are for comparing baseline characteristics of treatment and paired t test was applied for continuous variables; Change from baseline = visit x pre-therapy.

Fig. 2: Mean change in Haemoglobin concentration across visits on treatment with C.E.R.A.

Concentration of 10 g/dL or above and prior ESA therapy. Therefore, the maintenance of Hb levels in conversion patients with prior ESA therapy was not evaluated. Maintenance of Hb levels after achievement of target Hb was evaluated. In both the ITT and PP populations, 72 patients (78.2% in ITT and 80.8% in PP) were able to maintain Hb levels within the target range of 10-12 g/dL during the study and the mean (SD) duration of time spent in the target range was 16.69 ± 4.124 weeks (Table 3).

Safety

Total 572 doses of mean dose of 75.5 ± 26.79 mcg C.E.R.A were administered through subcutaneous route in all the patients. In the study population, 74.3% of the patients received a monthly dose and 25.7% received fortnightly dose of C.E.R.A.

Overall, 4 patients (3.7%) experienced 5 AEs during the study of which two patients (1.9%) experienced mild AEs; 1 patient (0.9%) each experienced moderate and severe AE. All the AEs were considered not related to the study drug.

Two patients (1.9%) experienced 3 SAEs during the study. These included pancreatitis, device related infection, and urinary tract infection. All the SAEs were considered not related to the study drug. One patient (0.9%) tested positive for HIV and was discontinued from the study. There was no death reported in the study population during the study.

Statistically significant increase was noted in Mean Corpuscular Hb Concentration (MCHC) at Visits 5 (p = 0.0079) and 7 (p = 0.0040). The occurrence of clinically significant abnormal values for RBC was found to be decreased (in 21.3% of patients at pre-therapy, in 8.3% of patients at Visit 5, and in 2.8% of patients at Visit 7).

There was no statistically significant change in serum iron, serum transferrin, BUN, serum creatinine and urea. The incidence of clinically significant abnormal values was 0.9% for serum ferritin, serum iron, and TSAT at Visit 5.

Eighty five patients had a history of diabetes and at Visit 7, statistically
significant decrease was observed in post-prandial blood sugar levels (PPBSL) (p = 0.0312) and HbA1c (p = 0.0301) with no significant change in Fasting Blood Sugar Levels (FBSL) and Random Blood Sugar (RBS) in these patients. The occurrence of clinically significant abnormal values for FBSSL, glycated haemoglobin (HbA1c) and PPBSL decreased from pre-therapy to Visit 7 (FBSSL: 8.3% of patients at pre-therapy to 2.8% of patients at Visit 7; HbA1c: 7.4% of patients at pre-therapy to 2.8% of patients at Visit 7; and PPBSL: 11.1% of patients at pre-therapy to 2.8% of patients at Visit 7). There were no clinically significant abnormal values observed for RBS at pre-therapy and Visit 7.

There were no statistically significant changes reported in vital signs, physical examination or hepatic profile parameters from pre-therapy to Visit 7. Therefore, in routine clinical setting treatment with C.E.R.A showed a favourable safety profile.

Discussion

This non-interventional study conducted in Vellore, Mumbai, Bhubaneswar, Vadodara, and Hyderabad in India aimed to describe the management of renal anaemia in CKD patients in stage III-IV, not on dialysis with C.E.R.A. in routine clinical practice.

The demographic and baseline characteristics of the enrolled patients were consistent with the general non-dialysis CKD population in India with vascular disorders in 83.3% of the patients as the most prevalent in recorded medical history.

A total of 90.2% of the subjects in the ITT and 93.2% in the PP population achieved target Hb of 10-12 g/dL and the mean time taken by the patients to achieve the target range for correction of anaemia by treatment with C.E.R.A was 9.6 weeks. This was comparable to that observed in the large-scale ARCTOS study in which the response rate in ESA-naïve patients was 97.5% and the median time to response was 43 days or about 6 weeks. The response rate in the ARCTOS study was defined as an increase of ≥ 1 g/dL from baseline and a concentration of ≥ 11 g/dL on treatment with C.E.R.A at every 2 weeks.

The mean change in Hb concentration over 24 weeks was 2.32 (0.174) g/dL in the ITT and 2.28 (0.029) g/dL in the PP population in our study. This was also in line with the ARCTOS study in which the mean change was 2.15 g/dL for a period of 10 weeks.

In this non-interventional study designed to evaluate routine clinical practice, none of the enrolled patients had pre-therapy Hb level of 10 g/dL or above or had received treatment with other ESAs. Therefore conversion to C.E.R.A in these Indian patients could not be assessed.

In routine clinical practice a steady level of Hb concentration was successfully maintained for mean duration of 16.69 weeks. Maintenance of Hb levels within the target range of Hb 10 - 12 g/dL was observed in 78.2% of ITT and 80.8% of the PP population. This implied successful correction of anaemia in Indian patients with C.E.R.A treatment as well as maintenance of Hb levels within the target range.

Incidence of adverse events was 3.7% majority of which were mild in intensity. None of the AEs were considered related to the study drug. Incidence of SAEs was 1.9%. These included pancreatitis, device related infection, and urinary tract infection. All the SAEs were considered not related to the study drug. One patient (0.9%) tested positive for HIV and was discontinued from the study. There were no deaths reported during this study. There were no clinically significant excursions in terms of vital signs, physical examination, or laboratory parameters.

In conclusion, subcutaneous fortnightly or monthly dosing with C.E.R.A corrected anaemia in CKD Stage III-IV patients, not on dialysis, in routine clinical practice in India. This study also showed that C.E.R.A. was well tolerated in Indian patients with no additional safety concerns specific to the Indian population at this dosage regimen. This less frequent dosing was successful in a significant increase in Hb levels and may offer clinicians and patients a simplified and convenient regimen (monthly or fortnightly) of anaemia management as compared to conventional frequently administered (thrice weekly to once weekly) ESAs.

Acknowledgments

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Conflict of interest

Dr. Anil Kukreja and Dr. Sachin Joshi are full time employees of RPIPL.

References


Pharmacovigilance is the art and science of detection, understanding and prevention of adverse drug reactions and not merely a critical analysis of prescriptions and errors. This field starts with reporting by clinicians of a suspected adverse drug reaction (ADR) to the pharmacologist followed by joint causality analysis and ends at the application of new information by a clinician for benefit of patients. There are a number of ways, which can be utilised for reporting adverse effects using pen and paper format to software applications for smart phones. Varied types of activities spreading from systematic reviews to the mechanistic evaluation of ADR can be performed under the umbrella of pharmacovigilance. It is of utmost importance for clinicians to understand how to identify, communicate and understand adverse effects of drugs with an aim to prevent harm to patients.

Pharmacovigilance is defined as the art and science of detection, assessment, understanding and prevention of adverse drug reactions or any other drug related problem. It is one of the least understood and lesser practised dimensions of medicine. A number of recent changes in regulations with regard to drugs (e.g. pioglitazone) and fixed-dose combinations (FDCs) have highlighted the role of this field in practice of medicine.

Pharmacovigilance aims at improving patient safety, by generating drug safety data from clinicians using them in diverse subsets of patients. The chronic use of medicines in such a heterogeneous patient population shows many adverse effects, which require analysis. The reporting of all these adverse effects by practising clinicians and their analysis by a team of clinicians and pharmacologists help in understanding the various aspects of drug safety. Communication of safety signals among clinicians modifies prescribing patterns and improves patient safety. Thus, pharmacovigilance begins with clinicians, with reporting of Adverse Drug Reactions (ADR), and ends at clinicians who use the data for improving patient safety.

Pharmacovigilance can be practised by spontaneous reporting of ADR, writing a narrative or systematic reviews on drug safety, undertaking research into mechanisms of ADR and conducting clinical trials for safety analysis.

Office of Central Drug Safety and Control Organisation (CDSCO) periodically publishes specific drug related adverse reactions to be noted. All physicians should remain vigilant about safety alerts from the national organisation.

Causality assessment of ADR establishes a relationship between suspected finding and drug use. This process is never complete without inputs and assessment by a practising physician. Scoring scales are used to assign causality category to the suspected finding. Practising physicians are expected to
Pharmacovigilance and its principles hold an important place in contemporary clinical practice. This subject improves patient safety, generates evidence refuting the use of a drug of interest or use a drug with precautions, and thus contributes to clinical therapeutics. The Indian College of Physicians supports the integration of pharmacovigilance in daily clinical practice and medical research. This position statement encourages physicians to remain pharmacovigilant and facilitates this practice.

Preamble

Pharmacovigilance has traditionally been considered as the practice of monitoring prescriptions for adverse effects of drugs and medication errors. Though it is considered by some clinicians to be critical of their activities and capabilities, the program is intended at improving patient safety and treatment outcomes while improving the level of trust between physician and patient.

Pharmacovigilance is a relatively new dimension of medicine which focuses on the use of epidemiological and research techniques to understand and prevent adverse effects of drugs. This dimension was not part of teaching curriculum of medical sciences a few years back. Recently due to many drug withdrawals from the market and growing concerns regarding patient safety among the general public and drug regulators, the interest in this field has gone up.

World Health Organisation defines Pharmacovigilance as “the art and science of detection, assessment, understanding and prevention of adverse drug reactions or any other drug related problem.” This definition describes the scope of this activity which extends from detection and reporting of ADR and to data analysis to information sharing with health care providers for prevention of adverse outcomes related to drug use. It encompasses the whole gamut of activities surrounding the safety aspects of drug use.

The increase in chronic morbidity has meant an increase in drug use. There has been an increase in a number of drugs, fixed-dose combinations and polypharmacy. Hence Indian College of Physicians has brought out this multidisciplinary position statement on Pharmacovigilance.

Scope of Pharmacovigilance

As discussed above, a variety of activities can be taken up under the umbrella of pharmacovigilance. The profile of activities routinely done are detection and reporting of ADR, data entry in software (VIGIFLOW), data analysis at the local, national and global level, signal generation and communication of newly detected adverse outcomes to health care providers through various channels. The profile of activities begins with clinicians/health care providers and concludes with them receiving new information intended to improve patient outcomes. This process involves the use of a number of epidemiological and research tools and mass communication skills. Pharmacovigilance is a self-sustaining process which starts with clinicians and ends at clinicians.

Practicing Pharmacovigilance

The practice of pharmacovigilance and allied activities by clinicians is an area which suffers from a lack of clarity and vision. We propose a simple operational framework to enhance understanding. Any action aimed at individual or epidemiological for improving patient safety, whether associated with the use of drugs or devices, detection or communication is the practice of pharmacovigilance. Practising physicians are concerned about patient safety but are dependent on the interpretation of facts taught during the teaching of the medical curriculum. Pharmacovigilance helps them internalise these facts and utilise them in daily practice.

1. Spontaneous Reporting: Understanding epidemiology of adverse drug reactions begins by identification of ADR. Reporting ADR to nearest ADR Monitoring Centre or by calling up the telephonic helpline of Pharmacovigilance Program of India (PvPI) at toll-free number 1800-180-3024 is the next step in the process. Filling up of ADR reporting form can be done by staff trained in
reporting of ADR or by Patient Safety-Pharmacovigilance Associates (PSPvAs). Indian Pharmacopeia Commission, the organisation responsible for running and managing Pharmacovigilance Program of India has recently launched an application for smartphones dedicated to reporting of ADR by clinicians.²

Maintaining Registries: Maintaining a registry of subgroups of patients according to diagnosis e.g. hypertension or therapeutic areas e.g. biologicals or any other sub-group can be of help in identification of drug-related problems e.g. hypersensitivity and other immunological reactions to biological agents. The first indication regarding the probable association of use of pioglitazone with bladder carcinoma came from analysis of data from a registry of type 2 diabetic patients. This is easily possible with the use of computers with software for the patient management system.

2. Narrative or Systematic Reviews: Academically oriented clinicians can work on safety aspects of therapy by writing a narrative or systematic reviews or conducting a meta-analysis. This is routinely practised in the developed world and has contributed to a great deal in drug withdrawals. Special training in statistics is required for such kind of work and activities. Drug regulators across the globe depend on such work for their decisions on labelling and availability of the drug in the market.

3. Original Mechanistic Research: Mechanistic modulation of ADR either at the level of the individual or molecular level is also the practice of pharmacovigilance. The gamut of activities does not stop at reporting and generating signals only. It goes on until a solution to drug-related problem is found. Mechanistic evaluation can be done by pharmacological manipulation of ADR like in the case of use of proton pump inhibitors (PPIs) with non-steroidal anti-inflammatory drugs like ibuprofen for prevention of gastric symptoms. Additional investigations are required to understand the pathophysiology of ADR. Such studies are usually possible in academic institutes which have required infrastructure for molecular level research.

4. Original Clinical Research: Clinical trials conducted for comparing the safety of two drugs or for evaluation of proposed new solutions also fall under this category. Any such activity will require a lot of time of practising physician and resources dedicated to trial related activity. Additionally, with increasingly complicated and aggressive regulatory environment for clinical trials, this may not be feasible in many small clinics or nursing homes. However, in academic institutions, all these activities can be conducted with vigour. A number of other activities that can be easily undertaken by community health specialists for communicating the adverse effect of drugs and curbing self-medication based on the distorted and incomplete information.

Drugs of Interest for Safety Related Issues

Pharmacovigilance Program of India has released the list of drugs and specific ADR which are being monitored aggressively and has urged all clinicians to remain vigilant about them.³ The list is given in Table 1.

It must be noted that actions of these drugs and adverse effects span the entire spectrum of internal medicine and no system is immune.

Causality Assessment and Role of Clinicians

Assessment of causal association between a suspected event and drug use is a scientific process requiring medical and pharmacological input to rule out the possibility of the event being a manifestation of underlying pathology and manifestation of the disease process. Standard scales are available which assign a category (Definite, probable, possible, unlikely etc.) to the probability of an event being due to drug use and not due to other causes. A classic situation where causality assessment can play an important role is in cases suffering from drug fever where pyrexia can be either because of drug use or infectious in origin.

This kind of work requires intensive inputs from clinicians and is a team work before any change in labelling is proposed. The most recent example of such an activity leading to regulatory U-turn in India is the use of pioglitazone for the management of type 2 diabetes mellitus.⁴

It is expected that practising clinicians familiarise themselves with the process of differentiating the causality of suspected event being from drug use or disease process or some other unexplained confounding factor. Such knowledge will be helpful in better patient management by timely interventions in terms of use of drugs for managing an event or not an unnecessarily withdrawing suspect but effective drug.

Importance of Vigilance

Detection of adverse effects of drugs manifesting after long-term treatment e.g. urinary bladder carcinoma with pioglitazone, emphasises the role of continuous monitoring of patients for adverse outcomes. Additionally,
with the launch of new drugs for management of a variety of diseases like SGLT-2 inhibitors and DPP-4 inhibitors for type 2 diabetes mellitus etc. and lack of information following chronic use in a variety of population, being vigilant about any suspected adverse medical outcome becomes necessary. In patients with compromised renal, hepatic or cardiac functions, it is required to modify doses for minimising adverse effects. The process of approval of drugs in India presently relies a lot on the clinical trials done in the western world. Racial and ethnic factors make us different from other parts of the world. A drug safety database of India is the unmet medical need of the hour and clinicians can only help in creating such a database, which will be of immense help to drug regulators in enhancing patient safety. Through this position statement, Indian College of Physicians hopes to facilitate such activities.

**Summary**

Table 2 summarizes issues related to pharmacovigilance.

**Conclusion**

The practice of Pharmacovigilance aims to create a system where all ADR (ideally) are reported and drug-related problems taken care of scientifically using evidence-based-medicine. Presently there is a big gap between practice and achieving desired goals and a lot needs to be done in this field. Apprehensions of physicians need to be taken care of and ways need to be discussed for making this activity to bring out the desired outcomes.

**References**


Blood Pressure Variability in Patients with Diabetes Mellitus with Hypertension: Treatment Recommendations and Role of Amlodipine

Bipin Kumar Sethi¹, Manash P Baruah², A Sreenivas Kumar³

Abstract

Recently, blood pressure variability (BPV) has gained focus owing to its role in predicting cardiovascular (CV) outcomes. Additionally, alterations in BPV contribute to the progression of end organ damage and trigger vascular events in hypertensive patients. Therefore, amelioration of BPV is considered a potentially important target and different classes of drugs are used to achieve the desired blood pressure (BP) goal. Based on several studies and clinical trials, treatments with CCB such as amlodipine have been found to be most effective in the management of BPV in hypertensive patients with diabetes. Growing evidence substantiates the role of amlodipine in significant reduction of BPV, thus, lowering the risk of diabetes related complications. This review sheds light on the importance of BPV reduction and the effectiveness of amlodipine in preventing cardiovascular morbidity and mortality in hypertensive patients with diabetes.

Introduction

Clinical evidence suggests a correlation between blood pressure (BP) and cardiovascular (CV) complications in patients with diabetes mellitus (DM).¹ Patients with DM are already at an increased risk of developing cardiovascular diseases (CVDs) as compared to subjects without DM. As high as 80% mortality in patients with DM have been associated with CV complications.² Hypertension (HT) is considered a major comorbidity of diabetes and coexistence of these conditions further increases the risk of heart failure, nephropathy, and other micro- and macro-vascular events.³ Blood pressure variability (BPV) has been an important focus in recent times, especially since its role got established in predicting cardiovascular (CV) outcomes, especially stroke. There is enough evidence to implicate BPV as an independent risk factor, which needs to be identified, followed up, and got rid of. This review tries to throw some light on clinical trial based evidence focussing on BPV and therapeutic armamentarium addressing this largely modifiable risk factor with particular reference to patients with co-existing HT and DM.

Impact of HT - Indian Scenario

Recently published meta-analysis documents that approximately one-third and one-fourth of the adults in urban and rural India, respectively, are hypertensives.⁴ Prevalence of HT have been projected to reach 22.9% and 23.6% for Indian men and women respectively by 2025.⁵ Such a concerning rise in HT portrays a frightening scenario for the 17.8% of the world’s population residing in India. The World Health Report 2002 has predicted CVDs as the major cause of mortality and disability among the Indian population by 2020 ⁶ and HT is considered as a crucial risk factor for increased incidence of CVDs in India.⁷ In sync with such predictions, an alarming role of HT has already been reported as the primary cause of 57% and 24% of all deaths due to stroke and coronary heart disease (CHD), respectively, in India.⁸

Blood Pressure Variability – The Next Big Target in HT

Blood Pressure (BP) control is highly important for CV protection as it is considered as a leading risk factor for CVDs.⁹ Blood pressure variability (BPV) has been defined as an average BP variation throughout the day, which is measured as the standard deviation of ambulatory BP readings. BPV is characterized based on two forms

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of fluctuations—short-term BPV, occurring over minutes or hours, as detected by 24-hour ambulatory blood pressure measurement (ABPM), and long-term BPV, in which fluctuations occur over prolonged periods of time, as detected by repeated recordings over days, weeks, months, and years, often referred to as visit-to-visit BPV.

