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Pulmonary Renal Syndrome

Aman Sharma¹, GSRSNK Naidu²

Pulmonary renal syndrome (PRS) is a rare, severe and life-threatening condition characterized by presence of diffuse alveolar haemorrhage (DAH) and glomerulonephritis. Common causes of PRS include autoimmune diseases like ANCA associated vasculitis (AAV) including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) and antiphospholipid syndrome (APS). Infections like leptospirosis, dengue and drugs like hydralazine, propylthiouracil and d-penicillamine have also been associated with the development of PRS.¹ Rarely, PRS can be seen associated with other autoimmune diseases like systemic lupus erythematosus (SLE), IgA vasculitis, mixed cryoglobulinaemia and antiphospholipid syndrome (APS). Infections like leptospirosis, dengue and drugs like hydralazine, propylthiouracil and d-penicillamine have also been associated with the development of PRS.¹ In patients with PRS as it is associated with high mortality.

Even though AAV are the most common causes of PRS, exact disease specific incidence of PRS is not known. DAH has been reported to occur in 8-36% of patients with AAV and among them, 25% to 57% of patients require renal replacement therapy.³ We previously reported PRS in 10 out of 92 patients with AAV, 5 among GPA and 5 among MPA patients.⁴ Anti-GBM disease is a rare disease with an incidence rate of around 1 per million.⁵ Among patients with anti-GBM disease, 60-80% of them have lung and kidney involvement suggestive of PRS.⁶ Lung involvement in the form of DAH is very rare in SLE patients, however, 40-100% of these patients have coexisting lupus nephritis.⁷ In IgA vasculitis, renal involvement is common and manifested as IgA nephropathy but DAH is a rare manifestation.⁸ DAH and renal involvement in APS are seen as a part of catastrophic APS and is characterized by thrombotic microangiopathy and rarely capillaritis on histology.⁹ Up to 90% of patients with mixed cryoglobulinaemia have glomerulonephritis while DAH is present in 3.2% of patients.⁹

Data exclusively on clinical features, etiology, management and outcomes of PRS is scarce. In a study reported in this issue of the journal, Gokhale et al. have described the etiology and short-term outcomes of 25 patients with PRS from a tertiary care centre in Mumbai, India. Out of 25 patients, 18 patients had underlying autoimmune diseases while 7 patients had PRS secondary to infections. Among the autoimmune diseases, AAV was the most common etiology, noted in 12 patients (7 with GPA, 4 with MPA and 1 with EGPA). PRS was secondary to SLE in 5 patients and anti-GBM disease was the cause in one patient. Leptospirosis and dengue fever were the infections noted among the other 7 patients.

Clinical features of DAH include breathlessness, haemoptysis, fall in haemoglobin level and respiratory failure. It is important to note that in about a third of the patients with DAH, haemoptysis may be absent hence, a high index of suspicion is required to diagnose DAH.⁹ Gokhale et al. have also reported that haemoptysis was present in only 68% of patients in their cohort of 25 patients. Chest radiology shows infiltrates in perihilar areas with peripheral sparing but in 25% of patients, chest radiography may be normal.¹ Gokhale et al. reported that 14.3% of chest radiographs were normal in their study. Renal involvement is characterized by presence of active urinary sediments and proteinuria with or with out deranged renal functions. Serological tests for ANCA, anti-GBM antibodies, ANA and cryoglobulins help in differentiating various causes of PRS. Most common finding on histopathology is the presence of small vessel vasculitis. Pattern of immune complex deposition also helps in differentiating the etiology of PRS. AAV are characterized by minimal or no immune deposits while the immune deposits are in a liner fashion in anti-GBM disease.³

PRS is associated with high mortality if not treated early and aggressively. In the study by Gokhale et al., 32% of the patients died despite aggressive immunosuppressive therapy and other supportive measures. Early initiation of immunosuppression is essential in patients of PRS with underlying autoimmune disease. High dose intravenous methylprednisolone and cyclophosphamide or rituximab help in achieving remission among these patients. Steroids were used in all patients by Gokhale et al. while cyclophosphamide was given in 72% of patients and rituximab in 8% of patients. Plasma exchange has been proven to be effective in reducing progression to end stage renal failure among patients with severe renal involvement in AAV and anti-GBM disease.¹⁰,¹¹ The results of PEXIVAS trial are awaited and the trial may help in providing more definitive evidence on role of plasma exchange in severe manifestations of vasculitis.¹² Antimicrobial should be initiated if the underlying etiology is infection. Other supportive measures like mechanical ventilation, renal replacement therapy and blood transfusions may be required in these patients. In the report by Gokhale et al., all 8 patients who received invasive ventilation died, indicating poor prognosis in patients who present with severe manifestations like respiratory failure.

References


¹ Professor, ² Assistant Professor, Clinical Immunology and Rheumatology Services, Department of Internal Medicine, PGIMER, Chandigarh


Pulmonary Renal Syndrome: Experience from Tertiary Centre in Mumbai

Yojana Gokhale1, Raosaheb Rathod2, Trupti Trivedi3, NT Awadh4, Utkarsh Deshmukh5, Lalana Jadhav3, Amol Pawar2

Abstract

Introduction: Pulmonary Renal Syndrome (PRS), is characterized by diffuse alveolar haemorrhage (DAH) and glomerulonephritis (GN), occurring simultaneously. It has high mortality and dialysis dependence at one year, if not timely diagnosed and aggressively treated.

Objectives: To study etiology and short term outcome of PRS in India

Materials and Methods: This study included patients of PRS seen in a tertiary care center in Mumbai, by one consultant from 1997-2013, analyzed retrospectively and from January 2014 to December 2015 collected prospectively from six medical units, intensive care unit, nephrology and respiratory units. Patients with DAH (haemoptysis, breathlessness and x-ray chest with bilateral alveolar shadows with sparing of apices) and glomerulonephritis (Proteinuria, heamaturia, hypertension with or without raised serum Creatinine) were included in the study after carefully excluding other causes of haemoptysis and breathless like tuberculosis, pulmonary oedema, pneumonia, ARDS. During prospective enrollment of patients, in all admitted patients with haemoptysis, urine examination was carried out to specifically look for proteinuria and red blood cells in urine, same was also followed in those admitted for breathlessness with chest x-ray suggestive of alveolar haemorrhage. Patients were extensively investigated for etiology and were treated with steroids and pulse cyclophosphamide (after ruling out infectious etiology). Supportive care with ventilator or dialysis was given as per usual indications. Palsmapheresis was initiated in those with serum Creatinine ≥ 5.7mg/dl. Rituximab was used in refractory cases, as per treating physicians’ choice. Final outcome was death or discharge.

Results: There were 25 patients of PRS (13 retrospective, 12 prospective), with following etiology: Granulomatosis with polyangiitis (GPA) 7, Microscopic polyangiitis (MPO) 4, Churg Strauss Syndrome (EGPA) 1, Goodpasture’s syndrome 1, lupus 5, leptospirosis 5, dengue 2. All were given steroids, 18 (72%) were given pulse Cyclophosphamide (barring those with leptospirosis and dengue), ventilator support in 14 (56%) patients (8 invasive, 6 non-invasive), haemodialysis 3, plasmapheresis 1, Rituximab 2. Seventeen (68%) patients survived, mortality was high in those requiring invasive ventilator.

Conclusions: Most common etiology of PRS is ANCA positive vasculitis in India. With high degree of suspicion for DAH in patients presenting with haemoptysis, breathlessness and alveolar opacities in chest x-ray and carefully investigating by simple urine examination for evidence of GN, timely diagnosis of PRS can be made. With timely appropriate treatment survival is 68%. Patients with PRS due to leptospirosis or dengue have features suggestive of underlying disease (like icterus with raised bilirubin but < 200U SGOT/SGPT, subconjunctival haemorrhage, typical rash of dengue with thrombocytopenia).

Introduction

PRS, is a combination of diffuse alveolar haemorrhage (DAH) and glomerulonephritis (GN), occurring simultaneously. Historically such combination of pulmonary haemorrhage and glomerulonephritis (GN) was first described by Goodpasture in 1919. The term Goodpasture syndrome was adopted in 1958 to define these patients and pathogenic role of anti-glomerular basement membrane (anti-GBM) antibodies in some cases of pulmonary haemorrhage and GN was proven 10 years later. In an interesting study from Massachusetts General Hospital, out of 88 patients’ sera sent for anti-GBM antibodies in the setting of PRS, 48 tested positive for ANCA, 6 for anti-GBM and 7 for both, whereas in 27 patients unrelated renal and pulmonary diseases were found. DAH is characterized by haemoptysis, breathlessness, fall in haemoglobin, hypoxia in severe cases, bilateral alveolar shadows with sparing of apices on chest x-ray. Whereas glomerulonephritis is generally rapidly progressive (hypertension, proteinuria-haematuria and rapidly rising serum Creatinine). All investigators have reported a prodrome, followed by an acute presentation. The prodrome consists of non-specific constitutional symptoms like malaise, fatigue, Fever, weight loss, arthralgias, myalgias, episcleritis, purpuric rash that precede acute presentation by an average of 3-6 months, but up to 8-12 months of prodrome has been reported. A remarkable feature of PRS is a rapid progression from a cough with haemoptysis to hypoxic respiratory failure over a few hours.
Dependence at 1 year in over 70%.

Recruitment of patients, retrospective observational study, with serial steroids, immunosuppressants and oedema, thus delaying instituting bronchopneumonia, ARDS, pulmonary disorders like pulmonary tuberculosis, may be confused with other common facility to confirm diagnosis. PRS of lack of awareness, rarity, lack of support (35-50%)

Table 1: Baseline characteristics of PRS patients N=25

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.12±13.5 yr (14-60 Yr)</td>
</tr>
<tr>
<td>Sex</td>
<td>11 M : 14 F</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>38 days (3-395 d)</td>
</tr>
<tr>
<td>Presenting Features</td>
<td>(respi/renal/both:12/2/11)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>22 (88%)</td>
</tr>
<tr>
<td>Cough</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>Oliguria</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Oedema</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Raised Creatinine</td>
<td>23 (92%)</td>
</tr>
<tr>
<td>Urine with proteinuria</td>
<td>25 (100%)</td>
</tr>
<tr>
<td>Fever</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Serum Creatinine mg/dl</td>
<td>2.78±1.7 (0.7-6.7)</td>
</tr>
<tr>
<td>Haemoglobin gm/dl</td>
<td>9.3±1.46 (6.8-12)</td>
</tr>
<tr>
<td>ESR mm at 1 hr</td>
<td>73.12±34.52 (18-132)</td>
</tr>
<tr>
<td>X-ray chest (N=28)</td>
<td>24 : 4</td>
</tr>
<tr>
<td>Abnormal: Normal</td>
<td>24 : 4</td>
</tr>
</tbody>
</table>

Fig. 1: Bilateral alveolar shadows with apical sparing in DAH

or days. Haemoptysis is common but not invariable, and its absence may delay the diagnosis. Those cases of PRS not related to Goodpasture’s syndrome usually have clinical features suggesting such diagnoses as vasculitis, acute synovitis, multiplex mononeuritis or previous history of SLE.

PRS is not a single disease, it has a differential diagnosis of its own, most common cause being ANCA positive vasculitis, others being connective tissue diseases, Goodpasture syndrome, infections, drugs, neoplasms. The diagnosis rests on the identification of particular patterns of clinical, radiologic, pathologic and laboratory features. Timely diagnosis of PRS is important, considering high mortality (25-50%)

Material and Methods

**Study design:** This is an observational study, with serial recruitment of patients, retrospective from 1997- 2013 (single consultant’s data) and prospective from January 2014- December 2015, from 6 medicine units, medical ICU, nephrology and respiratory units (ie from 9 areas), in a tertiary care centre from Mumbai.

Inclusion criteria: All patients of either sex and any age having [A] features suggestive of diffuse alveolar hemorrhage (DAH) in lung. Hemoptysis/ breathlessness not obviously attributable to tuberculosis, pneumonia, carcinoma and bronchiectasis. X-ray chest showing alveolar opacities with sparing of apices s/o DAH and [B] Glomerulonephritis / [RPGN] Hematuria (clinical or microscopic) RBC or RBC Casts in urine analysis, Hypertension, with or without raised serum Creatinine.

Exclusion criteria: Other causes of haemoptysis/ breathlessness, like tuberculosis, bronchopneumonia, pulmonary oedema, ARDS or of renal failure like septicemia with ARF

Material history, examination, urine routine, biochemistry, chest x-ray (wherever necessary HRCT chest), Anti Neutrophilic Cytoplasmic Antibody (ANCA) by immunofluoroscence which if positive anti-MPO or anti-PR3 antibody by ELISA, ANA (by IF), Anti-GBM antibody, Cryoglobulins, HBsAg, anti-HCV were performed. Kidney biopsy was performed in some cases, with patient’s consent. Daily chest x-ray were performed to observe response to Inj. Methyl Prednisolone (disappearance of alveolar opacities) for initial 3-5 days.

Investigations and management protocol for prospectively enrolled patients: For prospective enrollment of patients, during 24 months, all patients who were admitted to hospital for haemoptysis or for breathlessness with chest x-ray suggestive of DAH, immediate urine routine examination was performed on a non-catheterized urine sample to look for haematuria. Similarly for patients admitted with nephritis, history of haemoptysis in previous few months was specifically asked and chest film at admission and from recent past (if available) were specifically seen for any alveolar opacities.

All patients of PRS were treated with Inj. Methyl Prednisolone (followed by oral Prednisolone 1mg/kg), Inj. Cyclophosphamide 750-1000 mg pulse (barring those with PRS due to obvious infections like leptospirosis or dengue). Supportive care with ventilator, dialysis was given when indicated. For those with Creatinine ≥ 5.7mg/kg plasma exchange was given. Rituximab was used in refractory cases.

Outcome was survival or death.

**Results**

There were total 25 patients of PRS (13 retrospective, 12 prospective), M:F :: 11:14, average age 34.12 ± 13.5 years (14-60 yr), average disease duration before diagnosis of PRS 38 days (range 3- 395 days). Table 1 depicts baseline characteristics of these patients. Out of 25 patients, 12 had only respiratory complaints, 2 renal and 11 patients both respiratory and renal abnormality at presentation. In patients presenting with pure respiratory complaints, renal involvement was detected because of specifically looking for red blood cells in urine in all admissions with haemoptysis, or with alveolar shadows on chest x-ray (Figure 1). Haemoptysis, breathlessness and cough were present in 68%, 88%, and 68% patients respectively, whereas hypertension, oliguria, oedema in 56%, 16% and 16%. History of fever, joint pain and rash was given by 72%, 12% and 24% respectively. Five patients were known SLE patients, 3 of them with poor compliance and one with regular follow up but refractory disease for 9 years and one misdiagnosed outside as tuberculosis. In 5 patients clinical suspicion of leptospirosis (jaundice, fever, myalgia) and in 2 that of dengue (fever, rash, thrombocytopenia) with laboratory test confirmation was already done and during their hospital stay they developed DAH.
Discussion

This study included 25 patients of PRS, both prospective and retrospective, managed over 19 years in a single tertiary care centre in Mumbai. Out 25 patients of PRS, 13 are retrospective cases studied by single physician from 1997-2013 in one medicine unit (ie 13 cases in 204 months by one consultant) and remaining 12 cases are collected prospectively from 2014-2015, in the same institute from 6 medicine units, MICU, Nephrology and respiratory unit (ie 12 cases from 9 areas ie nine consultants, over 24 months). Thus with high index of suspicion, in a busy tertiary care centre, one case of PRS in 16-18 months was diagnosed by a consultant. Duration of symptoms before diagnosis of PRS was made was 38 days (3-395 days). Five patients were misdiagnosed before admission to our institution, 3 presenting with fever and haemoptysis were misdiagnosed as tuberculosis (later confirmed as PRS due to SLE 1, EGPA 1-with eosinophilia and waxing and waning infiltrates on chest x-ray and MPA 1), 2 with GPA with PRS, presenting with breathlessness were misdiagnosed as allergic rhinitis with ILD (on HRCT 1 and bronchial asthma 1. Both these patients had normal chest x-ray at some point of time during their illness.

Table 2: Chest Imaging in PRS

<table>
<thead>
<tr>
<th>Chest x-ray N=28</th>
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</thead>
<tbody>
<tr>
<td>Bilateral infiltrates</td>
</tr>
<tr>
<td>Unilateral infiltrates</td>
</tr>
<tr>
<td>Unilateral consolidation</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Waxing and waning infiltrates</td>
</tr>
<tr>
<td>HRCT Chest N=11</td>
</tr>
<tr>
<td>GGO</td>
</tr>
<tr>
<td>Consolidation</td>
</tr>
<tr>
<td>Fibrosis</td>
</tr>
<tr>
<td>Nodule</td>
</tr>
<tr>
<td>GGO- Ground glass opacities</td>
</tr>
</tbody>
</table>

Table 3: Etiology of PRS N=25

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCA positive</td>
<td>11</td>
<td>44%</td>
</tr>
<tr>
<td>GPA c-ANCA and anti-PR3 +ve</td>
<td>7</td>
<td>28%</td>
</tr>
<tr>
<td>MPA p-ANCA and anti-MPO +ve</td>
<td>4</td>
<td>16%</td>
</tr>
<tr>
<td>ANCA Negative</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Goodpasture syndrome</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Anti-GBM +ve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>5</td>
<td>20%</td>
</tr>
<tr>
<td>Churg Strauss syndrome / EGPA</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Infective</td>
<td>7</td>
<td>28%</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>5</td>
<td>20%</td>
</tr>
<tr>
<td>Dengue</td>
<td>2</td>
<td>8%</td>
</tr>
<tr>
<td>GPA- Granulomatosis with polyangiitis, MPA-Microscopic polyangiitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Treatment of PRS N=25

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>30 (100)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Ventilatory support</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

Our patients were a decade younger than reported in literature. Diagnosis of DAH is challenging. Triad of haemoptysis, radiographic abnormality (typically diffuse alveolar opacities/interstitial opacities/fibrosis), unexplained drop in haematocrit should make one suspect DAH. These features are individually present in 60-70%, 80-100%, 60-70% patients of PRS respectively, whereas the whole triad is reported in up to 38% in a meta-analysis of 112 cases. In our study the triad was present in 68% patients. Haemoptysis may be absent in about one third cases, alveolar shadows may be unilateral (10-20%) or chest x-ray may be normal in 10-20% patients and drop in haemoglobin may not be possible to document, if previous Hb is not available. Also, if haemoglobin <12 gm/dl is used as a cut off for anaemia as in western literature, most Indian patients are anaemic (100% in our study and with 10gm/dl as cut off 80% had low hemoglobin). Most consistent feature in the triad is alveolar opacities (reported in 93% in meta-analysis) was present in 96% in our study. So, in a patient with respiratory symptoms like haemoptysis, breathlessness, cough; if alveolar opacities are present on chest x-ray one should consider diagnosis of DAH and should specifically look for evidence of glomerulonephritis (Hypertension, proteinuria, haematuria with or without raised serum Creatinine). Though bronchoalveolar lavage is very useful in the diagnosis of DAH and also gives material for culture to rule out infection, and for biopsy, it is not always practical in non-respiratory units on an urgent basis, and often not performed by chest physicians in a patient with haemoptysis unless spumt AFB is negative. Carbon monoxide diffusion capacity (DLCO), is raised in 30% patients in first 48 hours after alveolar haemorrhage, the test may not be available at odd hours and at bedside in a critically ill patient. On high resolution CT chest, alveolar haemorrhage is seen as GGO's in acute stage and later as fibrosis, both these
features have a long list of differential diagnosis. Thus diagnosis of PRS (clinical+ radiological+ serological+ histological) is by suspecting DAH when x-ray chest reveals alveolar opacities in a patient with respiratory symptoms and documenting GN by urine examination, hypertension with /without raised serum creatinine, and sending serological test for ANCA (which is the most common cause for PRS), ruling out mimics by all possible means, and documenting quick response (disappearance) of alveolar opacities within 48 hours of administering Inj. Methyl Prednisolone, and then performing kidney biopsy to document GN. When bacterial infection is in doubt this can be done under cover of antibiotics (infiltrates of infectious etiology don’t disappear as fast as alveolar haemorrhage). PRS is generally not a presenting feature of SLE and develops in a known case of lupus. Infections like Leptospirosis, malaria, dengue would have their clinical features and laboratory tests for diagnosis. Low platelets occur in SLE and infections, whereas platelet count is normal or high in vasculitis and other CTD which can cause PRS.

In our patients breathlessness was most common presenting complaint (88%) followed by haemoptysis (68%), meaning thereby in 32% patients with DAH, haemoptysis was absent. Haemoptysis is reportedly absent in 30-40% patients of PRS16. Alveolar opacities were present at some point of time in (96%) 24 out of 25 cases, in one patient with normal chest x-ray, HRCT chest revealed GGOs and areas of fibrosis in lower and middle lobes, she was c-ANCA and anti-PR3 positive, Urine 100-120 RBCs /hpf, serum Creatinine 1mg/dl, kidney biopsy (Figure 2) was reported as most glomeruli sclerosed, 14 glomeruli relatively preserved and show mononuclear infiltrates, fibrinoid necrosis and crescents, biopsy consistent with Wegener’s granulomatosis in end stage renal disease. But her GFR was 30ml/min (persisted for 5 years and improved to 50ml/min after 5 years). She was symptomatic for 8 months prior to diagnosis.

Table 2 depicts features of chest imaging in our patients. Most common imaging finding was bilateral alveolar opacities with sparing of apices (Figure 1), 6 unilateral opacities (sparing apices, which are commonly involved in Tuberculosis) and 4 out of 28 chest x-rays were normal at some point of time, but 3 patients’ x-rays were at other times revealed infiltrates. Other investigators have reported 7-20% normal chest x-rays in DAH. There are few studies reporting HRCT chest findings in DAH. In acute stage of AH, HRCT shows lobar or lobular ground glass opacities16,17 (GGOs), later over 2-3 days may show interlobular septal thickening superimposed on areas of ground-glass opacity giving crazy pavement pattern, between chronic recurrent bleeding events ill-defined centriflobular nodules reflecting intra-alveolar accumulation of pulmonary macrophages usually uniform in size (1-3 mm) diffusely distributed may be seen, severe repeated haemorrhage may progress with features of interstitial fibrosis. CT chest is required in cases of suspected DAH with normal CXR findings. Table 3 depicts etiology, ANCA positive vasculitis being the most common cause of PRS in 11 out of 25 (7 GPA and 4 MPA), second being SLE (this may be due to referral bias as our unit is in-charge of rheumatology services, 1 was our regular follow up for 9 years, and on MMF for LN, 1 misdiagnosed outside as pulmonary tuberculosis, and three SLE patients were diagnosed cases but non-compliant with treatment), one patient was Goodpasture syndrome, 1 EGPA, 5 leptoauriosis and 2 dengue.

Table 4 depicts treatment given to these 25 patients. All were treated with immunosuppressants (Inj. MPS in all 25, Inj. Cyclophosphamide in 18 patients, barring those with infectious etiology for PRS. Total 14 patients required ventilator support. Six patients on non-invasive ventilator survived but eight on invasive ventilator died. Haemodialysis was given to 3 patients. There were 2 patients with serum Creatinine >5.7mg/dl, but only one could afford plasma exchange, he was a case of MPO, the other non-affording patient was of Goodpasture syndrome. He received haemodialysis, survived but became dialysis dependent. Both controlled and uncontrolled studies have suggested that routine addition of plasmapheresis is unnecessary. However, when renal
function is impaired to the point that dialysis is required, the addition of plasma exchange increases the chance of renal recovery. In the MEPEX trial the addition of PLEX to immunosuppressive therapy was found to improve 12-months renal outcomes in AAV patients presenting with severe renal dysfunction (serum creatinine > 5.8 mg/dl) Two out of 5 SLE patients were given Rituximab.

Seventeen (68%) patients survived. Cruz and Hugh have reported 61% and 64% survival respectively. In an Indian study, by Rajigopal et al 31% survival is reported. Mortality occurred predominantly in patients with severe respiratory distress requiring invasive ventilator (Table 5). There was no relation of serum Creatinine to mortality.

**Conclusion**

DAH should be suspected in a patient presenting with breathlessness, haemoptysis, alveolar opacities (on chest x-ray) and anemia. Look for RBCs in the urine of such patients to detect associated renal involvement. And vice a versa in patients of nephritis/ RPGN ask for history of haemoptysis and look for alveolar infiltrate, thus timely diagnosing PRS. ANCA positive vasculitis is the most common cause of PRS. With steroids, pulse Cyclophosphamide and supportive care, 68% survival can be achieved. In our cohort, outcome was better in infection associated PRS than vasculitis or CTD associated PRS.

**References**


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**Thrombolysis in Angiographically Proved Intermediate to High Risk Pulmonary Embolism**

**Rajeev Bhardwaji**, Malay Sarkar

**Abstract**

**Purpose of study:** Pulmonary embolism is a common emergency in the hospital setting. Main line of treatment is anticoagulant therapy. However, patients with right ventricular dysfunction are the subgroup with increased mortality and may have better outcome with initial treatment with thrombolytic therapy. The study was done to see the outcome of thrombolytic therapy in angiographically proved patients of pulmonary embolism

**Methods:** We performed systemic workup of patients suspected of pulmonary embolism(PE). Diagnosis of PE was ruled out in patients with low probability of PE, as defined by Wells score and negative d dimer assay. All patients were subjected to echocardiography. Those showing findings suggestive of PE, with right ventricular dysfunction, with or without hypotension, were subjected to pulmonary arteriography. Patients having evidence of PE were subjected to thrombolyis. Repeat angiography was done after the thrombolysis to see the effect of thrombolysis and fall in pulmonary artery pressures.

**Introduction**

Pulmonary embolism remains a major cause of morbidity and mortality in the general community, with an estimated incidence of 0.5 per 1000 people and a case-fatality rate of 15% at 3 months. Mortality is even higher for patients with “major” pulmonary embolism; registry data indicate in-hospital mortality of up to 30% in patients with acute pulmonary
Results: 27 consecutive patients with angiographically proved PE were thrombobilized. Mean age was 45.8±15.2 years. 18 were male and 9 were female. Average systolic and mean pulmonary artery pressure before thrombolysis was 71.2±14.4 and 47.5±10.5 mm Hg. Angiographic success was seen in 22 patients (81.5%). Average systolic and mean pulmonary pressure after thrombolysis was 47.1±21.7 and 29.4±16.5 mm Hg. Three patients with unsuccessful thrombolysis were successfully subjected to transcatheter thrombus extraction. One patient died during thrombolysis. None of the patients had major bleeding complications.

Conclusion: Thrombolysis is effective in majority of patients with pulmonary embolism with right ventricular dysfunction. The bleeding risk is low.

Pulmonary embolism who are hemodynamically unstable at presentation. The study was conducted to see the effectiveness of thrombolytic therapy (TLT) in patients with angiographically proved pulmonary embolism (PE).

Material and Methods

Patients coming to our hospital with symptoms suggestive of PE were subjected to detailed examination. ECG was done in all patients. Patients with low probability of PE on the basis of wells score and negative d dimer essay were excluded. All subjected were subjected to detailed echocardiography. Patients showing high risk features such as hypotension, dilatation of right atrium (RA) and right ventricle (RV), evidence of tricuspid regurgitation (TR) with TR velocity 3M/s and evidence of right ventricular free wall hypokinesia were included in the study. When study was started, our hospital did not have facilities of 64 slice CT.

Patients having contraindication to TLT were excluded. All patients were subjected to pulmonary arteriography with Pig tail catheter, through femoral vein puncture. Pulmonary artery pressures (PAP) were recorded. Patients showing evidence of occlusion or filling defect of proximal part of either pulmonary were subjected to TLT, through the same venous sheath. Most of the patients received streptokinasae (STK). Dose used was 2.5 lac units in 30 minutes and then infusion of one lac units/hour for 12-24 hours. Echocardiographic evaluation was done 6 hourly. Pulmonary angiography was repeated after 24 hours. PAP was again measured. Those showing partial recanalization were subjected to further infusion of STK for 12-24 hours and again angiography was repeated.

Results

27 consecutive patients who had evidence of PE on pulmonary arteriography with RV dysfunction on echocardiography were included in the study. Table 1 show patient characteristics. 18 were male and 9 were female. Mean age was 45.8±15.2 years. Breathlessness was most common presenting symptom, seen in 24 patients (88.8%). Table 2 shows ECG findings. Commonest ECG finding was T wave inversion in V1-V4, seen in 11 patients (44.7%), followed by S1Q3T3 pattern seen in 7 patients (25.9%). ST elevation was seen in V1-V4 in one patient. 4 patients had normal ECG. 13 patients had predisposing factors for PE, 3 of these had post partum state, 4 had long bone fracture in the past, one had past history of PE. 25 patients received STK. One patient had anaphylactic reaction to STK, and was given tenecteplase (TNK). Another patient with treated carcinoma of bladder received TNK. Average systolic and mean pulmonary artery pressure before thrombolysis was 71.2±14.4 and 47.5±10.5 mm Hg respectively. Main pulmonary artery was involved in one patient, right pulmonary artery in 12 patients and left pulmonary artery in 5 patients and both pulmonary arteries in 9 patients.

21 patients had complete resolution of thrombus, 3 of these required TLT for 48 hours. Out of 5 patients, who did not achieve successful thrombolysis, 3 had successful transcatheter thrombus extraction. One patient was subjected to surgical embolectomy outside the state. One patient died during thrombolysis due to cardiogenic shock. No patient had major bleeding.

Discussion

Pulmonary embolism should be suspected in all patients who present with new or worsening dyspnea, chest pain, or sustained hypotension without an alternative obvious cause. However, the diagnosis is confirmed by objective testing in only about 20% of patients. Depending on the clinical presentation, the case fatality rate for acute pulmonary embolism ranges from about 60% to less than 1%. To guide the management of acute PE, the European Society of Cardiology and the American Heart Association have proposed a three-level risk stratification scheme based on haemodynamic status and the presence of right ventricular dysfunction (RVD) or myocardial injury. High-risk (or massive) PE is defined as an acute PE with sustained systemic arterial hypotension. Intermediate-risk (or
submissive) PE is defined by the presence of RVD or injury in the absence of arterial hypotension. Finally, low-risk PE is defined by the absence of hypotension and of markers of RVD or injury. In 1970, the first randomized trial comparing urokinase with heparin for patients with PE was published and 7 years later streptokinase was approved by the US Food and Drug Administration (FDA) for the treatment of high-risk PE. The preferred fibrinolytic agent is alteplase as a 100-mg continuous 2-hour infusion. Alteplase is the only contemporary fibrinolytic drug approved by the Food and Drug Administration for massive PE.

Although systemic fibrinolysis is not worth the risk in all patients with acute PE, it is recommended as standard, first-line treatment in patients with massive PE. In an overview of the 5 randomized controlled trials that included patients with massive PE, fibrinolysis reduced the risk of death or recurrent PE by 55%.

Although thrombolytics are accepted as the standard of care for patients with hemodynamic instability, a great deal of controversy remains about the benefits of thrombolytic therapy for patients who present with acute PE, are hemodynamically stable, but have echocardiographic or other evidence of RV failure or strain. Registry data from the International Cooperative Pulmonary Embolism Registry indicated that patients with RV hypokinesis on echocardiography even in the presence of a normal systemic arterial BP were at a twofold increased risk of death compared to those patients who had normal RV wall motion. Another series of 162 consecutive patients presenting with acute PE reported that 31% had concomitant RV dysfunction that was associated with a 5% mortality rate compared to a 0% mortality rate in those with preserved RV function. Based on early data suggesting that patients with RV dysfunction are at an increased risk of PE-associated death, Konstantinides and colleagues designed a study that enrolled 256 hemodynamically stable patients (systolic BP > 90 mm Hg) with proven acute PE and evidence of RV dysfunction or pulmonary hypertension. Patients were randomized to receive rt-PA plus heparin or placebo plus heparin with a follow-up period of 30 days. The main outcome measure was a combined end point that included in-hospital death and clinical deterioration requiring escalation of care. The study results indicated that patients who received rt-PA were significantly less likely to deteriorate clinically and reach the combined clinical end point than those who received placebo (11% vs 25%, respectively; relative risk reduction, 55%; 95% CI, 21 to 75%; number needed to treat, eight). However, the groups did not differ in all-cause mortality with a 3.4% mortality rate in the rt-PA group compared to 2.2% in the placebo group (relative risk increase, 56%; 95% CI, 60 to 513%). The study has been criticized because it allowed treating physicians to break protocol and administer “rescue” thrombolysis if they judged that a patient’s clinical condition was deteriorating. The high rate of rescue thrombolysis may have driven the composite end point to statistical significance.

We thrombolized all patients with intermediate to high risk pulmonary embolism, with streptokinase, and got good results, though currently FDA has approved alteplase. This was done due to low cost of streptokinase and easy availability. In fact, STK is available free of cost in our hospital. Moreover, there are no conclusive findings from studies comparing different thrombolytic regimens in patients with acute pulmonary embolism. Short infusion times (2 hours or less) are recommended over prolonged infusion times, since they achieve more rapid thrombolysis and are probably associated with less bleeding. Conclusion Commonest presentation of PE is breathlessness. Most common ECG finding is T inversion in leads V1-V4. Thrombolysis with STK can be done in intermediate to high risk patients, with good results. There are no major bleeding complications. The patients not responding to TLT, can be subjected to mechanical thrombus extraction.

Limitations

It was not a randomized control trial and did not compare the results of TLT with heparin.

References

Co-relation Between Total Cholesterol, High Density Lipoprotein, Low Density Lipoprotein and Glycosylated Haemoglobin (HbA1c) in Diabetic Patients with Acute Coronary Syndrome (ACS)

DC Pant¹, AB Mowar², N Chandra³*

Abstract

Background: Patients with diabetes & dyslipidaemia are at increased risk of developing coronary artery disease that many time manifests as life threatening ACS.

Aim: To study co-relation between HbA1c & total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) in diabetic patients with acute coronary syndrome and also their co-relationship with severity of ACS independently.

Materials & method: Blood samples of 51 known diabetic patients presented to emergency with ACS were sent for HbA1c & lipid profile estimation. All patients underwent coronary angiography. Obtained results were statistically analysed & co-related.

Results: Patients were divided as having: 1. HDL <40, >40; 2. LDL <100, >100; 3. Total cholesterol <200, >200; 4. HbA1c 6.5-8.4, >8.4; 5. Single vessel disease (SVD) / multi vessel disease (MVD). Statistically significant direct co-relation was found between HbA1c, LDL, Total cholesterol, ACS severity (SVD/MVD) & inverse co-relationship with HDL.

Conclusion: Severity & incidence of ACS in diabetic patients can be minimised by maintaining adequate glycaemic control & also by keeping circulating lipids under control.

Introduction

The term acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with myocardial ischemia and covers the spectrum of clinical conditions ranging from unstable angina, non ST segment elevated myocardial infarction (NSTEMI) and ST segment elevated MI (STEMI).¹

Potentially modifiable risk factors for ACS - smoking, diabetes, hypertension, dyslipidaemia, obesity, psychosocial factors, lack of exercise, and a diet low in fruit and vegetables along with little or no alcohol consumption.²

HbA1c is a biomarker reflecting both fasting and PP plasma glucose concentration over preceding 3 months and also it has been regarded as an important tool in management of diabetes.³ HbA1c can be used to diagnose diabetes and the diagnosis can be made if HbA1c level is >6.5%.⁴ Diagnosis should be confirmed with a repeat HbA1c test, unless clinical symptoms and plasma glucose levels >200 mg/dl are present in which case further testing is not required. HbA1c just below 6.5% may indicate the presence of intermediate hyperglycemia. ADA has suggested HbA1c between 5.7-6.4% as the high risk range.⁵

Dyslipidaemia is a well established risk factor for the development of coronary artery disease, and this has been demonstrated in several clinical and epidemiological studies.⁶-⁸ High plasma low-density lipoprotein cholesterol concentrations are directly correlated with the development of coronary artery disease⁹ and low high density lipoprotein cholesterol concentration have been pointed out as one of the strongest independent risk factor for CAD.¹⁰

Levels of LDL, Total and HDL cholesterol:

LDL CHOLESTEROL <100 - Optimal, 100-129 - Near or above optimal, 130-159 - Borderline high, 160-189 - High, >190 - Very high. Total cholesterol <200 - Desirable, 200-239 - Borderline high, >240 - High. HDL cholesterol <40 - Low >60 - High.¹¹ Three categories of risk that modify LDL cholesterol goals:

Risk categories LDL goal (mg/dl)
- CHD and Risk equivalents* <100
- Multiple(2+) risk factors** <130
- 0-1 risk factor <160

*Diabetes is regarded as a coronary heart disease risk equivalent. **Risk factors - cigarette smoking, hypertension, low HDL, family history of premature CHD (in male first-degree relative <55 years of age, in female first-degree relative <65 years), age (men >45 years; women >55 years).¹¹

Significantly increased levels of cholesterol and lipids are also seen in type 2 diabetic patients with CAD as compared to diabetic patients without CAD. It has been observed that there is a direct correlation between HbA1c and the severity of CAD in diabetic patients.¹²
Table 1: Glycosylated haemoglobin (HbA1c) and coronary vessels involved

<table>
<thead>
<tr>
<th>Coronary vessels involved</th>
<th>Total</th>
<th>Single vessel</th>
<th>Multi-vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n%</td>
<td>n%</td>
</tr>
<tr>
<td>HbA1c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.5 - 8.4</td>
<td>31</td>
<td>79.5</td>
<td>0</td>
</tr>
<tr>
<td>8.5+</td>
<td>8</td>
<td>20.5</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>100.0</td>
<td>12</td>
</tr>
<tr>
<td>Mean</td>
<td>7.67</td>
<td>10.78</td>
<td>8.40</td>
</tr>
<tr>
<td>Std. deviation</td>
<td>0.71</td>
<td>1.44</td>
<td>1.62</td>
</tr>
<tr>
<td>Independent samples mann-whitney U-test p-value</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: High density lipoprotein (in mg/dl) and coronary vessels involved

<table>
<thead>
<tr>
<th>Coronary vessels involved</th>
<th>Total</th>
<th>Single vessel</th>
<th>Multi-vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n%</td>
<td>n%</td>
</tr>
<tr>
<td>HDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>19</td>
<td>48.7</td>
<td>11</td>
</tr>
<tr>
<td>40+</td>
<td>20</td>
<td>51.3</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>100.0</td>
<td>12</td>
</tr>
<tr>
<td>Mean</td>
<td>41.62</td>
<td>25.92</td>
<td>37.92</td>
</tr>
<tr>
<td>Std. deviation</td>
<td>11.12</td>
<td>8.67</td>
<td>12.48</td>
</tr>
<tr>
<td>Independent samples mann-whitney U-test p-value</td>
<td>&lt;0.001</td>
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</table>

Table 3: Low density lipoprotein (in mg/dl) and coronary vessels involved

<table>
<thead>
<tr>
<th>Coronary vessels involved</th>
<th>Total</th>
<th>Single vessel</th>
<th>Multi-vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n%</td>
<td>n%</td>
</tr>
<tr>
<td>LDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td>24</td>
<td>61.5</td>
<td>0</td>
</tr>
<tr>
<td>100+</td>
<td>15</td>
<td>38.5</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>100.0</td>
<td>12</td>
</tr>
<tr>
<td>Mean</td>
<td>96.15</td>
<td>162.83</td>
<td>111.84</td>
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<tr>
<td>Std. deviation</td>
<td>31.79</td>
<td>36.74</td>
<td>43.37</td>
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<tr>
<td>Independent samples mann-whitney U-test p-value</td>
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Table 4: Total cholesterol (in mg/dl) and coronary vessel involved

<table>
<thead>
<tr>
<th>Coronary vessels involved</th>
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<th>Single vessel</th>
<th>Multi-vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n%</td>
<td>n%</td>
</tr>
<tr>
<td>Cholesterol 200 - 239</td>
<td>3</td>
<td>7.7</td>
<td>6</td>
</tr>
<tr>
<td>240+</td>
<td>2</td>
<td>5.1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>100.0</td>
<td>12</td>
</tr>
<tr>
<td>Mean</td>
<td>164.13</td>
<td>216.35</td>
<td>176.41</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>33.44</td>
<td>41.22</td>
<td>41.52</td>
</tr>
<tr>
<td>Independent samples mann-whitney U-test p-value</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Materials and Methods

The study was cross-sectional study done from 1/1/2015 to 31/5/2016. Diabetic patients presented in cardiology unit of medicine at SRMIMS, Bareilly and were diagnosed to have acute coronary syndrome were taken in study.

Inclusion criteria: Known patients of diabetes mellitus on treatment with either insulin or oral drugs or both, presenting with acute coronary syndrome, in emergency.

Exclusion criteria: Patient already on hypolipidemic drugs, Old case of coronary artery disease, newly diagnosed cases of diabetes mellitus, Patients with conditions confounding lipid profile measurement such as known case of hypothyroidism, obstructive liver disease, chronic renal disease, nephrotic syndrome, Patient on medications such as estrogen, progestin, anabolic steroids, corticosteroids, retinoid, cyclosporine & anti-retroviral medication.

Sample size: 51 diabetic patients with acute coronary syndrome.

Methodology of data collection: Diabetic patients presented in cardiology unit of medicine at SRMIMS, Bareilly with symptoms of myocardial ischemia or atypical symptoms of ACS were taken for study. Detailed history of present illness with past history, personal history, family history was taken. General and systemic examination was done. Following which written consent was taken and patient was investigated with ECG, Cardiac troponins, Glycosylated haemoglobin, Fasting lipid profile, Liver function tests, Kidney function tests, Complete blood count, TSH estimation.

Diagnosis of ACS was made on the basis of ECG, cardiac troponins and clinical features.

All these patients undergone coronary angiography to find presence of whether single-vessel or multi-vessel disease on ARTIS-ZEE FLOOR CATH LAB OF SIEMENS.

HbA1c estimation was done by enzymatic assay method on automated analyser.

Total cholesterol was measured using liquid cholesterol reagent set for determination of total cholesterol based on enzymatic method using cholesterol esterase, cholesterol oxidase and peroxidase on automated analyser. Triglycerides were measured by glycerokinase peroxidase-peroxidase method on automated analyser, cholesterol was measured by enzymatic method using liquid cholesterol reagent set on automated analyser.

Statistical Analysis: Data was entered in Microsoft Excel 2010 and statistical analysis was done using IBM SPSS V 20.00. Categorical variables were analysed using proportion and percentages. Continuous variables were summarised by mean and standard deviation and association test was done by parametric tests.

Results

Significant co-relation between HbA1c and ACS severity depicted in form of single/multi-vessel disease. Mean HbA1c of patients with single-vessel disease was 7.6±0.71 and of patients with multi-vessel disease was 10.78±1.44 (Table 1).

Significant inverse co-relation was also found between LDL and ACS severity with mean LDL in SVD patients 41.62±11.12 and in patients with MVD it was 25.92±8.67 (Table 2).

Significant co-relation was also found between LDL and ACS severity with mean LDL in SVD patients 96.15±31.79 and in patients with MVD it was 162.83±36.74 (Table 3).

Significant co-relation was also found between total cholesterol and ACS severity. With mean total cholesterol 164.13±33.44 in patients with SVD and mean 216.33±41.22 in patients with MVD (Table 4).

Significant direct co-relation was also found between HbA1c and total cholesterol, LDL and inverse significant co-relation with HDL (Table 5).

Discussion

Our study showed direct co-relation
of HbA1c with ACS severity in the study patients. Similar type of relation was also observed in study “HbA1c level correlation as a predictor of coronary artery disease and its severity in patients undergoing coronary angiography” conducted by Baligar BD et al16 in 2016 on 100 patients presented with ACS. Coronary angiography was performed on all patients. Relationship between HbA1c and no of vessels involved was evaluated and it was found that most of the patients with single vessel disease had their HbA1c between 6.5%-8.5% and most patients with multi-vessel disease had their HbA1c level above 8.5%. In the end of study it was concluded that HbA1c may be a useful indicator for CAD risk evaluation.

In our study significant inverse relationship was found between HDL-cholesterol and ACS. In the study “Prevalence of conventional risk factors and lipid profiles in with ACS and significant coronary disease” by Gonzalez-Pacheco H et al14 in 2014 on 3,447 patients with a diagnosis of ACS and significant CAD with stenosis > or =50%, as shown in CAG. Lipid profile was sent in first 24 hours of admission and evaluated along with conventional risk factors such as smoking, dyslipidemia, diabetes and smoking. The lipid profile analysis revealed that 85.1% of patients had some type of dyslipidemia, and most frequent was low level of HDL-cholesterol.

Our study also showed significant co-relationship between LDL-cholesterol level and ACS. In a study conducted by “The lipid research clinics coronary primary prevention trial results”16 in 1984 showed that reducing total cholesterol by lowering LDL-C levels can diminish the incidence of CHD mortality and morbidity in men at high risk of CHD because of raised LDL-C. The trial provides strong evidence for a causal role for LDL-C in pathogenesis of CHD.

Our study also found significant relationship between total cholesterol and ACS, probably attributable to high LDL-C and low HDL-C. Results of our study showed mean cholesterol of >200 mg/dl in patients with multi-vessel disease which was considered high and risk factor for CAD as per adult treatment panel III(ATP III) guidelines. Our study showed significant co-relationship between HbA1c levels and LDL cholesterol and also significant inverse relationship with HDL. Similar type of co-relation has also been found in study conducted by Cho SW et al17 in 2016 on 708 patients who visited OPD and followed for a mean period of 28.5 months. Patients were divided in two groups, patients without major adverse cardiovascular event and patients with major adverse cardiovascular event, which included cardiac death, acute MI and newly diagnosed coronary heart disease. HbA1c and lipid profiles between the groups were compared. It was found that patients with major adverse cardiovascular events had significantly higher HbA1c, lower HDL when compared with patients with no adverse events. Significant inverse co-relationship was found between HbA1c and HDL-C on statistical analysis. It was concluded that poor glycaemic control and low HDL-C co-relate with each other and HbA1c could serve as simple and useful marker and predictor for lipid profile and major adverse cardiovascular events.

**Conclusion**

From this study we conclude that severity of ACS, as depicted in form of single or multi-vessel disease in coronary angiography, directly co-relates with poor glycaemic control depicted in form of raised HbA1c.

Severity of ACS also co-relates directly with deranged lipid profile like raised LDL, triglyceride/HDL ratio, total cholesterol and decreased HDL.

There is also significant co-relationship between poor glycaemic control and deranged lipid profile. Patients with raised HbA1c were also found to have deranged lipid profile and in result more severe ACS.

Thus we conclude that early therapeutic interventions, aiming to stabilize blood glucose levels along with reduction HbA1c and LDL, total cholesterol and to increase HDL, significantly reduce cardiovascular events and mortality in patients with diabetes.

**Limitations of study**

The sample size of patients in our study was less, further study regarding our topic is needed with more study subjects. We also did not studied other well known risk factors for ACS like smoking, lifestyle (sedentary/heavy working), dietary habits etc.

**References**

12. American Diabetes Association, Standards Of Medical Care In Diabetes. Diabetes Care 2004; 27

**Table 5: Correlation between Glycosylated haemoglobin and Lipid profile**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Pearson Correlation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>0.476</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>0.627</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
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The Multitasking Hepatobiliary Protector
Between the Person and the Pill: Factors Affecting Medication Adherence in Epilepsy Patients

Bianca Honneker1*, Schweta Rane1, Rajashree Vast1, Satish V Khadilkar2

Abstract

Background: The majority of people afflicted with epilepsy live in developing countries. Poor adherence to prescribed medication is considered the main cause of unsuccessful drug treatment for epilepsy. Our study aims to evaluate the factors influencing medication adherence in epilepsy patients at a public hospital in Mumbai, India.

Method: This cross-sectional study was carried out on a cohort of 313 epilepsy patients regularly attending an out-patient clinic at a tertiary-care hospital. A semi-structured questionnaire was used to assess demographic information, the level of medication adherence, and various factors that could influence adherence. Brief Illness Perception Questionnaire and WHO QoL-BREF Scale were also administered to the study population.

Results: Patients on anti-epilepsy medication reported an overall good quality of life and a good level of adherence. 90.1% of study participants reported being adherent with their treatment regimen. The main factors found to impact medication adherence were the duration of non-availability of medications in the public sector, and the monthly cost of the medications in the private sector. Other therapy-related, health system-related, socioeconomic, and psychosocial variables were not found to be significant determinants of medication non-adherence in our setting.

Conclusion: Ensuring that anti-epilepsy drugs remain available in the public sector, and/or making them more affordable in the private sector are the main interventions likely to improve medication adherence in clinical settings such as ours.

Introduction

Epilepsy is the second most common neurological disorder, affecting almost 50 million people worldwide.1 Antiepileptic drug (AED) therapy aims to achieve a balance between the prevention of seizure episodes, and the reduction of side-effects of AEDs to tolerable levels; to improve the patient’s quality of life, provide cost-effective care and ensure patient satisfaction.2,3 Good adherence to treatment and proper health education are fundamental to the successful management of epilepsy.4,5

Recent studies have shown that up to 70% newly diagnosed patients with epilepsy can be successfully treated (i.e. be seizure-free for several years) with antiepileptic drugs.5 After 2 - 5 years of successful treatment, drugs can be withdrawn in about 70% of children and about 60% of adults without relapse.6 Poor adherence to prescribed medication is considered the main cause of therapeutic failure in epilepsy patients.9,10

Approximately 85% of people afflicted with epilepsy live in developing countries.5 In a resource-limited setting like India and with pre-existing heavy chronic disease burden, successful treatment outcomes are essential to reduce morbidity and mortality, improve the quality of life, enhance earning capacity, reduce hospitalizations due to disease or its complications, and reduce societal and public health costs. Since medication non-adherence is the main cause for therapeutic failure in epilepsy,7 it is essential to assess the factors that influence adherence in common clinical settings in India. Clinicians and policymakers can then address these factors, while working in concert with patients, for better individual and overall treatment outcomes.

Aims and Objectives

To assess the level of medication adherence amongst epilepsy patients enrolled in the study.

To assess the factors affecting medication adherence in epilepsy patients.

To assess the quality of life of the study participants.

To study the perceptions held by the study participants about the illness.

Methods

This cross-sectional study was carried out over a study period of 6 months in the Department of Neurology at a tertiary-care public hospital in Mumbai, India. The study participants comprised of epilepsy patients on regular AED therapy. The study cohort of 313 epilepsy patients was obtained by consecutively enrolling all patients registered at our out-patient epilepsy clinic who met the criteria for participation.

The inclusion criteria were patients above the age of 18 years and of either sex, who had been taking AEDs for at least 6 months, and gave written valid informed consent to participate. The exclusion criteria were patients newly diagnosed with epilepsy, patients with

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Original Article
cognitive deficits or psychosis, patients who did not meet the inclusion criteria, and patients unwilling to participate.

The study was approved by the Institution Ethics Committee prior to commencement. Written valid informed consent was obtained from all participants before administering the study instruments.

**Study Material**

Demographic Questionnaire: Obtained information about the participant’s age, sex, education, income, occupation, area of residence, type of family, religion, alcohol consumption, and smoking status.

WHO QOL-BREF Scale\(^{11}\): Validated and reliable 26-item scale measuring the following broad domains of quality of life: physical health, psychological health, social relationships, and environment; with each question rated on a 5-point Likert-type scale.\(^{11}\) The four domain scores are scaled out of 100 each, in a positive direction; implying that higher scores reflect a higher quality of life.

Brief Illness Perception Questionnaire (B-IPQ):\(^{12}\) A 9-item validated and reliable instrument based on the original Illness Perception Questionnaire-Revised (IPQ-R), rated using a 0-to-10 Likert-type response scale.\(^{12}\)

A semi-structured self-report questionnaire obtaining information on factors perceived by study participants as contributing to their medication non-adherence behavior. This included treatment, hospital, health system, psychosocial, socioeconomic and provider-related factors.

**Statistical Analysis**

Statistical analysis was carried out using SPSS software after importing the data into MS Excel. The population was divided into two groups for analysis: adherent, and non-adherent. Categorical data was analyzed using Chi-square test, quantitative data was compared using Students’ ‘t’ test, and ordinal data was analyzed using Mann-Whitney Test. Bivariate and multivariate analyses using logistic regression were conducted to further evaluate the relationship between medication adherence status and the other variables under study.

### Results

**Demographics**

The mean age of the study sample was 37.4 years (SD 14.05). The youngest participant was 18 years old, and the oldest was 84 years old. In our cohort, 21% of the participants had studied up to college or further, 39% studied up to secondary school, 26% studied up to primary school, and 14% had not completed primary schooling. Of note, 40% of the participants were presently unemployed, and only 2% lived by themselves. In our study sample, 53% participants were married, 2% divorced/widowed and 45% were single. Further, 9% participants gave a positive history for routine consumption of tobacco in any form, and 5% reported routine alcohol consumption.

**Medication Adherence**

The patients were asked to self-report whether or not they were adherent with their AED therapy. In our cohort, 90.1% of participants reported being adherent with their treatment regimen (‘excellent’ or ‘good’ level of adherence), while 9.9% were non-adherent (‘somewhat’ or ‘poor’ adherence).

**Factors Affecting Medication Adherence**

Amongst health system-related and provider-related factors, the duration of non-availability of AEDs in the public sector (p-value: 0.027) and the monthly cost of medication in the private sector (p-value: 0.00036) were found to be significantly associated with medication non-adherence. Amongst socioeconomic factors, only the patient’s monthly income was significantly associated with medication adherence (p-value: 0.0047).

From the therapy-related factors under study, the number of times patient forgot to take medications (p-value: 0.0009) and the number of times the patient stopped taking medication on their own (p-value: 912E-0.9) were associated with non-adherence. The symptom control achieved, experience of adverse effects, mastery of complex techniques (inhaled/adherence to medication regimen, number of missed appointment- and physical impairments such as visual/ hearing impediments, problems with swallowing, and impaired mobility— were all found to be insignificant.

The patients were also asked about their attitudes towards treatment (i.e. belief that taking medication is important, regimen in easy to follow, fear of adverse effects, fear of dependence on medications, feeling stigmatized by disease), and these were found to have no significant influence on medication adherence.

**Quality of Life**

Patients on anti-epilepsy medication reported an overall good quality of life, with ‘environment’ being highest (83.56) and ‘psychological health’ the lowest (76.41) out of the four domains. On average, they rated their own quality of life as 3.1 out of a maximum of 5 points, and their health status as 3.21 out of a maximum of 5 points. Quality of life was not significantly associated with medication adherence.

**Psychosocial Findings**

Amongst psychosocial factors, perception of health status (p-value: 0.025) was found to influence medication adherence. However, other factors like stressful daily schedules, sleep quality, appetite quality, satisfaction in relationships and with work productivity, and perception of quality of life, were all insignificant.

Of the patients who self-reported experiencing depression symptoms, 44.2% were non-adherent to their medication regimen. Both male and female patients reported experiencing psychological ill-health (anxiety, depression, irritability) however these were not associated with non-adherence.

Features reported feeling significantly less social support than males (p-value: 1.61E-11). Amongst females, 62% reported not telling friends about their disease, while only 22% males withheld the fact. Female patients with epilepsy were also significantly less likely to use public transport independently (p-value: 2.53E-06).

**Perception of Illness**

The total BIP-Q Score, implying an overall poor perception of the disease, was significantly associated with adherence (p-value: 0.0143), as was the extent to which the illness affected the patient emotionally (p-value: 0.00032).
Discussion

This study is a step towards bridging the vast knowledge gap regarding medication non-adherence in chronic diseases, and to our knowledge, is the first study of its kind in the current setting.

The monthly cost of medications in the private sector was found to significantly influence medication non-adherence in our setting (p-value: 0.00036). This is consistent with a Chinese study which found that an inability to buy drugs significantly influenced non-adherence. The duration for which a patient was unable to obtain drugs in the government sector was also a significant factor (p-value: 0.027). Patients having a higher income reported better adherence (p-value: 0.047), which could be because purchasing AEDs in the private sector is more affordable for them. Patients with lower income may feel compelled to stop the medication when it is not available free of cost in the public sector. These results imply that making drugs available in the public sector, ensuring they don’t remain unavailable for long durations in the public sector, and/or making them affordable in the private sector are the main interventions likely to improve a patient’s adherence.

Patients with good medication adherence reported holding the perception of an overall poorer health status (p-value: 0.025), more negative emotional effects due to the illness (p-value: 0.00032), and an overall threatening perception of the illness (p-value: 0.01438), suggesting that patients with a more negative outlook towards the disease were actually more likely to comply with their medication.

Studies in international settings found that male gender, and younger age group were associated with non-adherence; however, we found no significant relationship with any sociodemographic variables under study (age, gender, family size, marital status, education level, occupation status). Symptom control (seizure-free period) was shown to significantly influence adherence in other study populations, but not in ours.

Having health insurance, access to healthcare facilities, access to pharmacy, distance of home from hospital, travel time from home to hospital, waiting period in hospital, quality of relationship with the doctor and education by the doctor; were all found not to be significant factors in our study.

Duration of illness has shown variable associations with adherence; with one study finding that a shorter duration results in poor adherence, and another finding the reverse to be true. Despite our study sample encompassing patient across a wide spectrum in terms of treatment duration- including those who have been on therapy for almost their entire lives, as well as patients who started therapy just 6 months before the study period- duration of illness was not found to be a significant factor.

Previous studies have found patients’ general attitudes towards drugs and the belief that drugs may be harmful correlated significantly with low adherence, as did regimen-related factors like older AEDs, monotherapy and more frequent dosing increasing regimen complexity and pill burden. Other reported factors include comorbid conditions, adverse effects or fear of them, and a poor patient-doctor relationship. None of these factors were found to be significant in our study.

Knowing which factors are not relevant in our clinical setting will prevent wastage of resources in futile interventions, and allow focused evidence-based interventions towards appropriately mitigating the relevant factors identified. Public health policymakers should consider the economic aspects (availability and pricing) of AED therapy in public hospital settings like ours, and accordingly devise interventions to retain patients in care, thus improving their clinical outcomes and reducing the cost of the disease burden to the patient and to society.

Conclusion

As medication non-adherence is the most common reason for failing AED therapy, addressing the factors affecting adherence will lead to positive treatment outcomes. Our study finds that ensuring that the antiepileptic drugs remain available in the public sector, and/or making them more affordable in the private sector, are the main interventions likely to improve patients’ adherence to therapy in clinical settings like ours.

Study Limitations

The study participants were from a single urban tertiary-care public hospital. This limits the ability to generalize our findings to all Indian epilepsy patients. Questionnaires are efficient data collection tools, but may have limitations due to inaccurate responses, problems with recall, and biases.

Acknowledgements

We gratefully acknowledge the Indian Council of Medical Research (ICMR) for supporting this study under the ICMR Short-Term Studentship (STS) Program.

References

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Abbreviated prescribing information: NovoMix™ 30 (biphasic insulin aspart P(L) 30/70). Presentations: NovoMix™ 30 NovoR, NovoMix™ 22 NovoR. All presentations contain insulin aspart and human crystalline insulin aspart 100 units in the ratio of 30:70, produced by recombinant DNA technology. A 30/70 pre-mixed insulin resembles pharmacological form suspendent for injection. Indication: treatment of patients with diabetes mellitus complicating insulin—depletion indices as outlined above — insulin showing is maintained. In patients with type 1 diabetes, NovoMix™ 30 can be given in monotherapy in combination with oral antidiabetic drugs (OADs) or the patients blood glucose is inadequately controlled with these OADs alone. For patients with type 2 diabetes, the recommended starting dose is 4 to 8 insulin units and is titrated to achieve the target HbA1c level. NovoMix™ 30 can be used as insulin substitution with 12/11 units depending on the need. NovoMix™ 30 can be used for up to 3 months, after which time insulin should be given according to the need for diabetes. Comparisons: No significant differences in terms of efficacy or safety have been reported using NovoMix™ 30 compared to its individual components, insulin aspart and human crystalline insulin aspart 100 units in the ratio of 30:70, produced by recombinant DNA technology. Contraindications: Hypersensitivity to one or both components of the insulin. For patients with type 1 diabetes, NovoMix™ 30 can be used in monotherapy in combination with oral antidiabetic drugs (OADs) or the patients blood glucose is inadequately controlled with these OADs alone. For patients with type 2 diabetes, the recommended starting dose is 4 to 8 insulin units and is titrated to achieve the target HbA1c level. NovoMix™ 30 can be used as insulin substitution with 12/11 units depending on the need. NovoMix™ 30 can be used for up to 3 months, after which time insulin should be given according to the need for diabetes.

Effect of Linagliptin on Incretin-axis and Glycaemic Variability in T1DM

S Mukherjee1, SK Bhadada1*, N Sachdeva1, D Badal1, S Bhansali1, P Dutta1, A Bhansali1

Abstract
Backgrounds & Objectives: Short-term studies have demonstrated potential therapeutic efficacy of dipeptidyl peptidase 4 inhibitors (DPP4 inhibitors) in patients with poorly controlled T1DM. In this study we evaluated the effect of DPP4 inhibitor, linagliptin, on glycaemic control and variability, and incretin-axis in well controlled T1DM patients to mitigate the effect of glucotoxicity on incretin secreting cells.

Methods: Twenty T1DM patients were randomized to receive either linagliptin (10 patients, dose-5 mg/day) or placebo (10 patients), in addition to insulin for 3 months. HbA1C, continuous glucose monitoring (CGM) and mixed meal test (MMT) were performed before and at the end of the study period.

Results: HbA1C reduction and change in glycaemic variability and insulin requirement in the linagliptin group did not attain the level of statistical significance. The increase in AUC_glucagon (Area under curve for glucagon) and decrease in AUC_glucagon (Area under curve for glucagon) during the MMT in linagliptin group were also statistically insignificant.

Interpretations & Conclusions: Linagliptin is not effective in reducing HbA1C and glycaemic variability in relatively well controlled T1DM patients.

Introduction
Type 1 diabetes mellitus (T1DM) is the commonest endocrine disorder of young adult population. Although, reduction in HbA1c is important in improving diabetes-related microvascular complications; glycaemic variability is increasingly recognised as an important contributing factor. T1DM is characterised by absolute insulin deficiency and hence insulin is the mainstay of treatment. Insulin therapy is challenging and often complicated with frequent hypo- and hyperglycaemic episodes. To overcome these difficulties, investigators have used oral anti-diabetic drugs as an adjunct to insulin therapy in T1DM with limited benefit. Dipeptidyl peptidase 4 (DPP4) inhibitor increases endogenous glucagon-like peptide 1 (GLP1) levels by inhibiting its rapid metabolism through the DPP4 enzyme. The raised GLP1 level causes increase in insulin release from the β-cells and decrease glucagon secretion from the α-cells; thereby, resulting in better glycaemic control. These drugs are currently Food and Drug Administration (FDA) approved for the treatment of T2DM as they have been shown to be GLP1 deficient. Hyperglucagonemia has been reported in patients with T1DM in many studies; hence, incretin-based therapy has been tried to target this pathophysiological defect in T1DM.

In a pilot study sitagliptin, a DPP4 inhibitor, when used along with insulin was found to be effective in poorly controlled T1DM patients. However, the mechanism of action remains elusive as the incretin response was not assessed in this study. Further, Lugari et al. has demonstrated blunting of GLP1 response during mixed meal test (MMT) in T1DM subjects and proposed chronic hyperglycaemia could have resulted in intestinal ‘L cell failure’ due to glucotoxicity. Linagliptin, another DPP4 inhibitor, which unlike sitagliptin does not require dose modification in renal failure patient, has not been studied yet in T1DM patients.

In the present study we investigated the effect of linagliptin on HbA1c and glycaemic variability in patients with T1DM who are relatively well controlled to obviate the effect of glucotoxicity on intestinal L cells.

Subjects and Methods
The research proposal was approved by the Institute Ethics Committee and registered in ClinicalTriall.gov (id.NCT02725502). Written informed consent was obtained from each of the patient participating in the study. The study was conducted according to the Declaration of Helsinki and ICH-GCP (International Conference on Harmonization-Good Clinical Practice) guidelines. During the study ICMR’s Ethical guidelines for biomedical research on human participants (2006) were strictly followed.

It was a 12 week randomized double-blind placebo control prospective study conducted in PGIMER, Chandigarh from 2013-2016. Euthyroid individuals with T1DM of either gender with age between 15-30 years, duration of DM between 6 months to 7 years, having BMI of < 25 kg/m² and HbA1c < 8% were enrolled in this study. The diagnosis of T1DM was based either on diabetic ketoacidosis (DKA) as the 1st presenting manifestation of the disease or on insulin requirement since the diagnosis along with anti-GAD65 Ab positivity.

All the participants were on stable doses of insulin for the last one month. Patients with creatinine >1.5mg/dl or calculated creatinine clearance of < 50 ml/min or having overt proteinuria, celiac disease, pregnancy, serious illness and gastroparesis were excluded from the study. Those, who were on metformin, GLP-1 agonist, DPP 4

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inhibitor, prokinetics and proton pump inhibitors, were also excluded from the study.

A flow diagram for participant recruitment has been shown in the Figure 1. Twenty T1DM patients were included for analysis. The primary end point of the study was reduction in HbA1c. From the previous pilot study (Estimated difference of HbA1c in HbA1c. From the previous pilot end point of the study was reduction included for analysis. The primary

**Fig. 1: Flow diagram for participant recruitment**

**Results**

A total of 20 patients (n=10 in each group) completed 3 months follow-up period without any dropout. The baseline parameters were similar between the two groups (Table 1).

**Change in Weight and BMI**

There was no significant change with respect to body weight and BMI after 3 months of treatment with linagliptin [51kg (IQR,45-55)] to 50.5kg (45-61), p=0.43 and 18.9 kg/m² (17.5-20) to 18.4
kg/m² (17.5-20.9), p=0.72, respectively] and placebo [49kg (45-54) to 49.5kg (44-54), p= 0.26 and 18.9 kg/m² (17.3-
Change in FBG, PPBG and HbA1c

There was a modest decrease in HbA1C from 54 mmol/mol (50-55) [7.1% (6.7-7.2)] to 50 mmol/mol (45-54) [6.75% (6.3-7.1)] in linagliptin group; whereas there was a mild increase in HbA1C from 52 mmol/mol (48-56) [6.9% (6.5-7.3)] to 54 mmol/mol (46-69) [7.1% (6.4-8.5)] in placebo group; however, these changes were statistically insignificant (p=0.39, 0.2; respectively, Figure 2). Similarly, in linagliptin group FBG remained unchanged [6.3 mmol/L (4-7.5) to 6.1 mmol/L (5.1-6.9), p=0.8]; whereas, PPBG showed a decreasing trend [9.7 mmol/L (8.0-9.9) to 7.6 mmol/L (6.7-10.7), p=0.45] after 3 months of therapy and in placebo group both FBG and PPBG showed a rising trend [6.7 mmol/L (5.8-8.1) to 7.1 mmol/L (5.7-8.1), p=0.77 and 9.3 mmol/L (8.3-10.1) to 11.4 mmol/L (9.2-12.0), p=0.10, respectively]; however these alterations were statistically insignificant.

Changes in CGMS Parameters

CGMS data which represents glycaemic control and variability remained similar even after 3 months of treatment (Table 2). Neither the time spent in euglycemic range (4-10 mmol/L) nor the time spent in hypo- or hyperglycaemic range changed significantly in both the groups from baseline to completion of the study (Table 2).

Glucose and C-Peptide level during MMT

Five patients in linagliptin and 3 patients in placebo group had undetectable C-peptide level (0.01 ng/ml). Changes in AUC Glucose during MMT in linagliptin group [3583 mmol/L X minute (2906-3717) to 3458 mmol/L (2896-3717), p=0.36] were not significant, whereas, AUC Glucagon showed a decreasing trend [7164 pg/m X minute l (2811-9257) to 2231 pg/m X minute l (1424-5477), p=0.15] in linagliptin group; whereas, in placebo group both AUC Glucagon and AUC C-peptide showed the same rising trend [AUC Glucagon: 7164 pg/m X minute l (2811-9257) to 2231 pg/m X minute l (1424-5477), p=0.15; AUC C-peptide: 776 ng/ml X minute l (419-940) to 287 ng/ml X minute l (186-377), p=0.82].

Table 1: Baseline study subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Linagliptin (n=10)</th>
<th>Placebo (n=10)</th>
<th>P value</th>
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</thead>
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<tr>
<td>Age (year)</td>
<td>20 (17-24)</td>
<td>20 (18-22)</td>
<td>0.84</td>
</tr>
<tr>
<td>Duration (year)</td>
<td>4.3 (1.5-7)</td>
<td>2 (1-4)</td>
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<td>Weight (kg)</td>
<td>51 (45-55)</td>
<td>49 (45-54)</td>
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<td>BMI (Kg/m²)</td>
<td>18.9 (17.5-20)</td>
<td>18.9 (17.3-19.8)</td>
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<tr>
<td>FBG (mmol/L)</td>
<td>6.1 (5.6-9)</td>
<td>6.7 (5.8-8.2)</td>
<td>0.11</td>
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<tr>
<td>PPBG (mmol/L)</td>
<td>9.7 (8.0-9.9)</td>
<td>9.3 (8.3-10.1)</td>
<td>0.68</td>
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<tr>
<td>HbA1C (mmol/mol)</td>
<td>54 (50-55)</td>
<td>52 (48-56)</td>
<td>0.42</td>
</tr>
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Table 2: Comparison with in each group with respect to CGMS parameters after 3 months

<table>
<thead>
<tr>
<th>CGMS parameters</th>
<th>Baseline</th>
<th>After 3 months</th>
<th>P value</th>
<th>Baseline</th>
<th>After 3 months</th>
<th>P value</th>
<th>Baseline</th>
<th>After 3 months</th>
<th>P value</th>
<th>Baseline</th>
<th>After 3 months</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Mean Glucose (mmol/L)</td>
<td>7.1 (5.8-7.9)</td>
<td>7.1 (6.7-7.9)</td>
<td>0.39</td>
<td>7.5 (5.7-9)</td>
<td>8.5 (7.6-10.7)</td>
<td>0.85</td>
<td>0.31</td>
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<td>Glucose standard deviation (mmol/L)</td>
<td>2.6 (2.3-3)</td>
<td>3.4 (2.4-4.8)</td>
<td>0.11</td>
<td>2.9 (2.2-4.4)</td>
<td>3.5 (2.5-3.9)</td>
<td>0.78</td>
<td>0.46</td>
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<tr>
<td>J Index</td>
<td>33.7 (24.1-31.6)</td>
<td>34.8 (22.8-75.4)</td>
<td>0.28</td>
<td>23.1 (11.9-23)</td>
<td>23.1 (11.9-23)</td>
<td>0.96</td>
<td>0.37</td>
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<tr>
<td>LBGI</td>
<td>6.6 (2.5-8.3)</td>
<td>6.9 (4.4-22.1)</td>
<td>0.28</td>
<td>6.9 (4.4-22.1)</td>
<td>6.9 (4.4-22.1)</td>
<td>0.28</td>
<td>0.96</td>
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<tr>
<td>HBGI</td>
<td>4.3 (2.9-7.1)</td>
<td>5.2 (3.7-11.4)</td>
<td>0.36</td>
<td>5.2 (3.7-11.4)</td>
<td>5.2 (3.7-11.4)</td>
<td>0.36</td>
<td>0.41</td>
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<td>GRADE</td>
<td>5 (4.3-9.1)</td>
<td>5.9 (4.5-8.1)</td>
<td>0.60</td>
<td>5.9 (4.5-8.1)</td>
<td>5.9 (4.5-8.1)</td>
<td>0.60</td>
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<tr>
<td>M value</td>
<td>8.9 (5.3-15.4)</td>
<td>21.4 (5.6-39.7)</td>
<td>0.14</td>
<td>21.4 (5.6-39.7)</td>
<td>21.4 (5.6-39.7)</td>
<td>0.14</td>
<td>0.35</td>
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</tr>
<tr>
<td>Time spent &gt;10 mmol/L (%)</td>
<td>17.5 (7-29)</td>
<td>18.5 (12-34)</td>
<td>0.55</td>
<td>23.5 (9-29)</td>
<td>31.5 (19-56)</td>
<td>0.64</td>
<td>0.25</td>
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<tr>
<td>Time spent 4-10 mmol/L (%)</td>
<td>65.5 (59-77)</td>
<td>60.5 (38-76)</td>
<td>0.30</td>
<td>60.5 (38-76)</td>
<td>60.5 (38-76)</td>
<td>0.30</td>
<td>0.71</td>
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<td>Time spent &lt;4 mmol/L (%)</td>
<td>8.5 (3-31)</td>
<td>5.5 (0-35)</td>
<td>1.00</td>
<td>5.5 (0-35)</td>
<td>5.5 (0-35)</td>
<td>1.00</td>
<td>0.94</td>
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</table>

Fig. 2: Median HbA1C level in both the group
GLP-1 Level during MMT

The median GLP-1 levels during MMT between the two groups were similar at baseline and at the end of the study (Figure 3). The AUC$_{GLP-1}$ during the MMT showed a rising trend in linagliptin group [1549 ng/ml X minute (345-5339) to 1821 ng/ml X minute (524-5650), p=0.13]; while it showed a decreasing trend in placebo group [2087 ng/ml X minute (974-2822) to 1459 ng/ml X minute (1057-2165), p=0.57], however these changes were statistically insignificant.

Glucagon Level during MMT

One patient in linagliptin group and two patients in placebo group had undetectable glucagon level (0.1 pg/ml). Although glucagon levels were not significantly different between the two groups during the MMT at baseline and after 3 months (Figure 4), the median AUC$_{glucagon}$ tend to decrease in linagliptin group [7164 pg/ml X minute (2811-9257) to 6103 pg/ml X minute (2946-10244), p=0.35], while it showed rising trend in placebo group [2231 pg/ml X minute (1424-5477) to 5688 pg/ml X minute (1790-9497), p=0.15], but these changes were statistically insignificant.

Insulin Requirement

Daily total insulin requirement decreased from 40 unit (34-48) to 32 unit (20-46) in linagliptin group after 3 months (P=0.58), while in the placebo group it decreased from 40.5 unit (28-48) to 35.3 unit (29-46) after 3 months (P=0.11). Insulin requirement per kg body weight did not change significantly in both linagliptin [0.84 unit/kg (0.75-1.12) to 0.66 unit/kg (0.44-0.81), p=0.84] and placebo group [0.86 unit/kg (0.53-1.05) to 0.73 unit/kg (0.48-0.91), p=0.09].

Adverse Events

No serious side effects related to linagliptin (nausea, vomiting or pancreatitis) therapy were observed during the study period.

Discussion

In this study, we examined the effect of linagliptin on incretin-axis and on glycaemic variability in relatively well controlled T1DM patients. Although we observed a decreasing trend in HbA1c and PPBG in linagliptin group; it did not attain statistical significance. Neither the glycaemic variability nor the insulin requirement changed significantly with linagliptin therapy. The increase in AUC$_{GLP-1}$ and decrease in AUC$_{glucagon}$ during the MMT in linagliptin group were also statistically insignificant.