BPV is of particular importance in patients with HT. The amplitude of BPV in patients increases progressively with increasing levels of HT. A study on intra-arterial BP monitoring of patients stratified into three major categories (mild, moderate, and severe HT) based on the mean 24-h BP revealed that the degree of BPV increased progressively with worsening HT. The relationship between BPV and the complications of a HT has been explored in a study by Kikuya et al., and there is a body of evidence of an association between the degree of BPV and HT-induced end-organ damage, CV morbidity and CV mortality.

Although most studies have focused on mean BP measured in clinic or “out of office” settings as the CVD risk indicator, there is a strong body of evidence on noticeable oscillations in BP over both short and long term. Such variability poses a hindrance to the accurate measurement of mean BP and has been recognized as a potential risk factor. Further, analysis of cohort studies and randomized trials revealed long term BPV as a predictor of stroke and coronary events in high risk patients. Increased stress on the walls of the blood vessels and heart are considered as contributing factors to such variability. Both cross-sectional and longitudinal studies have confirmed the correlation between BPV and target-organ damage, and also demonstrated that such an effect is independent of the mean BP.

**Impact of BPV in Patients with Diabetes and HT—A Double-Edged Sword**

In India, amongst patients with diabetes, about 50% are affected with HT. Hypertensives with diabetes are at a significantly high risk for premature microvascular and macrovascular complications. The presence of HT is responsible for about 7.2-fold increase in mortality in patients with diabetes.

Analysis of data from a factorial randomized controlled trial (ADVANCE trial) of lowering blood pressure and control of blood glucose in 8811 T2DM patients without major macrovascular and microvascular events revealed that visit-to-visit systolic BPV and maximum SBP were independent risk factors for macrovascular and microvascular complications in such patients and were positively associated with myocardial infarction (MI) and CV death. Additionally, the findings of a study on the effect of short-term BPV, assessed in 36 T2DM patients with overt nephropathy who were subjected to ambulatory BP monitoring, revealed that elevated night-time BPV was associated with more than 3 folds increased risk of CAD and proportional sympathetic activation in diabetes related nephropathy. These findings corroborate that BPV is an important predictor of microvascular complications and development of nephropathy among patients with diabetes.

There are several possible mechanisms that can explain the link between BPV and macrovascular and microvascular events in patients with diabetes. High BPV in T2DM patients suggests possible deleterious effect of hyperglycaemia on the blood vessels, that is responsible for large BP fluctuations. The population-based Hoorn Study reported an association between T2DM with increased arterial stiffness in both elastic (carotid) and muscular (femoral and brachial) arteries. Additionally, structural changes such as increased carotid intima-media thickness have also been reported. As a consequence, patients with diabetes undergo large systolic and diastolic BP fluctuations (Figure 1) which in turn can accelerate end-organ damage.

It is highly important to effectively manage BPV to mitigate the risk of future CVD events in

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*Fig. 1: Systolic and diastolic blood pressure variations in patients with type 2 diabetes mellitus and normal individuals (controls). Based on Mokhtar et al. Asian Cardiovasc Thorac Ann. 2010;18:344-8. T2DM: type 2 diabetes mellitus; SBPV: systolic blood pressure variation; DBPV: diastolic blood pressure variation*
such high-risk population. There are reports that even moderate BP reductions can substantially reduce CV morbidity and mortality. A meta-analysis of data from 61 prospective observational studies on vascular disease related deaths in individuals without known vascular disease at baseline demonstrated that even 2 mmHg SBP reduction could decrease stroke mortality by 10% and ischemic heart disease or other vascular events by 7%. In line with such findings, another observational study with diabetes patients found that 10 mmHg reduction in SBP to be positively associated with reduced risk of diabetes-related complications and deaths. Therefore, early detection followed by effective treatment of BPV in hypertensive patients with diabetes mellitus is paramount for reducing risks of CVD.

**Therapeutic Interventions for the Management of BPV: Role of CCBs**

Therapeutic intervention should be targeted not only towards reducing mean BP levels but also to stabilize BPV with the aim of achieving consistent BP control over time. Several classes of antihypertensive drugs are used for the control of BPV in diabetes patients with hypertension, namely angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide diuretics. Study by Webb et al., on the effect of antihypertensive treatment on inter-individual BP variance demonstrated that BPV was effectively reduced by CCBs and non-loop diuretic drugs, while it was increased by ACEIs, ARBs and beta blockers (Figure 2). Authors also found that CCB was responsible for maximum BPV reduction when compared with placebo. Similar findings, were also reported by Levi-Marpillat et al., in a study on the efficacy of mono and combination therapy on short-term BPV as assessed in 2780 hypertensive patients, in which CCBs and diuretics were associated with lower BP when compared to ACEIs, ARBs or β blockers. A meta-analysis by Ettehad et al., of 123 studies and 613,815 participants, further confirmed the superiority of CCBs over other classes of drugs in stroke prevention. Ushigome et al. conducted a study with 954 T2DM patients to investigate the effectiveness of antihypertensive drug class in managing BP. Their results confirmed the distinct advantage of selecting CCBs in hypertensive patients with diabetes mellitus for the reduction of home BPV.

**Amlodipine - Gold Standard in Reducing BPV**

Amlodipine is considered a well-established and long-acting CCB for the treatment of HT, including patients with diabetes. The well-known Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) study on 5137 patients with T2DM, reported lower risk of stroke when treated with amlodipine as compared to the treatment with atenolol (hazard ratio 0.78, 95% CI 0.67-0.90), and was attributed to the effectiveness of amlodipine in lowering of BPV. A post-hoc analysis of 710 patients, with known status of diabetes, was conducted by Jeffers et al. Data was pooled to determine the incremental effect of amlodipine titration to a daily dose of 10 mg daily on BP-lowering efficacy in hypertensive patients with diabetes, unresponsive to a daily dose of 5 mg amlodipine. The findings revealed that increasing amlodipine from 5 mg to 10 mg accounted for observed incremental reduction in BP (−12.5 mmHg/8.3% reduction in SBP, −6.0 mmHg/6.8% reduction in DBP) in hypertensive patients with diabetes, thus decreasing the risk of diabetes related complications. Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was conducted to determine the pharmacological effect of amlodipine, chlorthalidone and lisinopril on visit-to-visit BPV, recorded over a period of 6-28 months. Findings of these studies confirmed the marked lowering of visit-to-visit BPV by amlodipine and chlorthalidone in comparison to lisinopril.
Although there is limited evidence of the association of BPV with the microvascular complications in diabetes, a cross-sectional study of 422 Japanese T2DM patients demonstrated close association between Systolic BPV and the prevalence of albuminuria. The Diabetes Control and Complications Trial also reported that in patients with type 1 diabetes, the standard deviation in SBP and diastolic blood pressure (DBP) were predictive of future development of nephropathy. These studies indicate an association between BPV and impaired renal function in patients with diabetes. Previous studies on patients with diabetes have confirmed the renoprotective role of amlodipine. In the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial with 11,506 HT patients, amlodipine based regimen was successful in 48% reduction in the progression of nephropathy. A Study of Assessment for Kidney Function by Urinary Microalbunin in Randomized (SAKURA) trial was a prospective, multicentre, open-labelled, randomized trial, in which the anti-albuminuric effects of clindipine and amlodipine were examined. The findings suggest similar effects of clindipine and amlodipine on changes in urinary albumin to creatinine [Cr] ratio (UACR) after 12 months of therapy and successful renoprotection in RAS inhibitor-treated hypertensive patients with T2DM and microalbuminuria. Another study compared the effects of amlodipine versus fosinopril on urinary albumin excretion (UAER) in 147 elderly (60 to 75 years) elderly HT patients T2DM. The findings suggested that long-term treatment with both amlodipine and fosinopril effectively reduced UAE in elderly hypertensive patients with diabetes and suffering from microalbuminuria.

**Conclusion**

Given the alarming rise in the prevalence of HT in patients with DM, combined with the observed and increased macro and microvascular risk attributable to HT, effective BP management strategies are paramount for reducing risks of future CVDs. BPV has now emerged as an independent risk factor the development of chronic diabetes related complications. Several antihypertensive drugs are suggested for BPV control, out of which, treatment with CCB has been found to be more beneficial than treatment with ARBs or ACEIs. Based on several studies and clinical trials, the CCB amlodipine has been reported to reduce both mean BP levels and BPV, and therefore is most effective in the management of HT in patients with diabetes. There is growing evidence on the ability of amlodipine in significantly reducing SBP and DBP variability in T2DM patients, which can translate to meaningful reductions in diabetes related complications and improved renoprotection in the high-risk patients. Thus, amlodipine as a therapeutic option can safely be advocated for patients for the effective management of BPV in patients with DM and HT.

**References**


Changing Adolescent Sleep Patterns: Factors Affecting them and the Related Problems

Harpreet Kaur¹, Harpreet Singh Bhoday²

Abstract
Sleep affects physical growth, behavior and emotional development besides determining cognitive functioning, learning and attention especially of a growing child. Adolescence represents one of the critical transitions in the life span and is characterized by a tremendous pace in growth and change that is second only to that of infancy. Adolescent sleep patterns deserve particular attention because of the potential impact on school performance. Average sleep period in adolescents is reduced during school days to around seven hours. The reasons may be biological mainly the sleep phase delay or psychosocial and environmental. These include academic demands, social activities, sports, internet, television viewing, part-time employment, and use of mobile phone at night, peer and parental influence and socioeconomic status. These changing patterns of sleep in adolescents lead to many behavioral sleep problems like Delayed Sleep-phase Syndrome; Difficulties in falling asleep (insomnia); excessive daytime sleepiness, poor academic performance. Decreased sleep in adolescents also causes obesity and other cardio-metabolic abnormalities. This needs an integrated approach involving adolescents themselves, their parents, teachers and specialized physicians to help improve the sleep quantity and quality and lead to a better quality of life and daytime functioning in adolescents.

Sleep
Sleep is a naturally recurring state characterized by reduced or absent consciousness, relatively suspended sensory activity, and inactivity of nearly all voluntary muscles. Sleep is divided into two broad types: Rapid eye movement (REM) and Non-rapid eye movement (NREM or non-REM) sleep. The American Academy of Sleep Medicine (AASM) describes the stages of sleep as follows (Table 1).

An adult reaches REM approximately every 90 minutes, with the latter half of sleep being more dominated by this stage. The function of REM sleep is uncertain but a lack of it will impair the ability to learn complex tasks. One approach to understanding the role of sleep is to study the deprivation of it. A hypnogram is a graph that represents the stages of sleep as a function of time. It is an easy way to present the recordings of the brain wave activity from an electroencephalogram (EEG) during a period of sleep (figure 1).

Both these sleep states develop before birth. Infants cycle through many sleep periods throughout the day. As they develop, they sleep longer at night and have fewer sleep periods during the day. Newborns sleep almost all the time. By six months they sleep about 13 hours a day with the longest sustained period being about seven hours. By 24 months children sleep for 12 hours, including naps, and by four years children sleep 10–12 hours with one daytime nap at most. Throughout childhood children typically get about ten hours of sleep a night. This drops significantly at adolescence. National sleep Foundation (NSF) has given expert recommendations regarding the sleep durations according to the various age groups (Table 2).

Adolescents Sleep Patterns
World Health Organization identifies adolescence as the period in human growth and development that occurs after childhood and before adulthood, from ages 10 to 19. It is characterized by a tremendous pace in growth and change that is second only to that of infancy. Adolescent sleep patterns deserve particular attention because of the potential impact on academic performance, social behavior and cardiometabolic system. As per the NSF, the recommended sleep duration is 8 to 10 hours. However, studies show that in

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adolescence, the average sleep duration timings tend to be lower than the recommended especially school going children. The reasons may be biological, psychosocial or environmental. These shall be discussed one by one below.

### Biological Factors

In adolescents, the circadian rhythm that also controls sleep and wakefulness tends to undergo biological changes. This natural shift is called “sleep phase delay.” On weekdays, the adolescents tend to be sleep for a lesser duration, so they have a longer sleep duration on weekends because of the rebound effect. The irregularity that results from adolescents’ typical sleep patterns (i.e. sleep phase delay, decreased nocturnal sleep, irregular sleep-wake schedule, late bedtime and rise time, poor perceived sleep quality) is associated with many sleep related problems like Delayed sleep phase syndrome (DSPS), insomnia, excess daytime sleepiness, reduction in concentration levels, alterations in mood and temperament, and risk taking behavior.

### Psychosocial Factors

A primary psychodevelopmental task of adolescents is to achieve independence in many areas of their lives. One area where this striving for autonomy is displayed is the decision of when to go to sleep. Different psychosocial and environmental factors influence these changes in adolescents sleep patterns. These include academic demands, social activities, sports, media usage and part-time employment. In addition, decreasing parental involvement due to modernization may play a role as well.

### Academic Pressures

Studies have shown the influences of academic pressures on these sleep patterns. It has been seen that the combination of delayed circadian sleep phase and early start times at high schools causes adolescents to lose sleep during the school week. This causes day time sleepiness, inattentive behavior and poor academic performance. It also leads to negative effects on neurocognitive performance, mood and health and even put adolescents at risk for accidents or injury. A study by Hansen et al showed that there was a delay of about two hours in the sleep onset of adolescents on weekdays but not on weekends. It was associated
with the same pattern of poor morning performance, compared with afternoon performance (P < .001), and all students felt less vigorous in the morning (P < .0001) than in the afternoon. Fulgini and Hardway in 2006 conducted a study using the Daily Diary system to assess the effects of activities of daily living on the variations in the adolescent sleep and their psychological wellbeing and found out variability among individual adolescents’ sleep time in addition to the phase delay and also in the daily activities, and psychological well-being among adolescents. Studying and stressful demands were among the most important factors that caused sleep deprivation. Daily feelings of anxiety, depression, and fatigue were the most consistent feelings of anxiety, depression, and caused sleep deprivation. Daily activities of daily living on the system to assess the effects of medium to high-tech media has in one way increased our awareness, but on the other hand is also a risk factor for irregular sleep habits, shorter sleep duration, and sleep disorders especially in adolescence. A recent review by Cain and Gradisar noted shorter, late, and/or more disrupted sleep in adolescents who have greater television watching, computer/Internet/electronic games use, or mobile phone use in the evening before bed time. These adolescents also tend to have more day time sleepiness or disruptive behavior.

Addictions

Adolescent age is marked by acquaintance of various new things in life but comes with addictions to alcohol, cigarette smoking and various drugs. All these behaviors have an effect the sleep onset timings and other consequences. A large survey of 12- to 15-year-old subjects showed correlations between sleep problems, rebelliousness, depressive symptoms and cigarette smoking. It is also shown that there is an increase use of caffeine in adolescents nowadays. High school students who have high intake of caffeine have nearly 2 times more difficulty in sleeping and more day time sleepiness as compared to those with low intake. Caffeine especially reduces the percentage of time spent in deep sleep and alters the temporal relation of REM/ non REM sleep. Since both deep and REM sleep are essential for learning and memory consolidation, caffeine interrupts that and can cause serious concentration deficits in growing adolescents.

Modern life style and its influence on adolescent sleep

An important consequence of our modern-day society is that it is difficult for children and caregivers both to get adequate sleep. Sleep involves reciprocal interactions between all members of a household as well as with the environment of the home and outside. Changing work schedules and increasing night shifts of parents do influence a child’s bed time and sleep duration. As children grow, they want to be more independent and want to sleep alone. Studies have shown that children generally have better age-appropriate sleep in the presence of household rules and regular sleep-wake routines. Neighbourhood noise from vehicular traffic, commercial, or industrial activity and neighbour’s night parties also create disturbances in sleep. Gangwich and colleagues examined from a large epidemiologic data set gathered from adolescents (grades 7 to 12) in the US during the mid-1990s. The analysis showed that young people whose parent set their bedtime at midnight or after relative to those with bedtimes set earlier, were significantly more likely to suffer from depression or suicidal ideation.

Socioeconomic Status

In developing countries, where people from all kinds of socioeconomic strata reside, differences in the socioeconomic status and availabilities of sources of distraction also influence the sleep patterns. Only a single study could be found in Indian literature, where sleep patterns were studied only in urban school going adolescents.

Sleep Related Disorders

Studies indicate that these changing patterns of sleep in adolescents lead to many behavioral sleep related disorders. Sleep disorders in adolescents are highly prevalent, with prevalence rates ranging from 25% to 40%, and they are often persistent. Behaviorally-based sleep disorders typically present with at least 1 of the following complaints:

1. Delayed Sleep-phase Syndrome;
2. Difficulties in falling asleep (insomnia);
3. Disturbed daytime performance.
4. Obesity and its effects

Delayed sleep phase syndrome (DSPS)

Delayed sleep phase Syndrome (DSPS) is a circadian rhythm disorder that usually appears during adolescence. First described by Weitzman and colleagues, it is characterized by a cluster of features including a chronic inability to fall asleep and wake at a desired clock time, consistency in reported sleep times at later hours than other individuals, and otherwise normal sleep when measured by all-night polysomnography if the delayed schedule is allowed. It is associated with a wide range of problems, including inability to work or attend school, which can lead to school failure, daytime sleepiness, social difficulties, and depressed mood. Etiological mechanisms of DSPS include abnormalities of the circadian timing system with delayed timing of melatonin secretory patterns, the sleep homeostatic system, systems coordinating circadian and sleep processes, behavior, psychological traits and features.
Obesity and its effects

**Insomnia**

**Insomnia Disorder** is characterized by difficulties in initiating or maintaining sleep or by non-restorative sleep with these symptoms lasting at least one month and causing clinically significant distress or impairment in daytime functioning. Insomnia can be primary where there is no antecedent medical or psychiatric cause or it may be secondary. Insomnia is most likely caused by a combination of physiological/genetic factors and psychosocial factors. Only a few studies assessed the prevalence and development of insomnia among adolescents. A possible contributing factor during adolescence is the change in circadian rhythm, causing a delay in sleep onset and therefore sometimes misdiagnosed in them with DSPS. Chronic insomnia increases subsequent risk for somatic health problems, interpersonal problems, psychological and emotional problems, high incidence of anxiety and risk taking behavior.