In a study liraglutide, a GLP 1 agonistic analogue, when used in T1DM patients for 4 weeks period showed a trend towards lowered HbA1c with significantly lower total daily insulin requirement. In a pilot study sitagliptin, another DPP4 inhibitor was shown to be effective in reducing HbA1c and glycaemic variability in T1DM patients. But it was a short duration (4 weeks) cross-over trial and the baseline mean HbA1c was around 9.5% (80 mmol/mol). Our study was of 12 weeks duration and showed a decreasing trend in PPBG and HbA1c with no alterations in insulin requirement and glycaemic variability with linagliptin therapy. The baseline median HbA1c in our study group was around 7% (53
mmol/mol). The non-significant change in glycaemic profile in our study may be explained by inclusion of well controlled DM patients, and hence the magnitude of HbA1C reduction was too meagre to attain the level of statistical significance.

Linagliptin is a DPP4 inhibitor. DPP4 is an enzyme which is responsible for degradation of GLP 1. So DPP4 inhibitor increases GLP1 level which in turn increases insulin release from pancreatic β cells and decreases glucagon release from α cells. Kielgast et al. showed that GLP-1 infusion reduces gastric emptying rate and glucagon levels in T1DM patients and increases fasting C-peptide in C peptide positive T1DM patients. Lugari et al. evaluated endogenous GLP 1 concentrations, both at fasting state and in response to nutrient ingestion, in type 1 and 2 diabetes patients and in healthy controls. They observed that there was no increase in postprandial GLP-1 in patients with T1DM and proposed that chronic hyperglycaemia could result in desensitization of the L-cells with consequent peptide failure response i.e. “L cell glucotoxicity”. The AUC GLP-1 tended to increase in the linagliptin group, while in the placebo group it tended to decrease after 3 months of study period; however, these changes were statistically non significant. Chronic hyperglycaemia and consequent L cell failure or relatively small sample size may be responsible for this. In our study AUC glucagon tend to decrease in linagliptin group; while it tend to increase in placebo group, however these changes were also statistically insignificant. Farngren J et al. have shown that during the meal, glucagon levels were lower with vildagliptin treatment, (another DPP4 inhibitor) than with placebo. However, they took relatively less well controlled T1DM subjects than we did [Baseline mean HbA1C 7.5% (58 mmol/mol) and fasting blood glucose 10.5 mmol/L vs. baseline median HbA1C 7.1% (54 mmol/mol) and FBG 6.1 mmol/L in linagliptin group in our study]. Decrease in glucagon level could not attain level of statistical significance in linagliptin group. This is possibly due to use of supraphysiologic dose of insulin which can suppress α-cells.

This fact is further substantiated by frequent hypoglycemic episodes and undetectable glucagon level in some of the patients.

Limitations of our study are inclusion of relatively well controlled diabetes patients, small sample size and heterogeneity in β-cell reserve with respect to C peptide positivity. Further, we have used total GLP1 assay; however, intact GLP1 assay may be more useful to assess the DPP4 effect. The status of incretin-axis in patients with T1DM remains elusive. DPP-4 inhibitor may not be effective in well controlled patients with T1DM possibly because of α-cell inhibition of supraphysiologic dose of exogenous insulin.

Acknowledgment

We acknowledge Indian Council of Medical Research, New Delhi for funding the study.

References

3. Hamilton J. Metformin as an Adjunct Therapy in Adolescents with Type 1 Diabetes and Insulin Resistance. Diabetes Care 2003; 26:138-143.
Incidence and Spectrum of Opportunistic Infections Among HIV Infected Patients Attending Government Medical College, Kozhikode

PK Vinod¹, Chandni Radhakrishnan²*, Sasidharan PK³

Abstract

Background: People with advanced human immunodeficiency virus (HIV) infections are vulnerable to opportunistic infections because of a weakened immune system. Early diagnosis of Opportunistic infections and prompt treatment definitely contributes to increased life expectancy among infected patients and delays the progression to AIDS.

Aims and Objectives: are to study the incidence, clinical spectrum and outcome of opportunistic infections and relation between opportunistic infections and CD4 count.

Materials and Methods: The study was carried out in the Anti Retroviral Treatment (ART) clinic and medical wards of Government Medical College, Kozhikode. The study period was from January 2012 to January 2013 till 100 opportunistic infections are identified in newly diagnosed retro positive patients. This was a clinical observational study. 424 newly diagnosed retro positive patients were screened to identify 100 patients having opportunistic infections and they were studied in detail.

Results: Out of the 100 patients, 71 were males and 29 were females. 67% were in the age group of 30-49 years. The most common symptom of presentation was weight loss (77%) followed by fever (67%) and mucocutaneous lesions (60%). The commonest opportunistic infection detected was candidiasis (52%) followed by tuberculosis (50%). Majority of the patients had a CD4 count between 50-200/μL. Out of the 100 patients 19 patients expired. Among them 10 patients had disseminated tuberculosis. Incidence of opportunistic infection was 23.59/100 person years.

Conclusions: This study demonstrates that Oral candidiasis is the commonest opportunistic infection in HIV patients and Tuberculosis is the second most common. The incidence of opportunistic infection is higher in the older age groups, males and patients with lowCD4 count.

Introduction

People with advanced HIV infections are vulnerable to opportunistic infections (OI) because of a weakened immune system. OI cause substantial morbidity and mortality. The common OI that affecting people living with HIV infection in India are Tuberculosis, Candidiasis, Pneumocystis jiroveci pneumonia (PCP), Bacterial pneumonia, Herpes simplex, Herpes zoster and chronic diarrhea.

Early diagnosis of OI and prompt treatment definitely contributes to increased life expectancy among infected patients and delays the progression to AIDS (Acquired immunodeficiency syndrome) and it also helps to stop the spread of Tuberculosis and other transmissible OI.1,2 The relative frequencies of specific OI may vary in different countries and even in different areas within the same country. The pattern of OI in HIV patients in south Indian context is relatively less studied. This study was done to estimate the burden of OI and its pattern in HIV patients in North Kerala.

Materials and Methods

This is a clinical observational study carried out in the Anti retro viral treatment (ART) clinic and medical wards of Government Medical College, Kozhikode. The study was done after getting institutional ethics committee approval and informed consent from the patients. The study period was from January 2012 to January 2013 till 100 subjects with OI are enrolled. All patients above 12 yrs of age who found to be HIV positive after testing from ICTC (Integrated counseling and testing centre) during the study period were included in the study. Patients who were already had other immune compromised state before contracting HIV like diabetes mellitus and patients on chemotherapy were excluded from the study.

424 newly diagnosed consecutive retro positive patients were clinically assessed to identify 100 patients having opportunistic infections and they were studied in detail.

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A total of 424 newly detected HIV patients were clinically assessed for opportunistic infections in the study. The source of the cases was either ART clinic of the Department of Medicine or Medicine wards in Government Medical College, Kozhikode. Of the 424 newly detected HIV patients screened, 100 patients had opportunistic infections and a detailed study of them was done. In this study majority of the patients were male hetero sexuals. The age and gender distribution is shown in Table 1. It was observed that the majority were between the age groups of 30-49 yrs (67%) and 71% were males and 29% were females with a male to female ratio of 2.44:1.

All patients were presented with multiple symptoms. Symptoms at presentation were weight loss (77%), fever (67%), muco-cutaneous lesions (33%) and diarrhea (16%). 22% patients had headache and 19% had seizure. Altered sensorium was present in 14% patients (Table 2).

Most common skin manifestation was candidiasis (52%) followed by seborrhoeic dermatitis (12%). Tuberculosis (26%) was the frequent respiratory problem followed by PCP (15%).15 patients had isolated pulmonary tuberculosis and 11 patients had disseminated tuberculosis (DTB). Eight patients had extra pulmonary tuberculosis. Fourteen patients had CNS tuberculosis and 2 patients had pericardial effusion which was tuberculous in aetiology. Sputum AFB was negative in 76% of pulmonary tuberculosis cases. Among the patients with tuberculosis 11 patients had non homogenous opacity in chest x-ray and 5 had miliary mottling, 6 had pleural effusion. Oral candidiasis (52%) was the commonest gastrointestinal manifestation. Chronic diarrhea was present in 9 patients. There were 9 patients with HBsAg positivity. Stool examination of the patients with chronic diarrhea showed cryptosporidium in 5 patients and Isospora belli (Figure 5) in 2 patients. Most frequent CNS manifestation was tuberculosis (14 patients). CNS toxoplasmosis was present in 5 persons and 2 patients had Cryptococcal meningitis (Figure 4). The various clinical manifestations were shown in Table 2.

Oral candidiasis (Figure 3) was the commonest opportunistic infection. It was present in 52 patients. Among the 100 patients with OI, 50 patients had tuberculosis. Pneumocystis carinii. Pneumonia (PCP) was present in 15 patients. Ten patients had bacterial pneumonia. Other infections are shown in Figure 1.

CD4 count ranged between 2/microL to 892/microL. Majority of the patients had a CD4 count between 50-200/ microL. The CD4 count at various OI presented were shown in Table 3.

Out of the 100 patients 19 patients expired. Most common cause of death was tuberculosis (10 patients). 3 patients with PCP expired. All cases of PMLE (2) and cryptococcal meningitis (2) died.2 patients with toxoplasmosis also did not survive (Figure 2).
had opportunistic infections. Incidence calculated as 23.59/100 person years in this study.

**Discussion**

In the present study, among OI in HIV infected people at presentation, age group ranged from 20-50 yrs which represents the most active and productive group of the society. Majority were males (79%). These observations are comparable to another study from India by Nilanjan chakraborty et al.\(^3\) In the present study most common symptom of presentation was weight loss (77%) followed by fever (67%) and skin and mucosal lesions (60%) which is similar to a study by Singh A et al.\(^4\) The high proportion of weight loss, fever and cough can be due to the high incidence of tuberculosis in this study group.

The most common muco-cutaneous manifestation was oral candidiasis. This was present in 52% of patients. In many of the unsuspected cases of retroviral infection oral candidiasis prompted the diagnosis. Some of the patients had multiple muco-cutaneous lesions like candidiasis, oral ulcers, seborrhoeic dermatitis. Kaposi’s sarcoma was not detected in any of the subjects in the present study. This may be due to the decreased prevalence of the causative organism HHV-8 which predominantly spreads through homosexual contact. Homosexual mode of transmission is reported only in 6 patients in our study.

Pulmonary tuberculosis was the commonest respiratory infection. Eleven patients had disseminated tuberculosis (DTB) and 8 had extra pulmonary tuberculosis.\(^5\) The major symptoms at presentation were weight loss, fever and cough. 75% of patients with tuberculosis were Mantoux test negative. This can be attributed to the immune suppression in HIV-TB co-infection and Mantoux test will not be a useful aid in tuberculosis in HIV infection. Sputum AFB was negative in 76% of the tuberculosis cases. It was observed that many patients became positive for AFB in sputum after starting on HAART. This shows the improving immunity of these patients. Patients with high CD4 count have classical findings in chest x-ray. When CD4 count is low X-rays have lower zone involvement, miliary shadows and pleural effusion.\(^6\)

Most of the patients with PCP infection had a lower CD4 count and it was diagnosed clinically. Main symptoms were dry cough and breathlessness. Typical interstitial pattern of chest x-ray, high serum LDH (Lactate dehydrogenase) and ABG (Arterial blood gas) abnormality were present in these patients. There is a 5-7 fold increase in bacterial pneumonia in HIV patients compared to the general population. The clinical presentation was similar as in the HIV non infected patients.\(^7\)

Chronic diarrhea was present in 9 patients, which is much less when compared to the incidences reported by other Indian studies. This could be the reflection of better sanitary and environmental hygiene present in Kerala. In a study by Anant A Takalkar et al\(^8\) about OI in HIV 30.1% patients had chronic diarrhea. The mainstay of therapy in chronic diarrhea of HIV positive individuals in countries where it is economically and socially feasible is with highly active ART (HAART) which was instituted in our patients also. In our study, most common organism was cryptosporidium. In a study on chronic diarrhea in HIV patients by S.V. Kulkarni et al\(^9\) showed that commonest organism was cryptosporidium. Nine patients had HBsAg positivity. HIV infection increases the risk of chronic carriage of HBV infection and we need to ensure the screening of Hepatitis B in HIV patients.\(^10\)

Neurological manifestations were present in 23% of the cases. There was higher incidence of tuberculous meningitis when compared to western reports due to the increased incidence of this disease in general population. The clinical course of CNS tuberculosis in HIV patients is different from HIV negative patients. Cryptococcal meningitis was present in 8.7% of patients with neurological manifestation. The world wide incidence is 6-12%. Toxoplasmosis was present in 5% of the patients with opportunistic infections. In Europe the most common OI involving CNS is toxoplasmosis affects 20-40% of all the AIDS patients.

Progressive multifocal leucoencephalopathy (PMLE) was present in 2%. The worldwide incidence is 2-3%. Patients with this disease showed cognitive impairment and a sequence of variable focal deficits. Various studies showed that PMLE is exclusively seen in immune compromised groups. It is currently one of the AIDS defining illnesses in HIV infected patients.

The CD4 cell count is an important investigation in the clinical evaluation of any patient with HIV infection as it helps to decide the stage of the disease and in decisions regarding anti retroviral treatment and prophylaxis against OI. As the tuberculosis is endemic in India it may occur at any CD4 count. Most of the disseminated tuberculosis and CNS tuberculosis had a CD4 count below 100.

Majority of the bacterial pneumonia had a CD4 count 200-500/microL and the clinical presentation was similar to general population. Oral candidiasis was occurred in a wide range of CD4 counts and the incidence is very high when CD4 count is below 200. Patients with CD4 count below 100 had OI like cryptococcal meningitis and

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**Table 3: Relation between CD4 count and OI**

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>OI</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500</td>
<td>Bacterial pneumonia</td>
<td>2</td>
</tr>
<tr>
<td>200-500</td>
<td>Pulmonary tuberculosis</td>
<td>8</td>
</tr>
<tr>
<td>200-500</td>
<td>Bacterial pneumonia</td>
<td>8</td>
</tr>
<tr>
<td>200-500</td>
<td>Oral candidiasis</td>
<td>7</td>
</tr>
<tr>
<td>200-500</td>
<td>Extrapulmonary tuberculosis</td>
<td>7</td>
</tr>
<tr>
<td>200-500</td>
<td>PCP</td>
<td>2</td>
</tr>
<tr>
<td>200-500</td>
<td>Varicella</td>
<td>2</td>
</tr>
<tr>
<td>100-200</td>
<td>Oral candidiasis</td>
<td>21</td>
</tr>
<tr>
<td>100-200</td>
<td>Pulmonary tuberculosis</td>
<td>7</td>
</tr>
<tr>
<td>100-200</td>
<td>PCP</td>
<td>7</td>
</tr>
<tr>
<td>100-200</td>
<td>CNS TB</td>
<td>5</td>
</tr>
<tr>
<td>100-200</td>
<td>Extrapulmonary tuberculosis</td>
<td>4</td>
</tr>
<tr>
<td>100-200</td>
<td>Chronic diarrhea</td>
<td>4</td>
</tr>
<tr>
<td>100-200</td>
<td>Disseminated tuberculosis</td>
<td>3</td>
</tr>
<tr>
<td>100-200</td>
<td>Toxoplasmosis</td>
<td>2</td>
</tr>
<tr>
<td>100-200</td>
<td>CMV retinitis</td>
<td>1</td>
</tr>
<tr>
<td>100-200</td>
<td>Esophageal candidiasis</td>
<td>1</td>
</tr>
<tr>
<td>100-200</td>
<td>PMLE</td>
<td>1</td>
</tr>
<tr>
<td>50-100</td>
<td>Oral candidiasis</td>
<td>12</td>
</tr>
<tr>
<td>50-100</td>
<td>CNS TB</td>
<td>5</td>
</tr>
<tr>
<td>50-100</td>
<td>PCP</td>
<td>5</td>
</tr>
<tr>
<td>50-100</td>
<td>Extrapulmonary tuberculosis</td>
<td>3</td>
</tr>
<tr>
<td>50-100</td>
<td>Toxoplasmosis</td>
<td>2</td>
</tr>
<tr>
<td>50-100</td>
<td>Chronic diarrhea</td>
<td>2</td>
</tr>
<tr>
<td>50-100</td>
<td>CMV retinitis</td>
<td>1</td>
</tr>
<tr>
<td>50-100</td>
<td>PMLE</td>
<td>1</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Oral candidiasis</td>
<td>12</td>
</tr>
<tr>
<td>&lt;50</td>
<td>CNS TB</td>
<td>5</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Disseminated tuberculosis</td>
<td>5</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Cryptococcal meningitis</td>
<td>2</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Toxoplasmosis</td>
<td>1</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Chronic diarrhea</td>
<td>1</td>
</tr>
<tr>
<td>&lt;50</td>
<td>PCP</td>
<td>1</td>
</tr>
</tbody>
</table>
Toxoplasmosis. These observations are comparable to another study by Vinay KV et al.11

Out of the 100 patients 19 patients expired. In this study most of the expired patients had lower CD4 count. Cryptococcal meningitis and PMLE had 100% mortality. Disseminated tuberculosis had a high mortality rate in this study. Most of the expired patients with CNS tuberculosis expired. Toxoplasmosis also had a high mortality. Even if initiation of ART results in the suppression of OI, issues of non adherence, ART drug resistance and treatment failure also exist and might not be able to totally prevent or avert OI among the HIV infected patients. In this study incidence calculated as 23.59/100 person years. In a study by Manisha Ghate et al12 the incidence was 36.8.

In another study from Brazil, had an incidence 51/100 person years. In other studies incidence ranges from 10.7-69.7/100 person years. Oral candidiasis and tuberculosis had a high incidence rate in this study. The incidence of OI is higher in the older age group, in males and among patients with low CD4 count.

**Conclusion**

Oral candidiasis is the commonest opportunistic infection in HIV infected patients and is the first indicator of underlying immunodeficiency in majority of the cases. Tuberculosis is the second most common opportunistic infection and major cause for meningitis, lymphadenitis and respiratory disease. Chronic diarrhea is rare in our people compared to other states of India and HBV co-infection is common in HIV patients. The incidence of opportunistic infection is higher in the older age groups, males and patients with low CD4 count.

Limitations of the study are PCP is diagnosed mainly by clinical assessment...
Osteoarthritis: Clinical and Radiological Correlation

Shilpa P Karande¹, Seema Kini¹

Abstract

Background: Osteoarthritis (OA) is a slowly progressive degenerative joint disease, characterized by pain and functional disability. Various outcome measures for radiographic and clinical OA are described in studies. A limitation of radiographic evaluation is that, except for the direct evaluation of bone, the tissues involved in the OA process are either evaluated indirectly (cartilage) or not at all (synovium). In evaluation of clinical OA, the scores for pain, stiffness and function are commonly used outcome measures. The objective of this study was to co-relate the clinical status with activity and radiological score in osteoarthritis of various joints.

Materials and Methods: A Cross-sectional study was conducted including 100 consecutive patients of osteoarthritis of various joints. A thorough clinical examination of affected joint was performed and relevant laboratory investigations and radiology of the affected joint was done in all patients. Grading of severity of osteoarthritis was assessed by following clinical indices: Knee/ Hip by Lequesne, Articular Index of Doyle for osteoarthritis and modified WOMAC index – KGMC index. Radiological indices used were: Kellgren and Lawrence global grading scheme for the severity of osteoarthritis of the knee, hip, lumbar disc degeneration and apophyseal joints of the cervical spine, Kallman grading scale for individual features of the hand and Individual radiographic features assessed in radiographs of the hip and lumbar spine.

Results: Knee joint was commonly involved (89%), followed by lumbar spine (49%). Knee joint tenderness was significantly co-relating with KGMC and radiological index. Lequesne and KGMC Indian index were co-relating positively with each other for knee joint. All clinical indices showed significant co-relation with radiological indices for knee joint. Clinical and radiological indices were also co-relating positively in cervical and lumbar spine. Visual analogue scale (VAS) co-related significantly with Lequesne and Indian KGMC index with respect to knee joint, but showed no co-relation with Doyle index. Also for hands, cervical and lumbar spine VAS and clinical indices did not co-relate.

Conclusion: KGMC index is best applicable to assess the osteoarthritis knee joint. Radiological progression in OA co-relates well with all clinical indices including KGMC index. This study highlights the usefulness of visual analogue scale and various radiological and clinical indices to assess osteoarthritis especially for knee joint.

Introduction

Osteoarthritis (OA) is the most common joint disease of mankind and is also the leading cause of chronic disability in developed countries. It is a slowly progressive degenerative joint disease, characterized by pain and functional disability. The larger joints are commonly affected and specifically involvement of the hip and knee joint has a great health (care) and economic burden. Diagnosis of OA is usually based on symptoms (clinical OA) and is confirmed by radiography. An inconsistent association between radiographic and clinical OA hampers diagnosis however.

In clinical practice expression of disease varies significantly between patients, possibly implying the existence of different types of OA. Despite this inconsistency and the development of magnetic resonance imaging, with which a relation between pain and structural damage like bone marrow lesions and bone attrition was found, radiographs are still the gold standard for demonstrating structural changes since image acquisition is non-invasive, cheap, fast, and generally available.

Various outcome measures for radiographic and clinical OA are described in studies. Common outcomes for radiographic OA are Kellgren and Lawrence grading (KL) and in recent years actual measurement of joint space width (JSW) has been increasingly applied. A limitation of radiographic evaluation is that, except for the direct evaluation of bone, the tissues involved in the OA process are either evaluated indirectly (cartilage) or not at all (synovium). In evaluation of clinical OA the visual analogue scale (VAS) for pain, and the Western Ontario and McMaster Universities OA Index (WOMAC) scores for pain, stiffness and function are validated and commonly used outcome measures.

The objective of this study was to correlate the clinical status with activity and radiological score in osteoarthritis of various joints.

Materials and Methods

A Cross-sectional study was conducted at Department of Medicine of a tertiary care hospital, Mumbai after approval from institutional ethics committee. We studied 100 consecutive patients of osteoarthritis of various joints over a period of one year either attending OPD or admitted for various reasons.

Inclusion Criteria

1. Primary osteoarthritis of various joints in either sex.
2. Those who gave informed consent.
Table 1: Distribution of patients according to joint involvement

<table>
<thead>
<tr>
<th>Joints</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>89</td>
<td>89%</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>49</td>
<td>49%</td>
</tr>
<tr>
<td>Cervical spine</td>
<td>31</td>
<td>31%</td>
</tr>
<tr>
<td>Hands</td>
<td>26</td>
<td>26%</td>
</tr>
<tr>
<td>Ankle</td>
<td>16</td>
<td>16%</td>
</tr>
<tr>
<td>Hip</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>Elbow</td>
<td>6</td>
<td>6%</td>
</tr>
<tr>
<td>Shoulder</td>
<td>9</td>
<td>9%</td>
</tr>
</tbody>
</table>

Table 2: Co-relation of knee joint swelling and tenderness with other parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Swelling*</th>
<th>Tenderness*</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>0.204</td>
<td>0.055</td>
</tr>
<tr>
<td>Lequesne Index</td>
<td>0.109</td>
<td>0.311</td>
</tr>
<tr>
<td>KGMC Index</td>
<td>0.05</td>
<td>0.644</td>
</tr>
<tr>
<td>Doyle Index</td>
<td>-0.092</td>
<td>0.394</td>
</tr>
<tr>
<td>Radiological index</td>
<td>0.103</td>
<td>0.335</td>
</tr>
</tbody>
</table>

*Swelling vs Tenderness: r= 0.21; p= 0.049

Exclusion Criteria
1. Patients with secondary osteoarthritis due to trauma, RA, congenital or developmental defect, metabolic, endocrine, inflammatory neuropathic and endemic diseases.
2. Patients less than 12 years of age.

A thorough clinical examination of affected joint was performed and relevant laboratory investigation like ESR, CRP, IgM rheumatoid factor and radiology of the affected joint was done in all patients, which is the standard of care. Grading of severity of osteoarthritis was assessed by following indices:

Clinical Indices
1. Knee / Hip by Lequesne et al
2. Articular Index of Doyle et al. for Osteoarthritis (the higher the score the worse the osteoarthritis)
3. Modified WOMAC index – KGMC index

Radiological Indices
1. Kellgren and Lawrence global grading scheme for the severity

Table 3: Co-relation between clinical and radiological indices for knee joint

<table>
<thead>
<tr>
<th>Knee indices</th>
<th>r-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lequesne I. and KGMC I.</td>
<td>0.436</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lequesne I. and Doyle I.</td>
<td>0.14</td>
<td>0.192</td>
</tr>
<tr>
<td>Lequesne I. and Radiological index</td>
<td>0.429</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>KGMC I. and Doyle I.</td>
<td>0.171</td>
<td>0.109</td>
</tr>
<tr>
<td>Doyle I. and Radiological index</td>
<td>0.259</td>
<td>0.0165</td>
</tr>
</tbody>
</table>

Table 4: Co-relation of hand, cervical and lumber spine features with other parameters

<table>
<thead>
<tr>
<th>Joint</th>
<th>Parameters</th>
<th>r-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand</td>
<td>Swelling vs Tenderness</td>
<td>0.004</td>
<td>0.983</td>
</tr>
<tr>
<td></td>
<td>Swelling vs Clinical Index</td>
<td>-0.13</td>
<td>0.536</td>
</tr>
<tr>
<td>Cervical Spine</td>
<td>MR vs Clinical Index</td>
<td>0.193</td>
<td>0.294</td>
</tr>
<tr>
<td></td>
<td>MR vs Radiological Index</td>
<td>0.0735</td>
<td>0.694</td>
</tr>
<tr>
<td></td>
<td>Clinical vs Radiological Index</td>
<td>0.651</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Lumber Spine</td>
<td>MR vs Tenderness</td>
<td>0.61</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>MR vs Clinical Index</td>
<td>0.206</td>
<td>0.1554</td>
</tr>
<tr>
<td></td>
<td>MR vs Radiological Index</td>
<td>0.112</td>
<td>0.443</td>
</tr>
<tr>
<td></td>
<td>Clinical vs Radiological Index</td>
<td>0.6076</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

MR - Movement Restriction

Table 5: VAS and clinical indices

<table>
<thead>
<tr>
<th>Joint</th>
<th>r-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS and Lequesne I.</td>
<td>0.4708</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>VAS and KGMC I.</td>
<td>0.2569</td>
<td>0.0151</td>
</tr>
<tr>
<td>VAS and Doyle I.</td>
<td>0.1794</td>
<td>0.0924</td>
</tr>
<tr>
<td>Hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS and Clinical index</td>
<td>0.1407</td>
<td>0.493</td>
</tr>
<tr>
<td>Cervical spine</td>
<td>0.1547</td>
<td>0.9342</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.1820</td>
<td>0.2108</td>
</tr>
</tbody>
</table>

Results

Out of 100 patients of osteoarthritis, 73% were females and rest were males with mean age of 54.2 and 57.3 years respectively. Knee joint was commonly involved (89%) followed by lumbar spine (49%), cervical spine (31%) and hand (26%) (Table 1).

Knee joint swelling and tenderness had significant positive co-relation with each other. However no co-relation was observed between swelling and VAS, clinical indices (Lequesne, KGMC, Doyle) and radiological index. Knee joint tenderness was significantly co-relating with KGMC and radiological index while no co-relations was observed between tenderness and VAS, Lequesne and Doyle index (Table 2).

Knee joint’s clinical and radiological indices co-relation showed that, Lequesne and KGMC Indian index were co-relating positively with each other but Lequesne and Doyle index in this study were not co-relating. Lequesne, KGMC and Doyle’s Index, all showed significant co-relation with radiological indices suggesting that clinical and radiological indices for knee joint co-relate with each other (Table 3).

On observing co-relation of hand, cervical and lumbar spine, we found that clinical and radiological indices were co-relating positively in cervical and lumbar spine. Movement restriction and tenderness were also co-relating with each other in lumbar spine (Table 4).

Statistical Analysis of data was done by using SPSS software ver. 21. The association of clinico-radiological association was assessed by unpaired ‘t’ test, chi square test and Pearson’s co-efficient of correlation.

Discussion

Several studies have been conducted all over the world to note various parameters of OA with special emphasis on the knee joint as it is the most commonly involved joint. Present study is an attempt to find out the co-relation between clinical and radiological indices in osteoarthritis of
various joints. Hundreds of patients of primary osteoarthritis following up in rheumatology and medical OPD of a tertiary care hospital were studied. Most commonly involved joint was knee joint (89%). Both Indian and Western literature shows that knee is the most commonly affected joint in mono or pauciarticular pattern. The results are also attributed to habit of squatting in Indian population during day to day activity. The second common involvement was lumbar spine (49%) which can be attributed to lifting heavy weights on heads, manual labor which is common in Indian population. Spine osteoarthritis is seen in areas of maximum spinal motion in middle aged and elderly best manifested by pain on bending backwards. In the present study, hand affection was seen in 26% patients. In Indian scenario of vibratory tools in industries, and other occupations attributes to hand involvement as osteoarthritis. Hip joint involvement was seen in 7% patients. In India, hip joint involvement was found in one study in Karnataka described as Handigodu disease. Hip joint involvement is not commonly seen in India as compared with Western countries which are still unexplained.

In present study, we tried to co-relate various disease parameters viz. visual analogue scale, clinical profile, clinical indices and radiological indices with each other for various joints to find out their reliability in assessing the status of osteoarthritis. In case of osteoarthritis of knee cases the association between swelling and tenderness was significant. Knee joint tenderness co-relates with KGMC clinical index and radiological index suggesting that tenderness can be a reliable indicator of knee osteoarthritis. Knee joint clinical indices like Lequesne co-relate with Indian KGMC index and radiological index positively, however, the same is not true for Doyle’s index, suggesting that Indian KGMC index for assessing severity of knee osteoarthritis is reliable. Worldwide WOMAC scale is being use to assess knee joint osteoarthritis, but, we did not find it applicable in Indian population. KGMC scale is modified WOMAC scale which is best applicable in Indian scenario. The positive co-relation between KGMC scale and radiological indices further validates the reliability of KGMC score that it can be used to assess the progression of osteoarthritis of knee. Doyle index was not co-relating with KGMC and Lequesne, thus should not be advocated in Indian population.

In the present study, hand osteoarthritis and clinical indices didn’t co-relate with each other. Doyle’s clinical and radiological indices of cervical and lumbar spine co-relates well with each other and can thus be taken as a good marker for assessment of clinico-radiological presentation in patients. Movement restriction and tenderness were also co-relating well with each other in lumbar spine. Visual analogue scale (VAS) as given by patients at the time of presentations in outpatients department when co-related with clinical indices suggested that it had a good co-relation in knee joint only. VAS co-related significantly with Lequesne and Indian KGMC index with respect to knee joint, but showed no co-relation with Doyle index. Also for hands, cervical and lumbar spine, VAS and clinical indices did not co-relate. Hence there is a need to study the clinical indices for other joints like hands, wrist, cervical and lumbar spine in Indian population.

Conclusion

We thus conclude that KGMC index is best applicable to assess the osteoarthritis knee joint followed by Lequesne index while Doyle index is not suited. Radiological progression in OA co-relates well with all clinical indices including KGMC index. This study highlights the usefulness of visual analogue scale and various radiological and clinical indices to assess osteoarthritis especially for knee joint.

References

Platelet Indices as a Marker of Severity in Non-diabetic Non-Hypertensive Acute Ischemic Stroke Patients

Rathindra Nath Sarkar¹, Chandan Kumar Das², Urmimala Bhattacharjee³, Moumita Banerjee²

Abstract

**Background**: Platelet activation & aggregation are critical in pathogenesis of acute ischemic stroke. Mean platelet volume (MPV) & Platelet distribution width (PDW) are markers & determinants of platelet function. Larger platelets are metabolically more active, produce more prothrombotic factors, aggregate more easily & act as index of homeostasis and its dysfunction thrombosis.

**Material**: We studied 70 non diabetic non hypertensive ischemic stroke patients without previous thrombotic events & not on anti platelet medications within 24 hour of onset of symptoms & compared with equal number of age and sex matched controls. Severity of stroke was calculated by Canadian neurological scale (CNS).Platelet indices were obtained from SYSMEX KX-21.

**Observation**: Mean age of patients was 55 ± 7.11 and of controls was 52 ± 5.37. According to CNS patients were divided in two groups; with comprehension deficit (1st group, 32 patients) & without comprehension deficit (2nd group, 38 patients).Mean value for PDW & MPV in 1st group was 18.675 ± 3.494 & 12.894 ± 1.270 respectively and in 2nd group was 18.62 ± 3.387 & 12.42 ± 0.984 respectively and was significantly higher than mean value of 15.694 ± 3.127 & 10.46 ± 1.273 of PDW & MPV respectively in controls. In both study groups PDW & MPV was found to be significantly associated with severity of motor deficit.

**Conclusion**: In patients of ischemic stroke platelet indices may be used for predicting severity of motor deficit. Although larger sample size and multivariate analysis is required before this can be used regularly in clinical practice.

Introduction

Acute ischemic stroke results from sudden loss of blood circulation to an area of cerebral hemisphere leading to irreversible brain injury and neurological deficits persisting for more than 24 hours or until death. It accounts for 80–87% of all strokes.¹ Several risk factors like hypertension, diabetes mellitus, dyslipidaemia, tobacco smoking are instrumental in the pathogenesis of acute ischemic stroke largely by their link to atherosclerosis.²

Platelets are small, discoid and non-nucleated structures derived from fragmentation of megakaryocytes. Platelets play a pivotal role in the pathogenesis of atherosclerosis. Platelets secrete a large number of substances that are important mediators of coagulation, inflammation, thrombosis and atherosclerosis. Within an individual there is a wide variation in platelet size and density. Larger platelets contain more dense granules and produce more thromboxane A2. Thus larger platelets are metabolically more active and have greater prothrombotic potential.³⁴

Mean platelet volume (MPV) is a commonly used biomarker of platelet function and activation.⁵⁶ Increased MPV has been associated with greater in vitro aggregation in response to ADP and collagen.⁷ Mean platelet volume is a cost-effective and routinely available test. Elevated MPV levels are associated with increased risk of myocardial infarction in patients with coronary artery disease, as well as death or recurrent vascular events after myocardial infarction.⁸⁹ Also higher MPV is observed in patients with diabetes⁸¹ mellitus, hypertension,¹¹ hypercholesterolemia,⁶ smoking and obesity.¹²

Platelet distribution width (PDW) represents variation in platelet size. Larger PDW also indicates prothrombotic status.¹³ So far there is a paucity of data on the association between MPV, PDW and stroke severity or stroke outcome.¹⁴⁻¹⁶ The aim of our study was to investigate the relationship between platelet indices, MPV and PDW, and severity and outcome of acute ischemic stroke.

Material and Methods

This prospective observational cohort study comprising 70 acute ischemic stroke patients was conducted at the Department of medicine, Medical College, Kolkata during the study period between January 2015 and June 2015. The only inclusion criteria was the diagnosis of Acute Ischemic Stroke based on history, physical examination and computed tomography (CT) scan that was performed at the Emergency Department within 24 hours of symptom onset. Exclusion criteria were:

a. Age <18 years
b. CT features of cerebral haemorrhage
c. Presence of hypertension, diabetes mellitus and other co morbidities like liver and kidney failure, cardiac dysfunction.
d. Recent episode of infection
e. Histories of transient ischemic attacks (TIA), stroke, autoimmune disorders and peripheral vascular disease.
f. Patient on anti-platelet medications, medications for dyslipidaemia, immunosuppressants.

The control group comprised of 40...
healthy age and sex matched subject from our own hospital which included doctors, nurses and other staffs who did not have any past history of stroke/ TIA or other vascular risk factors.

All patients were subjected to detailed physical and neurological examination at the time of presentation. Severity of the stroke in the form of impaired neurological status was calculated for all patients using the Canadian Neurological Scale (CNS). The patients were divided into two broad groups, with comprehension deficit (1st group) and without comprehension deficit (2nd group), based on CNS.

During the first day of admission blood samples for the measurement of platelet indices were collected in ethylenediaminetetraacetic acid (EDTA) tubes and sent to the hospital laboratory. The blood samples were analysed by the SYSMEX KX-21 automated haematological analyser which is based upon the Coulter principle.

All the data collected were tabulated in the Microsoft Office Excel Worksheet and all the statistical evaluation were done using the Microsoft Office Excel tools.

**Results**

Out of 70 study subjects, fifty-two were male and 18 were female. Mean age of patients was 55±7.11 and of controls was 52±5.37. Based on Canadian Neurological Scale (CNS), thirty-two patients had comprehension deficit (1st group) with a mean CNS score of 1.87±0.25. While 38 patients had no comprehension deficit (2nd group), mean CNS score 8.89±0.39. Table 1. shows the demographic characteristics of cases and controls.

The mean values for PDW in 1st group, 2nd group and controls were 18.675±3.494, 18.62±3.387 and 15.694±3.127 respectively. Whereas the mean values for MPV in 1st group, 2nd group and controls were 12.894±1.270, 12.42±0.984 and 10.46±1.273 respectively. Thus the mean values of PDW and MPV in acute ischemic stroke patients were significantly higher compared to the control subjects (Figure 1).

Correlation coefficient between the values of motor deficit scores (based on CNS) and platelet indices of stroke patients were calculated. The severity of motor deficits was significantly correlated with the values of PDW (r=-0.556, p<0.01) and MPV (r=-0.46, p<0.05). Thus patients with lower CNS scores for motor deficits (indicating more severe deficits) had higher mean platelet volumes and platelet distribution widths. Figures 2 and 3 shows the scatter dot diagram between the values of motor deficits and MPV and PDW respectively.
Discussion

The Canadian Neurological Scale (CNS) is a simple and validated tool for assessing stroke severity. The scale amalgamates the following components: comprehension, level of consciousness, speech and motor function of arms, legs and face. Lower CNS scores indicate greater stroke severity. Generally CNS score 28 is mild, score 5-7 is moderate and 1-4 is severe stroke.\textsuperscript{17,18}

Our study revealed that platelet indices such as MPV and PDW are significantly raised in acute ischemic stroke patients compared to controls. Also increased values of MPV and PDW are significantly associated with greater functional impairment as indicated by motor deficits. All these implicate the role of platelet activation as an important underlying principle in the pathogenesis of stroke.

MPV and PDW are simple indices which are readily available and easily measured. During activation platelets undergo a change of shape from discoid to spherical. There is pseudopodia formation as well. Automated haematological analysers based on impedance technology can easily measure the platelet volume by deformation of electric field, which depends on platelet vertical diameter.\textsuperscript{15}

The association between platelet indices and acute thrombotic events have been investigated by researchers all over the world. The association of MPV with the risk of stroke was assessed in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) which revealed that MPV was positively associated with the risk of stroke, with an 11% increased relative risk (95% CI, 3% to 19%) of stroke per standard deviation of MPV.\textsuperscript{13} Another study by Slavka et al.\textsuperscript{20} showed that subjects with higher MPV (>11.01 fl) had 1.5 times higher vascular mortality risk than patients with low MPV (<8.7 fl). Arevalo- Lorido et al.\textsuperscript{21} in their study concluded that higher values of platelet indices are associated with overall mortality and morbidity including cardiovascular mortality. However a study conducted by Cho et al.\textsuperscript{22} failed to show statistically significant difference between patients and controls in terms of MPV values.

Both type II diabetes mellitus and hypertension are important risk factors of acute ischemic stroke. Several studies have demonstrated that type II diabetes mellitus and hypertension are associated with endothelial dysfunction leading to platelet activation and altered platelet-endothelial interaction. The uniqueness of our study lies in the fact that it deals with non-diabetic and non-hypertensive stroke patients. Thus it clearly upholds the view that increased platelet activity is itself an independent risk factor of acute ischemic stroke.

Conclusion

Our study supports the view that increased values of platelet indices, MPV and PDW is associated with increased platelet activity and can be considered as independent risk factor in stroke patients who are non-diabetic and non-hypertensive.

References

Spectrum of Cerebral Venous Thrombosis in Uttarakhand

Sunil Jee Bhat¹, Priyanka Vikas Kashyap²*

Abstract

Background: CVT is an uncommon but important cause of stroke that is often misdiagnosed delaying its treatment. High suspicion is essential in early recognition and treatment.

Objective: To study the clinical features and etiology of patients with Cerebral Venous Thrombosis (CVT) and relation between septic and non septic CVT if any.

Patients and Methods: A prospective study was done in SMIH that enrolled 40 patients of CVT in 2 years duration (Jan 2014 to Dec 2015). The patients were diagnosed as CVT according to Magnetic Resonance Venogram (MRV) and clinical status.

Results: Forty (40) patients of CVT were enrolled during 2 years period, most were females (22/30) and aged between 18-50 years (mean age 30.2±4.9). Most common presentation was headache followed by seizures and focal deficit. Other symptoms encountered were cranial nerve palsies, meningeal signs, papilloedema. Most common headache type was tension type headache. Most common cranial nerve involvement was abducens nerve. Superior Sinus Thrombosis (SSS) involvement was most commonly thrombosed followed by its involvement with other sinuses. Isolated lateral sinus involvement also seen. On screening for cause, non septic CVT outnumbered septic CVT (22/8) and the most common cause of non septic CVT was unknown followed by coagulation defect. Among septic CVT group puerperal sepsis in females and mastoiditis in males were the dominant cause.

Conclusion: Septic CVT prognosis had better than non septic CVT. Hence, CVT presents with wide range of presentations and anticoagulation is the treatment. Septic CVT if intervened timely with proper antibiotics have better prognosis. Antibiotics are the mainstay of therapy for septic CVT.

Introduction

Cerebral venous thrombosis (CVT) is an uncommon cerebrovascular disease presenting with a remarkably wide spectrum of signs and mode of onset. It was first described by Ribes in 1825. The disease is characterized by headache, papilloedema, seizures and focal neurological deficit culminating to coma and death and pathophysiologically by hemorrhagic infarction. Advent of conventional angiography and more recently MRV allowed frequent recognition of CVT cases. We present a series of CVT patients with varied etiology.

CVT may occur as a complication of infectious or noninfectious processes. Although the majority of CVT is actually due to non infectious causes, however septic thrombosis is still a potential life threatening complication that needs to be recognized and treated on emergency basis. The incidence of CVT has dropped dramatically in recent years. In the past, before the introduction of antibiotics, infection was the main cause of CVT, early suspicion and recognition is very crucial to reduce mortality and morbidity rates of this potentially fatal disease. Unlike non septic CVT, intravenous wide spectrum antibiotics and early surgical drainage of primary site of infection whenever possible are essential in septic CVT.

In this series, we highlight the early use of antibiotics for CVT. The vast majority of cases of septic CVT have an acute presentation associated with prominent features of sepsis.
suggestive of CVT, such as headache, altered mental status, seizures, focal neurological deficits, especially in the absence of the usual vascular risk factors were considered for inclusion into study. Past medical history was obtained for each case. All medications that were used by patients including contraceptives use were noted.

All the participants were subjected to a detailed physical examination, including general physical examination, a detailed neurological examination, Glasgow coma scale and examination of other systems.

In all the patients, the following laboratory testing were carried: complete haemogram, coagulation profile [bleeding time, clotting time, prothrombin time with international normalized ratio (INR) and activated partial thromboplastin time]; workup for other prothrombotic disorders (protein C and S, homocysteine levels); rheumatological work-up including rheumatoid factor (RF), antinuclear antibody (ANA), anti-double stranded deoxyribonucleic acid antibody (anti-dsDNA), anticardiolipin antibody (AcLa); and serological testing for human immunodeficiency virus (HIV) infection.

All patients were subjected to Magnetic Resonance Imaging (MRI) of the brain [T2 weighted (T2W) and diffusion weighted (DWI) images] and MR Venogram. Patients whose scans were suggestive of other pathologies such as arterial infarcts, tumors, arteriovenous malformations were excluded from the study. All the patients were managed according to standard guidelines. All the patients who have definite evidence of CVT were admitted in the neurology Intensive Care Unit. The treatment included management of predisposing/precipitating conditions, antithrombotics, lowering intracranial pressure and symptomatic treatment for seizures, headaches. Patients with CVT without contraindications for anticoagulation were treated with dose-adjusted intravenous heparin with an at least doubled activated partial thromboplastin time.

Analogous to patients with a first episode of CVT, oral anticoagulation was given for 3 months if CVT was secondary to a transient risk factor, for 6–12 months in patients with idiopathic CVT and in those with mild thrombophilia. Indefinite oral anticoagulation was given in patients with two or more episodes of CVT and in those with one episode of CVT and severe thrombophilia. Other symptomatic measures such as intravenous mannitol (100 ml, 6th hourly), were instituted. Antiepileptic drugs were started based on need. Large haemorrhages and infarcts associated with extensive cerebral oedema with progressive deterioration in sensorium were managed with decompressive craniectomy. Further course of illness, from hospital admission to the time of discharge, was assessed by progression of presenting complaints, neurological deficits and mental status assessment by Glasgow Coma Scale. We also assessed the treatment outcome in Septic versus non septic group. All the patients recruited in the study were assessed for functional status at the end of their hospital stay using Modified Rankin Scale (mRS) which were classified as complete recovery - 0 to 1, partial recovery independent - 2, partial recovery dependent - 3 to 5 and death - 6.

**Table 2: Sinuses involved in CVT patients**

<table>
<thead>
<tr>
<th>Sinuses involved</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSS</td>
<td>78%</td>
</tr>
<tr>
<td>SSS with other sinuses</td>
<td>14%</td>
</tr>
<tr>
<td>Isolated Lateral sinuses</td>
<td>5%</td>
</tr>
<tr>
<td>Straight sinus</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Table 1: Cardinal manifestations in 30 CVT patients**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>No. of patients (30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>27</td>
</tr>
<tr>
<td>FND</td>
<td>5</td>
</tr>
<tr>
<td>Seizures</td>
<td>3</td>
</tr>
<tr>
<td>Cranial nerves</td>
<td>2</td>
</tr>
<tr>
<td>Meningeal signs</td>
<td>6</td>
</tr>
<tr>
<td>Papilloedema</td>
<td>8</td>
</tr>
<tr>
<td>Stupor</td>
<td>1</td>
</tr>
</tbody>
</table>

40 patients of CVT were enrolled, 10 were excluded not satisfying inclusion criteria. Thirty patients satisfying the inclusion criteria were included in the study.

Out of 30 patients, 8 were males, 22 were females, and their age ranged from 18 to 50 years. Their mean age was 27.67±9.1 years. Most of the patients were in the third decade of life; majority was women (70%). Headache was the predominant and first symptom to bring patients to medical services, in 90% of patients. Headache was moderate to severe in 70%, and in rest it was mild but nagging and not relieving by any measures like sleep, analgesics or rest. 10% of patients had seizures and focal deficit in 16% of patients as shown in Table 1.

Headache was tension type in 40%, migrainous in 30% patients, 10% had mixed type and 20% had Chronic Daily Headache. Visual blurring was seen in 12 cases (40%). Focal neurologic deficit was seen in form of hemiparesis was noted in 2 patients (6%), aphasia in 2 (6%) and 1 had hemisensory loss. Cranial nerve involvement was seen in 4 (13%) patients and 3 (10%) had unilateral VI palsy and on had associated VII nerve along with abduccens palsy. Seizures seen in 3 (10%) patients and all had focal with secondary generalization. The mode of onset of symptoms was also highly variable–acute (<30 hrs) headache in 16 (53%) patients, subacute (>1 month) headache along with visual blurring and cranial nerve involvement in 8 (26%) patients and progressive in 6 (20%) patients over months and had exacerbation of headache intermittently. Neuro imaging in form of Magnetic Resonance Imaging of Brain with venogram was done in all patients. The results were as follows. Venous sinus thrombosis was present in all the patients. Hemorrhagic infarction was seen in 22/30 (73%) patients, non hemorrhagic infarct was present in 8/30 (26%) patients. Saggital Sinus Thrombosis (SST) was the most common sinus involved (78%) with either partial or complete occlusion. Its involvement with other sinuses was seen in 14 % patients and isolated lateral sinus thrombosis was seen in 5% and lateral and straight sinus thrombosis was seen in rest 3% patients as shown in Table 2.
Table 3: Spectrum of etiology in CVT patients

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraceptive pills</td>
<td>5/22 females</td>
</tr>
<tr>
<td>Post partum period</td>
<td>6/22 females</td>
</tr>
<tr>
<td>Puerperal sepsis</td>
<td>3/6 females</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>3</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Mastoiditis/otitis</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
</tr>
<tr>
<td>Furuncle over face</td>
<td>3</td>
</tr>
</tbody>
</table>

Etiology

Among twenty-two females patients, contraceptive pills were used by 5 females and rest 6 were in post partum state with duration varying from 2 weeks to 8 weeks. Evidence of puerperal sepsis was seen in three postpartum females, diagnosis made on basis of history of foul smelling discharge per vaginum, lower abdomen pain and culture of vaginal swab. Culture from vaginal swab grew staphylococcus aureus and pseudomonas aeruginosa.

Among all 30 CVT patients, 8 had septic cause, 5 were females and 3 were males. One male had mastoiditis and rest two males had furuncle over face area. Three females had puerperal sepsis as mentioned above and 2 had furuncle over upper lip region. These septic CVT patients presented with high grade fever, facial erythema and swelling and headache. Among non CVT patients, no cause could be attributed in 14 patients and 4 were found to have coagulation disorder, most common being antithrombin III (3 patients) and protein S deficiency (1 patient). Collagen vascular profile was negative in all patients so as anti phospholipid antibody workup as shown in Table 3.

Septic CVT patients had more acute presentation, more severe, they responded to treatment early and dramatic than non septic CVT pts. Two patients among non-septic CVT died of raised Intracranial pressure (ICP) and cerebral herniation underwent decompressive craniotomy but developed ICU complication in form aspiration pneumonitis.

Septic CVT patients had sudden onset erythema of eyelids and limitation of ocular movements which alerted the possibility of CVT. All patients received heparin. Septic CVT patients received antibiotics in addition to anticoagulants and short duration steroids and improved.

Discussion

Septic CVT can occur at any age but typically affect young adults, most commonly in the 3rd decade of life. The incidence is approximately 15% of all the cases of CVT that is 3 - 4 /1,000,000 with 3:1 female predominance. Although rare, septic vein thrombosis (SVT) remains a potentially lethal complication of infections that involve the sinuses, face, ears and oral cavity. The early recognition and differentiation from other diseases are keys to reducing mortality rates and long term sequelae. The dural sinuses and the cerebral and emissary veins have no valves, which allow blood to flow in either direction according to pressure gradients in the vascular system. This makes this venous system vulnerable to septic thrombosis resulting from spreading of infection from adjacent locations. Septic CVT involves mainly the cavernous sinus followed by lateral and then sagittal sinus. Infection may trigger the thrombosis directly by causing septic thrombosis or indirectly by precipitating thrombosis in people who suffer from a prothrombotic illness. Early diagnosis can be facilitated by prompt recognition of the clinical and radiological findings that are suggestive of venous occlusion of the cavernous sinus. Bacterial meningitis and parasal sinusitis can be a complication of superior sagittal thrombosis, resulting in an 80% mortality rate.

Septic CVT patients are more toxic with features of facial infection. They would present with acute onset of headache, fever, and vomiting, facial redness and painful eyelid edema. Fever is a constant finding as was in our patients as well as orbital symptoms may start in one side then very shortly within 24-48 hours become bilateral. Patients usually have the triad of chemosis, proptosis (due to orbital vein congestion) and painful ophthalmoplegia (due to involvement of III, IV, VI) with occasional ophthalmic branch of trigeminal cranial nerve involvement. Papilloedema is seen in some patients and is usually mild and late. It was present in 8 patients in our series. Decreased visual acuity is reported in less than 50% cases, pupils can be dilated (parasympathetic involvement) or smaller and immobile (both parasympathetic and sympathetic dysfunction). Impaired vision is uncommon. Nevertheless, visual loss may be caused by corneal ulceration secondary to proptosis and loss of the corneal reflex, occlusion of the internal carotid, ischemic optic neuropathy, orbital congestion, toxic neuritis of the optic nerve, or embolic phenomena.

In our series, septic thrombosis patients were much sicker than those with non septic thrombosis. The illness is almost always acute in nature and patients were sick, toxic and febrile. Some had focal symptoms and signs suggestive of raised intracranial pressure varying on site of CVT, but responded early and better with lesser morbidity and mortality as compared to non septic group.

Clinically, the differential diagnosis includes meningoecephalitis, orbital cellulitis, orbital apex syndrome and non septic CVT. In Sebire et al series, 23/42 patients had infection precipitated venous thrombosis emphasizing that people with prothrombotic conditions may develop thrombosis after having any systematic infection and blood culture was positive in 70% of cases. Reviews of large single center series from the pre-antibiotic and early antibiotic era had documented that infections of the middle third of the face were responsible for most cases of Septic CVT. It was seen in 4 patients of Septic CVT in our series. Approximately 60 to 80% of these nasal furunculus accounts for the most common cause. Organisms may reach the cavernous sinus from the face by an anterograde route along the ophthalmic veins, which is connected to the angular veins, or by a retrograde route along the emissary veins that are connected to the pterygoid venous plexus. In up to 25 percent of cases where a facial furuncle is responsible, it has either been previously manipulated by the patient or incised by the surgeon. Staphylococcus aureus is the most frequently cultured organism in these infections accounting for 70%, followed by Streptococcus species at 20%. In our cases, patients had different source of infections like furunculus, puerperal sepsis, mastoiditis. The most sensitive investigation of intracavernous occlusive defects is venography. Previously, Cerebral angiography with late venous views was considered.
to be gold standard in the diagnosis of CVT. but nowadays, it has been reserved for the definitive assessment of intracavernous aneurysms after they have been detected and monitored using CT or MRI. Diagnosis of cavernous sinus thrombosis is usually made with MRI scan with venogram; or contrast enhancement Computed Tomography. Fine -cut CT scan is less sensitive.  

Because it is often difficult to distinguish septic and non-septic causes of CST, the initial management is the same. Only when a septic etiology is ruled out definitively can antibiotics be withdrawn. Antibiotics are the mainstay of CST therapy. Anticoagulation, corticosteroids, and surgery are adjunctive treatment in appropriately selected patients. Undoubtedly, antibiotics have the greatest impact on the prognosis of SVT. The overall mortality and morbidity associated with cavernous sinus thrombosis (CST) continue to be high. Consequently, institution of intensive treatment at the earliest suspicion of disease should be emphasized. Postmortem studies have shown that there is less extensive thrombosis within the cavernous sinuses since the advent of antibiotics. Case reports and expert opinion recommends antibiotics have the greatest impact on the prognosis of septic CST. High-dose intravenous antibiotics should be instituted emergently at the earliest suspicion of this diagnosis. Appropriate selection of empiric antibiotic regimens should be directed at the probable organisms implicated as the primary source of infection. Complications such as brain or orbital abscesses, meningitis or subdural empyema should be kept in mind as these need surgical intervention at the earliest.  

Staphylococcus aureus (MRSA) until the actual culture results are available plus a third-generation cephalosporin, such as ceftriaxone. Quinolones should be used in patients allergic to penicillin. Intravenous metronidazole should be added if dental or sinus infection is suspected. Antifungal therapy has been advocated only in cases of biopsy confirmed invasive fungal infection. Vancomycin is used routinely until culture results negate MRSA. It is also indicated for patients who have failed to respond to penicillins and cephalosporins. Empiric antibiotics can be switched to specific antibiotic therapy once culture sensitivities reports are available. Intravenous antibiotics are required because thrombus may limit penetration of antibiotics. Bacteria, sequestered within the thrombus, may not be killed until the durals sinususes have started to recanalise. Antibiotics also need to be administered over an extended period, for at least 2 weeks beyond the time of clinical resolution and in high doses. This insures complete sterilisation and prevents relapses. Supportive therapy is includes resuscitation, oxygen support, and local eye care. Considerable controversy exists concerning the efficacy of anticoagulation in the treatment of CST. As the condition is rare, prospective trials to establish any benefit from anticoagulation are unlikely to be performed. Anticoagulation carries the risk of hemorrhage, especially in patients with concomitant complications (e.g., cortical venous infarction, necrosis of intra-cavernous portions of the carotid artery, and cerebral or intra-orbital haemorrhages). Two retrospective reviews examining the use of anticoagulation for septic CST produced varying results (Level C evidence). However, some evidence says that the use of anticoagulation prevents propagation and contributes to re-canalisation of the thrombus. These are potentially beneficial effects, partly because the thrombus itself can harbour bacteria and sustain their growth.  

Two controlled trials comparing the use of placebo to anticoagulants in patients with cerebral sinus venous thrombosis. European Federation of Neurological Societies (EFNS) guidelines recommend either low molecular weight subcutaneous or intravenous heparin for aseptic dural venous thrombosis. European Paediatric Neurology Society (EPNS) in 2012 recommend the use of anticoagulants for dural venous thrombosis to lessen the risk of death and other sequelae. However, it should be noted that septic CST and aseptic dural venous thrombosis differ in many respects and that anticoagulation may be more hazardous in patients with septic CST. The differences include the presence of infective etiology, the site of the thrombosis, the acuteness of the process, and the presence of associated haemorrhagic complications. Anticoagulation should be cautiously used in patients with bilateral CST and/or concurrent intracranial haemorrhage. The types and protocols for anticoagulation have varied considerably in research protocols. Intravenous and intramuscular unfractioned heparin, subcutaneous low molecular-weight heparin (LMWH), and oral coagulation have all been used. Intravenous unfractionated heparin is rapidly reversible agent hence, advocated in the early stages of disease, followed by conversion to longer-acting agents, such as warfarin, when the patient’s condition has stabilized. New anticoagulants, including direct thrombin inhibitors and factor Xa inhibitors has a more predictable anticoagulant effect and an absence of induction of immune-mediated heparin-induced thrombocytopenia (HIT). But there is a paucity of reported cases of CST or other forms of dural sinus thrombosis that have been treated with these agents. The use of direct thrombin inhibitors, such as argatroban, can be considered as an alternative form of anticoagulation to heparin in patients with HIT (Heparin Induced Thrombocytopenia) or those at risk of HIT. Regarding duration of anticoagulation, some authors have suggested that anticoagulation should be continued until clinical or radiological evidence of complete resolution or until significant improvement of infection and thrombus. If a patient is considered suitable for anticoagulation but deteriorates despite this therapy, they may be considered for thrombolysis. This therapy is usually reserved for progressive, aseptic CST and carries with it the risks of intracranial haemorrhage, stroke, and the inability to re-cannalise. Patients commenced on anticoagulants...
are usually still in an unstable clinical condition and are therefore not candidates for surgical management. However, if the patient’s condition stabilises and surgical management is indicated, rapidly reversible anticoagulants can be discontinued to allow surgery. Corticosteroids has controversial role in many cases of CST because of their potentially harmful immunosuppressive effects. However, they are absolutely indicated in cases of pituitary insufficiency and Addisonian crisis secondary to ischaemia or necrosis of the pituitary that complicates CST. Steroids may be essential in the acute setting to prevent Addisonian crisis as well as in replacement doses in the long-term. Corticosteroids reduce intraorbital congestion in patients with orbital oedema and cranial nerve inflammation in patients with cranial nerve dysfunction. There are only a few anecdotal reports concerning the use of corticosteroids in CST in general and their efficacy has not been proved by these reports. Studies in which the use of corticosteroids has been reported, other treatments have been used concurrently. In one case, reported in 1962, cranial nerve dysfunction and orbital oedema failed to improve after 37 days of antibiotic and anticoagulant therapy but regressed dramatically 2 days after the addition of corticosteroid therapy, with eventual complete resolution in eye signs and symptoms. Prompt drainage of the primary site of infection (such as the para-nasal sinusitis, dental abscess) or other concurrent closed-space infection is advisable once patient condition permits. Different operations have been performed to decompress the sinuses, including transeptal sphenoidectomy, endoscopic sphenoidectomy and ethmoidectomy and external fronto-ethmoido-sphenoidectomy. In cases of otogenic CST, mastoidectomy has been performed, with decompression of sigmoid sinus thrombophlebitis.

Anticoagulation with heparin is the only modality with reasonable evidence to support its use in CVT, even in patients with cerebral hemorrhage. Endovascular thrombolyis is a promising option for patients with a severe form of CVT or following a failure of anticoagulation therapy. Mechanical thrombectomy is reserved for selected cases and decompression surgery for malignant CVT with impending herniation. With increasing awareness, not only is CVT being diagnosed more frequently, but less clinically severe cases of CVT are also being detected presently. However, despite substantial improvements, the diagnosis of CVT is often missed because of the remarkable variations in the clinical presentation and neuroimaging signs. Furthermore, existing studies on CVT patients are often limited by small numbers; their retrospective nature and short term follow-up periods. Thus, CVT remains a diagnostic and therapeutic challenge, and scanty information still exists on the natural history and long-term prognosis of this disease. Most patients with CVT have a benign prognosis. Only a minority of patients die during the acute phase or in the following months. Most patients surviving CVT recover completely, or have only mild functional or cognitive deficits.

Limitation of the study

The number of CVT patients was less and that of Septic CVT group further less which limits the definite conclusion on etiology causes and treatment guidelines.

But, despite of lower number, the study strengthens the fact that septic CVT should be kept as high index of suspicion and timely management with antibiotics and steroids can decrease the mortality in these patients.

Acknowledgement

We are thankful to the statistical department and computer department for their valuable help.

References

Subcutaneous Injection of Botulinum Toxin in Patients with Post Herpetic Neuralgia. A Preliminary Study

Pratik Jain¹, Meena Jain², Shailendra Jain³*

Abstract

Background: Post Herpetic neuralgia (PHN) is neuropathic pain that occurs after herpes zoster infection. Several treatments have been suggested in the management of PHN. This study evaluates the efficacy of subcutaneous injection of botulinum toxin in patients suffering from PHN.

Methods: Nineteen patients suffering from PHN for more than 2 months were enrolled in the study. The severity of pain was assessed by visual analog scale (VAS). A total dose 500 units of BTX-A was injected around the site of pain. This was administered in about 25 sub-cutaneous injection around the site, delivering approximately 20U/ml of BTX-A per injection. The patients were followed at 1, 2, 3, 4, 12 and 16 weeks after the administration of the drug.

Results: The mean age was 56 years (age range 36 to 63) for non-pregnant patients. The two pregnant patients of age 28 and 32 year old who were in their 28 and 30 weeks of gestation were also included. The mean duration of PHN was 4.78 wks. At each visit VAS was used to evaluate the degree of pain (0= painless; 10: maximum pain). There was a significant reduction in the severity of pain after the injection.

Conclusion: Botulinum toxin significantly decreases the severity of pain in PHN patients and last for 4-6 month of the period. This decrease is less prominent by passing time.

Introduction

Herpes zoster is an infection caused by varicella zoster virus. Anyone infected with varicella (chicken pox) virus in childhood is at risk for reactivation of dormant virus although it occurs with increasing frequency in the elderly as a result of waning of cell mediated immunity. Herpes zoster is rare in pregnancy and only found one in 20000 pregnancies. The most common complication of herpes zoster is post herpetic neuralgia (PHN) which can cause chronic and debilitating pain.¹ One of the reasons for the constant pain months after zoster infection is the increase in the number of P fibers and decrease in the number of the large fibers which suppress the pain transmission.² The early treatment of PHN with botulinum toxin type A has shown promise in the long term pain control without any cognitive side effects.³ Due to large size of molecule botulinum toxin A is not expected to be present in systemic circulation and hence does not cross the placenta. It is safer to use in the pregnancy.⁴ One of the authors has the experience of using the Botulinum toxin in hyperhydrosis as dose dependent cosmetic effect.⁵ In this study we aimed to evaluate the effect of botulinum toxin type A in PHN patients in both general and pregnant patients.

Material and Method

Based on previous trial and experience in cosmetic effect of botulinum in hyper hydrosis (5-6) 19 patients men or women with severe PHN resistant to usual therapeutic modalities in order to evaluate the efficiency of BTX-A in this conditions were studied. Two women were pregnant. Written informed consent was obtained from each patient. Clearance from ethical committee was obtained. The mean age was 56 years (age range 36 to 63) years in the non-pregnant group. 2 pregnant patients were 28 and 32 year old in their 28 and 30 weeks of gestation respectively. The mean duration of PHN was 4.78wks. Herpes zoster has been diagnosed in all patients based on the presence of unilateral dermatomal clinical findings. Three patients had herpetic eruption in ophthalmic division of trigeminal nerve, six in T4-T5 dermatome on anterior side and five in T3, T4 dermatome on posterior side, one T6, T7 and four in T12 -L1 dermatome distribution. Both the pregnant patients did not receive oral antiviral (Acyclovir) therapy.

Patients were counseled regarding the nature of the drug, its possible complications. Method of injection was explained and written consent obtained. Severity of symptoms determined through a visual analogue scale (VAS) as standard criteria for assessment of severity of pain.⁶ At each visit VAS was used to evaluate the degree of pain (0= painless; 10= maximum pain).

Each sterile viral containing 500 units of BTX-A (Dysport, Speywood UK -Bharat serum and vaccine, India) was diluted with 5ml of sodium chloride, resulting in a concentration of 100 U/ml. The entire 500 units of the drug was delivered through subcutaneous route in a chess board fashion over the affected area at 25 points. Each of the injection delivered about 20U/ml subcutaneously. The patients were followed at 1, 2, 3, 4 and 12 and 16 weeks.

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Table 1: Patients demographic distribution, duration of PHN and VAS score at base line and follow up visits (weeks) after BTX-A therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Affected dermatome</th>
<th>PHN duration in months</th>
<th>VAS score baseline</th>
<th>1 wk</th>
<th>2 wk</th>
<th>4 wk</th>
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Software SPSS 16.0 version (Significant at 0.01 i.e. 1 % level of significance)

Result

There was decrease in the intensity of pain in all the patients including the pregnant patients. The magnitude of relief from pain varied from the patient to patient. It had no correlation with age of the patient, dermatomal involvement and duration of PHN. Except for erythema at the site of injection in 3 patients, no other immediate side effects were noted up to an observation for 24 hours. Table 1 shows dermatomal distribution and the changes in VAS score during follow up period in weeks. Mean VAS score dropped from 8.3 at base line to 2. The decrease in the severity of pain was noted after 2 weeks of administration and the peak effect were noted at 4-6 weeks. In both the pregnant patients, the pain lasted up to 16 weeks. Further follow up of the pregnant patients could not be under taken in the study. The pain recurred in the other patients (n=17). The drug was re-administered in 5 patients along with carbamazepine. However the pain intensity was less in these five patients as compared to pre-study period. The remaining patients (n=12) did not consent for re-administration in view of the cost involved.

Discussion

PHN pain is considered neuropathic in nature. It has a very complex mechanism, so different modalities of treatment medical and surgical has been suggested. The variable pain relief with BTX-A, with or without combinations of drugs such as in our patients was reported in literature.Use of BTX-A in pregnancy is considered safe and our goal was to achieve a reduction in various substances that sensitize nociceptors. This anti-nociceptive effect is associated with the inhibition of forminal-induced glutamate release and a possible reduction of the peripheral nociceptive input by inhibiting the release of substance P and calcitonin gene-related peptide, which plays a significant role in neurogenic inflammation. However, some investigators believe that the beneficial of BTX-A in treating neuropathic pain is related not only to acetylcholine inhibition but also to a blocking action on the parasympathetic nervous system.

Temporary erythema which was observed could be due to multiple injections in a limited area. However, it disappeared by passage of time. The dose of BTX-A was fixed in all the cases in spite of variable dermatomal involvement, intensity of pain and duration of PHN as it was observed in one of the study of one of the author that effect of BTX-A was dose dependent and our goal was to achieve in the reduction of pain intensity to a certain extent as to make patient comfortable.

The encouraging results of this small clinical study lead us to conclude that BTX-A could be an alternative therapeutic modality in treating PHN if not complete but at least in reducing the intensity. It can be given safely to pregnant patients as well.

References

5. Jain S, Tamer SK, Hiran S, Dwivedi MD. Cosmetic effect of BTX-A in pregnancy is considered safe and our goal was to achieve a reduction in various substances that sensitize nociceptors. This anti-nociceptive effect is associated with the inhibition of forminal-induced glutamate release and a possible reduction of the peripheral nociceptive input by inhibiting the release of substance P and calcitonin gene-related peptide, which plays a significant role in neurogenic inflammation. However, some investigators believe that the beneficial of BTX-A in treating neuropathic pain is related not only to acetylcholine inhibition but also to a blocking action on the parasympathetic nervous system.

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Immunogenicity, Safety, and Tolerability of Live Attenuated Varicella-Zoster Virus Vaccine (ZOSTAVAX™) in Healthy Adults in India

L Sreenivasamurthy1*, Sudhanshu Pandey2, Bharija Subhash Chandra3, Monisha Sharma2, SR Ranganathaiah4, P Vaidya5, Rajiv Naik6

Abstract
Background: Herpes zoster (HZ) is caused by varicella-zoster virus (VZV) reactivation. In the United States, Zoster vaccine (ZOSTAVAX) is indicated for HZ prevention in patients ≥50 years.

Aims: To evaluate the immunogenicity, safety, and tolerability of ZOSTAVAX in healthy Indian subjects, to support its registration in India.

Methods: This open-label, single-arm study was conducted at 10 sites in India. Healthy Indians (≥50 years) received a single ZOSTAVAX dose. Immunogenicity was assessed by VZV-specific antibody titer using gpELISA assay. VZV-specific antibody geometric mean titers (GMT; Day 1 pre-vaccination, Week 6 post-vaccination) and geometric mean fold-rise (GMFR; Week 6 post-vaccination) were assessed. Safety was evaluated by the incidence of adverse events (AEs) and serious adverse events (SAEs) within 42 days of vaccination. Two-sided 95% confidence intervals (CIs) were evaluated using t-distribution with natural log-transformed values.

Results: Of the 250 subjects (mean age, 58.6 years) enrolled and vaccinated, 244 subjects completed the 6-week follow-up. Overall, subjects in the per-protocol population had GMT of 149.8 gpELISA units/mL (n=250; 95% CI: 132.6, 169.2) at Day 1 pre-vaccination, and 410.8 gpELISA units/mL (n=243; 95% CI: 373.0, 452.6) at Week 6 post-vaccination. GMFR of VZV-specific antibody from Day 1 pre-vaccination to Week 6 post-vaccination was 2.8 (95% CI: 2.5, 3.1). Overall, 67 subjects (26.8%) experienced AEs, with 48 (19.2%) reporting injection-site AEs and 38 (15.2%) reporting non-injection-site AEs. SAE—abdominal pain and bronchitis—was reported in one (0.4%) patient each. There was one death, which was unrelated to the vaccine.

Limitations: Since ZOSTAVAX introduces a new live attenuated virus, clinical reactivation of ZOSTAVAX virus and wild-type VZV will need to be differentiated.

Conclusion: In healthy Indians ≥50 years, ZOSTAVAX was well tolerated and resulted in expected VZV-specific antibody titer levels at 6 weeks post-vaccination.

Introduction
Herpes zoster (HZ) is caused by the reactivation of varicella-zoster virus (VZV), which causes chickenpox. Hope-Simpson hypothesized that, in some individuals, VZV remains latent in the sensory ganglion after primary infection and reactivates or replicates, perhaps as a consequence of advancing age and waning cell-mediated immunity.1–3 HZ is associated with pain, which may occur during prodrome, the acute eruptive phase, and the postherpetic phase of the infection (postherpetic neuralgia; PHN). Serious complications, such as PHN, scarring, cranial and motor neuron palsies, encephalitis, visual impairment, hearing loss, and death can occur as a result of HZ.4–6 A systematic review of 130 studies conducted in 26 countries showed that the incidence of HZ ranges between 3 and 5 per 1,000 person-years in North America, Europe, and Asia-Pacific regions. The risk of recurrence of HZ ranged from 1% to 6%, whereas the risk of developing complications such as PHN varied from 5% to more than 30%.7 Moreover, the risk of developing PHN increases markedly with age.4–6 However, the HZ Global Awareness Survey of 8,688 subjects ≥50 years, conducted in 22 countries, evaluated the existing levels of awareness and knowledge of HZ and reported that <20% participants were aware of HZ and its symptoms in Turkey, Chile, and India.8

The live attenuated Zoster (Oka/Merck) vaccine (ZOSTAVAX) for adults can boost host immunity to VZV. It contains the same virus strain as the varicella vaccine for children, but is 14.4 times more potent (1,350 plaque-forming units [PFU] vs. 19,400 PFU).9,10 ZOSTAVAX is approved by the US Food and Drug Administration for prevention of HZ (shingles) in individuals ≥50 years,9,11 supported by the results of the ZOSTAVAX Efficacy and Safety Trial (ZEST)12 and Shingles Prevention Study (SPS).13 In ZEST, ZOSTAVAX significantly reduced the risk of developing zoster by 69.8% in comparison to placebo and increased the VZV-specific antibody geometric mean titers (GMT) by 2.3 fold at 6 weeks post-vaccination in a random 10% subcohort.9,12,14 In SPS, ZOSTAVAX significantly reduced the risk of developing HZ, the burden of illness,
Methods

Study design

This open-label, single-arm study (Clinicaltrials.gov NCT01527370; protocol number 025-00) was conducted at 10 sites in India between November 1, 2012 and April 9, 2013. Healthy Indians ≥50 years old received a single dose of ZOSTAVAX™ (Zoster Vaccine Live; Oka/Merck strain; Merck & Co., Inc., West Point, Pennsylvania, USA) on Day 1. The study was conducted in accordance with the Declaration of Helsinki and in compliance with the approved protocol and Good Clinical Practice Guidelines issued by the Central Drugs Standard Control Organization, Ministry of Health, of the Government of India. The study protocol was approved by the Institutional Review Boards of the respective investigational centers. All participants provided written informed consent.

Study population

Subjects ≥50 years, who were afebrile (<38.0°C oral) on the day of vaccination and did not have underlying chronic illness were eligible for the study. Additional eligibility criteria are included in the supplemental section.

Vaccination procedure

Subjects were assigned an allocation number and received a single dose subcutaneous injection of ~0.65 mL ZOSTAVAX in the deltoid region—preferably in the nondominant arm—on Day 1. Dose was based on previously demonstrated acceptable safety and immunogenicity responses in subjects ≥50 years in clinical studies. ZOSTAVAX is a single-dose, sterile, lyophilized, live attenuated virus vaccine reconstituted in sterile water (without preservatives or other substances that might inactivate the vaccine) as a diluent. Study vaccine was stored at 2°C to 8°C, and the sterile diluent was stored at room temperature at 20°C to 25°C or refrigerated at 2°C to 8°C. All subjects were evaluated for safety for 42 days post-vaccination.