**Daytime sleepiness and poor daytime performance**

As discussed earlier, since most of the adolescents get insufficient sleep because of the tendency to delay sleep, they experience what is called excessive daytime sleepiness (e.g. an increased tendency to fall asleep during wakefulness). It has many negative effects on their academic performance, cognitive and neurobehavioral functioning, emotional regulation and risk taking behavior.

**Obesity and its effects**

Adolescents gain greater autonomy and independence in their eating and sleeping habits and are therefore more vulnerable to over-nutrition and sleep disorders. For this reason, reduced sleep duration may lead to metabolic and hormonal deregulation, thus favoring food intake, obesity and cardiometabolic risk. A systematic review and a meta-analysis of studies conducted on adolescents indicated a reverse association between sleep duration and obesity. Ruiz et al. analyzed the possible association among nocturnal sleep duration, the presence of overweight and metabolic alterations in a group of adolescents. It was found that among ninety adolescents, adolescents with excessive weight had, in average, fewer sleep hours \( p < 0.05 \) and a higher rate of sleep deficit and sleep debt \( p < 0.05 \). Low HDL cholesterol and insulin resistance was significantly associated with sleep debt \( p < 0.05 \). Among adolescents with sleep debt, the risk of having excess weight was 2.70 times higher (95% CI= 1.09-6.72; \( p = 0.032 \)) regardless of age, gender, sexual maturity, sleep deficit and history of cardiovascular disease and diabetes in first-degree relatives.

Obese children tend to have interrupted sleep with snoring, sleep disordered breathing called obstructive sleep apnea and therefore they have excessive daytime sleepiness. This causes poor academic performance and bad social impact.

**Sleep Hygiene and Management of Sleep Related Disorders**

Adolescents around the world are experiencing a decreased amount of sleep time, which is in clear contrast to their sleep needs. This has many physical, neurobehavioural, academic and social implications on their mental and physical growth. Therefore, adolescents should be made aware of their growing sleep needs, the developmental shift in the circadian clock and such implications of chronic sleep insufficiency. This can be done by proper sleep hygiene and management of sleep related disorders.

### a. Sleep Hygiene: Adolescents should be encouraged to:

1. Keep consistent regular bedtimes and rise times, also on weekends.
2. Avoid sleeping late into the noon hours on weekends. Also napping in the early afternoon hours should be avoided or limited to 30 minutes.
3. Use the bed only for sleeping.
4. Create a routine before bedtime that will include calming and relaxing activities to break the connection between the stimulating activities of the day and sleep.
5. Reduce or avoid exposure to bright light in the evening.
6. Avoid using any drugs, alcohol, caffeine, or stimulating substances.
7. Maintain regular food habits.
8. Keep regular exercise in the beginning of the day and avoid exercise in late evening hours.

Besides the steps adolescents can take by themselves, parents, teachers and health care practitioners should be aware of the high prevalence of problematic sleep patterns and sleep difficulties in adolescents.

### b. Clinical approach to sleep disorders: Chronically sleepy adolescents, who are late for school and perform poorly at school without any clear reason, should be carefully examined for sleep disorders. If the adolescent shows excessive sleepiness even though he/she gets sufficient time to sleep, the presence of possible underlying physiological sleep disorders with potentially obstructive effects on daytime functioning, such as breathing related sleep disorders, should be examined. Such children are usually obese and should be counselled for weight reduction by increasing physical activity of at least 30 to 45 minutes per day along with limiting sedentary lifestyle to less than two hours in a day. These children should also
be screened for large adenoids, nasal polyps or any other causes of upper airway obstruction (retrognathia, macroglossia, neuromuscular weakness) and should be managed accordingly. These recommendations may help to improve sleep quantity and quality and lead to a better quality of life and daytime functioning in adolescence.

Conclusions

To summarize, adolescence is a dynamic phase and needs special attention. It is marked by a phase to be independent and try out new things. Most common problem in adolescents is delayed sleep onset and duration. Many biological, psychosocial and environmental factors contribute. These include academic pressures, changing lifestyles with increased modernization leading to progressively decreasing parental influences, presence of media and its late night use and neighbourhood noise. All these factors cause increasing sleep deficits and therefore many sleep related problems ensue. These sleep related problems include the physiological delayed sleep phase syndrome or the pathological insomnia, excessive day time sleepiness, poor academic performance, obesity and other cardiometabolic derangements. Management includes proper parental guidance and set sleep times, a good sleep hygiene, avoidance of stimulating drugs and foods and a healthy lifestyle. A coordinated effort by parents and children can lead to healthy and stress free living.

Abbreviations

REM: Rapid eye movement; NREM: Non-rapid eye movement; AASM: The American Academy of Sleep Medicine; SWS: Slow-wave sleep; EEG: Electroencephalogram; DSPS: Delayed sleep phase Syndrome; ICSD: International Classification of Sleep Disorders; CBT-I: Cognitive-Behavioral therapy for Insomnia; HDL: High Density Lipoprotein; NSF: National sleep Foundation

References

Principles of Correlation Analysis

NJ Gogtay, UM Thatte

Introduction

The field of medicine often requires drawing inferences regarding the association or relationship between two or more variables. In an earlier article on “Measures of Association” we introduced the concept of finding associations [relationships] between two variables that were binary and categorical in nature. Therein, we explored several possible relationships between these binary variables and understood metrics such as absolute risk, relative risk and odds ratio.

In the present article, we discuss how to establish a relationship or an association between two quantitative variables, i.e., variables that can be “measured”. As an example, we could perhaps ask the question “Is there a relationship between the number of hours of work put in by a sales representative and the actual sales of a product?” Or “Is there a relationship between maternal age [measured in years] and parity [total number of pregnancies that a woman has carried past 20 weeks of pregnancy]? Correlation analysis helps answer questions such as these.

Definition of Correlation, its Assumptions and the Correlation Coefficient

Correlation, also called as correlation analysis, is a term used to denote the association or relationship between two (or more) quantitative variables. This analysis is fundamentally based on the assumption of a straight –line [linear] relationship between the quantitative variables. Similar to the measures of association for binary variables, it measures the “strength” or the “extent” of an association between the variables and also its direction.

The end result of a correlation analysis is a Correlation coefficient whose values range from -1 to +1. A correlation coefficient of +1 indicates that the two variables are perfectly related in a positive [linear] manner, a correlation coefficient of -1 indicates that two variables are perfectly related in a negative [linear] manner, while a correlation coefficient of zero indicates that there is no linear relationship between the two variables being studied. These are depicted in Figures 1 and 2.

Eyeballing and Analyzing the Data for Correlation - Construction of the Scatter Plot/Scatter Diagram

A correlation analysis begins with the construction of a scatter plot or scatter diagram [a graphical representation of the data] with one variable on the X-axis and the other on the Y-axis. Let us understand this with an example.

We had carried out a study earlier that evaluated whether two modalities of the informed consent process – the written informed consent process, and the audio visual [AV] recording of this (in the same clinical trial) were different from each other in terms of the extent of understanding of the study by the participant using a pre-validated questionnaire. This questionnaire gave a “total score” [a quantitative measure] at the end of administration. One of the study objectives was to see if there was a relationship between the time (in minutes) taken to administer the consent in the two groups [again a quantitative measure] and the total score. Table 1 gives data on individual participants in both groups for time taken to consent [measured in minutes] and the total scores. Table 1 gives data on individual participants in both groups for time taken to consent [measured in minutes] and the total score.
The scatter plot or scatter diagram of the total score on the Y axis with the time taken to administer consent on the X axis, enables us to get a feel of the relationship (if any) between the two. Each point on the scatter plot represents the values of X and Y as a single coordinate. The closer the points are to a straight line, the stronger is the linear relationship between two variables.

Two scatter plots, one for each group can be easily constructed using Microsoft Excel and those for our example are shown below.

Both scatter plots from our study show a weak, positive, linear relationship between the total scores and the time taken to administer the consent.

The advantage of the scatter plot is that it is simple to construct, is non-mathematical in nature and is unaffected by any extreme values that may be present in the data set. It also tells us immediately if there are outliers or if the relationship is actually non-linear or not entirely linear. A line is usually drawn through the points on a scatter plot to identify linearity in the relationship. This line is called the regression line or the least squares line, because it is determined such that the sum of the squared distances of all the data points from the line is the lowest possible. This will be discussed in greater detail in the next article on regression analysis.

The disadvantage of a scatter plot is that it does not give us one single value that will help us to understand whether or not there is a correlation between the variables.
A correlation coefficient is that single value or number which establishes a relationship between the two variables being studied. Two methods are used to calculate this value, viz. the Karl Pearson’s product moment correlation coefficient r or more simply Karl Pearson’s correlation coefficient r and the Spearman’s rank correlation coefficient rho (q) or Spearman’s rho (q) in short.

The Pearson’s correlation coefficient establishes a relationship between the two variables based on three assumptions. These are:

1. Relationship is linear
2. Variables are independent of each other
3. Variables are normally distributed.4

On the other hand, the Spearman’s rho (q) is based on the ranks given to the observations and not on their actual values and is used when the assumptions of the Pearson’s coefficient are not met. It can be thus considered as the non-parametric equivalent of the Pearson’s coefficient. This is a robust coefficient and can also be used when one of the variables is ordinal4 in nature. For example, if you want to find the relationship between the weight (measured in kg, continuous, quantitative data) and socioeconomic stratum (ordinal data – higher, middle, lower, etc.) the Spearman rho (q) could be used.

Normality, we know from an earlier article on distributions is commonly tested using the Kolmogorov Smirnov test.5 In this example, when the variables in the two groups were tested for normality and were found not to follow a normal distribution, we calculated the Spearman’s rho (q). The q value obtained in our study for the written informed consent group was 0.2 while that for the AV consent group was 0.15.

Figure 2 describes the interpretation of this correlation coefficient and places the relationship in perspective. In our case, the values of 0.2 and 0.15 indicate a weak positive correlation between the two variables interpreted to mean that the time taken to administer consent is weakly, though positively related to the understanding of consent as assessed by the total scores.

When the relationship or association between more than two quantitative variables is to be studied, other correlation coefficients such as the Sample Multiple Correlation Coefficient can be used.

What Correlation Coefficients do NOT do

Correlation coefficients do not give information about whether one variable moves in response to another. There is no attempt to establish one variable as “dependent” and the other as “independent”. We shall discuss the concept of independent and dependent variables in the next article on regression analysis. Relationships identified using correlation coefficients should be interpreted for what they are: associations, and not causal relationships (see below).

Testing for Significance after Calculating the Correlation Coefficients

Any relationship or association between two variables should be assessed not just for the strength and direction [as given by the correlation coefficients r or q], but also by whether the relationship is “significant” [given by the p value]. Hence testing for significance answers the question “how reliable is the correlation analysis?”

When we calculate correlation coefficients from the given data, what we calculate really are the sample correlation coefficients. We now need to apply “tests of significance”5 to see how close these sample correlation coefficients are to the true population value; i.e., the population correlation coefficients. Both the p values obtained in our study were > 0.05 indicating a lack of a significant relationship between the time taken to administer consent and the total score. It is important to remember here that if the sample size is sufficiently large, even small correlation coefficients will achieve statistical significance without being clinically meaningful.

Coefficient of Determination – $r^2$ [r square]

This is the square of the coefficient of correlation r, which is calculated by squaring the value of the “r” obtained. In our study, this would be 0.2 x 0.2 = 0.04 or 4% for the written, informed consent group and 0.15 x 0.15 = 0.02 or 2% for the AV Consent group. This would mean that only 4% and 2% variability respectively in the total score can be accounted for by the time taken to administer the consent.

Correlation and Causation

One common error that often occurs is confusing correlation with causation. All that correlation shows is that the two variables are associated and nothing more. Any judgment regarding cause and effect must be made on the basis of the investigator’s knowledge and biological plausibility. This is easily seen in an interesting study by Messerli FH7 who showed that
greater a country’s annual per capita chocolate consumption, more were the number of Nobel Laureates per 10 million population and thus established a “relationship” or “association” between chocolate consumption and getting a Nobel prize!

Factors that Affect a Correlation Analysis

Several factors must be considered when a correlation analysis is planned. These include:

i. Correlation analysis should not be used when data is repeated measures of the same variable from the same individual at the same or varied time points. For example, if you have measured pain scores in patients with Rheumatoid arthritis at monthly intervals over 2 years in a study, it is inappropriate to find out a correlation coefficient for this data.

ii. It is useful to draw a scatter plot as an important prerequisite to any correlation analysis as it helps eyeball the data for outliers, non-linear relationships and heteroscedasticity.

iii. An outlier is essentially an infrequently occurring value in the data set. It is important to remember that even a single outlier can dramatically alter the correlation coefficient.

iv. If there is a non-linear relationship between the quantitative variables, correlation analysis should not be performed. For example, during the growth phase in adolescence, there would a linear relationship between height and weight, as both increase. However, this relationship ceases once a person enters adulthood.

v. If the dataset has two distinct subgroups of individuals whose values for one or both variables differ considerably from each other, a false correlation may be found, when none may exist. An example given by Aggarwal and Ranganathan illustrates this point well. If you were to plot heights (on X-axis) and hemoglobin levels (on Y-axis), of a group of men (n=20) and women (n=20), most women may end up in the left lower corner (shorter and lower hemoglobin) and most men in the right upper corner (taller and higher hemoglobin). Analysis would suggest a relationship with a positive “r” value between height and hemoglobin levels!

vi. The sample size should be appropriately calculated à priori. Small sample sizes may show a false positive relationship.

vii. If one data set forms part of the second data set, for example, height at age 12 (X - axis) and height at age 30 (Y-axis) we would expect to find a positive correlation between them because the second quantity “contains” the first quantity.

viii. Heteroscedasticity is a situation in which one variable has unequal variability across the range of values of the second variable. For instance, if one were to plot time on the X-axis and the Sensex on the Y-axis, one would find a great variability in the Sensex as compared to the relative stability in time.

Conclusion

In summary, correlation coefficients are used to assess the strength and direction of the linear relationships between pairs of continuous variables. When both variables are normally distributed we use Pearson’s correlation coefficient “r”. Otherwise, we use Spearman’s correlation coefficient rho (ρ), which is non-parametric in nature, and is more robust to outliers than is the Pearson’s correlation coefficient “r”.

Correlation analysis is seldom used alone and is usually accompanied by the regression analysis. The difference between correlation and regression lies in the fact that while a correlation analysis stops with the calculation of the correlation coefficient and perhaps a test of significance, a regression analysis goes ahead to expresses the relationship in the form of an equation and moves into the realm of prediction. The next article in the series will deal with regression analysis.

References

Science Bashing: Is it a global In-thing?

Sadananda Naik

Abstract
Ridiculing the well established knowledge and norms in the various branches of science like medical science, physics, chemistry, astrophysics, genetics etc. has become a new fashion all over the world. Look at the loose comments by the US senator Rand Paul on a study done by NIH on “origami condoms” as waste of tax payer’s money. Unfortunately, it is not just the politicians who are into this kind of science bashing but many eminent scientists, physicians; molecular biologists are also engaged into this. Physician and molecular biologist Dr. Henry Miller commented on the prevention research, specifically CDC’s Community Transformation Grants as poor choice. But, it is a well known fact that “more than half of the cancer occurring today is preventable by applying knowledge that we already have.” and the CDC was planning exactly that. Anti-vaccine movement is yet another form of science bashing in the USA. India is no different, look at the atrocious comments by an honorable member of parliament in support of the use of tobacco.

There are enough examples of eminent clinicians who are into this business of science bashing.

It is humanly impossible for any one individual to master various branches of science. At the most one can have a superficial knowledge of other forms science in addition to the deep knowledge of the form science which he is involved with. Hence, comments, critical analysis of complex scientific topics should be left to the experts in the respective scientific field. Otherwise, armed with the superficial knowledge of a subject, a good and outspoken orator could inflict devastating and irreparable damage to the existing and accepted scientific knowledge. All of us do have personal theories and prejudice on every matter but projecting them as the gospel truth using our extraordinary vocabulary and oration skills is nothing but self promotion. They thrive by sensationalizing and promoting their personal dogmas and they should not be taken lightly, as their words could create unnecessary confusions, apprehensions, overt anxiety and wrong notions in the minds of general public who do not understand these scientific facts. Nobel laureate, Chemist, Venkatraman Ramakrishnan’s recent comments stating that “Homeopathy is bogus, harmful” is just another example.2

It is very surprising that these ‘experts’ have no solutions for the problems and their role is just restricted to malign the existing well established scientific norms. It is not that these ‘masters’ can go on and on, one fine day, people will definitely get the measure them but by then they could have inflicted enough harm. In democracy, everyone has intellectual freedom but with right comes greater responsibility which these “wise” people show none.

The modern science is not so facile that it could be decimated by handful of “wise” orators or writers. It has evolved over the last few centuries by the hard work, dedication, sacrifice of thousands of scientists all over the world. Historically, the modern science has witnessed enough tortures, immolations, executions etc by its detractors. The great scientists of yester years who laid the foundation for modern science, achieved great innovations for the betterment of human life and not for the publicity, monitory gain or the media coverage but for the very passion of it. Now, it is testing time for this great tool of enlightenment into the mystery of the nature and universe at large. There is no doubt that it will come clean in this test. It is the time to show our
gratitude and acknowledge the great scientists like Edward Jenner, for whom we are grateful, for the discovery of vaccine against smallpox, an innovation which has saved more lives than the work any other human. Hundreds of scientists acted as their own guinea pigs, did not care for their lives with the quest to discovery which would better the lives of their fellow countrymen. We have Jonas Salk who risked the lives of himself and his entire family for the polio vaccine trial, Werner Forssmann who inserted catheter into his vein to reach the heart, August Bier, Sir Humphrey Davy, so on and the list is endless. None cared for publicity or money. Surely, their sacrifice will not go in vain. It is very ungrateful on our part, not to give credit to the modern science for what it is due. Those who want to blame the modern science for all our misery is better prepare themselves to be a cave man.