Assessments

Efficacy/immunogenicity

Immunogenicity endpoints included immune response measured by VZV-specific antibody titer using gpELISA assay[17] (PPD Vaccines and Biologics, LLC, Wayne, PA, USA). The VZV-specific antibody GMT (Day 1 pre-vaccination and Week 6 post-vaccination) and its geometric mean fold-rise (GMFR) at Week 6 post-vaccination were assessed. Subjects were also evaluated by age category (50-59 years and ≥60 years). For assessing VZV-specific antibody titer, 5 mL of whole blood was collected from all subjects before vaccination (Day 1) and post-vaccination (Week 6; Days 43-49). Subjects who had protocol deviations that may have interfered with the assessment of VZV-specific antibody response, developed suspected varicella or HZ rashes before a blood sample was taken, or reported an exposure to varicella/HZ were excluded from the analysis of VZV-specific antibody responses.

Safety

All subjects who were vaccinated and had any safety follow-up were included in the safety evaluation. The primary safety endpoint was the incidence of serious adverse events (SAEs) observed within 42 days post-vaccination. Key safety measures included any adverse experience, injection-site AEs, systemic AEs, SAEs, vaccine-related SAEs, and discontinuation due to an AE within 42 days post-vaccination. A vaccination report card (VRC) was maintained by the subjects in which they recorded subject-reported safety parameters such as systemic adverse experiences, varicella-like and HZ-like rash, injection-site complaints such as redness, swelling, and pain/tenderness/soreness occurring Days 1-5 after vaccination, and elevated temperature (oral ≥38.0°C) during the 42-day follow-up period. The VRC was examined by study personnel between Days 43-49. Subjects reporting suspected varicella/varicella-like or HZ/HZ-like rashes were evaluated by the investigator at the study site within 72 hours of rash onset (preferably within 24 hours) for clinical evaluation, and then every 3 days for evaluation of complications and for rash and pain assessments until no new lesions appeared. Provisions were made for the administration of antiviral medication (e.g., acyclovir, famciclovir, or valacyclovir) and the clinical assessment of the rash, including collection of a lesion specimen for VZV identification by polymerase chain reaction (PCR; PPD Vaccines and Biologics, LLC, Wayne, PA, USA) to differentiate between vaccine-strain and wild-type VZV.

Statistical analysis

This was an open-label descriptive study, and no hypotheses were tested. No formal statistical considerations were employed in determining sample size. Vaccinated subjects with any safety follow-up were included in the safety evaluation. The primary immunogenicity analysis was based on the per-protocol population. For immune responses measured by VZV-specific antibody responses, if 225/250 subjects (90%) were included in the per-protocol population, the half-width of the 95% CI for the GMFR would be 0.13 in the natural log-scale, assuming the standard deviation of the natural log of the fold rise was 1.0. For example, if the observed GMFR was 2.0, then its associated 95% CI would be 1.75, 2.28, if the estimated standard deviation matched the assumption. The final observed GMFR and its 95% CI depended on actual study results. The immunogenicity of the vaccine was evaluated overall and by age group (50-59 years and ≥60 years). The GMT and the GMFR of VZV-specific antibody values from pre-vaccination to 6 weeks post-vaccination were summarized, along with two-sided 95% CIs, which were evaluated on the basis of a t-distribution with natural log-transformed values. For safety analyses, if no vaccine-related SAEs were observed among the 250 subjects, this study was expected to provide 97.5% confidence that the true vaccine
related SAE rate was ≤1.47% (1 in every 68 subjects). The incidence rate and its associated 95% CI were provided for broader safety measures. Counts and proportions on SAEs, the overall safety profile, and injection-site AEs were also provided by age category (50-59 years and ≥60 years).

**Results**

**Patient disposition and baseline characteristics**

Of the 250 subjects enrolled and vaccinated, 244 subjects completed the 6-week follow-up. A summary of subject disposition is presented in Table 1. Subjects (mean age, 58.6 years) were mostly men (73.6%; Table 2). The most frequently used concomitant medications were metformin (12.0%) and glimepiride (9.6%; Table 2), and the most frequently reported medical conditions were hypertension (18.8%) and diabetes mellitus (14.4%).

**Immunogenicity**

Overall, subjects in the per-protocol population had an estimated VZV-specific antibody GMT of 149.8 gpELISA units/mL (n=250; 95% CI: 152.6, 169.2) at Day 1 pre-vaccination, and 410.8 gpELISA units/mL (n=250; 95% CI: 373.0, 452.6) at Week 6 post-vaccination. The estimated GMFR of VZV-specific antibody from Day 1 pre-vaccination to Week 6 post-vaccination was 2.8 (95% CI: 2.5, 3.1; Figure 1). In subjects 50-59 years old, the 6-week GMFR was 1.7 (95% CI: 1.4, 2.0). When summarized by age, 27.5% subjects 50-59 years old and 6.2% ≥60 years old experienced injection-site AEs. Most injection-site AEs occurred within 5 days of vaccination. A majority of injection-site erythema (13.2%) and injection-site swelling (10.4%) measured by subjects were 0 to ≤1 inch in diameter.

Overall, the frequency of systemic AEs was low; 38 (15.2%) subjects experienced at least one systemic AE post-vaccination. The most frequently reported specific systemic AEs were pyrexia (4.4%) and cough (2.8%). A total of 11 (4.4%) subjects reported at least one vaccine-related systemic AE post-vaccination. The most frequently reported vaccine-related systemic AE was pyrexia (2.8%). When summarized by age, 17.0% subjects 50-59 years old and 12.4% subjects ≥60 years old experienced systemic AEs (Table 5). A total of 6 (2.4%) subjects reported elevated temperatures (≥100.4°F [≥38°C] oral). There were no reports of varicella/varicella-like or HZ/HZ-like rashes during this study.

**Discussion**

Results of this phase 3 study show that ZOSTAVAX was immunogenic as measured by an increase in VZV antibody titer—149.8 gpELISA units/mL pre-vaccination to 410.8 gpELISA units/mL 6 weeks post-vaccination; GMFR at Week 6 was 2.8. The 6-week GMT and GMFR were higher in subjects 50-59 years old compared to subjects ≥60 years old, although the CIs overlapped between the groups. The primary safety endpoint was met, as the SAEs reported for 2 subjects (0.8%) were not vaccine-related. Overall, ZOSTAVAX was generally well tolerated. The types of AEs reported by subjects were consistent with those reported in earlier studies. To our knowledge, this is the first study evaluating ZOSTAVAX in an Indian population.

Immunogenicity in the current study was slightly higher than in previous studies. In SPS, involving 38,000 subjects ≥60 years old, GMFR was 1.7 in the ZOSTAVAX group at 6 weeks.
post-vaccination in a subset of 1,395 subjects\textsuperscript{9,13} compared to 2.5 for subjects ≥60 years old in this study. Similarly, in the ZEST study with 22,000 subjects 50-59 years old, a subcohort population of 1,136 reported a GMFR of 2.3 at 6 weeks post-vaccination, compared to 2.9 for subjects 50-59 years old in this study. Since the fold increase in antibody titer is a better marker for protection than absolute values of VZV-specific antibody titers at 6 weeks,\textsuperscript{10} the results of the current study are encouraging.

We report a lower rate of injection-site AEs in healthy Indian adults. Overall, 19.2% subjects reported at least one vaccine-related injection-site AE; these were more frequent in subjects 50-59 years old (27.5%), compared to subjects ≥60 years old (6.2%). The most frequently reported injection-site AEs were injection-site erythema (14.0%), swelling (12.4%), and pain (8.8%). The most frequent injection-site AEs in the SPS AE sub study were comparatively higher and included injection-site erythema (35.8%), pain or tenderness (34.5%), swelling (26.2%), and pruritus (7.1%).\textsuperscript{11} The rate of injection-site AEs in the ZV group reported in ZEST was 64%.\textsuperscript{12} In the current study, the rate of injection-site AEs was higher in subjects 50-59 years old versus ≥60 years old, which is similar to reports of the same age-specific populations in ZEST (50-59 years) and SPS (≥60 years).

Overall, we report a lower rate of systemic AEs in healthy Indian adults. In this study, 15.2% subjects experienced at least one systemic AE; pyrexia (4.4%) and cough (2.8%) were the most frequently reported. Systemic AEs occurred in 17.0% subjects 50-59 years old and 12.4% subjects ≥60 years old. In ZEST, systemic AEs were reported in approximately 35% and 34% of ZOSTAVAX and placebo recipients, respectively; vaccine-related systemic AEs were reported in 6.7% and 4.7% subjects, respectively. The most frequent systemic AE was headache (ZOSTAVAX, 9.4%; placebo, 8.2%), which was considered vaccine-related in ~3% and ~2% in the ZOSTAVAX and placebo groups, respectively.\textsuperscript{12} The SPS reported systemic AEs in 24.7% and 23.6% subjects in the ZV and placebo groups, respectively; vaccine-related systemic AEs were reported in 6.3% and 4.9% subjects, respectively.\textsuperscript{13} We did not receive reports of any varicella/varicella-like or HZ/HZ-like rash during this study; however, the identification and differentiation of viral subtypes is imperative in vaccinated subjects reporting breakthrough varicella zoster.\textsuperscript{16-21}

For the potential of this vaccine to be fully realized, it is important to ensure there is adequate knowledge among healthcare providers about HZ. An HZ global awareness survey, conducted in 2010 in 22 countries, reported an overall poor knowledge of the causes
and symptoms of the disease. In India, <20% individuals surveyed were aware of HZ in India compared to 97%-100% individuals in New Zealand, Brazil, and Malaysia. The study recommended a population-wide effort to improve global awareness of HZ. Since then, immense progress has been made towards raising awareness of HZ among healthcare providers and expanding its treatment options. Since this survey was conducted before the launch of the vaccine globally, the numbers are likely to improve in countries where the vaccine is being marketed.

In conclusion, in healthy Indian subjects ≥50 years old who received ZOSTAVAX, the VZV-specific antibody titers as measured by GMT and GMFR at 6 weeks post-vaccination were consistent with what has been observed previously in the clinical development program. The AE profile suggests that ZOSTAVAX was generally well tolerated. With greater use, ZOSTAVAX is expected to prevent the pain and suffering due to HZ disease in elderly population in India.

Acknowledgements

We acknowledge the efforts of Drs. D.N. Mishra, Anu Gaikwad, Hemant Talnikar, Neeraj Pandey, and Monica Gupta as investigators on the study. Medical writing assistance was provided by Suchita Nath-Sain, PhD, and Disha Dayal, PhD, of Cactus Communications, Mumbai, India. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The study was funded by MSD, India.

Conflicting interest

MS and SP are permanent employees of MSD, India. LS, BSC, SRR, PV, and RN have no conflicts of interest.

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Correlation of Thyroid Hormone Profile with the Acute Physiology and Chronic Health Evaluation II Score as a Prognostic Marker in Patients with Sepsis in the Intensive Care Unit

VA Kothiwale†, Pournima Patil‡, Saurabh Gaur§

Abstract

Objectives: Thyroid hormones regulate metabolism and homeostasis, and variations in thyroid hormone levels are common in chronically ill patients. Thyroid dysfunction, especially in critically ill patients admitted to the intensive care unit (ICU), is associated with adverse outcomes. This study was conducted to find a correlation between thyroid profile and sepsis and associate it with the acute physiology and chronic health evaluation II (APACHE II) score.

Methods: A cross-sectional study was conducted from January 2015 to December 2015 at the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Center, Belagavi. A total of 100 patients aged 18 years or more fulfilling the sepsis criteria were included in the study. Patients were subjected to clinical examination followed by systemic examination. The clinical severity as well as the prediction of outcome was assessed by APACHE II score. Based on the outcome, the patients were divided into two groups, namely survivors and nonsurvivors. The data obtained were coded and entered into Microsoft excel spreadsheet and analyzed using SPSS 21. Continuous data were compared using independent sample t-test. The correlation of free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) with APACHE II score was done using Pearson's correlation coefficient. At 95% confidence interval, \( p < 0.05 \) was considered as statistically significant.

Results: Out of 100 patients, 57 patients were men and 43 were women. The mean age of patients was 48.55 ± 18.09 years. Type 2 diabetes mellitus was the most common comorbid condition. Pneumonia was the primary diagnosis noted in 31 patients followed by pyelonephritis. Most of the patients had APACHE II scores between 15 and 19. The mean APACHE II score was higher in nonsurvivors as compared to survivors (30.5 ± 7.24 vs. 16.92 ± 8.11; \( p < 0.001 \)). In the study, 68 patients survived, while 32 of them died. Among nonsurvivors, APACHE II was inversely correlated with fT3 and fT4 levels, while TSH was positively correlated.

Conclusion: In ICU patients with sepsis, thyroid profile in combination with the APACHE II score may prove to be a better indicator of ICU morbidity and mortality more accurately than the APACHE II score alone.

Introduction

Sepsis is a complex syndrome and is defined as the body’s systemic inflammatory response to infection.\(^1\) It results in systemic manifestations, hypoxia and tissue hypoperfusion, and eventually death.\(^2\) Sepsis affects the endocrine system causing alterations in the thyroid function. The abnormal thyroid activity is referred to as euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS), which is often observed in critically ill patients with no history of intrinsic thyroid disease. Patients present with low serum levels of free triiodothyronine (fT3) and thyroid-stimulating hormone (TSH), and low or normal levels of free thyroxine (fT4).\(^3\) Also, high levels of reverse T3 (rT3) are observed in nonthyroidal illness due to the reduced conversion of rT3 to diiodothyronine (T2) due to the inhibition of 5’-monodeiodinase activity.\(^4\)

Critically ill sepsis patients admitted to the intensive care unit (ICU) exhibit thyroid dysfunction, which is associated with morbidity and mortality. Thyroid hormones modulate the metabolism and immune system in the body\(^5,6\) and, the magnitude of the thyroid dysfunction depends on the duration and severity of the disease.\(^7\) Based on the previous research studies, fT3 levels are significantly reduced in nonsurvivors when compared to survivors. Reports were also published in which there no association between rT3 and outcome was observed in ICU patients. Hence, there are several conflicting results regarding the association of thyroid hormones with the morbidity and mortality in ICU sepsis patients.\(^8,10\)

The acute physiology and chronic health evaluation II (APACHE II) scoring system is a widely accepted method to determine the outcomes in ICU patients with an accuracy level of 77%.\(^11\) It is a point score system based on the initial values of 12 routine physiologic measurements, age, and previous health status, which provide a measure of severity of the disease. APACHE II is the preferred method, as it involves simple calculations and the...
TABLE 1: Clinical profile of study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate (per min)</td>
<td>118.14 ± 10.87</td>
<td>100–150</td>
</tr>
<tr>
<td>Respiratory rate (per min)</td>
<td>37.35 ± 7.44</td>
<td>24–66</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>79.9 ± 11.76</td>
<td>40–100</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>59.56 ± 9.01</td>
<td>40–70</td>
</tr>
<tr>
<td>Temperature (°F)</td>
<td>101.35 ± 0.80</td>
<td>99–103</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>62.85 ± 14.59</td>
<td>16–80</td>
</tr>
<tr>
<td>pH arterial</td>
<td>7.18 ± 0.15</td>
<td>6.8–7.45</td>
</tr>
<tr>
<td>Oxygenation (%)</td>
<td>81.14 ± 15.93</td>
<td>9–100</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>136.15 ± 6.40</td>
<td>108–157</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>4.15 ± 0.94</td>
<td>2.22–7.13</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>3.52 ± 12.87</td>
<td>0.51–129</td>
</tr>
<tr>
<td>Hemocrit (%)</td>
<td>33.35 ± 8.79</td>
<td>9–54</td>
</tr>
<tr>
<td>WBC (cells/mm³)</td>
<td>19072 ± 8590.68</td>
<td>1200–58400</td>
</tr>
<tr>
<td>Glasgow coma score</td>
<td>11.93 ± 2.73</td>
<td>4–15</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>21.26 ± 10.07</td>
<td>2–46</td>
</tr>
<tr>
<td>Free T3 (ng/dL)</td>
<td>1.81 ± 0.68</td>
<td>0.88–3.17</td>
</tr>
<tr>
<td>Free T4 (ng/dL)</td>
<td>1.76 ± 1.65</td>
<td>0.55–10.3</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>1.79 ± 1.51</td>
<td>0.1–10.8</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>7.05 ± 3.98</td>
<td>1–20</td>
</tr>
</tbody>
</table>

WBC, White blood cell; APACHE II, Acute physiology and chronic health evaluation II; fT3, Free triiodothyroxine; fT4, Free thyroxine; TSH, Thyroid stimulating hormone.

Best calibration technique to accurately predict mortality. It does not include hormonal responses, such as thyroid function in critical illness, although the levels of hormones are highly associated with mortality. However, the APACHE II scores, when combined with an accurate description of the disease, provide a prognostic profile of the critically ill patients.

Role of thyroid hormones in predicting the outcome in sepsis patients is still debatable. In India, correlation of metabolic parameters with the APACHE II score in sepsis patients is nonexistent. Hence, this study was designed to find a correlation between thyroid profile and sepsis and associate it with APACHE II score.

Methodology

Study Design and data collection

The study was conducted at the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. It was a 1-year cross-sectional study conducted from January 2015 to December 2015.

A total of 100 patients aged 18 years and more admitted to the intensive care unit (ICU) were enrolled in the study. Patients fulfilling sepsis criteria were included in the study. The criteria include hypothermia, leukocytosis or leucopenia, tachypnea or tachycardia, systemic inflammatory response syndrome (SIRS), and proven infection. Patients with known cases of thyroid disorder, adrenal insufficiency, and patients not fulfilling the criteria predefined for sepsis were exempted from the study. Before the commencement of study, ethical clearance was obtained from the Institutional Ethical Committee. After explaining the purpose of the study, a written informed consent was obtained from all the participants before data collection. The data were recorded in a predesigned and pretested proforma.

Statistics and data analysis

Selected patients underwent clinical examinations followed by systemic examinations. They were evaluated for body temperature, blood pressure, pulse rate, respiratory rate, and impairment of consciousness on the Glasgow coma scale. The various investigations performed included arterial blood gas analysis, thyroid profile (fT3, fT4, and TSH), complete blood count, liver function test, renal function test, chest x-ray, and ultrasonography. The clinical severity and the prediction of outcome were assessed by APACHE II score. Based on the outcome, the patients were divided into two groups, namely survivors and nonsurvivors. The data obtained was coded and entered into a Microsoft excel spreadsheet and analyzed using SPSS 21. The categorical data were expressed in terms of rates, ratios, and percentages and the continuous data were expressed in terms of mean ± standard deviation.

Continuous data were compared using independent sample t-test. The correlation of fT3, fT4, and TSH with APACHE II score was done using Pearson’s correlation coefficient. At 95% confidence interval, a p < 0.05 was considered as statistically significant.

Results

A slight male predominance was observed in the study population. Maximum patients were in the age-group of 18–30 years followed by 20 in 31–40 years age-group with a mean age of 48.55 ± 18.09 years. The most common comorbid condition was type 2 diabetes mellitus (DM) followed by ischemic heart disease with type 2 DM, and hypertension with type 2 DM. Right ventricular dysplasia (RVD), RVD with type 2 DM, and cerebrovascular accident (CVA) with type 2 DM were observed in 1 patient each. Remaining patients were devoid of any comorbid conditions. The clinical profile of the study population is shown in Table 1. Mean respiratory rate (37.35 ± 7.44/min) was high in the study population and mean diastolic blood pressure was as low as 59.56 ± 9.01 mm Hg. A high WBC count was observed in the study population with a mean of 19072 ± 8590.68 cells/mm³. The mean hospital stay was 7.05 ± 3.98 days.

Maximum number of the patients had an APACHE II score between 15 and 19 with a mean of 21.26 ± 10.07. The thyroid profile revealed low fT3 levels in majority of the patients, while low fT4 and TSH was observed in 11 and 18 patients, respectively. Improvement in the outcome was observed in most of the patients, whereas mortality was observed in few of the patients in the study population. The primary diagnosis was pneumonia followed by pyelonephritis in the patients.

Analysis of outcome with APACHE II scores revealed a statistically significant difference between mean values of APACHE II scores in survivors and nonsurvivors (p < 0.001) wherein, the APACHE II score was significantly high in the nonsurvivors as compared to the survivors (30.5 ± 7.24 vs 16.92 ± 8.11, p < 0.001; Table 2).

In survivors, the APACHE II was negatively correlated with fT3 (r = 0.38) and TSH (r = 0.07) levels, whereas, fT4 (r = 0.18) level was positively correlated. In nonsurvivors, APACHE II score was...
inversely correlated with fT3 ($r = -0.21$) and fT4 ($r = -0.29$) levels, whereas TSH ($r = 0.10$) level was positively correlated (Table 2).

Discussion

The present study aimed at evaluating the correlation between thyroid profile and ICU mortality predictability scoring system—APACHE II score. It revealed that fT3 levels were reduced in majority of the patients. A marked correlation was established between the APACHE II score and thyroid profile. The analysis of the study population showed slight male predominance with a male to female ratio of 1.32:1. Most of the patients were aged between 18–30 years with a mean age of 48.55 ± 18.09 years. The gender and age distribution pattern observed in this study was consistent with the study conducted by Kumar et al.,14 in which 52% of the patients were men and 48% were women. The mean age was 58.7 ± 16.9 years. Most of the patients had APACHE II scores between 15 and 19 with a mean APACHE II score of 21.26 ± 10.07. Also, the majority of the patients had low fT3 levels; however, low fT4 and TSH levels were observed in few of the patients only. The results were similar to the study conducted by Kumar et al.,14 who reported low fT3, fT4, and TSH levels in 61%, 14% and 7% of the patients, respectively.

In the present study, a marked difference in the thyroid hormone levels and the APACHE II score was observed in the survivors and the nonsurvivors. In the nonsurvivors, a significant increase in the APACHE II score ($p < 0.001$) was observed when compared to the survivors. Among the circulating thyroid hormones, mean fT3 and TSH levels were reduced in nonsurvivors as compared to survivors, with increased mean fT4 levels in the nonsurvivors.

In the survivors, APACHE II score was inversely correlated with the fT3 and TSH levels, whereas fT4 levels showed a direct correlation with APACHE II score. On the other hand, in the nonsurvivors, the APACHE II score was inversely correlated with fT3 and fT4 levels. Also, a positive correlation was observed between APACHE II score and TSH levels in the nonsurvivors. The positive correlation between APACHE II score and TSH level indicates initial recovery phase in the sepsis patients with central hypothyroidism. A significant negative correlation between APACHE II and fT3 level indicates that fT3 level measurement might prove beneficial in the assessment of morbidity and eventual mortality in critically ill patients with sepsis. So, in this study among the thyroid profile parameters, the fT3 can be considered to be linearly correlated as an independent indicator of ICU morbidity.

In a study conducted by Zaid et al.,15 similar results were observed with a significantly increased APACHE II score in nonsurvivors as compared to survivors ($20.71 ± 6.65$ vs $13.04 ± 6.06$). Researchers in previous clinical studies found that low fT3 level has a negative prognostic effect in critically ill ICU patients with poor cardiac function, indicating the development of cardiac dysfunction.15-17 Wang et al., conducted a study to investigate the relation between APACHE II score and thyroid profile in 480 critically ill patients including sepsis. They reported significant correlation ($p < 0.001$) between fT3 level and APACHE II score and also as a good indicator of mortality in ICU patients.1 In a similar study conducted by Ture et al.,16 levels of fT3 were markedly decreased in nonsurvivors, and reported a significant and negative correlation between fT3 and ICU mortality scores—APACHE II score ($p < 0.0005$) and SOFA score ($p < 0.0005$). The findings reported by Elvio et al.,19 reveal that the fT3 was significantly lower in nonsurvivors when compared to survivors. Hosny et al.,1 in a study including 80 critically ill patients assessed the predictive value of thyroid hormone in septic patients and reported fT3 level as a better predictor of mortality among other thyroid profile parameters.

The reason behind the decreased fT3 levels in majority of the critically ill patients with nonthyroidal illness is the inhibition of 5'-monodeiodinase which leads to decreased conversion of T4 to T3.20,21 Several factors are involved in the inhibition of 5'-monodeiodinase including cytokines,22,23 circulating deiodinase inhibitors (free fatty acids),24 and glucocorticoid therapy.25 In prolonged illness the hypothalamic-pituitary suppression leads to reduced secretion of TSH, decreased production of T4 from the thyroid gland, and eventually reduced fT4 levels. The reduced levels of TSH and fT4 are a sign of severe chronic illness and a prognostic marker of poor outcome.26,27

As the illness progresses, reduced TSH secretion leads to low total and free T4 eventually resulting in reduced fT3 levels. The decreased TSH, fT4 and fT3 contribute in the development of central hypothyroidism.28 This is one of the self-protective mechanisms adopted by the body during chronic illnesses such as sepsis. The normalization of the thyroid hormones is indicative of the recovery phase in the critically ill patients with sepsis, which is observed by the initial increase in the TSH levels followed by the normal levels of fT4.29 Also, the fT3 and fT4 levels are not affected by the binding ability of thyroxine-binding globulin (TBG), liver disease, pregnancy, and commonly used drugs such as nonsteroidal anti-inflammatory drugs, heparin and furosemide. Thus, fT3 and fT4 levels are considered better than total T4 and total T3 as well.3 Therefore, inclusion of the fT3, fT4 and TSH in the APACHE II scoring system will provide an early assessment of morbidity and mortality in patients with sepsis.

When compared to other studies the present study included patients without previous history of thyroid dysfunction, which did not interfere with the study outcomes and proves to be the strength of the study. The patients in the ICU are administered with several drugs that can interfere with thyroid functioning which can be a limitation of the study. Because, in critically ill patients it is difficult to adjust this factor, the blood samples were collected on the admission day of the patients. And also fT3 and fT4 are not affected by various drugs, so fT3 and fT4 can be used as indicators for morbidity and mortality in ICU patients.

Conclusion

The present study revealed an inverse relationship between low fT3 levels with high APACHE II scores. Higher APACHE II scores were associated with higher mortality rate. In sepsis patients, thyroid profile in combination with APACHE II score in ICU patients predicts the outcome more accurately than the APACHE II score alone. The inclusion of thyroid profile in the APACHE II scoring system can
Disease Activity in Spondyloarthropathy: Does it affect Vascular Health?

Shubhabrata Das1,2, Rathindranath Sarkar2, Rudrajit Paul3, Parul Bagri4, Ashutosh Dey5, Anindya Mukherjee6, Ankita Das7

Abstract

Background: Chronic inflammation in spondyloarthropathy (SpA) is associated with accelerated atherosclerotic cardiovascular disease (CVD). Flow mediated vasodilatation (FMD) and carotid intima-media thickness (cIMT) detects endothelial dysfunction and subclinical atherosclerosis respectively, responsible for atherosclerotic CVD.

Objective: We aimed to examine the association of disease activity in SpA with surrogate markers of CVD, i.e., FMD and cIMT.

Methods: Fifty patients of Axial SpA (Assessment of SpondyloArthritis Society-ASAS 2009 criteria) (<5 years disease duration) and 50 control subjects, matched for age (33.7±8.8 vs. 33.7±8.4 years) and sex, with no CV risk factors were recruited. Ultrasound assessment of FMD of brachial artery and cIMT of both common carotid arteries were performed. Measurements were compared between patients and controls by Student’s t test. Association of disease activity in SpA patients with FMD and cIMT, were

References

2. Qari FA. Thyroid function status and its impact on clinical outcome in patients admitted to critical care. Pakistan Journal of Medical Sciences 2015; 31:915.
Introduction

Cardiovascular disease (CVD) is one of the leading causes of death in spondyloarthropathy (SpA), a chronic inflammatory disease of sacroiliac joint and spine. Chronic inflammation, seen in rheumatologic diseases is thought to be involved in accelerated atherosclerosis through endothelial dysfunction. Given the inflammatory nature of SpA, atherosclerotic CVD is more prevalent in these patients than healthy subjects. Endothelial dysfunction, forerunner of atherosclerotic CVD, can be detected non-invasively by ultrasonographic analysis of brachial artery-flow mediated vasodilatation (FMD). FMD detects the impaired ability of the artery to dilate in response to a variety of physical and chemical stimuli, as a consequence of reduced nitric oxide bioavailability. On the other hand, carotid intima-media thickness (cIMT) measuring the width of intima and media layers of common carotid artery (CCA) by B-mode ultrasonography, can detect subclinical atherosclerosis. Both FMD and cIMT are early markers of CVD, with high predictive values for future CV mortality. In the present cross-sectional study we examined the association of disease activity in Axial SpA patients with surrogate markers of CV health, i.e., FMD and cIMT.

Study population

Inclusion criteria

Study group: Fifty patients of newly diagnosed Axial SpA, fulfilling Assessment of SpondyloArthritis Society (ASAS) criteria 2009 for Axial SpA, having disease duration of less than 5 years and, with no prior use of disease modifying anti-rheumatic drugs (DMARDs) as well as use of systemic glucocorticoids ≥10 mg were recruited. The participants were between 18-50 years age as there is higher prevalence of SpA in this age group.

Control group: Similar number of age and sex matched individuals which included healthy persons as well as those with chronic low back pain, however not fulfilling the ASAS criteria.

Exclusion criteria

Those with a body mass index (BMI) <20 kg/m² and >35 kg/m², diabetes mellitus types 1 and 2, hypothyroidism, treated hypertension or with a systolic blood pressure >140 mm Hg and diastolic >90 mm Hg, history of gestational diabetes, gestational hypertension or pre-eclampsia, and who have smoked (any type) in the past 5 years; additionally, those with history of liver disease, renal disease, Cushing syndrome, active infectious disease and neoplasm, and use of medications at study-entry: those affecting lipid metabolism, oral contraceptives and thyroxine.

Anthropometric measurements

Height (cm) and weight (kg) measurements were performed using standard protocol in light clothing using a balance and wall-mounted stadiometer.

Resting blood pressure assessment

After 10 minutes rest, heart rate and peripheral blood pressure were assessed by oscillometric method in sitting position.

Vascular studies

The participants were in the fasting state and abstained from alcohol, coffee, tobacco and food for a minimum of 12 hours. All vascular measurements, i.e., FMD as well as cIMT assessments were performed by Philips HD 7 ultrasound machine using a 3–12 MHz linear array transducer probe under standardized conditions in a quiet, controlled environment with room temperature at 20-25°C and 55-65 % humidity in the morning. The vascular studies of all participants and subsequent analysis of the stored images were conducted by single experienced examiner to avoid interobserver variation.

FMD Assessment

The FMD assessment was performed on the right arm, in supine position according to existing guideline. Timing of each image frame with respect to the cardiac cycle is determined by the ECG signal. The brachial artery was scanned longitudinally just above the antecubital crease and a segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall was selected for 2D grayscale imaging. To create a flow stimulus in the brachial artery, a sphygmomanometric (blood pressure) cuff was first placed 1 cm above the antecubital fossa. Blood flow at baseline was estimated by the pulsed Doppler velocity signal obtained from a midarterial sample volume.

For FMD evaluation, firstly, the systolic-diameter of the brachial artery was recorded by measuring the width of intima and media layers of common carotid artery (CCA) by B-mode ultrasonography, can detect subclinical atherosclerosis. Both FMD and cIMT are early markers of CVD, with high predictive values for future CV mortality. In the present cross-sectional study we examined the association of disease activity in Axial SpA patients with surrogate markers of CV health, i.e., FMD and cIMT.
Table 1: Participant characteristics at entry in the study

<table>
<thead>
<tr>
<th></th>
<th>SpA patients (n=50)</th>
<th>Control (n=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.7±8.8</td>
<td>33.7±8.4</td>
<td>0.96</td>
</tr>
<tr>
<td>Male/Female</td>
<td>35/15</td>
<td>33/17</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.3±1.0</td>
<td>21.1±1.0</td>
<td>0.33</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>121.0±3.9</td>
<td>119.9±5.5</td>
<td>0.26</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80.3±2.4</td>
<td>80.8±4.3</td>
<td>0.49</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>164.0±3.8</td>
<td>162.9±5.1</td>
<td>0.22</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>93±6±3.2</td>
<td>92.5±3.6</td>
<td>0.11</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>48.9±2.6</td>
<td>47.5±2.6</td>
<td>0.25</td>
</tr>
<tr>
<td>TGA (mg/dl)</td>
<td>98.2±10.4</td>
<td>96.4±5.7</td>
<td>0.31</td>
</tr>
<tr>
<td>ESR (mm)</td>
<td>32.7±8.6</td>
<td>15.2±3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>8.5±1.4</td>
<td>3.7±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FMD %</td>
<td>4.9±1.4</td>
<td>8.7±1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cIMT (mm)</td>
<td>0.52±0.04</td>
<td>0.44±0.11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data represented as mean±SD; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMI: Body mass index; cIMT: Carotid intima-media thickness; CRP: C-reactive protein; DBP: Diastolic blood pressure; ESR: Erythrocyte sedimentation rate; FMD: Flow mediated vasodilatation; HDL: High density lipoprotein; LDL: Low density lipoprotein; SBP: Systolic BP; TGA: Triglyceride.

as well as post-hyperemia diameters were used for the analysis. FMD was expressed as the relative increase in brachial artery diameter during hyperemia, and calculated as [(post-hyperemia diameter–basal diameter)/ basal diameter] × 100 %.

**cIMT measurement**

The cIMT ultrasound scan protocol was according to Mannheim consensus. It required the visualization of the near and far wall of the right and left common carotid artery (CCA) and carotid bifurcation (bulb). Longitudinal images of both CCA were obtained with the head rotated 45 degrees toward the opposite side. Simultaneous ECG tracing was taken and only end diastolic images were captured to compensate for change in cIMT at different phases of cardiac cycle. IMT were calculated by measuring the width of intima and media layers of CCA over a length of 10 mm on the far wall of the artery, 20 mm proximal to the carotid bulb. CCA intimal and intraluminal diameters were also measured. The maximum value of the cIMT measurements from each side, i.e., right and left CCA was recorded and the average of the maximum readings from 2 sides was calculated for each participant.

**Laboratory assessment**

Laboratory assessment included measuring erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete hemogram, fasting lipid profile, fasting blood sugar, urea, creatinine, liver function test, and estimation of human leucocyte antigen-B27 (HLA-B27). Chest x-ray, x-ray and/or magnetic resonance imaging (MRI) of sacro-iliac joint and/or lumbo-sacral spine of the patients were also reviewed. Severity of SpA was measured by Bath’s Ankylosing Spondylitis Disease Activity Index (BASDAI). ESR was measured by Westergren method. CRP levels were analyzed with a Cobas Integra system (Roche diagnostics, Switzerland). Serum lipid levels (total cholesterol, high density lipoprotein cholesterol, and triglyceride) were measured using Hitachi 912 analyser (Roche Diagnostic). Value of low density lipoprotein cholesterol was calculated using Friedewald’s equation. HLA-B27 was estimated by flow-cytometry.

**Statistical analyses**

Statistical tests were performed with GraphPad Prism 6 software (Version 6.03). Means and standard deviations were calculated for each parameter. Student’s t test was performed to compare parametric variables between case and control groups. Pearson’s or Spearman’s correlation coefficient was used to examine the association of disease activity and inflammatory markers in SpA with FMD and cIMT. A p-value less than 0.05 was considered as statistically significant.

**Results**

**Participant characteristics**

The two groups were similar with respect to age, sex, BMI, BP and lipid profile (Table 1). Sixty percent (n=30) of the SpA patients were positive for HLA-B27 with disease duration of 2.7±1.1 years and BASDAI score of 4.0±0.5. The laboratory parameters, i.e., ESR and CRP, and vascular

<table>
<thead>
<tr>
<th>Variables</th>
<th>r&lt;sub&gt;SpA&lt;/sub&gt;</th>
<th>r&lt;sub&gt;Control&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>-0.96</td>
<td>0.84</td>
</tr>
<tr>
<td>p value</td>
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<td>&lt;0.001</td>
</tr>
<tr>
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<td>0.46</td>
</tr>
<tr>
<td>p value</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>ESR</td>
<td>-0.34</td>
<td>0.37</td>
</tr>
<tr>
<td>p value</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.97</td>
<td>0.83</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Pearson/Spearman correlation; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cIMT: Carotid intima-media thickness; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; FMD: Flow mediated vasodilatation; SpA: Spondyloarthropathy.

assessments, i.e., FMD as well as cIMT were significantly higher in SpA patients than the control group. Four SpA patients had carotid plaques compared to none in the control group (Table 1).

**Correlation of FMD and cIMT with disease activity and inflammatory markers in SpA patients**

FMD and cIMT in SpA subjects correlated significantly with disease duration, BASDAI, ESR and CRP (Table 2)

**Discussion**

In this study we found SpA patients had significantly lower FMD and higher cIMT compared to healthy, age and sex matched controls. We also observed FMD and cIMT had significant moderate to strong correlation with disease activity (BASDAI) and markers of inflammation (ESR, CRP) in SpA patients. To date, studies examined the association between FMD and cIMT in SpA patients as well as investigated the association between SpA disease activity and CV markers.

A crosssectional study by Sari et al. observed significantly reduced FMD in 44 patients of Ankylosing spondylitis (AS) (a subgroup of SpA) when compared to healthy control subjects (n=31), however there was no difference of cIMT between the 2 groups nor there was any correlation between FMD and disease activity in AS patients. Nevertheless, another crosssectional study by Bodnar et al. noted both reduced FMD as well as increased cIMT in 43 patients of AS when compared to 40 healthy controls; in this study also there was no correlation between disease activity (BASDAI) as well as inflammatory markers (ESR, CRP) and vascular
parameters. Similarly, Mathieu et al. and Gonzalez-Juanatey et al. reported increased cIMT in AS patients compared to healthy individuals, however, disease activity scores as well as ESR and CRP levels did not show any correlation with cIMT in both these studies.