The antibiotics, insulin, corticosteroids have saved the lives of millions of patients across the world. Patients used to die like flies in the pre insulin, antibiotic era. Of course, any scientific innovation is a double edged weapon and it up to us, to use them rightly. The life expectancy of an average human being has gone up by leaps and bounds, thanks to the wonderful antimicrobial drugs, good nutrition and the vaccinations programme. It is not only medical science but also other branches of science which have made difference in our lives.

Hundreds of life saving drugs has been innovated by the MNCs. These pharmaceutical companies have contributed to people’s improved health and prolonged life. But, unlike, the scientists of yester years, the greatest motivation for these pharma giants are the profit. Testing and thorough clinical trials are fundamental to innovate good medical drugs. But, there could be pit falls like short cuts, pressure to researchers to have a favorable result, conducting drug trials without their consent and use of drugs for unapproved indications. There could be conscious or unconscious bias by the researcher because of the source of the funding. Even, the medical journals who publish these results may be erring in their responsibility to guarantee credibility and transparency of the scientific process. One cannot hold science responsible, for the greed of the scientist or the pharma giants yearning for patenting the products before actually confirming the efficacy of their scientific innovations. But, there are statutory bodies, watch dogs like FDA etc to monitor the safety profile of these innovations. But, we should remember that persons who run these institutions are also mortals like us.

Science is the only known “mantra” known to us to learn, understand and unfold the mysteries of this natural world of ours. Science doesn’t “believe” anything without verification and this method has done reasonably over the centuries. It is the well known that science keeps changing its mind and it is a good for all concerned. Scientific conclusions, discoveries are always provisional and these will have to change whenever, new clear evidence comes up. It is true that science doesn’t know everything but it does not mean that intuitions, imaginations, quotes from ancient religious books, dreams, self experiments, illusions of knowledge of a bunch of so called “wise” experts are to be believed. Comedian Dara O Briain said it best: “Science knows that it doesn’t know everything, otherwise, it’d stop. But just because science doesn’t know everything doesn’t mean you can fill in the gaps with whatever fairy tale most appeals to you.” There is always a place for constructive critics and scientists will be grateful to anybody who finds any other ways of knowing things and they will be greatly relieved to say good bye to the existing cumbersome, tedious scientific research methodology. Any discussion, critics, suggestions on complex scientific matter should be done at the appropriate official scientific platform rather trying to reach the lay press. A conscious attempt by the media to discourage these “experts” in indulging in science bashing, would do a world of good to the science and general public at large.

References
Dural Arteriovenous Fistula following Cerebral Venous Sinus Thrombosis

K Mugundhan¹, MC Vasif Mayan², PD Nidhin², G Prakash³, N Balamurugan⁴

A 45 year old previously healthy non-diabetic, non-hypertensive female presented with history of severe headache and vomiting in August 2011. She was not on any medications. She was conscious, oriented, pupils 3mm, equally reacting to light. Fundus showed bilateral papilloedema. No focal neurological deficits noted. CT brain showed cortical venous thrombosis. She was treated and discharged with oral anticoagulants. In April 2012, she again presented with vertigo and headache with bilateral papilloedema. MR Venogram (coronal view) showed thrombosis of left transverse sinus (Figure 1). MR Venogram (sagittal view) showed thrombosis of straight sinus (Figure 2). Blood investigations including protein C and S, Antithrombin-III, Antiphospholipid antibody and serum Homocysteine were normal. Anticoagulants and antiepileptics were continued. In August 2014, she presented with recurrent episodes of seizures with papilloedema. Digital subtraction angiography (DSA) was done. Right external carotid angiogram (ECA) AP view showed transverse sinus dural AV fistula (Figure 3). Right vertebral artery angiogram showed trocar dural fistula (Figure 4). The diagnosis of dural arteriovenous fistula Cognard classification Type II (a+b) following cerebral venous thrombosis was made and endovascular surgery planned. But the patient refused due to financial constraints. She developed recurrent seizures which was refractory to treatment and expired.

Dural AV fistula constitutes 10-15% of all intracranial arteriovenous malformations. It is more common in females. Symptoms develop during middle to late adulthood. Initiating events include trauma, infection, recent surgery and dural sinus thrombosis. The commonest predisposing factor is venous sinus thrombosis. It is formed by the opening up of microvascular connections within the dura following venous hypertension. Unless intervened, these channels become hypertrophied resulting in direct shunting between arteries and veins. The fistula gets pial blood supply from parenchymal vessels leading to an angiomatous network formation within the partially recanalised sinus. Thus dural sinus receives arterialized blood flow causing mechanical obstruction of the sinus resulting in retrograde drainage of blood from the sinus to the cortical veins. They can be classified based on the type of venous drainage as Type I (drainage into a dural sinus, with normal antegrade flow), type II (drainage into a dural sinus, with reflux into II a: other sinuses, II b: cortical veins, II a+b: sinuses + cortical veins), Type III (drainage into cortical

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Spontaneous Pneumocephalus

Suvrendu Sankar Kar1, Jyotirmay Pal2, Suvendu Jana3, Swati Kumar4, Partha Sarathi Karmakar3, Anindya Sarkar4, Cankatika Chowdhuiy4

A 33-year-old non-diabetic, nonmotensive female presented with sudden onset, diffuse and deep boring headache and vomiting for 15 days. She also had complaints of watering from nose which was present for 15 days. She also had complaints of watering from nose which was present on underlying cause air can be distributed by CT scan brain, which can detect air is low as 0.5 ml. Depending on underlying cause air can be distributed in epidural, subdural, subarachnoid, intraventricular or intracerebral space or combination of these.

Common clinical manifestations are headache (38%), nausea, vomiting, seizure, dizziness.3 Treatment depends on underlying cause. It can resolve spontaneously or evacuation may be needed in tension pneumocephalus. Inhalation with 100% oxygen may increase resorption.4

Pneumocephalus could be diagnosed by plain skull radiograph, CT scan, and MRI.

References

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Sickle Cell Disease Presenting with Chronic Tophaceous Gout

LK Meher¹, VP Tushar², PK Hui³, SN Nayak⁴

Case Description

A 32 year old male patient who was a known case of Sickle cell disease (SCD) presented with pain and swelling of small joints of both hands and feet for last 5 years. On general examination there was moderate pallor, mild icterus, splenomegaly (1 cm), swelling of proximal interphalangeal joints of both hands, swelling and tenderness over metatarsophalangeal joints of both feet with irregular hard nodular swellings (tophi) over dorsum of both feet (Figures 1, 2). Routine investigations revealed Hb-5.8 gm%, MCV-85 fl, MCH-28 pg, MCHC-33 g/dl, reticulocyte count-4%, DC-N(70) E(3)L(25)M(2)B(0), ESR-140 mm in first hr, TC-9800 cells/mm³, TPC-1.72 lakhs/mm³. Rheumatoid factor was negative, BUN-42 mg/dl and serum creatinine - 1.4 mg/dl with creatinine clearance of 53.57 ml/min, serum uric acid-6 mg/dl, 24 hour urinary excretion of uric acid-350 mg and liver function tests showed total bilirubin - 3.5 mg/dl, indirect-2.8 mg/dl, AST-25 IU/L, ALT-28 IU/L, ALP-110 IU/L. Hemoglobin electrophoresis showed HbS-88%, HbF-9%, HbA2-3%. Xray of both hands and both feet showed lytic and sclerotic lesions with destruction of 1st metatarsophalangeal joint and soft tissue deposition in both feet (Figures 3, 4). FNAC from the nodular swelling over interphalangeal joint of great toe demonstrated putty like material (Figure 5) which in cytosmear showed clumps of needle shaped crystals (Figure 6). It was consistent with a diagnosis of tophaceous gout. Patient was treated with colchicines, folic acid and the acute attack subsided. After the acute attack subsided he was put on febuxostat and colchicine.

Thus, it was a clear case of sickle cell disease with tophaceous gout. Though the incidence of hyperuricemia (defined as a serum urate concentration above 0.39 mmol/l or 6.5 mg/100 mL) is high in patients with SCD, development of gouty arthritis and presence of tophaceous deposits is rarely documented. There are many hypothesis trying to explain this peculiar complication, but none has been proven conclusively delineating the need for further studies in this topic. It is hypothesised that this association is rare due to circulatory impairment resulting from congestion and thrombosis of small vessels, in synovia. This prevents white blood cells from responding to chemotactic stimulus of uric acid crystals. Activity of the polymorphs is also reduced by anaerobic condition present in SCD. Another hypothesis is that ageing and degenerative changes in joint play a major role for urate crystallisation in joint fluid, but patient of SCD don’t survive for this to occur. Presence of hyperuricemia in a SCD patient warrants a detailed evaluation of the renal function as it might be one of the earliest marker of deteriorating renal function.

References

Pyomyositis Complicated by Deep Venous Thrombosis - A Unique Case of Reverse Lemierre’s Syndrome

Uthara Elsa Mathew¹, Animesh Ray², Manish Soneja³, Surabhi Vyas⁴, KJDB Sanker¹, Neeraj Nischal², Pankaj Jorwal², SK Sharma⁵

Abstract

We report a case of a young individual who presented with fever and swelling of right upper and lower limbs for 3 weeks. Subsequently he developed shortness of breath and decreased urine output and had to be mechanically ventilated. Ultrasound screening of the lower limb had shown deep venous thrombosis (DVT) and thus the diagnosis of pulmonary thromboembolism (PTE) seemed probable. However the workup for PTE was negative and patient’s fever continued and his condition deteriorated. Evaluation for an infective locus led to the diagnosis of pyomyositis and DVT appeared to have developed secondary to the muscle inflammation as a part of Reverse Lemierre’s syndrome. Thus this case highlights the importance of considering this diagnosis in a similar setting and not to ascribe every case of respiratory failure in a background of DVT to be due to PTE.

A 17 year old boy with no premorbid illness presented with low grade fever for the last 3 weeks. He was treated in a health care centre with empirical antimalarial therapy and antibiotics. After a week of therapy he developed progressive painful swelling of the right lower limb which later involved the right upper limb. Patient was treated with analgesics and oral antibiotics but continued to be symptomatic. He subsequently developed subacute onset of shortness of breath and decreased urine output and was referred to our institute.

At the time of presentation the history was reviewed where the patient reiterated his complaints. Any history of trauma to the swollen limbs or similar history occurring in the past was denied by the patient. General examination in our Emergency Room revealed a febrile patient who was significantly tachypneic with a respiratory rate of 42 per minute, tachycardia of 122 per minute and hypotensive with a blood pressure of 82/62 mm Hg. Patient had tender, indurated erythematous swelling of the right thigh and right upper limb with tender bilateral inguinal lymphadenopathy. Respiratory examination revealed bilateral fine crackles in the infra-scapular and infra-axillary areas. He also had moderate non-tender hepatosplenomegaly. Examination of the cardiovascular and the central nervous system was essentially normal. Arterial blood gas analysis revealed PaO2/FiO2 ratio of 176. The chest radiograph revealed bilateral mid zone and lower zone infiltrates. ECG showed sinus tachycardia and bed side echocardiography was normal. His laboratory parameters at presentation are shown in Table 1.

Peripheral blood smear revealed macrocytic anemia, with leucocytosis and presence of toxic granules. He had an elevated ESR (45 mm/1st hr), C-reactive protein

Table 1: Laboratory parameters at admission

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (gm%)</td>
<td>6.2</td>
</tr>
<tr>
<td>Platelet Count (m/m3)</td>
<td>80000</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>18</td>
</tr>
<tr>
<td>TLC (m/m3)</td>
<td>16700</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>160</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>2.1</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>13</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>7.7, 8.6(corrected)</td>
</tr>
<tr>
<td>Na (mEq/L)</td>
<td>135</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>6.5</td>
</tr>
<tr>
<td>Bilirubin (Total)(mg/dl)</td>
<td>0.5</td>
</tr>
<tr>
<td>Total Protein (gm/dl)</td>
<td>6.3</td>
</tr>
<tr>
<td>Albumin (gm/dl)</td>
<td>2.0</td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>23</td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>108</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>249</td>
</tr>
<tr>
<td>PT/INR</td>
<td>58 sec/4.833</td>
</tr>
<tr>
<td>Urine Routine and</td>
<td>Protein 1+, WBCs</td>
</tr>
<tr>
<td>Microscopy (R/M)</td>
<td>18-20/HPF, RBC/6/HPF</td>
</tr>
</tbody>
</table>

¹Junior Resident, ²Assistant Professor, ³Associate Professor, Department of Medicine, AIIMS, New Delhi; ⁴Associate Professor, Department of Radiodiagnosis, AIIMS, New Delhi; ⁵Ex - Professor and HOD, Department of Medicine, AIIMS, New Delhi

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of 30.2 mg/l, Serum Procalcitonin of 58.6 ng/ml with azotemia and hyperkalemia. He also had features suggestive of disseminated intravascular coagulation. The Quick SOFA (qSOFA) score was 2 with a lactate of 2.3 mmol/l. The differential diagnoses considered at the time of admission are outlined in Tables 2 and 3. As per the history and initial investigations of the patient, a provisional diagnosis of Sepsis with acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI) was made with the presumed source of sepsis being either urinary tract infection or cellulitis was made.

After obtaining appropriate samples for cultures (blood, urine, induced sputum), he was started on broad spectrum antibiotics (Piperacillin-Tazobactam, Levofloxacin) in renal modified doses. Investigations for common infectious diseases like typhoid, dengue, chikungunya, malaria, typhus, leptospirosis and filariasis were negative. Ultrasound (USG) and Doppler of lower limb venous system done in the emergency revealed right sapheno-femoral thrombosis extending into the common femoral vein with subcutaneous edema in right upper and lower limb. There were no significant lymphadenopathy, intra-abdominal mass or other vessel thrombosis in the ultrasonography performed.

No evidence of pulmonary embolism, heart failure, valvular insufficiency or tamponade was seen in echocardiography. The Wells score for pulmonary embolism was 6 but Computed Tomography Pulmonary Angiogram (CTPA) was withheld due to AKI. A non-contrast CT thorax revealed only bilateral infiltrates without any suggestion of pulmonary embolism. Troponin I was negative with a mildly elevated Pro-BNP.

Anticoagulation was initiated but patient’s condition deteriorated and he had to be intubated and mechanically ventilated. Antibiotics were upgraded to meropenem and linezolid. Workup for procoagulant factors revealed only megaloblastic anemia with folate deficiency (Table 4). He was started on folate supplements in dose of 5 mg daily. But there was progressively increasing blackish discoloration on the areas of erythema over right hand and leg (Figure 1) whereas all peripheral pulses were well palpable. X-ray of the above areas didn’t show any gases in soft tissues and muscles. After reviewing with our surgical colleagues, a clinical diagnosis of

**Table 2: Cause of fever with unilateral limb edema**

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>Cellulitis</td>
</tr>
<tr>
<td>Necrotising fascitis</td>
</tr>
<tr>
<td>Lymphedema with lymphangitis</td>
</tr>
<tr>
<td>Superficial or deep venous thrombosis with phlebitis</td>
</tr>
<tr>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>Septic arthritis</td>
</tr>
<tr>
<td>Vasculitis</td>
</tr>
<tr>
<td>External venous compression by tumours or lymph nodes</td>
</tr>
<tr>
<td>Ruptured inflamed Bakers cyst</td>
</tr>
<tr>
<td>Traumatic hematoma</td>
</tr>
<tr>
<td>Infectious myositis</td>
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</tbody>
</table>

**Table 3: Differential diagnosis of subacute dyspnea in the background of presumed sepsis**

<table>
<thead>
<tr>
<th>Pulmonary embolism</th>
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<tbody>
<tr>
<td>ARDS</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Myocarditis</td>
</tr>
<tr>
<td>Cardiomyopathy / Congestive heart failure</td>
</tr>
<tr>
<td>Acute valvular insufficiency (due to Infective Endocarditis)</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Pericardial Effusion / Tamponade</td>
</tr>
<tr>
<td>Shock: Septic, Cardiogenic,Hypovolumic</td>
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</tbody>
</table>

**Table 4: Work up for thrombophilia**

<table>
<thead>
<tr>
<th>Vitamin B12 : 100 pmol/L</th>
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<tbody>
<tr>
<td>Folate:2 ng/ml, Homocysteine: 14 µmol/L</td>
</tr>
<tr>
<td>Urine R/M: Protein 1+, RBC: 1-2/HPF, WBC: 1-2/HPF</td>
</tr>
<tr>
<td>Urine active sediments: Negative</td>
</tr>
<tr>
<td>Urine 24 hr protein: 12 mg</td>
</tr>
<tr>
<td>Lipid profile: TG:234 mg/dl, HDL:11 mg/dl, LDL:55 mg/dl, TC:82 mg/dl</td>
</tr>
<tr>
<td>LDH (Lactate Dehydrogenase): 530 U/L</td>
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<tr>
<td>TSH (Thyroid Stimulating Hormone): 3.4 U/L</td>
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<tr>
<td>DCT, ICT: Negative</td>
</tr>
<tr>
<td>HIV, HBsAg, Anti HCV: Negative</td>
</tr>
<tr>
<td>RF / ANA, Anti-dsDNA: Negative</td>
</tr>
<tr>
<td>APLA work up: Negative</td>
</tr>
<tr>
<td>Peripheral smear: No atypical cells / Schistocytes</td>
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<tr>
<td>Fundoscopy: Within normal limits</td>
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**Table 5: Causes of thrombophilia**

<table>
<thead>
<tr>
<th>Inherited</th>
<th>Acquired</th>
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<tbody>
<tr>
<td>Factor V Leiden mutation</td>
<td></td>
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<tr>
<td>Prothrombin gene mutation</td>
<td></td>
</tr>
<tr>
<td>Protein C, S deficiency</td>
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<tr>
<td>Primary Antiphospholipid syndrome</td>
<td></td>
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<tr>
<td>Anti thrombin III deficiency</td>
<td></td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td></td>
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<tr>
<td>Immobilisation</td>
<td></td>
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<tr>
<td>Surgery</td>
<td></td>
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<tr>
<td>Secondary Antiphospholipid syndrome</td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative disorders (Polycythemia vera, Essential thrombocytopenia)</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td></td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td></td>
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<tr>
<td>Inflammatory bowel disease</td>
<td></td>
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<tr>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td>Malignancies</td>
<td></td>
</tr>
<tr>
<td>Hormone replacement therapy, Oral contraceptives</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
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<tr>
<td>Presence of central venous catheter</td>
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</table>
Necrotising fasciitis was made and debridement was done for the same where evidence of necrosis was seen in skin but not underlying soft tissues. Table 5 shows the important predisposing factors for thrombosis.

The patient however remained febrile and all cultures were negative for both bacterial and fungal pathogens. Repeat serum procalcitonin was 8.2ng/ml while urine AFB and serum galactomannan were negative. CD25 and NK (Natural Killer) cell activity in serum was negative. Repeat Ultrasound and Doppler of right thigh revealed multiple abscesses in the vastus medialis in addition to the thrombosed veins. CECT (Contrast Enhanced) chest and abdomen showed similar multiple collections in the iliacus and gluteus muscles and in the anterior compartment of thigh with the largest collection in vastus medialis of 4.6×3.8 cm abutting the saphenofemoral junction and the common femoral vein (at the site of thrombosis) (Figure 2). Similar collections were also noted in the muscles of right upper limb. 15-20 ml of frank pus was aspirated from the collection under sonographic guidance which was subjected to tests as shown in Table 6.

Thus a definitive diagnosis of pyomyositis was made. Since we could not isolate any organisms; considering the clinical condition, common etiologies, and the resistance patterns; meropenem and linezolid were continued. He responded to the treatment and could be extubated within a week. Screening whole body MRI (Magnetic Resonance Imaging) after 2 weeks of intravenous antibiotics revealed resolving multiple collections in muscles of thigh and upper limb with dissolution of thrombus. After 3 weeks of intravenous antibiotics, patient became afebrile, pain and swelling of both limbs subsided. All available work up for immunodeficiency disorders (HIV, CD3, CD4 counts, immunoglobulin levels, DHR test) was negative.

The uniqueness of the case stems from the co-existence of fever, swelling of limbs and respiratory failure in a patient which we could not apparently explain by a single cause. The presence of deep venous thrombosis (USG Doppler) made us suspect pulmonary embolism. Though a CTPA could not be done, a non-contrast CT thorax together with a normal echocardiogram excluded significant pulmonary thromboembolic process. The persistence of high grade fever made us suspect the presence of an untreated septic process which was confirmed by the USG and MRI showing presence of pyomyositis.

But what seemed out of place was the almost contiguous presence of deep vein thrombosis along with pyomyositis in the lower limb. If the thromboembolic process was due to the systemic effects of sepsis (a hypothesis initially considered) – why was it present adjacent to the inflamed muscles? It could rather be completely explained by the inflammation and compression of the vessel wall by the ‘pus in the muscle’ which the MRI substantiated. Thus the final diagnosis made was primary pyomyositis complicated by suppurative saphenofemoral thrombophlebitis and secondary thrombosis, the so called ‘Reverse Lemierre syndrome’ along with folate deficiency.

Lemierre Syndrome (LS), also known as human necrobacillosis, was first described in 1900 by Courmont and Cade, but named after Dr. Andre Lemierre in 1936 (1). He described a series of lethal anaerobic septicemia following oropharyngeal infections caused by anaerobic bacterium known today as “Fusobacterium necrophorum”. When a similar condition presents in the lower limb, it is called Reverse LS. In our case, multiple abscesses in muscles (i.e., pyomyositis) of anterior compartment of thigh (especially vastus medialis) which were abutting the saphenofemoral vein and common femoral vein caused septic thrombophlebitis and subsequently thrombosis.

The basic pathophysiology of all septic thrombophlebitides are similar regardless of the vein involved. With regard to Virchow’s triad, endothelial dysfunction (contributed by inflammatory mediators and microbial toxins), stasis of blood (by compression of vein), platelet aggregation and hypercoagulable state (by sepsis) contribute to thrombus formation. This also acts as a source of septic emboli and the most common site is lung resulting in pulmonary abscesses and empyema (85%), pneumatoceles, pneumothorax, ARDS (10%).

Pyomyositis, classically an infection of the tropics, is defined as a primary suppurative infection of the skeletal muscle, first described by Scriba in 1885. Predisposing factors include conditions characterized by immunodeficiency (T cell deficiency, Chronic granulomatous disease, hyper-IgE syndrome, HIV, Malignancy, Diabetes, use of steroids and immunosuppressants), trauma, concurrent infection (with Toxocariasis, Varicella or Arbovirus) and malnutrition.

The common causative organisms are Gram positive bacteria, such as Staphylococcus aureus (90% in tropics and 75% in temperate regions) and Group A Streptococcus(1-5%). Three clinical stages of disease process have been described: invasive (bacterial seeding), suppurrative (abscess formation) and septicaemic stage (dissemination in blood with

<table>
<thead>
<tr>
<th>Table 6: Pus from right upper limb muscles</th>
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<tr>
<td>Pus for gram stain: negative</td>
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<tr>
<td>Bacterial c/s: sterile</td>
</tr>
<tr>
<td>Fungal c/s: sterile</td>
</tr>
<tr>
<td>Anaerobic c/s: negative</td>
</tr>
<tr>
<td>AFB: negative</td>
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<tr>
<td>GeneXpert: negative</td>
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<tr>
<td>MGIT culture: negative</td>
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The patient remained febrile and all cultures were negative for both bacterial and fungal pathogens. Repeat serum procalcitonin was 8.2ng/ml while urine AFB and serum galactomannan were negative. CD25 and NK (Natural Killer) cell activity in serum was negative. Repeat Ultrasound and Doppler of right thigh revealed multiple abscesses in the vastus medialis in addition to the thrombosed veins. CECT (Contrast Enhanced) chest and abdomen showed similar multiple collections in the iliacus and gluteus muscles and in the anterior compartment of thigh with the largest collection in vastus medialis of 4.6×3.8 cm abutting the saphenofemoral junction and the common femoral vein (at the site of thrombosis) (Figure 2). Similar collections were also noted in the muscles of right upper limb. 15-20 ml of frank pus was aspirated from the collection under sonographic guidance which was subjected to tests as shown in Table 6.

Thus a definitive diagnosis of pyomyositis was made. Since we could not isolate any organisms; considering the clinical condition, common etiologies, and the resistance patterns; meropenem and linezolid were continued. He responded to the treatment and could be extubated within a week. Screening whole body MRI (Magnetic Resonance Imaging) after 2 weeks of intravenous antibiotics revealed resolving multiple collections in muscles of thigh and upper limb with dissolution of thrombus. After 3 weeks of intravenous antibiotics, patient became afebrile, pain and swelling of both limbs subsided. All available work up for immunodeficiency disorders (HIV, CD3, CD4 counts, immunoglobulin levels, DHR test) was negative.

The uniqueness of the case stems from the co-existence of fever, swelling of limbs and respiratory failure in a patient which we could not apparently explain by a single cause. The presence of deep venous thrombosis (USG Doppler) made us suspect pulmonary embolism. Though a CTPA could not be done, a non-contrast CT thorax together with a normal echocardiogram excluded significant pulmonary thromboembolic process. The persistence of high grade fever made us suspect the presence of an untreated septic process which was confirmed by the USG and MRI showing presence of pyomyositis. But what seemed out of place was the almost contiguous presence of deep vein thrombosis along with pyomyositis in the lower limb. If the thromboembolic process was due to the systemic effects of sepsis (a hypothesis initially considered) – why was it present adjacent to the inflamed muscles? It could rather be completely explained by the inflammation and compression of the vessel wall by the ‘pus in the muscle’ which the MRI substantiated. Thus the final diagnosis made was primary pyomyositis complicated by suppurative saphenofemoral thrombophlebitis and secondary thrombosis, the so called ‘Reverse Lemierre syndrome’ along with folate deficiency.

Lemierre Syndrome (LS), also known as human necrobacillosis, was first described in 1900 by Courmont and Cade, but named after Dr. Andre Lemierre in 1936 (1). He described a series of lethal anaerobic septicemia following oropharyngeal infections caused by anaerobic bacterium known today as “Fusobacterium necrophorum”. When a similar condition presents in the lower limb, it is called Reverse LS. In our case, multiple abscesses in muscles (i.e., pyomyositis) of anterior compartment of thigh (especially vastus medialis) which were abutting the saphenofemoral vein and common femoral vein caused septic thrombophlebitis and subsequently thrombosis.

The basic pathophysiology of all septic thrombophlebitides are similar regardless of the vein involved. With regard to Virchow’s triad, endothelial dysfunction (contributed by inflammatory mediators and microbial toxins), stasis of blood (by compression of vein), platelet aggregation and hypercoagulable state (by sepsis) contribute to thrombus formation. This also acts as a source of septic emboli and the most common site is lung resulting in pulmonary abscesses and empyema (85%), pneumatoceles, pneumothorax, ARDS (10%).

Pyomyositis, classically an infection of the tropics, is defined as a primary suppurative infection of the skeletal muscle, first described by Scriba in 1885. Predisposing factors include conditions characterized by immunodeficiency (T cell deficiency, Chronic granulomatous disease, hyper-IgE syndrome, HIV, Malignancy, Diabetes, use of steroids and immunosuppressants), trauma, concurrent infection (with Toxocariasis, Varicella or Arbovirus) and malnutrition.

The common causative organisms are Gram positive bacteria, such as Staphylococcus aureus (90% in tropics and 75% in temperate regions) and Group A Streptococcus(1-5%). Three clinical stages of disease process have been described: invasive (bacterial seeding), suppurrative (abscess formation) and septicaemic stage (dissemination in blood with...
multiple organ dysfunction). The presentation of localised muscle pain, edema, low grade fever in first stage leads to misdiagnosis of muscle strain or contusion. Pain and swelling in the second stage leads to differentials of deep vein thrombosis, septic arthritis or osteomyelitis. By definition, pyomyositis never occurs secondary to contiguous infection of soft tissue or joints nor due to penetrating trauma. However in third stage as a part of septicaemia when it involves skin, leading to cutaneous gangrene, it can present as necrotising fasciitis like picture.

Aspiration of pus from the muscle or muscle biopsy (in case of absent macro abscess as in the early invasive stage) with culture and gram staining is the gold standard for diagnosis. But in tropical regions, pus cultures are sterile in 15-30% cases whereas 90-95% of patients in tropics and 70-80% in temperate regions have sterile blood cultures.

Radiologically, USG is useful during the purulent stage of pyomyositis when it may detect diffuse muscle hyperechogenicity with or without localized hypoechochogenicity (suggestive of collection) and diffuse hyperaemia. Contrast enhanced CT reveals segments of low attenuation with loss of muscle planes and a surrounding rim of contrast enhancement. Magnetic resonance imaging is considered the gold standard for the diagnosis of pyomyositis at any stage. It can differentiate pyomyositis from necrotising soft tissue infections. The MRI shows hyperintense signal on T2 –weighted images, hyperintense rim on T1-weighted images with peripheral enhancement on Gd-DTPA scan (Gadolinium –Diethylenetriaminepentaacetic acid) (Figure 3). In our case, the diagnosis of deep vein thrombosis led us to believe that it is the root cause of problems for our patient. The fact that it was rather a consequence (of infection), was realised later when the evaluation for pulmonary thromboembolism was negative and the diagnosis of pyomyositis was made.

The basic modalities of treatment include supportive therapy, antibiotics, and surgical drainage/debridement. If identified in first stage, antibiotic therapy covering Gram positive organisms is sufficient, while an immunocompromised patient would require additional gram negative coverage. But in later stages, broad spectrum antibiotics (covering Gram positive including MRSA and gram negative organisms) are used empirically, which can be de-escalated if indicated after culture reports. Clindamycin is indicated in severe cases as in necrotising infections or toxic shock syndrome and empirically in later stages in immunocompromised. In this case, combination of Linezolid and Imipenem-Cilastin were preferred, since several studies has shown their synergistic bactericidal activity in severe MRSA infections.

The duration should be tailored to clinical and radiographic features. The use of therapeutic anticoagulation along with intravenous antibiotics remains controversial. The inherent risk of the anticoagulation as well as the potential for metastatic spread of septic emboli has to be kept in mind before initiating anticoagulation. Moreover, there is spontaneous resolution of thrombus even without anticoagulation. Whether anticoagulation is beneficial for antibiotic penetration into the septic emboli and leads to faster resolution of thrombus is debatable.

Initially while evaluating the non genetic causes of venous thrombosis in this patient, the only positive finding was megaloblastic anemia caused by folate deficiency. A number of studies have identified the relationship between thrombosis, homocysteine and megaloblastic anemia caused by B12/folate deficiency. B12 and folate are required for metabolism of homocysteine. Analysing the causes of folate deficiency, it could be explained by either nutritional (chronic) or extensive tissue damage

Fig. 2: Coronal reconstruction contrast enhanced CT (A) and axial CECT images (B and C) showing a filling defect in the common femoral vein (arrow) with multiple collections in the proximal thigh(*)
due to sepsis (acute). Here in this case, normal homocysteine levels and localised area of thrombosis at site of abscess would support septic thrombophlebitis rather than folate deficiency as the prime cause for deep vein thrombosis.

A thorough literature search on reverse LS revealed only one documented case report in a soccer player who had pyomyositis of right obturator internus with evidence of septic iliak thrombophlebitis and pulmonary septic emboli resulted in ARDS. No definite criteria has been proposed for this condition probably on account of the paucity of cases.

The identification of Reverse Lemierre syndrome is a diagnostic challenge. Delay in treatment is the most important determinant of mortality in pyomyositis. Thus with early suspicion and diagnosis it can be cured with just antibiotics and/or by surgical drainage of the abscess.

References


**Fig. 3:** Coronal whole body spliced post gadolinium image showing peripherally enhancing collections in the right distal forearm, proximal thigh and ankle (*). Axial T2W images at the level just superior to the inguinal ligament (A) showing normal flow void of the right external iliac vein (arrow), whereas at the level of proximal thigh(B) showing loss of the normal flow void of the right common femoral vein (arrow). Note is also made of multiloculated intramuscular and intermuscular collections in the right proximal thigh and hemipelvis(*) with extensive subcutaneous tissue edema.
An Interesting Case of a Movement Disorder

K Ganesamoorthy¹, R Surendran², K Jamunarani¹, A Akila¹, CJ Selvakumar¹, G Suganthi², M Shalini², Usha³

Abstract

Neuroacanthocytosis is a genetic neurodegenerative disorder with syndromes of variable inheritance. These hyperkinetic movement disorders are reported to be very rare. It is associated with choreiform movements, orofacial and lingual dyskinesias and acanthocytes on peripheral smear and normolipoproteinemia. Here we present a similar case.

Case Report

A 38 year old male presented with insidious onset progressive involuntary movements for past ten months (Figure 1). He had irregular semipurposeful movements of limbs, flexion extension movements of neck, facial and oral movements, lip biting and tongue biting and unsteadiness while walking progressing to generalised choreoathetosis, orofacial dyskinesia, feeding dystonia, and lip biting. Over the last six months he developed truncal and gait ataxia. These involuntary movements disappeared during sleep. There was no history of behavioural changes like psychosis or obsessive compulsive neurosis. His cognition was normal with Mini Mental Status Examination score of 27 out of 30. No history suggestive of rheumatic fever, intake of anti-psychotic or anti-epileptic drugs was elicited.

Patient was born of a non-consanguineous marriage and had six siblings. Eldest brother was treated as a case of Parkinson’s disease and he was no more. Second brother was diagnosed to be a case of seizure disorder. His younger sister too had seizure and was on anti-epileptic medication. He had a son and a daughter without any history or signs of neurological disorder.

On examination patient was alert, co-operative, restless and with normal vital signs. There was no rash, muscle tenderness, muscle atrophy and skeletal deformity. Cardiovascular, respiratory system and abdomen examination were clinically normal.

On neurological examination, higher function, cranial nerve examination were normal except nasal quality of voice and occasional nasal regurgitation. Motor system examination revealed normal tone, muscle power of 4+/5 in proximal muscles of upper and lower limbs and 4/5 in distal muscles of upper and lower limbs absent biceps, triceps, supinator, knee, and ankle reflexes and bilateral flexor plantar. Sensory system examination, vibration and joint position sense were normal. Romberg sign and spurling sign were negative. Gait showed truncal instability and sudden extension movements of the trunk – rubberman gait. No fasciculation or muscle tenderness was present. Extrapyramidal system examination revealed involuntary, irregular, jerky, non-repetitive, ill-sustained, semi purposeful movements randomly distributed in character implying chorea. Orofacial dystonia or feeding dystonia, self-lip mutilation, sudden flexion and extension movement of the neck were present.

On investigation peripheral smear showed more than 30% of acanthocytes (Figure 2). EEG, ECG, ECHO, chest X ray, liver function test, renal function test, thyroid function test, serum lipids, lipid electrophoresis, serum

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ceruloplasmin, urinary copper, ESR, serum vitamin B 12 level, fundus examination were normal. Nerve conduction study revealed sensorimotor axonal polyneuropathy. The action potentials studied in EMG showed neuropathic changes (the motor unit potentials were of long duration, polyphasic and there was decreased recruitment). CPK level was elevated - 688 U/L. Muscle biopsy was not done since the patient was not willing. MRI brain showed normal study.

His positive family history, presence of acanthocytes in peripheral smear, normal lipids and lipoproteins, elevated creatinine kinase, peripheral neuropathy, normal Kell blood group expression, with characteristic orofacial dyskinesia, feeding dystonia, self-lip and tongue mutilation, chorea led to the diagnosis of neuroacanthocytosis. Patient was treated with anticholinergics, benzodiazepine, tetrabenazine and dopamine antagonists to control his involuntary movements and patient responded well to treatment.

On examining the peripheral smear of the patient’s second brother it was surprising to find acanthocytes confirming the genetic basis of the disease (Figure 3).

Discussion

The leading cause of adult onset chorea would be Huntington disease [HD]. Other causes of chorea include thyroid disease, lupus, drug-induced, pregnancy, stroke, and an idiopathic type. Our patient with very peculiar feature of “feeding dystonia” with tongue protrusion, orofacial dyskinesias, dystartria, involuntary tongue and lip-biting and generalized chorea favoured the diagnosis of neuroacanthocytosis. The patient also had “rubber man” gait with truncal instability and sudden, violent trunk spasms. The presence of acanthocytes on peripheral smear proved it to be neuroacanthocytosis. The identification of acanthocytosis in peripheral blood smears may be negative in a standard setting and a negative screen does not rule out neuroacanthocytosis syndrome. A more sensitive and specific method for detecting acanthocytes uses a 1:1 dilution with physiological saline and phase contrast microscopy.