The observation of deranged vascular parameters in AS patients compared to healthy individuals, in the above-mentioned studies, was similar to our current study. However, in contrast to these reported results, interestingly we observed moderate to strong correlations between disease activity and inflammatory markers and CV markers (FMD and cIMT) in SpA. Our results could explain the role of inflammation in the endothelial dysfunction and subsequent atherosclerotic CVD. The disease activity (BASDAI) and levels of inflammatory markers (ESR or CRP) in our SpA patients was markedly higher in comparison to other published studies, this might explain significant association between disease activity and impaired vascular markers in our study, not evident in other studies.

Gonzalez-Juanatey et al. also reported carotid plaque in 19 out of 64 AS patients where as 4 out of 50 SpA patients in our study reported plaques by carotid ultrasound examination. Carotid plaque being the final stage of atherosclerosis, higher disease duration (19.1±11.2 vs. 2.65±1.13 years) reported by Gonzalez-Juanatey et al. in AS patients than our study population might be responsible for this result.

Endothelial dysfunction and subclinical atherosclerosis were also reported in psoriatic arthritis, another subgroup of SpA, emphasizing the importance of investigating these surrogate markers (FMD and cIMT) of CVD in the whole disease-spectrum of SpA.

Several studies investigated changes of FMD and/or cIMT with intervention of anti-tumor necrosis factor (anti-TNF) agents in SpA. Short term (1 month) as well as long term (4.9 years) intervention of anti-TNF agents has been found to either improve or stabilize the disease activity and vascular parameters, suggesting the role of these anti-inflammatory agents in controlling inflammation, thereby improving CV health in SpA.

In contrast to the above-mentioned studies, some studies did not observe any significant difference of CV markers between SpA patients and healthy controls. Ceccon et al. reported no difference of cIMT between AS patients and healthy subjects; AS patients in this study had a superior metabolic profile than the controls which might have masked the difference of cIMT between the two groups. Although AS patients in comparison to their healthy counterparts had better lipid parameters, Malesci et al. and Divecha et al. observed inflammation driven worse metabolic parameters in SpA patients compared to healthy controls. However, the lipid levels of the SpA patients in our study did not differ from the controls, probably because of small disease duration (2.65±1.13 years).

Our study was limited by small sample size. A larger population would further confirm the association of disease activity in SpA with CVD surrogate markers. Secondly, crosssectional design of our study did not allow us to determine the actual inflammatory or metabolic burden of the SpA patients over time. Similarly, being an observational study, the results were indicative of association of disease activity in SpA with endothelial dysfunction and sub-clinical atherosclerosis, instead of establishing probable causation. A prospective or interventional study would perhaps shed light on the mechanisms behind these abnormal vascular findings.

Despite these limitations, our study demonstrated endothelial dysfunction and subclinical atherosclerosis in SpA. Further research is needed to clarify the mechanisms involved behind adverse CV outcomes in SpA patients.

References

The leading causes of adult disability. Death worldwide and it is also one of the leading causes of adult disability. Sudden death often lasts longer than several seconds. Cerebral ischemia is caused by reduction in blood flow that is attributable to a focal vascular cause. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. Cerebral ischemia is caused by reduction in blood flow that last longer than several seconds. Ischemic Cerebrovascular Accident

Introduction

A stroke or cerebrovascular accident is defined as an abrupt onset of a neurological deficit that is attributable to a focal vascular cause. A definition of stroke is clinical and laboratory studies including brain imaging are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. Cerebral ischemia is caused by reduction in blood flow that last longer than several seconds.

Stroke is the second leading cause of death worldwide and it is also one of the leading causes of adult disability. Numerous risk factors are involved in the development of stroke such as hypertension, smoking, dyslipidemia and diabetes mellitus. Hyperuricemia has been reported to be an independent predictor of stroke.

There is a pressing need to identify these treatable risk factors that can be easily measured and are highly prevalent, in order to identify patients at high risk for stroke.

Hyperuricemia have also been suggested as one of the factors in the pathogenesis of an atheroma. Significant association was found between serum uric acid and serum triglycerides. This implicates that a rise in serum uric acid and serum triglyceride may play some part in the etiology of ischemic cerebrovascular disease.

Uric acid is the breakdown product of purines. Increased uric acid levels promote oxygenation of low-density lipoprotein cholesterol and facilitate lipid peroxidation. Uric acid may stimulate vascular smooth cell proliferation, and reduce vascular nitric oxide production. Moreover, higher uric acid levels may be associated with increased platelet adhesiveness predisposing to thrombus formation. SUA has also been found to stimulate the synthesis of pro-inflammatory factors like monocyte chemo attractant protein-1, interleukin-1β, interleukin-6, and tumor necrosis factor-α. It has been suggested that serum uric acid may cause endothelial dysfunction. Even a mild elevation of serum uric acid was associated with cerebral ischemia in adults. It was suggested that impaired vascular tone and endothelial dysfunction could contribute to ischemic changes, because they permit cerebrospinal fluid to cross the blood-brain barrier and cause areas of edema.

How dyslipidemia is related to atherosclerosis is well known but there is less data about hyperuricemia and atherosclerosis. We undertook this study to evaluate serum uric acid and serum lipid levels in patients with ischemic cerebrovascular stroke.

Materials and Methods

Study Design: Cross-sectional study.
Sample Size: 60 cases

Abstract

Background: Stroke is a growing disease and it is the second common cause of death in the world after coronary heart disease especially in the elderly. In patients with acute stroke hyperuricemia was significantly higher than normal population with associated dyslipidemia. Hyperuricemia has been associated with decreased amount of HDL cholesterol and increased amounts of triglycerides and LDL cholesterol.

Aim: Serum uric acid levels and serum lipid levels in patients with ischemic cerebrovascular accident.

Material and Methods: This was a cross-sectional study carried out between January 2015 - June 2016, which included 60 cases of acute ischemic stroke. Serum uric acid levels and serum lipid levels was done in all the patients and was statistically analyzed.

Result: A total of 60 patients with ischemic stroke were included in the study. Out of which 43 (71.7%) were males and 17 (28.3%) were females. The mean age of the patients was 63.2 ± 14.8. Mean serum uric acid levels in the patients studied was 5.5 ± 1.7, and 18 patients (30%) were hyperuricemic. Serum uric acid levels were significantly higher in females (6.2 ± 1.9) compared to the males (5.2 ± 1.6). It was predominant in the age group between 56-70 years. Dyslipidemia was seen in 49 (81.7%) patients (Males were 36 and females were 13). More than one lipid parameter was seen to be deranged in 10 male patients and 4 female patients. Of them 87.75% of patients had low HDL levels, 36.73%, 10.20% and 8.16% patient had high cholesterol, triglycerides and LDL levels respectively. The study also showed that 15 patients had both hyperuricemia and dyslipidemia.

Conclusion: Hyperuricemia and its accompanying dyslipidemia can be considered as the risk factor for acute ischemic stroke.
Duration of Study: 18 months (January 2015 - June 2016).

Inclusion Criteria
- All patients with Ischemic cerebrovascular accident identified based on clinical as well as laboratory and radiological evaluation (including CT/MRI) admitted in our hospital.

Exclusion Criteria
- Age < 18 years
- Patients with chronic intake of hyperuricemic drugs
- Patients with conditions which alter serum uric acid levels (lymphoproliferative diseases, polycythemia, myeloproliferative disorders, diabetic ketoacidosis, lactic acidosis)

Statistical Analysis
- All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. Chi-square (χ²)/Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables was tested with the unpaired t-test. If the p-value was < 0.05, then the results will be considered to be significant. Data were analyzed using SPSS software v.23.0.

Results

In present study, 60 patients of ischemic cerebrovascular accident are considered, out of which 43 were males and 17 were females. Mean age of patient was 63.2 ± 14.8.

Table 1 and Figure 1 shows the distribution of cases according to age and it was predominant in the age group 56 – 70 years.

Table 2 and Figure 2 shows mean distribution of uric acid according to sex and p value <0.05 was considered significant.

Table 3 and Figure 3 shows hyperuricemia and sex distribution and p value <0.05 was considered significant.

Table 4 and Figure 4 shows relation between abnormal lipid profile and hyperuricemia and p value <0.05 was considered significant.

Discussion

Stroke continues to have a great impact on public health. Stroke is frequent, recurring, and is more often disabling than fatal. Although some determinants of stroke, such as age, gender, race, ethnicity and heredity cannot be modified, they are risk markers. However controlling the more important modifiable factors like serum uric acid and lipid levels may reduce the incidence of the disease.

In our study a total of 60 patients with ischemic stroke were included. Out of which 43 (71.7%) were males and 17 (28.3%) were females. The mean age of the patients was 63.2 ±14.8. Mean serum uric acid levels in the patients studied was 5.5 ± 1.7, and 18 patients (30%) were hyperuricemic. Serum uric acid levels were significantly higher in females (6.2 ± 1.7) compared to the males (5.2 ±1.6).

A study by Mehrpour et al. was done in 55 patients with acute ischemic stroke. Of which, 25 of those were females and 30 were males. The mean age of the patients was 67 ±14 years. Mean serum uric acid level was 5.94±1.70 mg/dl. 47.3% of patients were hyperuricemic. Urac acid levels were significantly higher in males than females. Hyperuricemia was associated with increase in levels of triglycerides and LDL-C.

Bhadra J et al. evaluted 38 patients with mean age 59.28±12.31. Serum uric acid levels were significantly higher in study subjects and statistically significant correlation was seen with TG and VLDL and inverse association with HDL in the cases.

Study by Biyani VV et al. studied 100 patients among which 68 were males and 32 females. The patients with hyperuricemia were mostly in the age group of 60-69 years. 49% of the patients with hyperuricemia were females and 51%were males.
Hyperuricemia

![Fig. 3: Hyperuricemia and sex](Image)

**Table 4: Abnormal lipid profile and hyperuricemia**

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>Hyperuricemia</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N</td>
</tr>
<tr>
<td>Increased TC</td>
<td>3 (16.7)</td>
<td>15 (83.3)</td>
</tr>
<tr>
<td>Increased TG</td>
<td>2 (40)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Decreased HDL</td>
<td>16 (37.2)</td>
<td>27 (62.8)</td>
</tr>
<tr>
<td>Increased LDL</td>
<td>2 (50)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Increased VLDL</td>
<td>2 (33.3)</td>
<td>4 (66.7)</td>
</tr>
</tbody>
</table>

patients had hyperuricemia. Similar results were concluded in studies by Millinois et al and Patil T et al.

In the present study dyslipidemia was seen in 49 (81.7%) patients (Males were 36 and females were 13). It was predominant in the age group between 56-70 years. More than one lipid parameter was seen to be deranged in 10 male patients and 4 female patients. Of them 87.75% of patients had low HDL levels, 36.73%, 10.20% and 8.16% patient had high cholesterol, triglycerides and LDL levels respectively. The study also showed that 15 patients had hyperuricemia and dyslipidemia can lead to acute ischemic stroke and they both are modifiable risk factors. Hyperuricemia and its accompanying dyslipidemia can be considered as the risk factor for acute ischemic stroke.

**Conclusion**

The study concludes that hyperuricemia and dyslipidemia can lead to acute ischemic stroke and they both are modifiable risk factors. Hyperuricemia and its accompanying dyslipidemia can be considered as the risk factor for acute ischemic stroke.

**References**

Use of Ambulatory Glucose Profile for Improving Monitoring and Management of T2DM

Banshi Saboo1, Shruti V Sheth1, Shashank Joshi2, Sudhir Bhandari3, Jothydev Kesavadev4, Anuj Maheshwari2, Manish Agrawal1, Dhruti Hasnani1, Feny Patel1, Dharmendra Panchal1, Rutul Goklani1

Abstract
Aim: To demonstrate glycemic variability in type 2 diabetic patients and consequent control of the same.
Methods: 108 patients with type 2 diabetes with an HbA1c level of 7.5-8.5% were selected for the study. A Freestyle Libre Pro AGP sensor was applied to the patients after explaining the patient about the same. Next, they were called for follow up at 3rd, 7th, 11th and 14th days. Based on the readings and graph obtained, diet and treatment changes were made on various follow-up days. The sensor was removed at the end of 14 days.
Results: Out of the 108 subjects, 106 completed the study. There were no adverse device effects. 98 patients had therapy changes while the rest had diet and lifestyle modifications. The mean HbA1c decreased from 7.96% to 7.03% by the end of 15 days. The glycemic variability curves helped in recognizing and treating masked or asymptomatic hypoglycemic events. It also graphically shows intervals of optimal and sub-optimal glycemia.
Conclusion: AGP is one of the most recent, innovative developments that are being used to monitor Glycaemic variability in DM patients. AGP is generated from the Flash Glucose Monitoring device which is like a CGM device attached to the patient for a maximum period of 14 days, which checks the ISF glucose at every 15 minutes. We are able to get a Glycaemic variability curve, a median, a modal, various percentiles and statistical data generated through this.

AGP study in the patient provides the doctor with an opportunity to have a complete glycemic picture of the patient. It offers a reliable, predictive, standardized visualization of the glucose data. We were able to not only reduce the Glycaemic variability but were also able to improve their Quality of Life by reducing the frequency of hypos. The data lead to breaking of the clinical inertia and provided a valuable insight into Glycaemic patterns. The achievement of near to normal Glycaemic status at the end of 14 days reflected the use of AGP as an interventional tool.

Introduction
Diabetes mellitus is estimated to rise 171 million (2.8%) in 2000 to 366 million (4.4%) in 2030.1 due to lack of awareness and proper patient education diabetes is usually poorly controlled and there still are many undiagnosed sub-clinical cases of diabetes.2 SMBG forms an integral part in diabetes care and management. A good metabolic control can be achieved by a combination of regular blood glucose monitoring, good patient education and appropriate treatment. HbA1c has been used to assess a good glycemic control. However, it has been seen that it is a poor predictor of glycemic variability. For example a patient with HbA1c of 7% may experience significant glucose fluctuations.3 increased glucose variability is associated with oxidative stress which plays a significant role in the pathogenesis of diabetic complications.4

Figure 1 shows the AGP sensor and the reader
The Ambulatory Glucose Profile consists of a small, round sensor – around the size of a 10 rupee coin that has to be applied on the back of the arm; it measures the interstitial blood glucose every 15 minute with the help of a small filament that is inserted subcutaneously. The glucose readings can be obtained by a reader. Each result shows ISF glucose value, showing the glycemic trend of the patient. It functions for a maximum of 14 days.

Figure 2 represents five curves of AGP represents five curves which demonstrate the median level of control and provide an index of variability in control at every hour of a typical day, both inter as well as intraday variability.5

The following study has been done to show the glycemic variability in apparently well controlled type 2 diabetic patients and consequent decrease in the glycemic variability with appropriate dietary and medical

1 Diacare – Diabetes Care and Hormone Clinic, Ahmedabad, Gujarat, India; 2 Consultant Endocrinologist, Lilavati Hospital and Research Centre; 3 Professor of Medicine, SMS Medical College, Rajasthan; 4 Chairman and Chief Diabetologist, Jothydev’s Diabetes Research Centre, Trivandrum, Kerala; 5 Associate Professor in Medicine, Babu Banarsi Das University, Lucknow, Uttar Pradesh
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management. Thus, it can be used as a comprehensive tool to understand the patient’s metabolic fluctuations.

**Methods**

The study was conducted at Diacare-Diabetes care and Hormone clinic, Ahmedabad, Gujarat. An informed consent was taken from all the patients prior to the application of AGP for the study.

**Inclusion criteria:** T2D patients with an HbA1c level between 7.5-8.5% of the age group 35-55 years with a diabetes duration of 1 year or more.

**Exclusion criteria:** Adult and adolescent Type 1 diabetic patients, patients with Gestational diabetes.

**Visit Schedule:** At visit 1, there was HbA1c estimation and explanation about the AGP device, its mechanism of blood glucose measurement and the graphs obtained thereafter. The subjects were examined and based on the individual patient profile, appropriate dietary and therapeutic changes were done.

After 5 days, at Visit 2, there was anthropometric data measurement (Height, weight, waist and hip circumference), regular general examination (temperature, pulse, blood pressure). After the regular preliminary work up the AGP device was applied.

At visit 3 (day 3) dietary modifications were prescribed based on the patient’s hypoglycemic-hyperglycemic variability and diet recall. Major hyperglycemic and/or hypoglycemic episodes were managed by changes in the treatment regimens. Doses of insulin and oral agents were changed or added accordingly.

At visit 4 (day 7), after reviewing the AGP report, pharmacotherapy changes were made in the treatment regimens. OHAs and insulin were either uptitrated or reduced or changed. Insufficient control was managed by initiation of new agents - oral or injectable.

At visit 5 (day 11), the same procedure of reviewing AGP graphs and consequent management of treatment protocol was done.

At visit 6 (day 14), overall change in glycemic variability of the patients blood sugar was noted. Further, patients were explained regarding the changes in improvement of the glycemic variability in comparison to the initial visit. Their diet and therapy changes were reviewed and the AGP sensor was removed.

Fasting, pre-prandial and post prandial blood glucose levels were analyzed. Any hypoglycemic tendencies were noted too. Potential causes of any major hypoglycemia or hyperglycemia was looked for and treated in the first visit. However, in most cases the glycemic pattern were noted and appropriate dietary modifications were made. In the forthcoming visits, dietary modifications were accompanied by pharmacotherapeutical changes. The main consideration during interpreting the AGP data is to evaluate whether the readings are within the target range, shape of the median curve, hypoglycemia pattern and width of the interquartile range.

**Results**

Out of the 108 subjects, 106 completed the study. Out of the 2 patients who did not complete the study 1 withdrew on their own discretion while the other subject had the sensor fall off before the completion of 14 days. The mean age of the enrolled subjects was 47.2 ± 7.08 years. Their BMI was 29.52 ± 4.73 kg/m² and mean duration of diabetes was 9.2 ± 6.9 years. Clinically relevant hyperglycemia (RBS->350mg/dl) was observed in 35.18% patients and frequent hypoglycemia (<70 mg/dl) in 53.7%.

A1c and sensor glucose values: On the initial visit, the baseline HbA1c calculated of all subjects was 7.96 ± 1.21%. At the end of the study, i.e, at the end of 14 days the HbA1c mean had reduced to 7.03 ± 1.09% (Figure 3).

**Dietary and Therapeutic modifications:** At least 2 therapy changes were done in 98 (90.74%) patients. Of the 98 patients that underwent the therapy change the mean reduction of HbA1c was 0.78% from baseline. Of the 10 subjects who did not require any therapeutic modifications the mean decrease of HbA1c was 0.33% from baseline.

On the 3rd day, 37 (34.26%) subjects required dietary modifications. Major therapy changes due to significant hyperglycemia and/or hypoglycemia was done in 7 (6.48%) patients. Basal insulin was decreased in 2 (1.85%) patients and OHAs (Pioglitazone, gliptin and SGLT, inhibitor) were added in 5 (4.62%) patients.

On day 7 and 11, theoreutical changes were made. New OHAs were added in subjects with suboptimal control of blood glucose. Patients who were on insulin had their basal and/or bolus dose increased or reduced based on reviewing the fasting and post prandial sugars.

Initially, 32.4% (35) patients were only on oral agents, 36.11% (39) patients were on Basal and OHAs, 17.6% (19) patients were on Basal Bolus plus OHAs therapy, 11 (10.18%) patients

![Fig. 2: AGP graph depicting median, 10th to 90th percentile and 25th to 75th percentile graphs](image-url)

![Fig. 3: HbA1c change in the 1st (7.96±1.09%) and the 6th visit (7.03±1.09%).](image-url)
were on premixed insulin regimes plus OHAs and 2 (1.85%) patients were on metformin alone (Figure 4).

Out of the 35 patients on oral agents, 28 patients were on sulfonylureas alongwith other OHAs. The rest were on medications other than sulfonylureas. Most frequently taken sulfonylurea was Glimeperide, others used were gliclazide, glibenclamide, glipizide.

Most commonly used sulfonylurea with Insulin was found to be Glipizide (n=48) followed by Gliclazide (n=17).

On the first visit, 4 of the 11 patients on premixed insulin were shifted to basal bolus regime due to persistent nocturnal asymptomatic hypoglycemia (<70mg/dl). 8 of the 35 patients only on OHAs had to be started with basal insulin due to persistently high blood glucose levels. The second visit showed multiple treatment changes in the form of further shifts from premixed insulin to basal plus OHAs, Basal insulin doses were reduced, OHAs were reduced (sulfonylureas were stopped in 37 (35.57%) patients). Other OHAs were started in patients with metformin alone. The third visit showed few minor titrating changes in the patients’ insulin and OHA doses. The diet therapy was reinforced and modified further according to the patients’ individual requirement. The final visit showed the overall 14 day improvement in the patients’ glycemic variability.

The most frequent change observed was increase in insulin doses; many subjects also had their treatment regimens changed with respect to oral medications, diet and exercise.

Discussion

The study results support the previous studies that HbA1c may not be an appropriate indicator of glycemic variability. The glycemic variability observed can thus be a good judge for subsequent treatment decisions.

The study helped in identifying the mismatch between HbA1c and the patient’s complete glycemic profile. It also helped in visually categorizing the patient’s glucose levels versus the target range and easily correlated with the patient’s individual dietary pattern. After the various changes made in the medications on day 7 and day 11, the graphical changes helped to monitor the changes that occurred in the glyemia, thus making it easier to adjust OHA and/or insulin doses.

Furthermore it acts an educational tool for the patients themselves to be able to see and determine the causes and results of their diabetes self-management.

Analysing Glucose Variability

SMBG is an important tool that empowers the patient to judge their own glucose levels, thus making it more educative and comprehensive than an HbA1c level. However, due to its episodic nature it may miss the in between hypo or hyperglycemias. For SMBG to adequately show a true representation of glycemic variability, it would take 7-10 capillary glucose measurements per day.

On conducting a CGM, data reflects significant hypoglycemias and mealt ime hyperglycemic excursions that are missed in SMBG. Studies show a lower HbA1c level with CGM than patients who use SMBG. However, alongwith CGM, AGP can make HbA1c potentially more useful in clinical practice. Different patients with the same or similar HbA1c values have markedly different rates of hypo and hyperglycemias throughout the day and overnight, as well as different rates of hypoglycemia.

In a study, review of serial AGPs obtained for sequential 2-wk periods for 23 non-pregnant individuals with type I diabetes and 10 women with gestational diabetes revealed changes in AGP corresponding to alterations in regimen. In a study by Roger Mazze et al, Blood glucose levels showed that HbA1c levels were not consistent with the individual’s glycemic variability. AGPs provided a visual representation of improved glucose responses to exenatide once weekly showing that results of treatment alterations can be best visualized graphically by the AGP.

The role of AGP in diabetes management is not only useful for the health professional but also provides an actual insight to the patients about their glucose control. AGP serves as an educational tool in categorizing the patient as having optimal glycemic control not only in terms of their HbA1c levels but also by their glycemic variability pattern.

As was recently shown in the ICMR - INDIAB study, less than a third of patients in India are able to achieve A1C values <7%. AGP provides a systematic method of presenting an SMBG data, i.e. the complete glycemic profile of the patient. It reflects the glycemic control of a typical day. The data can thus be used for individualizing patient care and diabetes management in relation to control, complications, impact of therapeutic management and adjustment of insulin doses.

References

Current Status of Delamanid in the Management of MDR Tuberculosis

Sonali Rajiv Karekar¹, Padmaja Anil Marathe¹

Abstract

Delamanid is a nitro-dihydro-imidazooxazole compound which was developed by a Japanese company, Otsuka Holdings inc. and has shown in-vitro and in-vivo activity against drug resistant tuberculosis. The drug exerts its anti-mycobacterial activity by inhibition of mycolic acid biosynthesis, leading to defective cell wall formation ultimately leading to bacterial death. Following the promising results in Phase 2 trials, Delamanid received approval in European Union in 2014, following which it was also approved in Japan and Korea in the same year. It was approved in India recently in August, 2017. Though relatively well tolerated, there have been concerns due to QT prolongation associated with the use of Delamanid. WHO has currently recommended use of Delamanid in combination with optimized background regimen in patients with pulmonary TB (conditional recommendation). More data from clinical trials and observational studies is awaited regarding use of Delamanid in children, HIV co-infection, pregnant women and use in combination with Bedaquiline.

Introduction

Tuberculosis (TB) has been one of the leading causes of mortality and morbidity worldwide. It has been ranked among the top 10 causes of death globally by the World Health Organization (WHO).¹ In 2015, it was estimated to have caused 10.4 million new cases and 1.4 million deaths all over the world.² Out of seven countries accounting for 64% of the total TB burden, India is in the lead, followed by Indonesia, China, Philippines, Pakistan, Nigeria, and South Africa.³ The emergence of Multidrug Resistant (MDR) and Extensively Drug Resistant(XDR) strains have made the treatment of TB more challenging. MDR TB is defined as resistance to both Isoniazid and Rifampicin.⁴ XDR TB is defined as resistance to Isoniazid and Rifampicin, one of the fluoroquinolones and at least one of the second-line anti-TB injectable drugs.⁴ In 2016, there were 600 000 new cases of Rifampicin resistant TB, of which 490 000 had MDR-TB.⁴ Among the 30 countries which had the highest number of TB cases, 90% cases belonged to the MDR/RR TB category.⁵ MDR TB accounts for approximately 4% of the new cases and 20% of the retreated cases of tuberculosis in India.⁶ About 6.2% of MDR-TB cases in India had XDR-TB in 2016.⁷

The WHO End TB strategy which was approved by the World Health Assembly in 2014 aims to reduce TB deaths by 90% and TB incidence rate by 80% by 2030. Globally, though the incidence of TB is declining at about 2% per year however a targeted decline of 4–5% annually is needed to reach the End TB Strategy targets.⁸ There is continuing research with eight new drugs and 12 vaccine candidates in the pipeline.⁹ The current treatment regimens for MDR TB are lengthy, requiring at least five drugs to be given for a duration of 18-24 months.⁸ They are also associated with a number of side effects and have shown a lower success rate, often less than 50%.¹⁰ Currently only 54% of MDR-TB patients and 30% of XDR-TB have been treated successfully worldwide.¹¹ As a result of the drawbacks of the current MDR TB regimens, extensive research is being carried out in this domain and several new compounds have been discovered.¹² Delamanid is one such compound, which appears to be a promising addition to the current treatment regimen for MDR TB. This drug was recently approved by the Drug Controller General of India in August, 2017. In view of this development, it is pertinent to discuss the pharmacology, recent updates and current status of Delamanid in management of MDR TB.

History

In 1982, Akihiko Otsuka (former Chairman of Otsuka Holdings inc., Japan) initiated a programme to develop a new anti-TB agent that would be effective against both drug-susceptible and drug-resistant strains of M. tuberculosis. They focused on 6-nitro-2,3-dihydroimidazo[2,1-b] oxazoles (Nitroimidazoles), synthesized various compounds to enhance anti-tuberculosis activity, and carried out studies to eliminate mutagenicity and general toxicity. After investigating in vitro activity, acute in vivo efficacy, and the bacterial reverse mutation (BRM) test, compounds that passed the acceptance criteria were evaluated for in vivo efficacy in a chronic mouse model. Compounds that showed superior therapeutic efficacy in the chronic mouse model compared to Rifampicin were then evaluated for their safety profiles in rats. Otsuka’s targeted strategy for screening new TB candidates has led to the discovery of Delamanid, which was subsequently validated and developed through preclinical and clinical studies.¹³

Mechanism of Action

Delamanid is a dihydro-imidazooxazole compound, [(2R)-2-methyl-6-nitro-2-[(4-[4-(trifluoromethoxy)phenoxy]-1-
piperidinyl[phenoxy)methyl]-2,3-dihydropyrimidazino[2,1-b][1,3]oxazole).11 In vitro, Delamanid has shown mycobacteria specific antibacterial activity with no action on other gram positive or negative bacteria.8 It exerts its anti-mycobacterial activity by inhibiting mycolic acid biosynthesis. Delamanid disrupts the cell wall of the mycobacterium and facilitates increased drug penetration through it. It is a prodrug that is activated by bioreduction of its nitro group by M. tuberculosis enzyme, deazaflavin-dependent nitroreductase to produce reactive species. The reactive intermediate such as nitrogen oxides formed between Delamanid and its desnitro-imidazooxazole derivative have been associated with significant mycolic acid synthesis inhibition.12 Delamanid inhibits the keto mycolic and methoxy mycolic acid components of the cell wall but not the alpha mycolic acid.13,14 However, alpha-mycolic acids are predominant components of mycobacterial cell wall followed closely by methoxymycolic acids, beta mycolic acid with significantly less contribution by ketomycolic acids.13 Isoniazid inhibits the synthesis of the major mycolate component viz alpha-mycolic acid, methoxymycolic acid, and beta-mycolic acid. This may explain the difference in efficacy of both these drugs. 

In vitro and In vivo Activity

Delamanid has been shown to exhibit very high anti-TB activity in comparison to other anti TB drugs, with a minimum inhibitory concentration (MIC) against standard drug susceptible and resistance strains of tuberculosis ranging between 0.006 microg/ml and 0.012 microg/ml. Moreover, these concentrations were between 2 and 512 times lesser than the MICs of established first line anti TB drugs.9 The intracellular killing activity of 0.1 microg/ml of Delamanid was similar to that of 3 microg/ml of Rifampicin at a certain concentration, indicating more potent action of Delamanid.8 A study by Matsumoto et al further substantiated that Delamanid exhibits the most potent bactericidal activity, similar to Rifampicin and superior to Isoniazid.8 It also possesses in vitro activity against M. kansasi and M. bovis but not against M. avium, M. chelonae, M. abscessus, or M. fortuitum.7 Thus, Delamanid showed promising results in vitro and in vivo studies against both drug susceptible and drug resistant strains, which led to its further development. Post antibiotic effect has been demonstrated in preclinical studies after pulsed therapy on intracellular organisms, which was comparable with that of rifampicin, which may be of additional benefit in increasing the efficacy of treatment of MDR-TB.14

Pharmacokinetics

As opposed to the other first line drugs which are to be taken on an empty stomach, Delamanid is to be taken along with food as its absorption increases with food.12 The oral availability of the drug is 2.7 times higher in fed state as compared to fasting state. The peak plasma concentrations are obtained at 4 hrs after administration.8 Delamanid and its metabolites exhibit high plasma protein binding (>99%). It has a large volume of distribution of around 1,100 litres after 100 mg twice daily oral administration.8 Delamanid is primarily metabolised rapidly to a metabolite DM-6705 by a reaction between the amino acid groups present in albumin and the 5-C of 6-nitro-2,3-dihydropyrimidazino[2,1-b]oxazole moiety of Delamanid. Some metabolism occurs via liver microsomal Cytochrome (CYP) 450 3A enzyme.9 Four major metabolites(M1-M4) of Delamanid have been identified. These metabolites have limited anti-mycobacterial activity however they may contribute to QT prolongation.7 Delamanid has a plasma half-life ranging between 30 to 38 hours, while its metabolites have a half-life ranging between 122-322 hours.8 Steady state concentrations are reached 10-14 days after administration.14 It is excreted primarily via faecal route, urinary excretion being less than 5%.9 No dose modifications are required in mild to moderate renal impairment, but data regarding severe renal impairment is not available. Though it can be used in mild hepatic insufficiency, it should be avoided in moderate to severe liver disease.15

Dosage and Administration

Currently, Delamanid has been recommended to be used orally at a dose of 100 mg twice daily for 24 weeks. It has to be administered with optimized background regimen and has shown to improve the sputum conversion and decrease mortality in patients with MDR TB.16 It is recommended to be administered as directly observed therapy.15 At present its use is limited at a few centres in India.

Adverse Events and Monitoring

The most commonly adverse events associated with Delamanid include nausea(38%), vomiting(33%) followed by dizziness(30%).13 A dose dependent QT prolongation was observed in the Delamanid group as compared to placebo in phase II trials. This QT prolongation was found to have an association with hypoalubuminemia. The QT prolongation was not associated with arrhythmia or syncope. It is recommended that electrocardiography is to be done at 2 weeks, 12 and 24 weeks and Delamanid should be stopped if QT interval is more than 500ms.17 Also, serum potassium, calcium and magnesium levels need to be monitored in view of concerns regarding QT prolongation. However, there was no significant difference between Delamanid and placebo groups with respect to occurrence of overall serious adverse events.13

Drug Interactions

Delamanid has not been shown to be a substrate for P- glycoprotein transporter. At therapeutic concentrations, it is unlikely to have any clinically significant interactions with drugs metabolised via CYP enzymes.9 Delamanid was studied in a trial involving healthy volunteers at a dose of 200 mg daily dose with and without Rifampicin (300mg daily)/ Isoniazid (720mg daily)/Pyrazinamide (1800mg daily) or Etbambutol (1100mg daily) for 15 days. Concomitant use of Delamanid did not change the levels of all the first line drugs except Etbambutol which showed increased plasma concentrations by 25%. Trials conducted for testing drug interactions with anti-retrovirals demonstrated the lack of clinically significant drug-drug interactions with Tenofovir, Efavirenz, Lopinavir, and Ritonavir.18

Delamanid Resistance

Resistance to Delamanid has been thought to be associated with mutations in mycobacterial F420 genes (Rv3547, fgd, fbiA, fbiB, fbiC) which are linked to
Table 1: Current status of delamanid approval16,20

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Union (EU)</td>
<td>2014</td>
<td>Approved</td>
</tr>
<tr>
<td>Japan</td>
<td>2014</td>
<td>Approved</td>
</tr>
<tr>
<td>South Korea</td>
<td>2014</td>
<td>Approved</td>
</tr>
<tr>
<td>India</td>
<td>Aug, 2017</td>
<td>Approved</td>
</tr>
</tbody>
</table>

the activation of the prodrug. A cut off of 0.2 microg/ml was used to delineate mycobacterial resistance in clinical studies however this needs more validation.16 The frequency of Delamanid resistance in vitro is comparable to isoniazid, ranging from 1/10² to 1/10³ organisms.19 In vivo resistance could be observed in patients treated with few or ineffective anti-TB drugs.5,20 Hence, appropriate companion drugs should be used when Delamanid is administered.19 Although it acts by inhibition of cell wall synthesis, Delamanid does not exhibit cross resistance to Isoniazid.5 It also does not exhibit cross-resistance to rifampicin, ethambutol, or streptomycin as well as no antagonistic activity to these drugs.8

**Delamanid in Children**

MDR TB as well as XDR TB is often harder to diagnose in children due to lower number of bacilli present in the sputum. Hence, there is limited reporting and diagnosis of TB in children. There is evidence of a case report where Delamanid was used for a case of XDR TB in Italy on compassionate use basis. Delamanid is being studied in paediatric population and trials are going on in several countries.16 However, according to WHO recommendations given in 2016, Delamanid can be added to the longer regimen in children and adolescents with MDR/RR TB who are not eligible for shorter regimen. (conditional recommendation).21 A recent systematic review revealed that Delamanid in children seems to be promising, and was well tolerated and effective, as 13 out of 16 children undergoing treatment for more than a few days achieved smear and culture conversion. However, no information is currently available on the combined use of Delamanid and Bedaquiline in children.22

**Delamanid in Pregnancy**

There is limited data regarding use of Delamanid in pregnant women. Animal studies have shown reproductive toxicity. It is not recommended for use in pregnant women or women of child bearing potential in the absence of reliable form of contraception.15

**Delamanid in TB with HIV**

Clinical trials are ongoing with respect to use of Delamanid in HIV patients. Some trials have shown lack of drug interactions with antiretroviral drugs which is an important aspect favouring its introduction in treatment regimens for HIV co-infected subjects.16 As per the interim policy guidance released by WHO, the current recommendation for the use of Delamanid applies to adults (≥18yrs) with pulmonary MDR-TB disease, including people living with HIV.17 However, due to lack of published evidence so far on the use of Delamanid in HIV-infected MDR-TB patients on Anti-Retroviral Treatment (ART), patients receiving Delamanid as part of MDR-TB treatment should have their ART regimens designed after careful discussion with clinicians and specialists in the respective fields.17

**Current Status of Delamanid in MDR TB**

Table 1 shows that Delamanid first received conditional approval in the EU for use in combination with optimised background therapy.5 It has been granted Orphan drug status in both EU and Japan.6 By September 2017, out of 688 patients who received Delamanid from over 40 countries, only 51 were from India. Delamanid has not yet been launched by Otsuka in India. Otsuka licensed Mylan to market the drug in India and South Africa through a conditional access program to enroll 400 patients on delamanid by early 2018 was planned.23,24

Delamanid is also currently undergoing phase III trial in seven countries (Estonia, Latvia, Lithuania, Moldova, the Philippines, Peru, South Africa) in patients with pulmonary MDR-TB.25,26 It has not been approved in the United States. The first-ever phase III randomized controlled clinical trial, by the name of ‘Trial 213’ for MDR-TB treatment was completed in October 2017. A position statement was released in by the WHO Global Tuberculosis Programme on the use of Delamanid in MDR-TB, following an expedited review of this trials results which were released at the 48th UNION World Conference on Lung Health in Mexico in October 2017. The robust phase II trial with Delamanid 100 mg twice daily for 2 months had demonstrated a significantly higher rate of sputum culture conversion than placebo, which led to its approval.3 However, Trial 213 did not confirm the efficacy findings from the phase II trials, although the safety conclusions were the same.26

Table 2 summarizes the ongoing clinical trials for Delamanid.