Neuroacanthocytosis (NA) syndromes were known previously under the eponym “Levine-Critchley syndrome”. In 1991, Hardie and colleagues studied a series of 19 NA patients, which for years was the pioneering work on NA. However, with recognition of the molecular genetics of the different NA syndromes, this case series turned out to be heterogeneous, including patients with Chorea acanthocytosis (ChAc), McLeod syndrome (MLS) and Pantothenate Kinase - Associated Neurodegeneration (PKAN).

The “core” NA syndromes are - autosomal recessive ChAc caused by mutations of the VPS13A gene, and X-linked MLS, caused by mutations of the XK gene. There are several other genetic disorders in which acanthocytosis is occasionally seen, such as PKAN and Huntington disease – like 2 (HDL2). Occasional cases are reported where acanthocytes are present in other extrapyramidal features, such as paroxysmal dyskinesias or mitochondrial disease.

ChAc is a progressive autosomal recessive neurodegenerative disease with onset of neurological symptoms usually in the second decade, thus representing a late onset for an autosomal recessive disorder. The initial presentation may be subtle cognitive or psychiatric symptoms, and in retrospect patients might have related psychiatric complaints several years before the neurological symptoms. Administration of neuroleptics for psychiatric disease may confound the scenario to a neurodegenerative process. In some cases, seizures may precede the appearance of involuntary movements by as much as a decade. Most develop generalized chorea and a minority develops Parkinsonism. In addition to orofaciolingual dystonia, limb dystonia is also common. In at least one third of cases, seizures typically generalized, are the first manifestation. Memory disturbances and cognitive impairment is frequent, although not invariable. Most ChAc patients have elevated levels of creatine phosphokinase (CK). In contrast to MLS, myopathy and axonal neuropathy are usually mild. Clinical neuromuscular manifestations include areflexia, sensorimotor neuropathy, and variable weakness and atrophy. Muscle biopsy and electromyography commonly demonstrate neuropathic changes and rarely myopathic alterations. Disease usually slowly progresses over 15-30 years, but sudden death, presumably caused by seizures or autonomic involvement, may occur.

The differential diagnosis of NA syndromes depends upon the presenting symptoms, which can be protean. Initial symptoms may suggest psychiatric disease, including schizophrenia, depression, obsessive - compulsive disorder, tics, Tourette’s syndrome, cognitive impairment, personality change, or may consist of parkinsonism, chorea, dystonia, peripheral neuropathy, myopathy, cardiomyopathy, or seizures. Persons harboring the McLeod blood group phenotype are sometimes identified upon blood donation, many years or even decades prior to development of neurological symptoms. Both MLS and ChAc may be detected incidentally by the elevation of CK or liver enzymes. Recognition of the syndrome may avoid the need for invasive and non – diagnostic tests such as muscle, bone marrow, or liver biopsy. ChAc, MLS, and HDL2 all present in young to middle adulthood, but MLS has usually the latest onset of neurological symptoms. Presence of self–mutilating lip and tongue biting, or other self–mutilation such as head–scratching or finger – biting is strongly suggestive of ChAc.

So far no curative or disease – modifying treatments are available and management of the NA disorders is purely symptomatic. Recognition of treatable complications such as seizures, swallowing problems, and heart involvement is essential. Neuropsychiatric issues, particularly depression, can have a major impact upon quality of life, and these symptoms may be more amenable to pharmacotherapy than others. Dopamine antagonists or depletors such as tiapride, clozapine or tetrabenazine may ameliorate the hyperkinetic movement disorders. Anticonvulsants may have the benefit of multiple parallel effects upon involuntary movements, psychiatric symptoms, and seizures.

Non – medical therapies with a multidisciplinary approach are often helpful.

Conclusion

This case illustrates that it is...
worthy to have a clinical approach to a movement disorder, carefully ruling out the causes with simpler investigations done to diagnose a major disease like neuroacanthocytosis. Neuroacanthocytosis is to be considered as a differential diagnosis in adult onset chorea with classical presentations like orofacial dyskinasias, feeding dystonia, flexion and extension dystonia of neck, self-lip mutilation etc.

References

Neoplastic Fever: All who Shiver are not Infected
Yogesh B Sharma¹, Aparna Vishal More²

Abstract
We report the case of previously healthy 14 years old male who presented high grade fever and headache. There was a history of convulsion at age of 7 years, so MRI Brain was done. It was suggestive of a central nervous system neoplasm. Our patient had only two days of fever which is an unusual presentation of a neoplasm. The paper should be of interest to the clinicians as neoplastic fever as cause of acute febrile illness is considered as a remote possibility.

Introduction
Neoplastic fever is a challenging yet essential clinical diagnosis. Neoplastic fever is a well-recognized phenomenon occurring in certain patients with cancer. It has been seen in Hodgkin’s disease, non-Hodgkin’s lymphomas, acute and chronic leukemia, multiple myeloma, and other solid tumors. Neoplastic fever has been the major cause of fever of undetermined origin in patients with cancer.

Case Report
14 years old male was admitted with complaints of fever with chills and headache since two days. He did not have any other complaints. On admission, patient was febrile, (temp =101° Fahrenheit), pulse -120/min, BP: 120/80 mm Hg. RR: 16/min, with Hepatosplenomegaly. Other systemic examination was normal. There was no neck stiffness. Patient gave history of left eye ptosis since childhood. Patients was started on injections–Artesunate and Ceftriaxone. Complete Blood Count – report showed Hb – 12 g/dl, WBC count 14000 per microliter, platelet count 480000 per microliter, peripheral smear for ‘Malarial parasite was negative, Urine routine and microscopy normal, X-ray chest normal. Sonography of abdomen showed hepatosplenomegaly. Patient still continued to have fever with chills two days after admission so higher antibiotic Ceftazidime and quinine was started. Blood culture was sterile. 2D echocardiography was normal. Fundoscopy showed no evidence of papilledema. Patients ESR was 54, Mantoux test was negative. Inspite of being on antibiotics and antimalarials, patient was still having fever spikes and showing no focus of infection. In view of raised ESR, we decided to start on empirical antituberculosis treatment. Patient’s father revealed that patient had one episode of generalized convulsions at age of 7 years, which was treated as febrile convulsions. So we performed an do MRI brain which showed heterogeneously enhancing extraaxial lesions along the left anterior temporal lobe with involvement of left orbit, left cavernous sinus and left temporal fossa. This finding were suggestive of a neoplastic etiology.

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The differential diagnosis were lymphoma, sarcoidosis or metastasis. Patient was referred to neurosurgery department for surgical intervention. Subsequently to Tata hospital where he was diagnosed as suffering from ALK positive Anaplastic Large cell Lymphoma. Patient was started on chemotherapy and radiotherapy. Patient is now currently in palliative care.

Discussion

Fever is a common presenting complaint in clinical practice. Fever of unknown etiology still remains a perplexing problem to both clinicians and investigators. Acute fever or acute febrile illness (a rapid onset of fever and symptoms such as headache, chills or muscle and joint pains) is common can be caused by very diverse pathogens. Differential diagnosis include dengue, malaria, typhoid/paratyphoid, and investigators. Acute fever or acute febrile illness (a rapid onset of fever and symptoms such as headache, chills or muscle and joint pains) is common can be caused by very diverse pathogens. Differential diagnosis include dengue, malaria, typhoid/paratyphoid, and pneumonia (FIND, 2012). Our patient had presented with only two days of high grade fever with headache which is a rare presentation of neoplastic fever. All investigation were normal ruling out common causes of acute febrile illness.

Classic adult pyrexia of unknown origin is fever of 38.3°C or greater for at least 3 weeks with no identified cause after three days of hospital evaluation or three outpatient visits. Common causes are infections, neoplasms, and connective tissue disorders. A thorough history and physical examination, along with basic investigations usually provides clue to a possible diagnosis that can guide the choice of further investigations. If the initial evaluation provides no diagnostic clues, further investigations including imaging studies and serological tests may be indicated.

In appropriate clinical settings, therapeutic trials of antitubercular drugs may be accepted. It is particularly helpful in cases where there is a history of prolonged low-grade fever with evening rise along with raised ESR, a positive tuberculin test.

Neoplastic fever, i.e. fever arising solely as a manifestation of malignancy, is a troublesome symptom and is difficult to manage. The mechanism of neoplastic fever production involves cytokines such as tumor necrosis factor (TNF), interleukins 1 and 6 (IL-1, IL-6) and interferon (IFN), produced either by host macrophages in response to tumor, or sometimes by the tumor itself. The cytokines stimulate production of prostaglandins which act on the hypothalamus causing a change in the thermostatic set point.

Naproxen was very effective in suppressing tumor fever and this property may be useful in elucidating the clinician’s suspicion of cancer in patients with prolonged, undiagnosed fever. Naproxen has unique ability to suppress tumoral cytokines in preference over infectious cytokines. While the “naproxen challenge” may be useful in evaluating prolonged fever suspected to be of neoplastic origin, it must be performed when there is high degree of clinical suspicion. In our case the patient had only 2 days history of high grade fever.

This case report is unique in a way: A healthy 14 years old male who presented with only two days history of high grade fever with chills and headache was diagnosed as a case of central nervous system neoplasm. In our case, patient was diagnosed early on day 7 of fever and referred to Cancer care unit for further workup and management.

Conclusion

Any case presenting with acute fever not responding to standard line of treatment and having all primary routine investigations normal, workup for neoplasm as a cause of fever should be kept in mind.

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References

Double Chambered Right Ventricle: A Rare Diagnosis

Nitesh Pansari¹, H Raghavendra¹, Hemant Mahur², Mahesh Dave³

Abstract
A 27 years old female was admitted to our hospital with complaints of swelling of feet and abdomen, pain abdomen and exertional dyspnea from last 1 week. On examination she was found to have congestive heart failure. Chest x-ray revealed mild cardiomegaly with left pleural effusion and electrocardiography showed right axis deviation with right ventricular hypertrophy. By echocardiography she was diagnosed to have double chambered right ventricle without any other congenital heart anomaly. She was started on medical treatment following which she recovered well and she was advised for surgery. This case is unique as usually double chambered right ventricle is associated with other cardiac malformations, common ventricular septal defect, pulmonary stenosis and aortic stenosis but no such association was present in this case.

Introduction

Double-chambered right ventricle is a developmental cardiac anomaly characterized by aberrant muscular bands which obstruct the body of the right ventricle dividing it into a high-pressure proximal chamber and a low-pressure distal chamber.¹ It typically presents in infancy or childhood but has been reported to present rarely in adults as in our case.

Case Summary

A 27 years old female patient admitted with complaints of swelling of feet and abdomen, pain abdomen and exertional dyspnea for past 1 week. She had a full term normal vaginal delivery before 3 months without any adverse event.

On examination she had pallor, raised jugular venous pressure, bilateral pitting pedal edema, ascites and congestive hepatomegaly. Clinical examination of cardiovascular system revealed a palpable P2 with a systolic thrill at pulmonary area with left parasternal heave and a grade IV/VI systolic murmur at mitral and tricuspid area. So a clinical diagnosis of right ventricular failure was established.

We performed a routine blood work up which showed anemia with a hemoglobin level of 7.5 g/dl and raised erythrocyte sedimentation rate with normal liver and kidney function tests. Chest x-ray displayed cardiomegaly with right ventricular dilatation and left pleural effusion (Figure 1). Electrocardiography was suggestive of right axis deviation and right ventricular hypertrophy. Ultrasound of abdomen demonstrated congestive hepatomegaly with mild to moderate ascites and prominent hepatic veins and inferior vena cava indicating a cardiac pathology.

Echocardiography showed dilated right atria and ventricle with prominent muscle bundle in distal right ventricle body near infundibular os (PSG=120 mm of hg between proximal and distal right ventricular chambers) which led to a diagnosis of double chambered right ventricle with right ventricular dysfunction (Figure 2). Medical therapy with diuretics and hematinics helped the patient to get rid herself of symptoms. Then she was advised to consult a cardiac surgeon for further management.

Discussion

The double-chambered right ventricle is a rare congenital heart disorder involving two different right ventricle pressure compartments that is often associated with malalignment ventricular septal defect (VSD). Usually, the obstruction is caused by an anomalous muscle bundle crossing the right ventricle from the interventricular septum to the right ventricle free wall.² It can be caused by the presence of anomalous muscle tissue, hypertrophy of the endogenous trabecular bands, or an aberrant moderator band; all of which will typically result in progressive obstruction of the outflow tract.³

Frequent associated lesions include ventricular septal defect (VSD), pulmonary valve stenosis, and discrete subaortic stenosis.

As outlined by Restivo et al, several subtypes of divided right ventricle are noted.⁴ These subtypes include anomalous septoparietal band, anomalous apical shelf, hypertrophy of apical trabeculations, anomalous apical shelf with Ebstein malformation, and sequestration of the outlet portion of the ventricle from a circumferential muscular diaphragm in patients with tetralogy of Fallot. Double-chambered right ventricle, the most common form, is noted by the presence of anomalous muscle bundles (AMB) that divide the right ventricle into 2 chambers. However, no uniformity is observed in the position of these anomalous muscle bundles or in the manner in which the right ventricle is divided.

The lesion makes up approximately 0.5-2% of congenital heart disease and occurs in as many as 10% of patients with ventricular septal defect (VSD). Male-to-female ratio is 2:1.

Clinically, patients with double-chambered right ventricle and no ventricular septal defect (VSD) resemble patients with isolated pulmonary valve stenosis. When a ventricular septal defect (VSD) is present, the clinical picture relates to a ventricular septal defect (VSD). Usually, the patient is diagnosed with a ventricular septal defect (VSD) or pulmonary outflow tract obstruction and, subsequently, may show signs of progression of the outflow obstruction, such as cyanosis, fatigue, and decreased exercise tolerance. Patients with severe right ventricle (RV) hypertension...
may present with cyanosis, right ventricle (RV) failure, failure to thrive, and fatigue. Association with other syndromes is well recognized, and double-chambered right ventricle may be found during their workup.

Most patients are nondysmorphic and acyanotic with normal peripheral examination findings. Auscultation reveals a variable intensity of the second heart sound. A holosystolic ejection murmur, which peaks in intensity near midsystole, with greatest intensity at mid-left and upper-left precordial areas, characterizes double-chambered right ventricle. An right ventricle heave, hepatomegaly, and tachypnea indicate right ventricle (RV) hypertension.

Electrocardiographic findings in double-chambered right ventricle were reviewed in one series of 30 patients. Almost 50% of the patients had evidence of right ventricular hypertrophy (RVH), 40% of them demonstrated an upright T wave in V3 R in the absence of other findings of right ventricular hypertrophy (RVH), and the remainder had normal electrocardiographic findings. Similar findings are reported in other series.

Chest radiography may reveal either a left-to-right shunt with increased pulmonary vascular markings or a severe right ventricle (RV) obstruction with diminished pulmonary vascularity. The usual arrangement includes atrial situs solitus, levocardia, and left aortic arch. Cardiomegaly may be seen in some patients.

Echocardiography currently enables diagnosis on a 2-dimensional Doppler echocardiogram; before its advent, diagnosis of double-chambered right ventricle (DCRV) could not be made noninvasively. In infancy, subxiphoid imaging is optimal; parasternal short-axis views may be more useful in older patients. The cardinal feature is demonstration of muscle bundles that traverse the right ventricle (RV) cavity, with an accompanying gradient starting proximal to the infundibulum. Wong et al described a “displacement index,” which is determined by dividing the distance from the pulmonary annulus to the septal insertion of the moderator band by the tricuspid annulus diameter. An index less than 1 may predict that infants with ventricular septal defect (VSD) are at risk of developing an obstruction from a displaced moderator band.

Transesophageal echocardiography has been used to define structures in older patients with poor windows.

Further evidence of double-chambered right ventricle includes the angiographic demonstration of a filling defect dividing the right ventricle, as well as the absence of infundibular hypoplasia. Double-chambered right ventricle should be differentiated from tetralogy of Fallot by the absence of infundibular hypoplasia and pulmonary artery anomalies in double-chambered right ventricle. Entering both components of the right ventricle is important; ideally, perform angiography from the right ventricle apex in the frontal and lateral projections with craniocaudal angulation. During cardiac catheterization recording of the pressure gradient (which widely varies in magnitude) within the right ventricle cavity, remote from the infundibulum, strongly suggests a diagnosis of double-chambered right ventricle.

Symptoms of double-chambered right ventricle (DCRV) that require therapy are generally an indication for operative repair. In the presence of a ventricular septal defect (VSD), a significant left to right shunt can be present, requiring antifailure treatment, particularly if the muscle bundles are not sufficiently obstructive to reduce pulmonary blood flow.

Indications for surgery: a simple dual-chamber right ventricle, the patient’s symptoms obvious, right ventricular hypertrophy, evidence electrocardiogram, chest radiograph, right heart pressure chamber systolic blood pressure reached 70mmHg average pressure reaches a pressure gradient of 25mmHg or more, or the high and low pressure chamber exceeds 40mmHg. Merge other the Correction heart malformations.

Conclusion

When a young patient presents with symptoms and signs of right heart failure, a differential diagnosis of Double chambered right ventricle should be considered and patient should be investigated keeping this diagnosis in mind. Double chambered
Introduction

Osmotic demyelination syndrome (ODS) also known as Central pontine myelinolysis (CPM) was described by Adams and colleagues in 1959 as a disease affecting alcoholics and the malnourished. The concept was extended from 1962 with the recognition that lesions can occur outside the pons, so-called extrapontine myelinolysis (EPM). Classically this is associated with rapid correction of hyponatremia but it can also occur in presence of normonatremia. We present a case of ODS in a normonatremic patient with chronic kidney disease.

Case Report

A 35 years old male from a remote village, who had hypertension and chronic kidney disease stage IV (serum creatinine 4.5 mg/dl) and was taking indigenous therapy from a quack, presented to us with complaints of anorexia since 4-5 months, nausea, vomiting and loose stools of 2 days duration and drowsiness since 6 hours. Diarrhoea was watery, copious, about 10 times per day and was not associated with blood or tenesmus. There was no fever, headache, head injury hematuria, dysuria or pyuria.

On examination, his blood pressure was 120/80 mm of Hg. On central nervous system examination, he was drowsy, spontaneously opening eyes and responding to commands slowly. Pupils were normal. There was no focal neurological deficit, no meningeal signs, and plantar were flexor. Other systemic examination was normal. His investigation showed haemoglobin – 8.2 gm/dl, (normocytic normochromic anaemia), total leucocyte count 9,600 cumm, polymorph 60%, lymphocyte 36%, platelet count 1,55,000 cumm. His serum urea –131 mg/dl, creatinine –9.1 mg/dl, serum electrolytes: sodium –136 meq/L, potassium 3.0 meq/L, calcium 9.6 mg/dl, phosphorous 2.0 mg/dl. PTH 940 pg/ml. He had bilaterally shrunken kidneys on ultrasonography (right –6.8 cm and left –5.5 cm). His stool examination was normal.

He was diagnosed as a case of chronic kidney disease of unknown etiology (bilateral contracted kidneys) with hypertension. He was managed with intravenous fluids (2 L of normal saline), parenteral antibiotics (ceftriaxone and metronidazole), recombinant erythropoietin, alfacalcidol, phosphate binders, calcitriol, amlodipine and hematins along with hemodialysis and other supportive therapy.

Over the next 24 hours his sensorium worsened with GCS dipping to E1V1M3. The pupils were equal and reacting to light, but horizontal conjugate eye movements were restricted. There was spasticity with grade 2/5 power in all limbs, brisk reflexes and bilateral extensor plantar response. An urgent computerized tomography of the brain showed diffuse hypodensities in the pons extending into the middle and superior cerebellar peduncle. Magnetic resonance imaging (MRI) of the brain showed hyperintense lesions on T2 weighted images suggestive of pontine myelinosis (Figures 1, 2).

He remained in hospital for 15 days and was treated with repeated sessions of hemodialysis and other supportive management but his sensorium did not improve and he finally expired after 1 month due to sepsicaemia and bilateral pneumonia.
Discussion

Rapid correction of hyponatremia is an important risk factor for the development of ODS, but ODS has been reported in normonatremic and hypernatremic patients also, especially in association with conditions like chronic alcoholism, liver transplantation, diabetes mellitus, hypokalemia, pituitary surgery, hepatocellular dysfunction, lithium toxicity, hypophosphatemia, chemotherapy and chronic renal failure. However, osmotic demyelination, does not occur with the frequency one would expect in renal dialysis. It is thought that urea acts in renal failure patients as an “ineffective solute” —i.e. it contributes to measured osmolality but as it easily crosses cell membranes does not contribute to tonicity, thus protecting from the rapid shifts in sodium which can occur in haemodialysis.

The signs of CPM include dysarthria and dysphagia (secondary to corticobulbar fibre involvement), flaccid quadripareisis (from corticospinal tract involvement) which later becomes spastic, all from involvement of the basis pontis, if the lesion extends into the tegmentum of the pons and papillary, oculomotor abnormalities may occur. There may be an apparent change in consciousness level reflecting the “locked-in syndrome” that a large lesion in this site is particularly liable to produce. In Extrapontine Myelinolysis (EPM) the pathological changes are identical to those of CPM. A variety of sites may be involved. The lesions are often strikingly symmetrical.

Proposed hypotheses of CPM include osmotic injury to the endothelium resulting in release of myelinotoxic factors or vasogenic oedema and brain dehydration resulting in separation of the axon from its myelin sheath with resultant injury of oligodendrocytes. ODS have predilection to involve areas of rich gray-white matter apposition. This is probably due to endothelial changes (due to osmosis) leading to the release of myelinotoxic factors from the gray matter. Magnetic resonance imaging (MRI) is the imaging technique of choice. Hyperintense lesions are seen on T2, and hypointense lesions on T1 weighted images. The lesions are noncontrast enhancing. The timing of the appearance of lesions on MRI may be significantly delayed, and if the diagnosis remains likely a repeat imaging study at 10–14 days may reveal lesions not apparent on early scans. Diffusion weighted imaging (DWI) may aid in early detection of disease. DWI might have the capability of detecting lesions undetectable on T2.

CPM has been reported in the presence of hypokalemia and hypophosphataemia. In a recent study, hypokalemia was found to be a predisposing factor in 7 cases of CPM seen amongst 22 cases of hyponatremia, even when rapid correction of hyponatremia and non-acuteness of hyponatremia were not found to be the risk factors. For this apoptotic hypothesis has been proposed. It is suggested that a depletion of the energy supply to glial cells might limit the function of their Na+/K+-ATPase pumps. This could reduce their ability to adapt to relatively minor osmotic stress caused by small changes in serum sodium concentration, and ultimately lead to apoptosis.

Our patient possibly developed ODS due to multiple factors that may have predisposed him to have osmotic shifts like diarrhoea, hemodialysis and hypokalemia, hypophosphatemia and malnutrition.

Conclusion

Our case show that ODS is not exclusively linked to hyponatremia and one must suspect ODS in susceptible patients with other electrolyte abnormalities like hypokalemia and hypophosphatemia.

References

Small Vessel Vasculitis, an Uncommon Presentation of Systemic Lupus Erythematosus

Madhumita Priyadarshini Das¹, Purabi Borah², Bhaskar Thakuria³, Sahidul Islam⁴, Ankit Patawari⁴

Abstract
We report a nineteen year old female with gangrene of toes as the only clinical feature of systemic lupus erythematosus. She was treated successfully with pulse cyclophosphamide and steroid.

Introduction
Systemic lupus erythematosus (SLE) is characterized by protean manifestations.

SLE is an autoimmune disease in which organs and cells undergo damage initially mediated by tissue binding autoantibodies and immune complexes. Clinical manifestations are heterogeneous, and ninety percent of patients at diagnosis are women of child bearing age.¹ It is characterized by the production of antibodies against a variety of nuclear antigens.

A web search on small vessel vasculitis as the sole presentation of SLE yielded scant reports.² We report a case presenting with gangrene of the toes due to small vessel vasculitis.

Case Report
A 19-year-old unmarried female was admitted to the hospital in November 2014 with history of pain of both limbs since 4 months, and blackening of 2nd and 3rd toes of right foot since 2 months (Figure 1). The pain was gradual in onset, progressively increasing in intensity, excruciating in nature, with no aggravating factors. On the next day of admission, she developed pain and blackening of right middle finger. This was associated with oral ulcers twice within the last 6 months, healing spontaneously. There was history of insignificant hair loss and photosensitivity of the same duration, for which medical consultation was never sought.

She denied any systemic symptoms like fever, joint pain, skin rash or fatigue. Neither was there any history of medications taken in the past. Nor any history of smoking, illicit drug consumption or high risk behaviour.

Bilateral dorsalis pedis, posterior tibialis and popliteal artery pulsations were not felt; bilateral brachial, radial and ulnar artery pulsations were well felt. Sharply demarcated dry gangrene was noted involving tip of 2nd and 3rd right toes, and the tip of right middle finger. (Figure 2).

Laboratory investigations are as tabulated (Table 1).

Vascular Doppler of right lower limb showed monophasic high resistance flow pattern in distal anterior tibial artery with no power Doppler detectable flow in distal anterior tibial and dorsalis pedis arteries - features suggestive of small vessel disease. Similarly, Doppler of right upper limb showed monophasic high resistance flow pattern in distal ulnar artery.

Patient did not consent for biopsy

Fig. 1: Disappearance of gangrene in the right leg 2nd and 3rd toes following treatment. A: Pretreatment and B: After treatment

Fig. 2: Disappearance of gangrene in the right hand middle finger following treatment. A: Pretreatment and B: After treatment

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Table 1: Investigations on presentation

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>10.3 gm/dl</td>
</tr>
<tr>
<td>Platelet count</td>
<td>1,30,000/cumm</td>
</tr>
<tr>
<td>ESR</td>
<td>75 mm at the end of 1st hour</td>
</tr>
<tr>
<td>CRP</td>
<td>50 mg/L</td>
</tr>
<tr>
<td>PT(INR), APTT</td>
<td>16.6 (1.34), 31.9</td>
</tr>
<tr>
<td>HBsAg, anti-HCV, HIV-1 &amp; 2</td>
<td>Non Reactive</td>
</tr>
<tr>
<td>Chest X-Ray (PA-view), ECG, Echoangiography</td>
<td>Normal</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Normal</td>
</tr>
<tr>
<td>24 hr urinary protein</td>
<td>124 mg/dl</td>
</tr>
</tbody>
</table>

of the affected tissue. Immunological reports are listed in Table 2.

On the basis of clinical and laboratory findings she was diagnosed as small vessel vasculitis with SLE as she satisfied 4 out of 11 criteria as per ACR guidelines (1-oral ulcer, 2-photosensitivity, 3-ANA positivity, 4-dsDNA positivity). She was treated with steroid-pulse dose (methylprednisolone 1 gm/day intravenous infusion on three consecutive days) and injectable cyclophosphamide (10 mg/kg/month for six doses) as per the NIH guidelines.

During first follow up i.e. four weeks after the 1st dose of cyclophosphamide, there was a dramatic response with halt in the progression of gangrene, overall well-being and reappearance of the peripheral pulses in lower limbs. ESR was 30 mm at the end of first hour, CRP-20 mg/L. These values came down significantly compared to the baseline as shown in Table 1. CT angiography of both lower limbs was placed on oral low dose steroid (prednisolone-10 mg/day), aspirin 75 mg od, pentoxyfylline 400mg tid, iron-500mg and folic acid-5mg od, calcium-carbonate 500 mg od, nifedipine 20 mg od, as maintenance therapy.

Table 2: Immunological reports

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear</td>
<td>Positive</td>
</tr>
<tr>
<td>Antibodies (ANA)</td>
<td>homogenous pattern (4+) with maximum dilution is 1:2560</td>
</tr>
<tr>
<td>Ant-Smith</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti-ds DNA</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti-histone</td>
<td>Positive</td>
</tr>
<tr>
<td>anti-La (SS-B)</td>
<td>Positive</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>Positive (maximum dilution is 1:540)</td>
</tr>
<tr>
<td>c-ANCA</td>
<td>Negative</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti-cardiolipin</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Discussion

We report a patient with digital gangrene as the primary presenting symptom of SLE with vasculitis. Gangrene and ischemia in the extremities have diverse causes. Small vessel vasculitis may be primary or secondary to diseases such as SLE, rheumatoid arthritis, Sjogren’s syndrome and systemic sclerosis. Small vessel vasculitis presenting as gangrene of digits in SLE is rare. This may be ANCA or immune complex associated. ANCA positivity has been reported in 3-69% in SLE.3,4 However p-ANCA can be false positive in SLE with anti-ds DNA antibodies. To differentiate this one needs to look into the subspecificities of p-ANCA mainly myeloperoxidase subspecificities which if positive rules out ds-DNA mediated false positivity of p-ANCA.

In a series of 6 patients of gangrene of the extremities in lupus, the diagnosis was suggested by a good response to immunosuppression.5 The manifestations included fingertip, toe or gangrene of the forefoot. The prevalence of digital or distal limb gangrene was reported to be 1.3% from a large series of 520 lupus cases.6

Lupus vasculitis requires an exclusion of antiphospholipid associated vascular occlusion or embolic vascular occlusion. Differentiation is often difficult as both can occur simultaneously. Our patient tested positive for lupus anticoagulant and was negative for anticardiolipin antibodies. However, in view of immediate arrest of progressive gangrene with pulse methylprednisolone, without any anticoagulation, we feel that the pathogenesis of her digital gangrene is due to SLE vasculitis. This is further supported by the CT angiography findings (Figure 3).

Conclusion

From this case report we can conclude that when a young female comes with gangrene of the digits as the principal presenting feature, we should keep in mind the possibility of vasculitis and work up for a connective tissue disease. It is important to remember that ANCA positivity has been reported in various studies, however p-ANCA can be falsely positive due to anti-ds DNA antibodies.

References

Granulomatosis with Polyangiitis (GPA) Mimicking Tuberculosis

Vikram Haridas¹, Kiran Haridas²

**Abstract**

Granulomatosis with Polyangiitis (GPA) is a rare disease with varied clinical manifestations. We present a case of GPA which manifested initially with symptoms suggestive of meningeal tuberculosis. High index of suspicion and collective review of all clinical features helped in the correct diagnosis. Treatment of this case with rituximab provided significant symptomatic relief.

**Introduction**

Granulomatosis with Polyangiitis (GPA) is a rare autoimmune disease, characterized by necrotizing vasculitis, leading to the classic triad of granulomatous inflammation of the respiratory tract, necrotizing glomerulonephritis, and systemic vasculitis predominantly affecting the small vessels.¹ Being a rare disease, with non-specific symptoms, early diagnosis of GPA is difficult.² Due to the involvement of respiratory tract, and the high prevalence of multi-drug resistant tuberculosis in India, many patients are initially misdiagnosed as having tuberculosis.³

Here, we present a case which manifested initially with symptoms suggestive of meningeal tuberculosis. However, the patient did not respond to antitubercular therapy and in view of the patchy meningitis, other symptoms, laboratory investigations and previous history, a diagnosis of GPA was made. This case report underlines the need for a high index of suspicion and continuous treatment monitoring in GPA to diagnose and manage non-responders.

**Case Report**

A 32 year female presented with complaints of right-sided throat pain. Endoscopic examination of the throat revealed suspected granulomatous lesion at the junction of the eustachian tube and nasopharynx. Laboratory investigations revealed elevated C-reactive protein (CRP)-10 mg/dl and erythrocyte sedimentation (ESC) rate=30mg /1st hour (ESR). The antineutrophil cytoplasmic antibodies (C-ANCA) were strongly positive in high titers (38 IU/dL; normal range: 0-5 IU/dL). Computed tomography (CT) scan of the paranasal sinuses was normal. Magnetic resonance imaging (MRI) of brain did not reveal any abnormality in the brain and brainstem. She was suspected to have an upper respiratory tract limited (ANCA associated) vasculitis (Granulomatosis with Polyangiitis). A biopsy of the lesion was planned; however, the patient refused. Since patient was symptomatic, she was started on low dose steroid (methyl prednisolone 5 mg daily) for 2 weeks with significant improvement. Since her ESR and CRP were still high and she required steroids to reduce the pain, methotrexate (10 mg/week) was started as steroid sparing medicine for 2 months. The patient improved; however, later she discontinued the medications and lost for follow up.

Six months later, the patient returned with severe pain in the throat, along with severe headache, dysphagia, dysphonia and pain in the ear. She had leukocytosis and, elevated ESR and CRP levels. An MRI of the brain revealed patchy meningitis in the basal region with obstructive hydrocephalus. (Figure 1) Left otitis media and mastoiditis were also noted. Her cerebrospinal fluid (CSF) analysis showed few lymphocytes with 1 gm of protein. With all the neurological features, a working diagnosis of tuberculosis was made as it is the most common cause for basal meningitis. She was started on antitubercular drugs (ethambutol hydrochloride, isoniazid, pyrazinamide and rifampicin), along with steroids. A ventriculoperitoneal (VP) shunt was placed for obstructive hydrocephalus. Even after one month of treatment with antitubercular drugs, steroids and post placement of VP shunt, her symptoms (dysphagia, dysphonia and headache) persisted.

A repeat MRI revealed similar findings. With a previous history of c-ANCA positivity, the ANCA was repeated which was strongly positive in high titers (34 IU/dL). Patient was diagnosed as having ANCA positive central nervous system vasculitis. She was started on intravenous cyclophosphamide (750 mg every two weeks) with pulse methylprednisolone (1 g daily for 3 days), followed by 50 mg/day oral methylprednisolone. Dysphagia and dysphonia improved within 2 weeks; however, she continued to have severe headache, which responded only to intravenous methylprednisolone (125 mg) intermittently. Since the patient continued to have symptomatic
Management of ANCA positive vasculitis consists of remission induction with initial immunosuppressive therapy, followed by maintenance immunosuppressive therapy to prevent relapse and control the disease. Cyclophosphamide and prednisolone are most commonly employed drugs for remission induction in patients with systemic or severe disease. Shifting to methotrexate or azathioprine can be considered for maintenance of remission, in order to avoid the side effects of continued cyclophosphamide therapy.

Once the diagnosis of ANCA positive vasculitis was made in this case, treatment was initiated with cyclophosphamide and prednisolone. However, even after four cycles of cyclophosphamide therapy, the patient had no improvement in symptoms. Rituximab was thus used as an alternative, to which the patient had significant response.

About 15-20% of patients with GPA have been reported to be refractory to standard treatment. Rituximab is now being increasingly used for various refractory autoimmune diseases, including refractory ANCA associated vasculitis or in patients with a contraindication to cyclophosphamide. A retrospective study that included 66 patients with GPA, treated with rituximab and glucocorticoid for remission induction, showed that 78.8% patients achieved response in 6 months. Low dose rituximab, when used for maintenance of remission, was associated with low rates of relapse (11.2 per 100 patient years) and was also safe. Further, it does not have infertility concerns or bladder toxicity associated with cyclophosphamide.

Conclusion

Granulomatosis with Polyangiitis, with its varied and non-specific manifestations, is often a missed diagnosis and confused with TB. Since the disease can be fatal if untreated, one should always keep a high clinical suspicion for a timely diagnosis of this rare disease. Once the diagnosis is established, patients should be closely monitored for treatment response, as identifying non-responders at an early stage can help save crucial time of disease progression. Promptly shifting the non-responders to the next line of treatment can help bring in substantial symptomatic relief, induce remission and reduce complications.

References

Seizures Due to Insulinoma- A Rare but Treatable Cause

Shubha Bhalla¹, VPS Punia², M Naran³, Pushpa Kumari⁴, Saurabh Gupta⁵

Abstract
Hypoglycemia can cause multiple neuroglycopenic symptoms; seizures being one of them. Misdiagnosis and delay in treatment are common and prolonged hypoglycemia can lead to permanent neurological deficit or fatal coma. Hypoglycemia caused by an insulinoma is a readily treatable condition that should be considered in the differential diagnosis of intractable seizures. The following case report highlights the need for careful reassessment of all seizures that are atypical and refractory to medication.