**Recommendations Regarding Delamanid use**

Despite the treatment of MDR TB gaining focus and advances in treatment modalities, a meta-analysis conducted by Kibret et al showed a low treatment success rate and failure to achieve the WHO target set for 2015. It was observed that 14% patients defaulted from treatment whereas 12.6% died, showing that the management of MDR TB is far from satisfactory.21

According to WHO, Delamanid should be retained in country guidelines, national essential medicine lists and the addition of Delamanid should be considered when an MDR-TB regimen with four effective drugs, consisting of a Fluoroquinolone (FQ) and an injectable agent in addition to Pyrazinamide, cannot be designed (additional resistance to FQ or an injectable agent, drug intolerance or contraindication). It may also be added for patients at higher risk of poor outcomes.26,28 WHO has laid down the following conditions for Delamanid
Table 2: Ongoing Clinical Studies on Delamanid15

<table>
<thead>
<tr>
<th>Title</th>
<th>Condition and interventions</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 6-Month Safety, Efficacy, and PK Trial of Delamanid in Pediatric Patients with Multidrug Resistant Tuberculosis</td>
<td>MDR TB; Pediatric Delamanid Doses = 5, 10, 25, 50, 100 mg (age-based doses)</td>
<td>II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Evaluating the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination With Optimized Multidrug Background Regimen (CBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-Infected and HIV-Uninfected Children With MDR-TB</td>
<td>TB; HIV Infections (Dose based on age and weight)</td>
<td>I/II</td>
<td>India - Not yet recruiting; Globally – Recruiting</td>
</tr>
<tr>
<td>Treatment Shortening of MDR-TB Using Existing and New Drugs</td>
<td>TB; MDR TB Levofoxacin, Pyrazinamide, Delamanid</td>
<td>II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Evaluating Newly Approved Drugs for Multidrug-resistant TB</td>
<td>TB; MDR Bedaquiline; Delamanid; Clofazimine; Levofoxacin; PMX-DHP</td>
<td>III</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Evaluating the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, For Drug-Resistant Pulmonary Tuberculosis</td>
<td>TB; HIV Infections Bedaquiline, Delamanid, Dolutegravir</td>
<td>II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Pharmacokinetic Study of Antitubercular Drugs and Related Drugs During and After Pregnancy</td>
<td>Antitubercular drugs (ARV) + Anti-TB, ARV, Anti-TB</td>
<td>IV</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

use15,26

i. careful selection of patients that are likely to benefit;
ii. informed consent of the patients;
iii. adherence to WHO recommendations in designing a longer MDR-TB regimen;
iv. close monitoring of clinical treatment response;
av. active TB drug-safety monitoring and management

In India, Delamanid has been approved for the use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.29 Delamanid can be a valuable addition to the available treatment options where no other drugs have shown effect.

Conclusion

The World Health Assembly has adopted the WHO End TB Strategy in May 2014 which aims to end the TB epidemic by 2030 and ensure that no family is burdened with catastrophic costs due to TB. It is also among the health targets of the newly adopted Sustainable Development Goals.31 There are still a number of hurdles in combating the burden of MDR TB which include timely detection of cases, providing quality assured treatment which is of a relatively shorter duration, cost effective and associated with minimal side effects in order to assure maximum compliance. Incorporation and judicial use of Delamanid in regimen of MDR TB is an important step in this direction.31 There will be more data available in near future to confirm role of Delamanid treatment regimens in paediatric population, HIV co-infection and regarding combined use with Bedaquiline. Data from observational studies following its use in limited access programs will also add to the evidence.

References

The Dilemma of Subclinical Hypothyroidism in Chronic Kidney Disease

Abhilash Chandra

Abstract
Thyroid hormones are important for growth and maintenance of kidney functions. Hypothyroidism has significant health consequences. Subclinical hypothyroidism has been less well defined clinically. Prevalence among women increases with age especially those with thyroid antibodies. Subclinical hypothyroidism carries the risk of developing overt hypothyroidism, subsequent cardiovascular health risks and renal dysfunction. Continuous clinical monitoring is recommended to evaluate the therapeutic response and possible adverse effects of over treatment requiring dosage adjustment. The present article reviews the complex interaction between subclinical hypothyroidism and kidney dysfunction.

Introduction
The definition of subclinical hypothyroidism (SH) is a biochemical one with elevated TSH levels (4.5-10 mIU/l) but normal FT4 level. It may have subtle symptoms of hypothyroidism. As against prevalence of subclinical hypothyroidism in general population of 4-10%, there is a higher prevalence in patients of chronic kidney disease not requiring dialysis, around 18%. Moreover the prevalence gradually increases as the GFR falls further. This stands true independent of age, gender, fasting blood glucose levels, total cholesterol and triglyceride levels. Multiple mechanisms have been cited to explain this association of SH and chronic kidney disease (CKD). This includes chronic inflammation altered iodine metabolism, decreased sensitivity to hormones and autoimmune thyroiditis.

Epidemiology
Thyroid autoimmunity and subclinical primary hypothyroidism are highly prevalent in CKD patients not requiring chronic dialysis treatment. Higher TSH levels are seen with increasing age. The percentage of individuals with positive antithyroid antibodies is roughly about 40% in over 80 yr. age group compared to 67.4% in 40-49 yr. age group. Women have greater degree of anti TPO antibodies leading to higher number of cases of subclinical hypothyroidism. Those with elevated TSH and positive thyroid antibody have a wide prevalence of 20-78% due to variation in method of selection of subjects. Seronegatives have a much lower risk of progression to overt hypothyroidism. 17-50% of patients with TSH value between 5-10 mIU/L are thyroid antibody positive. In euthyroids the seropositive state is about 10% which rises to 80% with TSH>10 mU/L. Epidemiological studies have shown that a number of subjects especially males of patients with TSH value between 5-10 mIU/L may actually be euthyroid outliers (healthy population falling outside TSH reference range). Altered renal physiology in thyroid hormone deficiency Various mechanisms are responsible for reduction of GFR in hypothyroidism. Reduced renal blood flow due to impaired left ventricular function, increased peripheral vasoconstriction, intrarenal vasoconstriction, decreased renal expression of various endothelium dependent vasodilators like VEGF, IGF are all responsible for a fall in GFR. Reduction in chloride reabsorption leads to tubuloglomerular feedback via macula densa causing fall in GFR. Apart from fall in GFR, rise in s. creatinine value in hypothyroidism can be due to decreased secretion in tubules or release from muscles. Rarely rhabdomyolysis as a part of thyroid myopathy can precipitate an acute worsening of GFR.

Hypothyroidism is linked to decrease in calcium reabsorption similar in a fashion as that of sodium.

In hypothyroidism there is reduction in sodium bicarbonate reabsorption owing to decreased activity of Na(+)/H(+) exchanger type 1 (NHE-1) leading to defective urine acidification, loss of medullary toxicity subsequently causing poor urinary concentrating ability. Hypothyroidism is also known to cause inappropriate increase in ADH levels causing fluid retention. This leads to hyponatremia whose incidence is all the more increased in presence of renal failure. Microscopically, there is glomerular basement membrane thickening, mesangial matrix expansion and renal parenchymal growth retardation.

Intrathyroidal and intrapituitary defect is also seen in some, leading to decreased thyroxine response to thyrotropin and decreased s. thyrotropin response to TRH.

Features of thyroid dysfunction in chronic kidney disease
Low T3 syndrome observed in CKD is possibly due to the state of chronic inflammation, malnutrition prevalent in CKD population. Impaired
renal handling of iodine leads to Wolf Chaikoff effect. There is also poor peripheral conversion of T4 to T3 (decreased expression of type 1, 5 deiodinase). However, the association of low T3 syndrome with endothelial dysfunction, cardiovascular and all-cause mortality, is controversial.7,33,34 Sometimes low T4 is seen probably due to poor protein binding. Total rT3 is normal despite low renal clearance due to redistribution from vascular to extravascular space. Free rT3 is mildly elevated due to poor renal clearance. TSH is often elevated in CKD in response to thyrotropin from pituitary as a result of uremic effect.37 TSH also looses its circadian rhythm along with compromised bioactivity due to poor glycosylation.

Patients on haemodialysis can have high free T4 levels due to heparin induced poor protein binding of T4.38 TSH is also mildly elevated although mostly below 10mU/ml indicative of non-thyroid disorder rather than thyroid dysfunction.39 Dose of erythropoietin is also higher due to redistribution from vascular to extravascular space.36 Free rT3 is mildly elevated due to poor renal clearance. TSH is often elevated in CKD in response to thyrotropin from pituitary as a result of uremic effect.37 TSH also looses its circadian rhythm along with compromised bioactivity due to poor glycosylation.

Effect of Treatment

One rationale given behind treatment of subclinical hypothyroidism is the prevention of progression to overt hypothyroidism. As per 20-year Wickham survey the progression occurs in 2-4.3% per year, more in cases with elevated TSH and presence of thyroid antibodies.43

Treatment of elevated TSH (4.5-10 mIU/L) has not found equivocal approval from all the societies as per available evidence.44 However, TSH>10 mIU/L has found more acceptance with regards to thyroxine treatment.3,9,12,13

Few studies that have shown improvement in cardiovascular profile after thyroxine mostly had TSH>15 mIU/L.61-64 Some uncontrolled studies have shown improvement in neuromuscular and cardiovascular parameters(cardiac systolic interval) after thyroxine replacement in subclinical hypothyroidism.65-67 But most of these improvements occur at a higher exercise intensity or at a higher baseline TSH levels (>15 mIU/L). Data from Framingham heart study has demonstrated that after adjustment of known risk factors, elderly people with ≥ 60 yrs. of age with low TSH have a 3.1 fold higher risk of atrial fibrillation over a 10 yr. period compared to normal TSH levels.68 This phenomenon may assume importance in the CKD population as it carries a higher risk of arrhythmias compared to the general population.

Cognitive and affective scores are also insignificantly affected by thyroxine replacement in SH.67,68 Improvement in quality of life or symptoms with thyroxine treatment has been reported in few studies.69,70

The impact of thyroid hormone replacement has not been extensively studied in CKD patients with SH. In particular, it still needs to be conclusively evaluated whether the restoration of euthyroidism is beneficial in terms of preserving renal function in these patients. Between 10-53% of individuals on thyroxine treatment have TSH values less than normal7.70-74 and approximately 1/3-1/2 of these are less than 0.1mIU/L.7.75

The risk of overzealous treatment of subclinical hypothyroidism are many like iatrogenic hyperthyroidism, arrhythmias, decreased bone mineral density, requirement of dose adjustment as per TSH levels (low TSH quite common). On the positive side the treatment is simple, cheap and effective when used appropriately. Possible indications of treatment in subclinical hypothyroidism can be: TSH>10 mIU/L on repeated measurements,5 clear symptoms and signs of thyroid failure, strong family history, pregnancy, severe degree of hyperlipidemia, associated with smoking66 and rapid worsening of renal functions.

Given the high incidence of oversupressed TSH levels, the negative effect on poor nitrogen balance because of increased protein catabolism can worsen the existent malnourished status in CKD population. The desirable level of TSH in this group of population is also not clear making clinical decision all the more complicated. The overlap in the symptomatology between symptoms of hypothyroidism and uremia makes evaluation challenging. The treating physician has to carefully
balance the positive and negative effects of hormone replacement therapy.

The prediction of transition to overt hypothyroidism can be made to some extent on baseline value of TSH. However, waiting period for spontaneous resolution of subclinical hypothyroidism is far from clear. Presence of anti TPO antibody decreases the possibility of its spontaneous resolution.

**Conclusion**

To achieve optimisation it is important to relate TSH levels to hypothyroidism is far from clear. One may follow individuals with overt hypothyroidism can be made of hormone replacement therapy.

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Gender Inequity in Cardiovascular Care - Global Perspective

Zamzamy Raniah E1, Kinsara Abdulhalim J2

Abstract
In the last decades, promotion of women’s health has become a growing field for health professionals. Although global society has recognized the importance of providing women with appropriate health services to maintain healthy families and communities, women are still underserved in every segment of health systems worldwide. The inequity in health services for women results from a lack of knowledge, stigma, and social norms for women. This gender inequity exists in every segment of the health system worldwide. In this paper, a review of online global research on an important health issue for women has been conducted. The findings indicate that women with cardiovascular disease are struggling with gender inequity in health services throughout the world. Recommendations for addressing this dilemma require more investment in research into women’s health; empowering women to have a role in decision making, and in global collaboration to replicate successful models and programs for women’s health.

Introduction
This paper provides data about women with cardiovascular disease to emphasize inequity of treatment. Cardiovascular disease accounts for more than half of women’s deaths globally.1 The definition of gender equality states that the processes for decision making and resource usage should provide the same initial level of opportunities and access for both male and female patients.2

Gender analysis of medical investigations and procedures carried out has been used to pinpoint and treat health inequalities that have resulted either from the different social norms and roles of women and men, or from the imbalanced authority in their relationships and the effects of these inequalities on their health.3-4

Gender inequity in social, economic, and environmental circumstances has led to huge disparities and inequalities for health outcomes for both genders; especially for women. Therefore, making more effort to improve gender equity and to reach for gender sensitivity is a core principle for women’s health. Women’s overall health is a result of the interaction of multiple factors that create a cycle of health, wellness, illness, and disability. The aim of this literature review is to introduce examples of how pandemics, chronic diseases, and physical disabilities are related to one another, and how they influence the nature of the health services available and cultural reactions towards women.

The most visible areas in which women face health disparities are due to cultural norms, medical bias, and health-policy ignorance. The awareness of gender equity varies according to countries and cultures.

Methods
This systemic review was conducted using two search engines: Google Scholar and Summon. The studies were not limited to a specific country or race because of the aim of attaining a global view of women’s health issues with respect to the health care services they receive. There was random selection for countries: random names of countries from each region were used with the key words until appropriate articles were found. All publications included were written in English and complied with the inclusion criteria of original research, studies, and meta-analyses for cardiovascular diseases and gender inequity.

Results
Studies of cardiovascular disease in Finland and Brazil have shown the disparity between women and men; women being consistently under diagnosed and undertreated compared with men.5-9 Women face difficulties in getting the help they need to prevent death from cardiovascular disease.1,8,10 The causes have ranged from differences in presenting symptoms to insufficient care during hospitalization period after surgery; where the death rate is high for women.5,11-14

Until recently, women were not included in clinical trials, which led to misdiagnosis and mistreatment of heart disease in women.9,15-16 For example, a meta-analysis for clinical trials of aspirin therapy to reduce the risks of cardiovascular disease-related deaths only included 20% female participants. Such a percentage cannot establish a strong dataset about the impact of this medication on women.17 Another example is coronary artery bypass graft surgery, with clinical trials for this procedure excluding women.18 Most symptoms of cardiovascular disease in women appear in advance of hospitalization and chest pain. These symptoms include edema, shortness of breath, lightheadedness, dry cough, and exhaustion.10-13 Due to these variations women are disadvantaged from the high technological procedures for diagnosis or treatment of cardiovascular disease.19

Although women are at higher risk of developing heart disease than men, there is still ignorance about the
In Asia and Australia, the risk of dying from cardiovascular disease in women is linked to high concentrations of triglyceride. Estrogen inhibits the formation of atherosclerosis and artery spasm, causes vasodilation, and improves endothelial function and so enhances the functioning of blood vessels. In Asia and Australia, the risk of dying from cardiovascular disease is higher for women; especially for smokers and ex-smokers. A study in Europe indicated that women have a lower risk of developing cardiovascular disease but women who smoke have a higher risk of disease than nonsmokers. Death from cardiovascular disease in women is linked to high concentrations of triglyceride. A study in Saudi Arabia indicated that the prevalence of cardiovascular disease is lower in females than in males. However, the number of female participants in this study was very small as compared with the number of male participants, which is more evidence of the lack of research into women’s cardiovascular health. There is some evidence for gender bias and inequity in using technological diagnostic methods and surgical procedures for women who have problems with heart disease.

Health services for women with heart disease should address every segment of health and wellbeing. However, rehabilitation programs for female patients with cardiovascular disease in Iran are more effective than for male patients.

Reproductive health faces significant limitations in addressing women with cardiac diseases; since contraceptives may negatively impact reproductive health. There is poor communication between health care providers and their female cardiovascular patients regarding reproductive health concerns and precautions. More attention in this area is needed to ensure that the reproductive health needs of this group of women do not affect their cardiovascular health.

In Indonesia, there is a gender behavior pattern that needs to be addressed regarding the awareness and prevention of cardiovascular disease. Mental health is an important factor in preventing heart disease. Social and cultural norms create various gender stereotypes for both men and women. Health inequity for women is the result of these stereotypes; since it impacts women’s ability to access health care services and shapes the negative attitude of some health care providers towards those women. Collaborative work across health and social care is the key factor to promote women’s health and eliminate gender inequity.

**Barriers and Factors for Health Inequity**

This huge gap in treating women’s health issues effectively is due in part to lack of research and also to the absence of policy to support gender-based medicine and gender sensitivity. In the 1970s, women were excluded from clinical trials because it was claimed that factors such as the menstrual cycle and menopause would change the response to the medicine. In addition, the possibility of pregnancy would increase the responsibilities of the researchers. It was assumed that there was no difference between men and women in the responses to a drug and any pathology it might cause, owing to the lack of knowledge of female physiology.

Another factor in the lack of gender-based research is that policy makers are ignorant about the gender differences between men and women, which lead to different health needs; even though several studies have indicated the need for a more gender-based approach to research and treatment. Existing plans to fund health care systems that address the unique problems faced by women seeking health services are not effective and the poor health outcomes for women subsequently impact the SES for women. Government should support working women by creating policies that support good health and quality of life, such as appropriate prenatal and dependent health-care leave policies. More women than men live in poverty and women are more likely to be unable to afford health care or to get treatment.

However, the cardiovascular health disparity in women is mainly due to inadequate knowledge about women and cardiovascular diseases. In addition, insufficient efforts are being made to increase women’s awareness of cardiovascular disease.

**Recommendations**

There is an urgent need to implement more strategies and models to minimize the gap in gender equity in health. The Center for Disease Control and Prevention has designed a Well-Integrated Screening and Evaluation for Women Across the Nation (WISEWOMEN) program for screening and prevention. The program has been shown to have a significant impact in promoting the health of populations at risk. Another successful model in the US is Heart Truth, which uses social media to reach women and increase their awareness of cardiovascular disease. The search did not find any successful models for promoting women’s cardiovascular health in Africa or the Middle East.

The Institute of Gender and Health in Canada has identified the national health priorities through brainstorming and interviewing sessions with the public and professionals. Combining these data with research reviews and analysis methods will increase national and international knowledge about the impact of sex and gender on health and ultimately influence policy, leading to implementation of programs to address gender inequity.

It is important that staff are trained in gender sensitivity and that institutes practice it. Appropriate training should be initiated after gender analysis guidelines have been used to evaluate for gender sensitivity. More research into the
genetic, physiological, and behavioral differences between sexes and genders is required. In addition, any research should consider cultural differences within different communities and ethnicities. It is critically important that governments should implement policies that include more women in decision making in health care systems to minimize gender inequality. The media and other organizations in society should be encouraged to participate in supporting women; especially vulnerable groups of women who suffer from cardiovascular disease. In addition, vulnerable subgroups such as the elderly, pregnant women, teenagers, and those with low income must be considered. Governments and other organizations should recruit more volunteers to engage the public with these vulnerable groups, and to eliminate the stigma and barriers that prevent society from reaching out to help. National and international collaboration will be needed to initiate these measures.

**Limitations**

It was difficult to find studies carried out in a number of different countries.

**Conclusion**

The inequity in health services that women face globally is directly linked with the knowledge and understanding of sex and gender by health professionals, governments, and society. Women are always at risk as they live under different types of inequity, even in the most developed countries. The lack of effort towards empowerment and informed decision making of women’s needs have a strong impact on current levels of health inequity. For society to be healthy, we must first have healthy women, and therefore strong global advocacy and collaboration is needed.

**Acknowledgement**

We would like to thank Dr Rodriguez Daniel, PH.D Associate Professor of Public Health, Philadelphia, USA for his help in Concept and revising the article.

**References**

Need for Insulin Stewardship Programmes

Sanjay Kalra1, Rakesh Sahay2, Mangesh Tiwaskar3

The Challenge

Indoor patients often present with severe community acquired infections, and are at high risk of nosocomial infections as well. This creates challenges for health care professionals who deal with such patients. Antibiotic policies and antimicrobial stewardship programmes have been created to manage such situations, and are now accepted as integral parts of intensive care and in-hospital medicine.1,2 These have helped improve efficiency of antibiotic use, and reduce antimicrobial resistance in hospital settings.

Similar challenges are faced in diabetes care in such settings. The diabetes epidemic means that a large number of hospitalized patients have comorbid diabetes, which needs to be treated. There is a high load of hyperglycemia in intensive care settings,3 which may be exacerbated by stress and by certain drugs used in intensive care therapy. This adds to the complexity of in-hospital management, and creates challenges for both patients and health care professional. Insulin injections for example,4 may be a health hazard for nursing care professionals, who run the risk of needle stick injuries (NSI).5 At the same time, the ever-increasing number of insulin regimes, preparations and delivery devices increases the chances of errors, in prescription dispensing and administration. This may compromise patient safety and well-being.

The Solution

There is, therefore, an urgent need to address these obstacles to patient and health care provider health.6 Creation of an insulin policy, specific for each intensive care unit (ICU) or ward, can help improve quality of indoor glycemic control, while mitigating professional hazards associated with insulin injection. A comprehensive insulin stewardship programme should address all aspects of safe and rational insulin use. Such a policy should lay down standard operating procedures which govern choice of insulin regimes, preparations and delivery devices. This will minimize the possibility of inappropriate prescription and administration. For example, suggesting only intravenous insulin regimes in an intensive care unit will obviate the need for, and the potential complications associated with, keeping premixed and basal insulin vials or pens in the premises. Listing a specific insulin preparation, with one concentration (e.g., 40 IU/ml or 100 IU/ml) reduces the risk of mismatch between vial and needle.

The points to be covered in a comprehensive sample are listed in Table 1. These include descriptions of the insulins available in the ICU or ward, their strengths and delivery devices; appropriate insulin technique;7 methods of reducing risk of NSI; and environment-friendly methods of disposal of sharps.8 Such a policy should also delineate responsibilities and duties of various staff, prescribe modes of patient, care-giver and hospital staff education, and factor in regular audits to ensure quality check and improvement. Pragmatic choice of insulin therapy, dose initiation, titration and intensification, should also form part of a complete insulin stewardship programme.

One may build upon comprehensive national and international guidelines5,9 to initiate insulin stewardship programmes in hospitals, wards and intensive care units. Revision of stewardship guidance, based upon objective and subjective feedback from all stakeholders, at regular intervals, will help improve the quality and relevance of such documents. Best practice sharing, facilitated by interdisciplinary and inter-institutional contact, will help expand the reach and utility of insulin stewardship programmes.

References

1. Van Gastel E, Balligand E, Costers M, Magerman K, Hospital Medicine Working Group of the Belgian Antibiotic Policy

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Table 1: Sample insulin policy

<table>
<thead>
<tr>
<th>Insulin availability</th>
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<tr>
<td>Short acting</td>
</tr>
<tr>
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</tr>
<tr>
<td>o Strength</td>
</tr>
<tr>
<td>o Delivery device</td>
</tr>
<tr>
<td>Long acting</td>
</tr>
<tr>
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</tr>
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</tr>
<tr>
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</tr>
<tr>
<td>o Record</td>
</tr>
<tr>
<td>o Dose titration</td>
</tr>
<tr>
<td>Insulin administration</td>
</tr>
<tr>
<td>o Staff-administered</td>
</tr>
<tr>
<td>o Self-supervised</td>
</tr>
<tr>
<td>Insulin technique checklist</td>
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<td>o Site choice/rotation method</td>
</tr>
<tr>
<td>o Site preparation</td>
</tr>
<tr>
<td>o Quality of insulin check/Re-suspension</td>
</tr>
<tr>
<td>o Dose check</td>
</tr>
<tr>
<td>o Injection technique</td>
</tr>
<tr>
<td>Health care provider safety</td>
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<td>o Avoidance of re-use</td>
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<tr>
<td>o Proper sharps disposal</td>
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<tr>
<td>o Reporting policy for needle sticks injury</td>
</tr>
<tr>
<td>Insulin Education policy</td>
</tr>
<tr>
<td>o Patient education</td>
</tr>
<tr>
<td>o Caregiver education</td>
</tr>
<tr>
<td>Storage and Disposal policy</td>
</tr>
<tr>
<td>o Insulin storage</td>
</tr>
<tr>
<td>o Sharps disposal: ward level</td>
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<tr>
<td>o Biomedical waste disposal: hospital level</td>
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</tbody>
</table>

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1. Van Gastel E, Balligand E, Costers M, Magerman K, Hospital Medicine Working Group of the Belgian Antibiotic Policy


Nicolau’s Syndrome (Embolia Cutis Medicamentosa)

Arun Agarwal¹, Anshu Kabra², Rahul Jain³, Gaurav Bhargava⁴

Nicolau’s Syndrome is an iatrogenic syndrome caused by intramuscular injection leading to variable degrees of tissue necrosis including the skin and deeper tissues and manifests as intense pain in the after injection along with purplish discoloration of the overlying skin, with or without a reticulate pattern. It has also been reported after subcutaneous, intravenous, and intraarticular injections. We report a case after intradermal injection of benzathine penicillin for skin allergy testing. Mr SG, 24 years had rheumatic fever in childhood and had been receiving intramuscular injections of benzathine penicillin 12 lakh units every month for secondary prevention and each time skin allergy testing was being done. This time after skin allergy testing in the right forearm, he developed intense pain around the injection site followed by local erythema, purple blue patchy and reticular areas of the overlying skin distally up to the finger tips (Figures 1, 2). Over the next two weeks, the skin has turned black with dehydration of the subcutaneous tissue, but hasn’t separated from the margins (Figure 3). The right distal half of thumb has developed dry gangrene (Figure 4). Presumed pathogenesis is ischemic necrosis caused by arterial vasospasm and/or thrombosis and/or drug embolism but still is largely an unidentified pathogenesis. Skin biopsy was not done as the diagnosis is clinical. There is no standard guideline for its management. He was managed with heparin and hydrocortisone. He is under close follow up and may need debridement/plastic surgery later. Clinicians must be aware of this iatrogenic adverse reaction and be cautious in the use of proper injection procedures, including appropriate needle length, in order to minimize complications.

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Crossed Aphasia

Mugundhan Krishnan¹, Balamurugan N², Thiruvarthelvan K³, Sivakumar S⁴

A 5 year old male, smoker, non-alcoholic, not a diabetic or hypertensive, admitted with history of acute onset of difficulty in speaking for 3 days. He is a right handed individual and there was no family history of left handedness. On examination, patient was Conscious, aphasic, PR 80/mt, BP 120/80 mm, pupil 3 mm equally reacting to light on both sides, fundus was normal. There was no weakness of limbs. All Deep tendon reflexes were normal with bilateral plantar flexors. Sensory, cerebellar systems were normal. Examination of language revealed, impaired repetition, normal comprehension, less fluency was noted. Naming, reading, writing was good suggestive of motor aphasia. MRI Brain (T2 axial, Flair coronal, DWI) showed infarct over right frontal region (Figures 1, 2, 3). Routine investigations including blood biochemistry was normal. ANA & vasculitic work up were normal. In view of the above clinical features and imaging, diagnosis of crossed aphasia was made. Patient was treated with antiplatelets, statins and speech therapy. On follow up after 6 months, patient’s language function recovered to become transcortical motor aphasia.

Discussion

Aphasia occurs due to disturbance of comprehension and formulation of language. Produced by damage of cortical regions related to language function. Speech is lost only when dominant hemisphere involved. Language dominance occurs in 95% humans are right handed individuals with left hemisphere dominant, 5% humans are left handed individuals, in which 80% are left hemisphere dominant, 10-15% are right hemisphere dominant and <5% are equidominant.

Crossed aphasia is an acquired language impairment following a lesion in the right hemisphere in a right-handed individual was described by Bramwell in 1899.¹ The incidence is between 0.4 percent and 2 percent.² Crossed aphasia may occur more frequently in women than men, perhaps because of sex differences in brain asymmetry. Precise mechanisms underlying language disorders of crossed aphasia are not yet completely understood.³ The accepted criteria for the diagnosis of crossed aphasia require 1) absence of left handedness or ambidexterity in the patients and family members 2) clear cut lesion of the right hemisphere diagnosed by computed tomography, 3) definite language disturbance.³ Proposed explanations for crossed aphasia include 1) a previously silent or unrecognized lesion in the left hemisphere that is somehow rendered symptomatic by a new lesion in the right hemisphere 2) ipsilateral control of the dominant hand 3) bilateral representation of linguistic functions 4) an arrested developmental stage in the lateralization of language function. The most common cause of crossed aphasia are trauma, and vascular disorders.

This case is being presented for its rarity.

References


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Lymphoma in Rheumatoid Arthritis – Catastrophic Sequela of a Common Disease

Swapan Deep Singh Nagpal¹, Narinder Pal Singh², Pravas Mishra³, Angad Singh⁴

Abstract
Rheumatoid arthritis (RA) is a common rheumatological condition affecting the joints and has a wide range of extra-articular manifestations. A 69 year old male, known case of rheumatoid arthritis presented to our OPD with right lower limb redness and swelling, and left axillary lymph node swelling. Lymph node biopsy revealed a high grade diffuse large B-cell lymphoma with co-expression of c-myc and bcl-2 (double expressor). RA increases the risk of both Hodgkin’s lymphoma (HL) and non-Hodgkin’s Lymphoma (NHL). The association with diffuse large B-cell lymphoma (DLBCL) has been found to be particularly strong, however double expressor DLBCL is an extremely uncommon occurrence. High disease activity of rheumatoid arthritis is a major determinant in development of lymphomas.

Introduction
Rheumatoid arthritis (RA) is a chronic immune-mediated, polygenic disease that causes chronic joint inflammation and deformity, with many extra-articular manifestations.¹ Incidence of malignancy in patients with RA has been studied in detail and it has been shown that patients with RA have an overall 10 % more risk of developing malignancies as compared to the general population, particularly lung malignancies and lymphomas.²

We report and discuss a case of rheumatoid arthritis who presented to OPD with lymphadenopathy and was diagnosed with high grade diffuse large B-cell lymphoma with co-expression of c-myc and bcl-2.

Case Summary
A 69 year old gentleman presented to our OPD with complaints of redness and swelling in the right lower limb, and swelling in the left axilla for the last 1 month. The patient was a known case of rheumatoid arthritis for the last 20 years. However he was not following up with any physician for his disease. He had however started consuming allopathic medicines, namely methotrexate and hydroxychloroquine only 2 months ago. Before that, he had been on medications of alternative medicine. Examination revealed typical deformities of the hands (swan neck, boutonniere and Z deformity). The right lower limb was red and swollen, the swelling extending from the mid-thigh up to the mid-leg and involving the knee. The right calf was tender. There was a large fixed swelling measuring 6 X 3 cm in the left axilla and multiple enlarged and matted right inguinal lymph nodes. The patient had normal vital signs barring an irregular pulse. ECG revealed occasional premature ventricular complexes. 2D echocardiography was normal. Blood investigations revealed high ESR (60), anaemia (Haemoglobin 9.8 g/dl), normal kidney and liver functions. A colour Doppler ultrasound of the bilateral lower limbs was done with showed thrombosis of the right superficial and deep veins and compression of the external iliac vein by multiple enlarged inguinal lymph nodes. An ultrasound of the left axilla confirmed the mass as a lymph node and also reported presence of multiple other enlarged axillary nodes. An excisional biopsy of the left axillary node was done. The patient was started on enoxaparin. An orthopaedic consultation was sought for the right lower limb swelling. Roentgenogram and MRI of the limb showed a mass involving the marrow, with evidence of cortical destruction, periosteal reaction and marked circumferential extra-osseous soft tissue component (Figure 1). Lymph node biopsy revealed diffuse effacement of nodal architecture by large lymphoid cells and a Non-Hodgkin’s Lymphoma was suspected. Immunohistochemistry (IHC) was performed which showed large cells to be diffusely positive for CD20, CD10, Bcl-6 and negative for CD3 and MUM-1 (Figure 2). Further, IHC showed large cells to be positive for c-myc and Bcl-2 (in 75% and 95% of cells respectively) (Figure 3). Thus, a diagnosis of a diffuse large B cell lymphoma; germinal centre subtype with co-expression of c-myc and Bcl-2 (Double expressor phenotype) was made. Bone marrow biopsy also showed infiltration by high grade NHL.

Fig. 1: Magnetic resonance imaging of the right lower limb showing a mass involving the marrow, with evidence of cortical destruction, periosteal reaction and marked circumferential extra-osseous soft tissue component
Fig. 2: A: HE section (400x) shows sheets of large pleomorphic lymphoid cells with prominent nucleoli and mitotic figures (arrow mark →). B: CD20 IHC showing strong membranous uniform staining (arrow mark →) around large lymphoid cells (400x).

Fig. 3: A: Immunohistochemistry for c-myc shows nuclear positivity in majority of lymphoid cells (arrow mark →) (400x). B: Bcl-2 immunostaining showing diffuse cytoplasmic positivity (arrow mark →) among all tumor cells.

The patient was transferred under the department of haematology and started on chemotherapy - rituximab plus cyclophosphamide, vincristine and prednisolone. The patient showed marked clinical improvement, including the decrease in size of swellings in the left axilla and right lower limb, after the initiation of chemotherapy.

Discussion

The WHO in 2001 classified lymphomas into three main types – B-cell, T-cell and Hodgkin’s lymphoma; which were further subdivided into over 40 categories. The classification was updated in 2008 and then in 2016; and many new categories were created.

A detailed meta-analysis noted that the increased risk of lymphoma varies with various rheumatological conditions and concluded it being highest in sjogren’s syndrome, rheumatoid arthritis and SLE – in that order. Other disorders like dermatomyositis, polymyositis and psoriasis also confer higher risk of developing lymphomas, but the rates vary in various studies.

Rheumatoid arthritis is a chronic immune mediated disease that involves the joints and has many extra articular manifestations. RA has been associated with many malignancies in individual case reports, however a meta-analysis concluded that true association existed only in lung malignancies and lymphomas. Both Hodgkin’s and non-Hodgkin’s lymphomas occur more frequently in patients with rheumatoid arthritis; the association being strongest with diffuse large B-cell lymphoma. Overall the risk of developing lymphoma in a patient with RA is two to three times the general population.

Many factors may contribute to the development of lymphoma in a patient with rheumatoid arthritis. These include genetic factors, environmental factors, high inflammatory activity and treatment related factors. Genetic factors were not found to be of no major importance in a study involving first degree relatives of patients with RA. Smoking is the only major identified environmental factor but the evidence for the same is weak and may even be conflicting. High disease activity has been found to have strong association with development of lymphoma in patients with RA in an elegant study. Disease activity in this study was measured using ESR, number of inflamed joints and the doctor’s global assessment. Another group found felty’s syndrome as marker of high disease activity and thus a risk factor for development of lymphoma in patients with RA. There is controversy regarding role of immunosuppressive therapy including methotrexate in the causation of lymphomas. In a study involving 1767 RA patients, spanning over two decades, it was showed that high inflammatory activity (elevated ESR) instead of therapy with methotrexate or prednisone, determined the risk of developing lymphoma. Hence, it is speculated that DMARD therapy may, conversely, lower the lymphoma risk.

Many studies have proposed various mechanisms involved in lymphomagenesis. It is believed that clonal proliferation of B-cells
may be a major pathogenic event.² The role of B-cell in development of RA-DLBCL was shown in a study that detected higher expression of APRIL (A Proliferation-Inducing TNF Ligand, also called TNFSF13) in RA-DLBCL patients with high disease activity.¹¹

Diffuse Large B-cell lymphomas with over-expression of c-myc and bcl-2 at a protein level (detected by immunohistochemistry) are referred to as “double-expressor” phenotype of DLBCL [12]. Over-expression is defined as greater than 40% c-myc expressing cells and greater than 50% bcl-2 expressing cells.¹² At a genetic level (detected by fluorescence in-situ hybridization), if dual re-arrangement of c-myc and bcl-2 is detected, it is called “double-hit” phenotype of DLBCL.¹³ This double-hit DLBCL has been reclassified as “high grade B-cell lymphoma (HGBL)” by WHO in 2016.¹³ Double-expressor and double-hit phenotypes may be related but the terms cannot be used interchangeably, as all double-expressor phenotypes may not have dual re-arrangement at the genetic level. The DLBCL in our patient had an over expression of c-myc and bcl-2, and is thus a double-expressor phenotype. The recognition of double-expressor is important for risk stratification and prognostication of the lymphoma. The poor prognostic effect was proved in an independent cohort of 140 double-expressor lymphomas.¹⁴

The double-hit and double-expressor phenotypes have a bearing on the treatment too. It has been shown that standard treatment with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone) may be suboptimal and R-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab) regimen might have more favourable outcomes.¹²¹⁵ Large prospective studies are, however, required to find the optimum treatment for such lymphomas.

**Conclusions**

Rheumatoid arthritis is a common connective tissue disorder, in which the risk of developing lymphomas is much more as compared to the general population. The most common lymphoma associated with RA is diffuse large B-cell lymphoma. High disease activity rather than therapy contributes significantly to the risk of developing lymphoma in RA. A physician must treat his patients with rheumatoid arthritis adequately; and strive to reduce the disease activity; thus reducing the risk of lymphomas. Lymph nodal swelling in patients with RA must alert the physician to look for an underlying lymphoma. When recognised as a diffuse large B-cell lymphoma, it is imperative to quantify c-myc and bcl-2 expression by IHC; which will in turn help to stratify risk, choose the appropriate therapy and prognosticate.

**Acknowledgements**

The authors thank Dr. Gaurav Aggarwal (Unit head) for his guidance. **Informed Consent**

A written informed consent was obtained from the patient.