Introduction
Insulinoma is the most common pancreatic islet cell tumors that arise from beta cells within the islets of Langerhans. The incidence is 4 cases per million per year. They are uncommon, with female preponderance; the average age of presentation being fifth decade of life. They are typically sporadic, solitary and less than 2 cm in diameter. The diagnosis relies on clinical features along with laboratory tests and imaging investigations to aid in localisation. We present a case of insulinoma in a 59 years old female who presented with history of recurrent seizures refractory to medication.

Case Report
A 59 year old female patient presented to ER in unconscious state since early morning hours. For the last 4 years she was having recurrent fainting episodes on awakening in morning between 5 am to 7 am sometimes associated with abnormal posturing, perioral and eyelid twitching and unresponsiveness. The attacks would usually last from few minutes to about half an hour.

Patient was on antiepileptic drugs for the last 4 years in view of recurrent seizures. The frequency of seizures had increased since last 5 months inspite of regular treatment. Patient also had complaints of headache, lethargy, diplopia, and blurred vision, particularly with exercise or fasting. She didn’t have history of fever, cough, breathlessness, weight loss or altered sleep pattern.

Patient’s serum insulin and c-peptide levels were checked. Her fasting plasma insulin level was 162.7 mU/L (Normal range 4.5- 40.5 mU/L) and c peptide level was 11.7 ng/ml (1.10 - 5.0 ng/dl) suggesting hypoglycaemia due to raised insulin levels and that too pancreatic origin.

Patient’s serum insulin and c-peptide levels were checked. Her fasting plasma insulin level was 162.7 mU/L (Normal range 4.5- 40.5 mU/L) and c peptide level was 11.7 ng/ml (1.10 - 5.0 ng/dl) suggesting hypoglycaemia due to raised insulin levels and that too pancreatic origin.

Abdominal ultrasound and abdominal CECT (triple phase) scan revealed a small lesion in body of pancreas of approximately size 11*15 mm, thought to be solitary benign insulinoma (Figures 1 and 2). Patient was then taken up for surgery and underwent distal pancreatectomy. Macroscopic pictures of the distal pancreas with the tumor mass are depicted in Figure 3. Histopathology pictures of the insulinoma are shown in Figure 4. Postoperative period was uneventful and she was discharged in stable condition.

Discussion
Insulinomas which are typically a beta-cell tumor are the commonest hormone-secreting tumor of the gastrointestinal tract; the incidence is 4 cases / million / year. Tumors may occur as a unifocal sporadic event or in 5–10% of patients with MEN-1. 10% are metastatic, and a further 10% are multiple but behave as benign tumors. Insulinomas are found throughout the pancreas and are small (usually less than 20 mm). The median interval from onset of symptoms to the diagnosis of insulinoma is 2 years with a wide range of one month to 30 years as reported by Service F et al.¹

Many patients with an insulinoma are overtly well individuals and do not report the adrenergic symptoms of hypoglycaemia and present with neurological or psychiatric symptoms.

Fig. 1: Triple phase CT abdomen showing the insulinoma (mass) of size 11*15 mm in the body of the pancreas and its relationship with the splenic artery and the superior mesentric artery

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manifestations that often lead to misdiagnosis. The delay in diagnosis is due to several factors. Firstly, the symptoms of insulinoma lack specificity, including various seizure disorders, personality change, bizarre behaviour, amnesia, convulsions, and incidentally dystonia and polyneuropathy; these symptoms are similar with many common neurological and psychiatric disorders. Secondly, fasting blood glucose level can be normal in some patients. Thirdly, hypoglycemia itself induces neuroglycopenic and autonomic unawareness.3,6

In a retrospective study with histologically confirmed islet cell adenomas, the interval between onset of symptoms ranged from one month to 30 years with the median of 24 months. A significant proportion (39%) were originally diagnosed with a seizure disorder. All these patients had symptoms of neuroglycopenia and three quarter reported relief of symptoms with ingestion of food.5

Insulinoma is one of the cause of post absorptive hypoglycemia also known as fasting hypoglycemia which occurs in non diabetic patients. Other causes being critical illnesses, hormonal (cortisol, growth hormone, glucagon or epinephrine) deficiency, alcohol consumption especially with empty stomach, other non islet cell tumors and certain medications. Diagnosis relies on key neuroglycopenic and sympathetic symptoms, blood glucose levels <50 mg/dl during monitored symptomatic episodes which improves with oral intake and a prolonged supervised fasting blood sugar test lasting upto 72 hrs. The above criteria along with increased c-peptide levels (>200 pmol/l), increased serum insulin level (>5 micromol/ml) in absence of sulfonylureas favoured a diagnosis of Insulinoma.4

Intraoperative palpation and ultrasound are the gold standard for localising an insulinoma with a reported success rate of 96 - 100%.7 MRI is said to be superior to CT for localisation of insulinoma among the non-invasive imaging modalities.

In Daggett and Nabarro’s review of 252 reported cases the most common neurological symptoms were confusion, coma, and seizures.3 Service FJ, Dale AJD, Elveback LR reported 12% of 60 consecutive patients of insulinoma presenting with grand mal seizure.1

The risk of recurrence of insulinoma is greater among patients with MEN-1(21% at 10 and 20 yrs) than in those without MEN-1 (5% at 10 yrs and 7% at 20 yrs).2

Risk of post pancreatectomy diabetes after distal pancreatectomy is around 7.5% in patients without pancreatitis.7

Neuroglycopenia should be considered in all patients with seizures and other neuropsychiatric symptoms especially if they do not conform to diagnostic criteria or respond to standard treatment. Taking full history (including relationship of attacks to foods, non stereotyped or atypical attacks and poor response to antiepileptic treatment) and clinical suspicion are key to making a diagnosis of insulinoma. Once suspected, confirming the diagnosis with a seventy two hour fast is relatively simple.

Conclusion

This case emphasizes the importance of evaluating the metabolic cause of the refractory seizure disorder. The possibility of atypical causes like insulinoma associated seizures should be considered in patients with history suggestive of close relationship to food intake, history of weight gain, atypical attacks, seizures refractory to treatment. Early diagnosis and treatment can free many patients from recurrent unpleasant hypoglycaemic attacks which could be fatal and from burdensome multiple antiepileptic treatment.

References

Marchiafava-Bignami Disease: A Rare Clinical Dilemma

Nitesh Pansari¹, Ravi Goyal¹, Manish Aswani¹, Shruti Agrawal¹, Heeralal Verma², Hemant Mahur³, Mahesh Dave⁴

Abstract

Marchiafava-Bignami Disease (MBD) is a progressive neurological disease, characterized by corpus callosal demyelination and necrosis and subsequent atrophy. It is usually seen in the context of alcoholism and malnutrition. Clinical diagnosis of this disease is quite challenging due to various presentations but a high degree of suspicion often leads to the correct diagnosis with help of neuroimaging. We report a case of MBD with a classical clinical course and typical radiological features. This case is highlighted in order to generate awareness regarding this uncommon but historic complication of chronic alcoholism.

Introduction

Marchiafava-Bignami Disease (MBD) is a progressive neurological disease, characterized by corpus callosal demyelination and necrosis and subsequent atrophy. It is usually seen in the context of alcoholism and malnutrition. In 1903, Italian pathologists Marchiafava and Bignami described 3 alcoholic men who died after having seizures and coma. In each patient, the middle two thirds of the corpus callosum was found to be severely necrotic. It can pose diagnostic dilemma in an appropriate scenario (such as heavy alcohol consumers/malnourished individuals) by mimicking the other common aetiologies of dementia, seizures, behavior disturbances and gait abnormalities.

MBD is a very rare condition. In 2001, Heleniuset al² wrote that they had found approximately 250 cases in published reports, although they also suggested that many cases had gone undiagnosed.

Case Report

A 40 years old healthy male was admitted to our medical ward with complaints of insidious onset gradually progressive gait instability for past 1 year and numbness of both lower limbs for past 15 days. There was no history of seizures, bladder-bowel-bladder disturbances or any history suggestive of cranial nerves involvement. There was no history of trauma in past. He had been a chronic alcoholic since last 15 years and he used to have 350-400 ml of country liquor daily. He was conscious, oriented to time, place and person but aggressive and irritable during the examination. He had severe spasticity of all four limbs with normal power. All deep tendon reflexes were exaggerated and bilateral plantar reflexes were flexor. He also had signs suggestive of cerebellar involvement like dysarthria and impaired coordination. He had sensory involvement in the form of reduced vibration and joint position sense. Gait was wide based and both spastic and ataxic type. There were no signs of inter-hemispheric callosal disconnection. Rest of the systemic examination was normal. On further laboratory evaluation he had a normal complete blood count with peripheral blood film. His liver function tests were deranged i.e. total bilirubin was 3.6 mg/dl, direct bilirubin was 1.9 mg/dl. Aspartate aminotransferase (AST or SGOT) was 275 W/L, alanine aminotransferase (ALT or SGPT) was 64 W/L, alkaline phosphatase (ALP) was 209 W/L, total protein was 7.9 gm/dl, albumin was 2.9 g/dl indicating albumin and globulin ratio reversal. His renal function tests, blood sugar, serum electrolytes were found to be within normal limits. He had normal thyroid profile with normal vitamin B12 levels. Blood HIV and VDRL tests were negative. His chest x-ray and electrocardiogram was normal. Ultrasonography revealed enlarged fatty liver with altered echogenicity without any evidence of portal hypertension. Magnetic resonance imaging (MRI) of brain with cervical spine was performed which revealed thinning of corpus callosum with abnormal signals within it, periventricular white matter and corona radiata, associated with changes of diffuse cerebral and cerebellar atrophy with normal cervical spinal cord (Figure 1). Based on the clinical scenario of the patient and neuroimaging findings a diagnosis of Marchiafava-Bignami disease was made. Patient was provided supportive treatment for his illness and advised complete abstinence from alcohol.

Discussion

Specific clinical characteristics of this case are chronic alcoholism, progressive gait imbalance, behavioral disturbances, dysarthria, spasticity, sensory involvement, deranged liver function tests and MRI findings of thinning of corpus callosum with diffuse cerebral and cerebellar atrophy.

MBD is most frequently seen in middle-aged or elderly chronic alcoholic males.² MBD was first reported in 1903 by Marchiafava and Bignami, who originally described the symptoms in Italian men with increased consumption of inexpensive manufactured Chianti wine¹. Currently, however, MBD is known to occur in patients with chronic consumption of other sorts of alcohol including whisky and French liquor³. MBD has also been found in severely malnourished people without a history of alcoholism.² In the present case, long-term consumption of alcohol in form of country liquor might have been related to the pathogenesis of MBD. Although the precise mechanisms underlying development of MBD remain unknown, effects of toxic agents present in alcohol, vitamin-B complex deficiency, or osmotic

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disorders have been considered as potential causes. The clinical spectrum of this disease is diverse which makes diagnosis difficult. In acute cases, prognosis is usually poor and mortality is high, even though there are case reports documenting complete recovery. Acute MBD and Wernicke’s encephalopathy clinically may occur together. Differentiating acute MBD from Wernicke’s encephalopathy is not difficult, because in the latter, MR imaging shows abnormal signal intensity and contrast enhancement in the mammillary bodies, peri-aqueductal region, and the walls of the third ventricle. Chronic presentation includes progressive dementia, behavioural abnormalities and an interhemispheric disconnection syndrome (limb apraxia, tactile agraphia, unilateral agraphia and hemialexia). An intermediate form has been described with an initial acute onset followed by regression to chronic form. It may be seen in combination with other manifestations of chronic alcohol abuse like Wernicke’s encephalopathy, Central Pontine myelinolysis and Morel’s laminar sclerosis. Our patient had signs of corticospinal tract, cerebellar and posterior column involvement simulating either subacute combined degeneration of cord or spinocerebellar ataxia with alcoholic neuropathy, however these two differentials were ruled out following laboratory investigations and MRI brain findings. In the past, cases of MBD were diagnosed only at autopsy, but with the advent of CT and MRI of brain, early and prompt diagnosis has resulted in improved survival and better prognosis. The characteristic MRI picture of acute MBD shows symmetrical lesions involving the central portion of the body of corpus callosum with sparing of dorsal and ventral layer; the ‘sandwich sign’. Sometimes, lesion extends into the genu and splenium, but only rarely is the entire corpus callosum involved. The lesions are hypointense on T1WI, hyperintense on T2WI and FLAIR showing diffusion restriction on DWI and variable reduction in apparent diffusion coefficient value. Recent MRI studies have shown that lesions may also be found in the cerebral hemispheric white matter, cerebellar peduncles or cortical grey matter. Our patient had typical lesions involving corpus callosum and additional extracallosal lesions involving periventricular white matter and corona radiata associated with changes of diffuse cerebral and cerebellar atrophy. In 2004, Heinrich et al. described 2 clinical subtypes of MBD as follows:

- **Type A** - This has predominant features of coma and stupor; this subtype is associated with a high prevalence of pyramidal-tract symptoms; radiologic features include involvement of the entire corpus callosum.
- **Type B** - Characterized by normal or mildly impaired mental status; radiologic features are partial or focal callosal lesions.

Our patient is categorised into Heinrich type A in view of the clinicoradiological picture. There is no specific therapy for MBD. Prompt diagnosis and early initiation of treatment with thiamine, vitamin B complex and folic acid expedite clinical recovery. High-dose steroids may aid in recovery by reducing oedema.

**Conclusion**

MBD is a disorder found in chronic alcoholics and malnourished patients. It should be included in differential diagnosis of an alcoholic patient presenting with neurological manifestations. MBD can mimic various neurological diseases and should be ruled out by neuroimaging of brain, which is a key to the diagnosis. Alcohol abstinence along with thiamine, vitamin B complex with vitamin B12 and folic acid can be given for treatment.

**References**

Bernardini Ramazzini-Father of Occupational Diseases

Jayant Pai-Dhungat

Bernardini Ramazzini (1633-1714) was born in Capri, northern Italy, during tumultuous period in European history characterized by deep recession affecting every aspect of life. Tribunal of inquisition had banned Galileo’s teaching and war was raging in the north.

Ramazzini studied at the University of Parma and became physician in 1659. Later for some time he practiced in the periphery of Rome, but subsequently chose Modena, which had recently established medical school. His hostile reception by the profession was counterbalanced by his successful practice and favor from Ducal Court. He was appointed to the chair of Professor Theory of medicine. Here, he became interested in the neglected occupational medicine and remained discharging his duties for almost 20 years. During this time he extensively studied workers in various industries and professions. Convinced that workers’ disorders had an important socioeconomic impact, he went to their workshops, talked to workers, and studied the conditions under which they worked. Ramazzini diagnosed health disorders with masterly clinical observations, and suggested measures to protect health. He proposed that physicians should extend the list of questions to ask the patients- “What is your occupation?”

Ramazzini published his principal treatise in Latin-De Morbis Artificum Diatriba - Diseases of Tradesman (Occupation), in 1700. In the De Morbis he outlined the health hazards of chemicals, dust, metals, repetitive violent motions, odd postures and other factors encountered by various workers in approximately 70 occupations leading to diseases. Hazards of the environment were distinguished from hazards of physical participation in the work. Mercury and lead are examples of the first group. Writer’s cramps, simian round shoulders of cobblers, and sciatica of tailors are some examples in the second group. De Morbis was one of the founding and seminal works on occupational medicine and played a substantial role in its further development. Ramazzini’s insights on prevention were no less significant. In fact he anticipated different issues within the framework of public health. The methodological approach, the interest towards vulnerable group, the concerns towards disabling disorders, and the need to cooperate with other physicians and hygienists was stressed in the treatise. Ramazzini clearly foresaw that prevention is better than cure.

As an epidemiologist, Bernardini contributed to the understanding of rinderpest and described epidemics of malaria. He was an early proponent of using cinchona bark in the treatment of malaria. As a meteorologist he noted the varying heights of Torecelian column of mercury with weather changes. In 1700, the senate appointed him to the first chair of the practice of medicine

Karl Marx cited Ramazzini’s work as a characteristic historic document of early manufacturing period in the beginning of industrial period, to support his anti-capitalist views.

De Morbis Artificum Diatriba’s first English edition appeared in 1705, just 5 years after Latin princeps edition. Historians’ claim the De Morbis Diatriba is to the history of occupational diseases what Vesalius’s book is to anatomy, Harvey to physiology, and Morgagni’s to pathology. Bernardino Ramazzini died in Padua in 1714. Many scientific societies on occupational hygiene have been named after Ramazzini in several countries including Italy and the USA.

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Steroid May be Beneficial in Patients with Pulmonary Leptospirosis

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Sir

We curiously read an article pertaining to the two cases that were presented and seen severe mold infection written by Hingorani et al.1 The two patients were given steroids which are suspected to be the risk factor for life-threatening invasive mold infection. They advise the physicians to be cautious in order to use steroids in pulmonary leptospirosis until its role is not clear whether the antibiotics were modified for the diagnosis or not after the detection of leptospirosis Ig M positive, supporting diagnosis of leptospirosis epidemic, pulmonary involvement in leptospirosis. However, in areas where there are cases of leptospirosis epidemic, pulmonary involvement can cause with 50%-70% mortality. Moreover, studies have shown that using steroids result in an important reduction in mortality.2,3 We can discuss whether steroids are beneficial adjuvant in the pulmonary leptospirosis, yet the two cases have not enough evidence for mold infection.

In both cases except leptospirosis Ig M positive, supporting diagnosis of leptospirosis was not given any further information.

We agree with the author about the fact that pulmonary leptospirosis has not been studied in sufficient level of evidence of steroid administration yet. However, in areas where there are cases of leptospirosis epidemic, pulmonary infection can cause with 50%-70% mortality. Moreover, studies have shown that using steroids result in an important reduction in mortality.2,3 We can discuss whether steroids are beneficial adjuvant in the pulmonary leptospirosis, yet the two cases have not enough evidence for mold infection.

References


Isolated Myocysticercosis

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Sir

Dear Editor, the article on “isolated myocysticercosis” is very interesting.1 Vignesh et al. noted that “most muscular cysticercosis are almost always associated with central nervous system involvement or with multiple intramuscular cysts or both.”1 Indeed, the isolated myocysticercosis is an uncommon type of cysticercosis2 and it can exist at any muscle including to small muscles such as ocular muscle.3 In the present case report, the assumption is made that there is no existence of other site of cysticercosis in the patient. The possibility of the existence of asymptomatic lesion in deep internal organ, soft tissue or very small organ (such as small muscle) cannot be ruled out.

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