**Abbreviations**


**References**

Large Submitral Aneurysm Compressing Left Main Coronary Artery: Rare Presentation of a Rare Disease

Parveen Kumar¹, Suryakant Jana², Kumar Kenchappa³, Geetesh Manik⁴

Abstract
Submitral left ventricular aneurysm is a rare cardiac anomaly that was first reported from African countries and initially termed as “annular left ventricular aneurysm”. Submitral aneurysm (SMA) causes out-pouching of the left ventricular wall, adjacent to the posterior leaflet of the mitral valve. Generally, SMA opens into left ventricle (LV) with a wide mouth and not into left atrium (LA). We report a case of Submitral Aneurysm with two openings: one into LV and the other into LA. This case also highlights the compression of coronary arteries by the submitral aneurysm. Large SMA can cause compression of left main coronary artery rarely. Having a knowledge of this point can help the clinician. SMA generally have an opening in LV but in this case SMA has two openings (One in LV and another in LA). This knowledge can help in proper surgical management.

Introduction
Submitral left ventricular aneurysm is a rare cardiac anomaly was first reported from African countries initially termed as “annular left ventricular aneurysm”.¹ The etiology is debatable; although the current consensus is that they are most likely due to a congenital weakness of the fibro-muscular annuli.²,³ Submitral aneurysm (SMA) causes out-pouching of the left ventricular wall, adjacent to the posterior leaflet of the mitral valve.⁴ Generally SMA opens into left ventricle (LV) with a wide mouth and not into left atrium (LA).

Case Report
A 19 years old girl presented to cardiology clinic with gradually progressive worsening shortness of breath on exertion associated with exertional palpitations and atypical chest pain for the past 2 years. There was no history of orthopnoea and paroxysmal nocturnal dyspnea. There was no history suggestive of rheumatic fever in past. On clinical examination, she was found to have mitral regurgitation. Chest X-ray revealed cardiomegaly with evidence of pulmonary venous congestion. On two-dimensional transthoracic echocardiogram (TTE), the significant finding was a submitral aneurysm of the LV with the mouth of the aneurysm just below the posterior mitral annulus opening into the LV and into the LA (Figure 1). Three dimensional TTE showed the same findings (Figure 2). LV angiogram showed significant mitral regurgitation (Figure 3). Coronary angiogram done showed systolic narrowing of the lumen of the distal left main, proximal left anterior descending artery & left circumflex artery due to extrinsic compression by a sub mitral aneurysm (Figure 4). This patient underwent successful surgical repair of submitral aneurysm and mitral valve replacement.

Discussion
Submitral aneurysm, although uncommon, should always be considered in differential diagnosis in young patients presenting with mitral insufficiency or signs and symptoms of heart failure. The main clinical manifestations of SMA are mitral regurgitation, thromboembolism, arrhythmias, sudden death and heart failure.⁵-⁷ In some cases, it presents as myocardial ischemia due to compression of the coronary arteries by the aneurysm or as cardiogenic shock.⁸,⁹ The mechanisms of mitral regurgitation are multifactorial and...
The definitive diagnosis is made by transthoracic echocardiography in the presence of an aneurismal dilatation in submitral location behind the posterior mitral leaflet that communicates with the left ventricular cavity through one or more necks. The spatial extent of these aneurysms can be challenging to delineate, thus resulting in surgical failure, which is often attributable to either failure to identify additional aneurysm necks (50% of failures) or inadequate closure of the aneurysm. Preoperative assessment has previously been done using transthoracic echocardiography, 2-dimensional TEE, and invasive angiography. Real-time three-dimensional echocardiography is not necessary for the diagnosis of SMA. However, it is very useful in the evaluation of the relationship of the aneurysm with the other cardiac structures. In the evaluation of the anatomical characteristics of the aneurysm allowing the identification of one or more apertures through which aneurysm communicates with the left ventricle, providing additional data to two-dimensional echocardiography, and improving the plan for surgery.

References

**Abstract**
**Background:** Panhypopituitarism due to compression of pituitary gland by internal carotid artery branch aneurysm is extremely rare.

**Case Presentation:** A 70 year old male presented with history of fall and altered sensorium. Investigations revealed hyponatremia, hypopituitarism and sellar mass. Evaluation of mass by MRI and CT angiography revealed a large internal carotid artery branch aneurysm.

**Case Report**
A 70-year-old male, known Hypertensive on Telmisartan 40 mg and Amlodipine 5 mg per day presented with a history of fall at home followed by headache & altered sensorium. His Blood pressure was 110/70 mmHg. The skin and mucous membranes were dry. Laboratory investigations showed hyponatremia (Na -126 mEq/L) and a potassium level of 3.5 mEq/L. His hemogram was normal. Random blood sugar was 95 mg/dl, serum creatinine was 1.2 mg/dl, Urine examination was normal. In view of hyponatremia, hypotension and altered sensorium, CT Brain was obtained which showed a suprasellar mass.

On further hormonal evaluation, he was found to have Panhypopituitarism. (Table 1).

MRI Brain and pituitary showed a space occupying lesion in Pituitary area. Aneurysm pressing over pituitary area (Figures 1 and 2).

Differential diagnosis of a Macro adenoma or Craniopharyngioma was considered. A CT angiogram was obtained for confirmation, which showed a huge aneurysm arising from internal carotid artery compressing the pituitary area (Figure 3).

The patient was rehydrated with normal saline to achieve euvolemia. Intravenous hydrocortisone 100 mg 8 hrly were started followed by levothyroxine 50 ugm which was increased to 75 ugm.His symptoms improved immediately, and the hyponatremia normalized. Interventional radiologist opinion was sought. The patient underwent further endovascular intervention for the aneurysm in the form of endovascular coiling with flow diverters. The patient has been on a daily replacement dosage of 5 mg prednisolone and 50μg thyroid hormone and he is off all anti-hypertensive medications and following up regularly.

**Discussion**
Sellar aneurysms form internal carotid artery, are an uncommon subtype of intracranial aneurysm and rarely cause hypopituitarism. The most common presenting symptoms of a patient with a giant intrasellar aneurysm are headache and visual

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### Table 1: Hormonal evaluation

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<th>Value</th>
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<tr>
<td>Free T4 (0.8-1.8 ng/dl)</td>
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field cuts or decreased visual acuity.² Mental changes can occur, albeit rarely, when they rupture. Clinically significant hyponatremia has been reported at presentation in 21% of patients with unruptured intrasellar aneurysms. The decreased mental status can be explained on the basis hyponatremia induced by secondary adrenal insufficiency and secondary hypothyroidism.

Various pathophysiologic mechanisms have been proposed to explain hypopituitarism in these patients.³ A parasellar mass can impinge on the hypothalamus or pituitary stalk and lead to hormone deficiencies due to interruption of releasing factors arriving at the anterior pituitary. Mass effect may lead to ischemia and necrosis of pituitary tissue.

Historically, the diagnostic dilemma between pituitary tumors and aneurysms has been common. Raymond in 1978 estimated that between 1.4-5% of aneurysms look like pituitary tumors. Many reports have described an aneurysm initially diagnosed as a pituitary tumor and only later properly identified by carotid angiography, or at the time of autopsy.

To ascertain the diagnosis, the gold standard continues to be angiography. Magnetic resonance imaging has also become a first-line diagnostic tool now because it helps to characterize location, size, lumen size and flow. On pre contrast T1 weighted images; aneurysms have a similar density as cerebrospinal fluid (Figure 1).⁴

The definitive management includes direct surgical clipping or endovascular coiling. Both the techniques eliminate the aneurysm from normal circulation and prevent further dilatation or hemorrhage.⁵ Patients with panhypopituitarism need appropriate hormonal replacement therapy and regular follow up.

Conclusion
Differentiating between pituitary adenoma and intrasellar aneurysm is crucial in order to avoid a potential surgical catastrophe. CT angiography and MRI are useful tools for the differential diagnosis.

References
Double - Trouble- Relapsing Leishmaniasis in a Virologically Suppressed HIV Positive Patient

Sumeet Prakash Mirgh1, Gajanan Panandikar2, Smrati Bajpai3, Kavita S Joshi4, Amar R Pazare5

Abstract
We present a case of a middle aged male, with long standing retroviral disease on second line ART (Anti-Retroviral Therapy) with three episodes of visceral leishmaniasis diagnosed on bone marrow examination treated with a combination of liposomal amphotericin B and miltefosine.

Introduction
Visceral leishmaniasis (VL) is endemic in some states of India. It is a known opportunistic infection in HIV positive individuals with high mortality if untreated and increased frequency of relapses. As per literature, relapses of VL have been observed in cases of ART (Anti-Retroviral Therapy) failure. Our patient was virologically well suppressed on second line ART but he still developed two relapses which as per our knowledge has not been reported from India. This case also highlights the importance of effective dosage of amphotericin and bone marrow examination post therapy to document cure.

Case
A 35 year old male, farmer from Bihar, known case of retroviral disease on ART (anti-retroviral therapy) since eight years, visited our outpatient department in March 2014 with a history of low grade fever, easy fatigability and dull aching left hypochondriac pain since six months. At other hospital, he was initially started on d4T+3TC+NVP (Stavudine + Lamivudine + Nevirapine) regimen in 2005 which was changed three years later in 2008 to d4T+3TC+LPV/r (Stavudine + Lamivudine + Boosted Lopinavir) regimen. His previous investigations were not available. He was diagnosed with visceral leishmaniasis (VL) in 2010 and treated with liposomal AMB (Amphotericin B) 15 mg/kg in 3 divided doses daily for 28 days. ART regimen was changed to AZT+3TC+LPV/r. Since d4T was phased out, it was replaced by Zidovudine (AZT). Patient improved clinically. Eight months later, patient had a relapse which was retreated with liposomal AMB 5mg/kg for 6 doses with Miltefosine 50 mg twice a day for 28 days after which he symptomatically improved. During this 4 years period, patient had effective HIV viral RNA suppression.

On examination, he was pale and had massive splenomegaly - 10 cm below left costal margin. His hemogram revealed pancytopenia. His CD4 count was low - 64 but HIV viral load was 72 copies/ml. Bone marrow aspirate showed macrophages studded with LD (Leishmania Donovani) bodies (Figure 1).

In March 2014, we treated his second relapse with liposomal AMB 4mg/kg/day from day 1 - day 5, then at day 10,17,24,31,38 with Miltefosine 50mg twice a day for 28 days. Hemogram, creatinine and electrolytes were monitored regularly. ART regimen consisting of AZT+3TC+LPV/r was continued. At the end of treatment, his splenomegaly regressed, cytopenias improved and bone marrow was normal. At 1 year follow-up, he was stable without any signs of relapse.

Discussion
Leishmaniasis is an important opportunistic infection in HIV patients, especially in severe immunodeficient patients. India, Nepal, Bangladesh, Sudan and Brazil account for 90% of world’s VL burden, with India being the worst affected. Almost all cases of VL/HIV co-infection have been found to have fewer than 200 CD4+ cells/ml blood, and about 50% meet the AIDS-defining criteria during their first episode of VL. Its incubation period is between 2 – 6 months transmitted through bites of phlebotomine sandflies.

VL is an AIDS defining condition and is an indication for starting ART irrespective of patient’s CD4 count.2 The clinical manifestations of VL in HIV-infected individuals may be similar to those seen in HIV-negative cases; fever, pancytopenia and hepatosplenomegaly, are found in 75% of all the HIV-positive cases. Following dissemination of the parasites, however, they may develop unusual, multi-organ pathology.1 The clinical case definition of Primary VL is fever for more than 2 weeks with malaria excluded or treated in the presence of splenomegaly or lymphadenopathy and wasting.2 Unusual manifestations like gastro-intestinal involvement, respiratory involvement, reactivation of arthritis, cutaneous involvement can be seen in such patients.10 Demonstration of amastigotes in smears of tissue aspirates is the gold standard for diagnosis. The sensitivity of splenic smears is >95%, whereas smears of bone marrow (60 – 85%) and lymph node aspirates (50%) are less sensitive. Serological tests are commonly negative.
in immunocompromised patients. Although rK39 ELISA is sensitive and important in epidemiological studies, it may remain positive up to 24 months after treatment. Hence, it was not done in our patient.

Treatment of VL-HIV co-infection is difficult as both HIV and Leishmania attack the immune system, they respond less effectively to ART and anti-leishmanial treatment like Sodium stibogluconate have unacceptable high mortality (16.33 %) during treatment. Liposomal AMB is the drug of choice for VL-HIV coinfection – both for primary treatment and for treatment of relapses. A total dose of 40mg/kg administered as 4mg/kg on days-1-5,10,17,24,31,38 is considered and approved by FDA. Almost all the cases of co-infection are very prone to VL relapses, even after carefully managed antileishmanial treatment. Most patients relapse within 1 year. These new episodes are usually recrudescences reflecting an inability of host’s immune system to control leishmanial infection. The characterization of leishmania isolates from same patients during different episodes of VL indicate that very few relapses are the result of post treatment infection. HIV patients who have demonstrable parasites will relapse much sooner than those who have achieved parasitological cure. In coinfected patients in East Africa, MSF recently demonstrated that high dose Liposomal AMB in Ethiopian HIV-Primary VL co-infected patients led to an initial cure in only 74% cases which was further reduced to 38% in relapsed patients. Combination of Liposomal AMB with Miltefosine in HIV positive VL patients enhances its effectiveness and lowers treatment failure rates as compared to monotherapy. Dose of Miltefosine - for children aged 2-11 years is 2.5mg/kg/day, for more than 12 years and < 25kg – 50 mg/day, 25-50 kg – 100 mg/day, >50 kg – 150 mg/day orally for 28 days. Initiation of effective HAART regimen is mainstay in HIV- VL co-infection and most relapses are due to ineffective HAART and high HIV viral replication. Our patient was treated with FDA recommended dose of liposomal AMB for 10 days along with oral miltefosine for 28 days. Our patient is unique as he developed two relapses while being virologically suppressed on second line ART. Our patient did not have documented evidence of parasitological cure after treatment in first two episodes. Only evidence of clinical cure was present with resolution of splenomegaly and clinical symptoms. Thus, it is strongly recommended to document “parasitological cure” after completion of regimen in form of bone marrow or splenic aspiration for absence of LD bodies, especially in HIV positive patients.

Secondary prophylaxis with Liposomal AMB has been shown to delay relapses but no regimen has been established as optimal. In a retrospective study of Pintado et al, it was shown that patients treated with monthly pentavalent antimonial or liposomal amphotericin were significantly less likely to relapse. In the only open, prospective and randomized clinical study till date where patients treated with ABLC (Amphotericin B lipid complex) (3 mg/ kg every 21 days) were compared to those not receiving prophylaxis, after 1 year follow up, 50 % patients treated with ABLC relapsed compared to 78% in nontreated patients.

Conclusion

VL is an AIDS defining illness and HAART should be initiated irrespective of CD4 count. Relapse is reported in HIV positive individuals with high HIV viral load and ineffective HAART. Our case signifies that relapse may occur even on effective HAART regimen but large case studies are needed to establish this. Documentation of cure post treatment is strongly recommended to prevent relapse. Liposomal AMB with Miltefosine combination regimen has been shown to prevent relapse.

References

Hemophagocytic Lymphohistiocytosis Secondary to Acute Hepatitis E Infection: A Rare Association

Asha Ranjan, Jatinder Mokta, Surinder Thakur, Rajesh Bhowani, Ivan Joshi, Shekhar Vohra

Abstract
Viral infections are commonest cause of secondary hemophagocytic lymphohistiocytosis (HLH) and Ebstein Bar Virus is associated with majority of cases. We report a rare case of HLH associated with acute hepatitis E virus infection.

Introduction
Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal condition, in which body’s own inappropriate hyperimmune response leads to hypercytokinemia (cytokine storm syndrome) and subsequently the vivid manifestations of syndrome. It may be primary (underlying genetic mutations) or secondary triggered by infections, malignancy or rheumatological disorders, immunumosuppressed states. Among viral infections, it is most commonly associated with EBV, CMV and HHV-8 infection. Here we report a rare case of HLH associated with acute Hepatitis E virus infection.

Case Presentation
A 20 year male resident of Jharkhand referred to us during the acute viral hepatitis epidemic in Shimla in December 2015 with yellowish discoloration of eyes for 1 month, vomiting for 4 days and fever for 1 day. He had associated pruritus, clay coloured stools, high coloured urine and decreased appetite. He did not consume alcohol. He was being treated for acute viral hepatitis at Zonal hospital on OPD basis for 3 weeks but no records were available. He did not take any indigenous drugs. On examination he was febrile with 103°F temperature, had icterus, cervical lymphadenopathy, hepatomegaly and moderate splenomegaly. Clinical possibility of acute viral hepatitis with pyrexia under evaluation was kept and investigations ordered. Haematological findings were anemia (Hb 8.5%), leucopenia with neutropenia (TLC 3700/mm³, ANC 900/mm³) and thrombocytosis (5,19,000/mm³). Peripheral smear showed anisocytosis, macrocytes with schistocytes. Biochemistry report revealed hyponatremia (130meq/l), conjugate hyperbilirubinemia(total bilirubin-29.11mg/dl, direct bilirubin-14.22 mg/dl), SGOT 80 IU, SGPT 33 IU, alkaline phosphatase 234 IU, hypoalbuminemia (2.8g/dl) and AKI (creatitine 1.4mg/dl). His IgM HEV was positive and rest all viral markers (IgM HAV, HBsAg, anti HCV and HIV) were negative. Pyrexia workup including blood cultures, LN biopsy, malarial antigen/smear and amoebic, scrub and leptospira serology were all negative. Patient’s Hb and platelet count fell down (8.5 to 3.4 g% and 3,19,000 mm³ to 2,10,000/mm³ respectively) on subsequent estimation at day 4, while TLC count remained on lower side (3500/mm³). There was no obvious bleeding from any site. Serum LDH levels was 715IU s/o hemolysis but DCT and ICT were negative. Radiological investigations (CXR, USG abdomen, CECT abdomen) were suggestive of hepatomegaly and splenomegaly with normal portal vein and no occult ascites. Patient was started at admission on empirical broad spectrum antibiotics with supportive therapy including blood transfusion. When, even after 7 days of antibiotics patient stayed febrile and counts remained low, bone marrow examination (BME) was done to rule out visceral leishmaniasis. BME did not reveal LD bodies but showed focally reticulendothelial cells with hemophagocytosis (Figure 1). At this stage, possibility of HLH was kept and further investigation were done to rule it out- fibrinogen level: 324 mg/dl, S.ferritin: 13578 μg/L, fasting S.TGs: 316 mg/dl. Our patient fulfilled 6 out of 8 diagnostic criteria for HLH (Histiocyte Society 2004). So final diagnosis of secondary HLH etiology: acute HEV hepatitis was kept. After definitive diagnosis patient was started on iv dexamethasone and antibiotics were continued. He responded to treatment and fever and counts improved (Hb 8.3 g/dl, TLC 4500/mm³) icterus decreased (bilirubin 10.51 mg/dl, C. bilirubin 2.95 mg/dl). He was discharged on oral dexamethasone for 8 weeks, was asked to come for follow up after 2 weeks but he did not come. Unfortunately he expired after 2 months when enquired on telephone.

Discussion
HLH is a rare entity of immune activation, which may be familial or sporadic, manifesting as symptoms and signs of severe inflammatory response. It has been associated with viral infections (29%), other infections (20%), malignancies (27%), rheumatological disorders (7%). Most common associated viral infection is EBV. Its association with HEV virus has been rarely documented. Less than 5 cases have been documented till date. Morbidities have been documented...
in three cases (hepatitis A co-infection,² splenic lymphoma,³ and rheumatoid arthritis treated with tocilizumab infusion.⁴ Three patients recovered with supportive treatment while the fourth one died due to fulminant hepatitis.

HLH is characterised by phagocytosis of blood cells and their precursors, mostly by monocytes and macrophages. Excessive activation of monocytes may be due to stimulation by high levels of activating cytokines, IFN-γ, IL-2 receptor, TNF-α, IL-1 and IL-6. The exact mechanism by which abnormal cytokine elaboration by T-lymphocyte results in HPS remains unclear.

It presents with cytopenias due to uncontrolled hemophagocytosis and laboratory findings resulting from disseminated immune regulation and cytokine storm. Clinically, HLH is characterised by high fever, lymphadenopathies, hepatosplenomegaly, liver dysfunction, pancytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, as well as coagulopathy and neurological manifestations (cerebral HLH) in many cases and is diagnosed based on HLH 2004 criteria.³ The diagnosis of HLH can be established if one of the two criteria is fulfilled: 1) A molecular diagnosis consistent with HLH 2) Diagnostic criteria for HLH: fulfilling 5 out of 8 criteria: 1) fever 2) splenomegaly 3) cytopenias (at least 2 of 3 lineages in peripheral blood, 4) hypertriglyceridemia (>265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL) 5) haemophagocytosis in bone marrow, spleen or lymph nodes 6) low or absent NK-cell activity 7) serum ferritin >500 µg/L 8) soluble CD25 ≥ 2400 U/ml. but these criteria are not very sensitive. Treatment of HLH involves immunosuppression and modulatory agents and treatment of the inciting illness, if it is secondary. Infection as such are most common cause of secondary HLH also common triggering factor in familial HLH. So, genetic mutations to rule out familial HLH must be done in very case. There is no standard protocol for treatment in infections. One must treat underlying infection. The HLH-94 and HLH-2004 trials protocols (dexamethasone, etoposide cyclosporine and methotrexate) used for genetic HLH can be applied to secondary severe or non responding cases. Although steroids have been commonly used in treating virus associated HLH, there have been cases reported showing failure.⁵ Our patient showed a drastic improvement with steroids initially. Patients without a clear diagnosis of familial HLH, bone marrow transplantation should be considered if remission is not attained by 8 weeks of chemotherapy and immunotherapy and patients in remission without a clear diagnosis of familial HLH should be monitored for signs of relapse. Without treatment, HLH has poor prognosis and with treatment also mortality ranges from 50-75% in acquired cases. EBV related HLH has mortality of 25-100% and other infections has recovery in 60%-70% cases.

**Conclusion**

HLH is an uncommon life threatening condition due to uncontrolled immune activation and bears high mortality. HLH is a rare extra-hepatic manifestation in acute HEV hepatitis and must be suspected if patient develops fever, hepatosplenomegaly and cytopenia. Early aggressive therapy with steroids must be started and patient must be followed closely.

**References**

Julius Axelrod & Neurochemistry

Jayant Pai-Dhungat

Julius Axelrod (1912-2004), an American biochemist and pharmacologist, was born in New York City in 1912. Graduate of the College of New York City (1933), he worked briefly as a laboratory technician at New York University. In 1935 he got a job with New York City Department of Health for testing vitamin supplements added to food (1935-45). He lost his left eye in a lab accident, and wore an eye patch for the rest of his life. While working at the department he attended night school, and received his master’s degree.

Axelrod joined research division at Goldwater Memorial Hospital (1946). He began his research on metabolism of analgesic medications, and began his studies on sympathetic amines. But, Julius came to realize that his research contributions would not be fully recognized unless he had a doctorate. It was at this stage that he took leave of absence from NIH (1954) to study in the Department of Pharmacology of George Washington University for his PhD, which he thought was vital for his further recognition. At the Washington University he was allowed to submit some of his earlier research towards his degree. Hence he graduated within a year in 1955. He returned to NIH and began some key research on nervous system and its main neurotransmitters-adrenalin and noradrenalin. Axelrod initially worked on mechanism and effect of caffeine. Working with Bernard Brodie, their research focused on non-aspirin analgesics. This analgesic caused methemoglobinemia in some individuals. The duo discovered acetanilide as the main culprit in the formulation and further, that one of the metabolite acetaminophen (paracetamol) was more effective and safer analgesic. During this time he also conducted research on codeine, morphine, methyl-amphetamine, ephedrine and performed first experiments on LSD-25.

Axelrod’s Nobel Prize winning research grew out of work done by Euler, especially Euler’s discovery of noradrenalin that transmits nerve impulses. Axelrod in turn discovered neuro-transmitter’s reuptake and storage by pre-synaptic nerve endings-research carried out by Euler and Hillarp earlier, unknown to Axelrod. His Key discovery for winning Nobel Prize was that noradrenalin could be neutralized when not needed, by an enzyme- catechol-O- methyl transferase, which he isolated and named in 1958. The enzyme proved critical in the understanding of the entire nervous system. It was shown to be useful in dealing with the effect of certain psychotropic drugs and in research on hypertension and schizophrenia.

Re-uptake and storage of neurotransmitters laid the ground work for later selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, which blocks the reuptake of serotonin. Axelrod also worked on dopamine, monoamine oxidase (MAO) inhibitors in 1957, which are used as antidepressants. Axelrod and Solomon Snyder elucidated and concluded that antidepressants work in a variety of ways. (1964).

Some of Axelrod’s later research focused on the pineal gland. He along with colleagues obtained hormone melatonin which is generated from tryptophan. Rate of synthesis and release follow body’s circadian rhythm driven by suprachiasmatic nucleus within hypothalamus. They went on to show that melatonin has wide ranging effects throughout CNS, allowing the pineal gland to function as a biological clock.

Axelrod was awarded the Nobel Prize in Physiology or Medicine in 1970, together with Von Euler and Bernard Katz “for their discoveries concerning humoral transmitters in the nerve terminals and mechanism for their storage, release and inactivation”
Giant Cell Arteritis Presenting as PUO – An Earlier Series

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Sir,

We read with interest, the report by Santhanam and Mani, on a patient with Giant cell arteritis presenting as PUO.¹ Though the authors have referred to four other papers from India on the subject of Giant cell arteritis, they appear to have missed out on our series on the same topic.² It is important to document this because there are few case series on giant cell arteritis from our country and our series was one of the earliest.

Besides, and this is more to the point, four of our nine patients presented with PUO, one for as long as for four months. Even in the series by Singh et al, nine of 21 patients presented with fever.³ Thus, the statement that the authors make, “PUO as a presenting manifestation is very rare and may be found in only 15 % of patients” is erroneous.¹ We emphasised the fact that PUO could be an important symptom in patients with Giant cell arteritis not only in the paper, but even in the abstract by stating “Pyrexia is a common presenting feature of the disease; temporal arteritis should be considered in the differential diagnosis of elderly patients with pyrexia of unknown origin. Thus, our paper should have been detected in a MEDLINE search and should ideally have been quoted as well.

References


Reply from Author

Sham Santhanam
Consultant Rheumatologist, Global Hospitals, Chennai, Tamil Nadu

Sir,

Thanks for the communication. We regret for missing out on the wonderful case series¹ by Vankalakunti M et al on Giant cell arteritis and it was not intentional. Or else, we would have definitely cited the article¹ as 4(50%) of the patients had presented with Pyrexia of unknown origin (PUO).

Regarding the discussion on PUO as the presenting manifestation, except for the case series by Vankalakunti M et al¹ others² have just mentioned fever as a constitutional symptom presenting along with other symptoms is not the same as PUO. Fever as a constitutional symptom presenting along with other symptoms is not the same as PUO. But, still in the previous paragraph the incidence of fever in Indian data has been discussed in our article.³

Most of the data are from western literature as it is more common there compared to Asian countries like India. Hence, our citation on PUO being rare as a presenting manifestation (15%) is from western literature⁴⁵⁻⁶⁻⁷ (Kelley’s textbook of rheumatology and others).

So, considering the paucity of data on PUO from India (except for one Indian case series of 8), we felt it was more appropriate to cite the western literature.

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Association of Serum Homocysteine, Vitamin B12 and Folic Acid Levels with Metabolic Syndrome

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Sir,

I read the article “Serum Homocysteine, Vitamin B12 and Folic acid levels in patients with Metabolic syndrome” with great interest.¹ Metabolic syndrome has drawn attention of researchers because of its association with athero vascular diseases. It has been found that there is a high prevalence of metabolic syndrome in Indians. A multisite study from India reported age adjusted prevalence of metabolic syndrome in men and women as high as 33.3% and 40.4% respectively.² Even vitamin B12 deficiency and hyperhomocysteinemia are common problems encountered in Indian population. One of the study from Pune, Maharashtra found that 81% of urban middle class individuals had low vitamin B12 concentrations and 79% had hyperhomocysteinemia.³ Interestingly, it has also been hypothesized that low levels of vitamin B12 and folic acid along with hyperhomocysteinemia are associated with athero vascular diseases. Supported by these facts, Narang et al conducted this study to determine the levels of these aforementioned parameters in individuals with and without metabolic syndrome. They concluded that Indian patients with metabolic syndrome have a strong association with elevated blood levels of homocysteine and reduced levels of vitamin B12 and folic acid. However, it is pertinent to note the limitations of this study enumerated below -

1. The authors have utilized the American Heart Association guidelines to define metabolic syndrome. It has been demonstrated that Asian Indians are likely to develop insulin resistance and cardiovascular risk factors at lower levels of Body Mass Index (BMI). The cut off levels of BMI

I would be grateful if you could provide more details about the study and its limitations. Furthermore, I would like to suggest that future research should focus on the role of vitamin B12 and folic acid in the development of metabolic syndrome in Indians.
for overweight and obesity have been revised for Asian Indians to 23.0 - 24.9 kg/m² and > 25 kg/m² respectively. The recommended action level 1 waist circumference cutoffs for Asian Indians are 78 cm for men and 72 cm for women [4]. Interestingly, the mean (± standard deviation) BMI for the controls was 23.04 (± 0.829) kg/m² and the waist circumference (± standard deviation) for controls was 78.8 (± 5.664) cm. If guidelines for Asian Indians were utilized in this study then all these controls will also fall in overweight category. Thus, it would have been more practical if guidelines pertaining to our country were put to use to identify this category of patients. This would have helped to identify the risk factors with an Indian perspective.

2. The inclusion criteria spells out that patients with metabolic syndrome were recruited as cases for the study. The mean (± standard deviation) fasting blood sugar for the cases was 137.72 (± 26.835) mg/dl. There is a high likelihood that the cases were started on metformin given that their mean (± standard deviation) body mass index was 29.316 (± 1.645) kg/m². It is known that long term metformin use increases the risk of vitamin B12 deficiency which in turn results in raised homocysteine concentrations. As the authors have not excluded cases taking metformin in their protocol, a significant bias may have been introduced into the study interpretation.

3. The authors have presented their non-normally distributed quantitative data as mean ± standard deviation. However, it is not recommended to assume that mean will be the middle of the sample or that most of the sample will lie within two standard deviation on either side of mean in a non-normally distributed data. It is recommended to utilize median with interquartile range to present quantitative variables in such a scenario to make it more meaningful for the readers. In fact Mann Whitney U nonparametric test, the one employed by the authors to test the significance, compares the medians of the two groups rather than the means.

The present study provides important data for the researchers to interpret and analyze the relationship between metabolic syndrome, vitamin B12, folic acid and homocysteine levels. Presentation of quantitative data as medians with interquartile range would have been more meaningful. However, it would have been more interesting to analyze metabolic syndrome as per the guidelines for Asian Indians. Besides, consideration for use of metformin as an exclusion criteria may change the results all together. Future studies may be planned accordingly.

References


Reply from Author

M Narang
Professor & Consultant, Department of Medicine, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi

Sir,

Dr. Gulati has reiterated the need for studies on vitamin B12, folic acid and homocysteine in patients with metabolic syndrome. Regarding the points mentioned as limitations of this study, we have following observations:

1. On the issue of definition of metabolic syndrome for Indians and other South Asians, we feel that the objection is unwarranted since the definition used by us, i.e. American Heart Association (AHA) definition with cut-offs for Asians as mentioned in footnote of its Table 2, defines abdominal obesity in the same manner as proposed by Misra et al in their consensus statement, i.e. waist circumference cut-offs of 90 cm for men and 80 cm for women (Table 2 of Misra et al). 1–3 These cut-offs are also recommended in the International Diabetes Federation (IDF) definition. 4 In 2009, a joint statement by IDF, AHA, National Heart Lung and Blood Institute and 3 more societies has been published to provide a harmonious definition of metabolic syndrome. 5 This statement also recommends the same waist circumference criteria for Asians. Most recent studies from India have also used these cut-offs. 6,7 Waist circumference cut-offs of 78 cm for men and 72 cm for women have been given by Misra et al for Action level 1 (avoid gaining weight and maintain physical activity) but not for defining metabolic syndrome. According to authors themselves, even these Action level 1 criteria need to be researched further. Body mass index is not used for diagnosing metabolic syndrome in any of these definitions.

2. Whether or not patients were taking metformin cannot be concluded on basis of fasting blood sugar and body mass index. Although, metformin has been reported to increase the risk of vitamin B12 deficiency, this is seen in only about 4% of patients taking metformin. Hence, it is unlikely that our findings would have been markedly different had we excluded patients on metformin. Even if vitamin B12 levels are reduced due to metformin, it is important to document, characterize and research this aspect, rather than excluding such patients from studies. Moreover, folic acid, which is also involved in homocysteine metabolism, was also low in patients with metabolic syndrome in our study.

3. Amongst the large data we reported in this study (27 variables are listed in Table 1 of our study), some were normally distributed and others were not. Hence, we gave mean and standard deviation for all for the sake of simplicity rather than mentioning medians with inter-quartile ranges for some of the data and mean with standard deviation for the rest. Non-parametric statistical tests, e.g. Mann-Whitney U test, were
used for analysis of non-normally distributed data.

References


Comments on:
Neoplastic Fever- All who Shivers are not Infected

Ankur Dalal
Assistant Professor in Medicine, The Sarvajanik Medical Trust Hospital, Surat, Gujarat
Sir,

I have read the case report titled, “Neoplastic Fever - All who shivers are not infected” written by Sharma YB et al.1 with great interest. The authors suggest that any case presenting with acute fever not responding to standard line of treatment and having all primary routine investigations normal, work up for neoplasm as a cause of fever should be kept in mind.1 However, there are few clarifications needed for the common readers, which I would like to highlight.

First of all, clinician commonly refers to any febrile illness without an initially obvious aetiology as fever of unknown origin (FUO).2 Now a day as better diagnostic techniques; including CT and MRI are widely available, only the cases that are more difficult to diagnose continue to meet criteria for classical FUO. The authors had mentioned in their conclusion about ‘acute fever not responding to standard line of treatment’. I would like to emphasise here that there is nothing like standard line of treatment for FUO, instead the treatment should be individualised. Now looking in to this particular case antibiotic (ceftriaxone) and antimalarial (artesunate), both treatments were started as empirical on presentation. Then after two days just because fever was not subsided even in absence of vital-sign instability change of antibiotic (cefazidime) and antimalarial (quinine) were done. This approach was not explainable. As we know that both antibiotics are third generation cephalosporins and the major difference is useful activity against pseudomonas aeruginosa for ceftazidime and antimalarial (quinine) were done. This approach was not explainable.

The emphasis in patients with FUO is on continued observation and examination, with the avoidance of “shotgun” empirical therapy. The antibiotic therapy, (even for tuberculosis) may irrevocably alter the ability to culture fastidious bacteria or mycobacterium and delineate ultimate cause. However, vital-sign instability or neutropenia is an indication for 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.3 However, they themselves started empirical antitubercular drugs in this particular patient with a very short duration of high-grade fever with negative tuberculin test just considering high ESR, which was also not convincing. If the tuberculin test is positive or if granulomatous hepatitis or other granulomatous disease is present with anergy (and sarcoid seems unlikely), then only a therapeutic trial for tuberculosis should be undertaken for classical FUO, with treatment usually continued for up to 6 weeks. A failure of the fever to respond over this period suggests an alternative diagnosis.2

Second, the authors discussed about “naproxen challenge”, which may be useful in evaluating prolonged fever suspected to be of neoplastic origin. However, author did not provide any references in support, which can be useful in clinical practice. Vanderschueren S et al.4 concluded that naproxen test is not specific for tumor-related fever and has no differential diagnostic role in the work-up of a patient with prolonged unexplained fever from their study. Ampel NM et al.5 also commented after reviewing Vanderschueren S et al.4 at NEJM journal watch that although the study was retrospective and few subjects had a malignancy, the results indicate that the naproxen test is neither sensitive nor specific for distinguishing cancer from other etiologies of occult fever. This makes sense, since the antipyretic mechanism of NSAIDs is independent of the etiology of the fever.

On concluding my comments; in my opinion the conclusion of standard line of treatment for acute unexplained fever; which was shown in this case, cannot be recommended as a general approach in routine practice as discussed above. I also opine that instead of in its presentation, uniqueness of the case is actually lies in its disease entity as anaplastic large cell lymphoma (ALCL) is a rare type of non-hodgkin’s lymphoma and primary involvement in the central nervous system of ALK positive ALCL, however,
is even rarer or exceptional. 6

References


Antidote for Non Vitamin K Antagonist Oral Anticoagulants

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Sir,

This refers to review article titled “Current Perspective on Use of NOAC in Clinical Practice in India” written by Jamshed J Dalal et al in JAPI 2016 April.1 The authors have made great efforts to review literature and enlighten readers about latest trends in safe use of these novel non vitamin K oral anticoagulants introduced recently in India. The authors mention that there is no antidote for Dabigatran. It may please be noted that monoclonal antibody “Idarucizumab” has been recently approved by US FDA as specific antidote for Dabigatran.5 Four grams of IV Idarucizumab (Praxbind) reverses Dabigatran induced anticoagulation in just few minutes. This accelerated approval by US FDA is keeping in view safety of the patients who need emergency surgery or have uncontrolled bleeding. It is possible that such specific antidotes for other NOACs [Rivaroxaban & Apixaban] may also become available in near future. It is very important for practicing clinicians to have these antidotes ready for emergency use. This is similar to keeping Protamin Sulfate ready to reverse action of heparin in emergency. Anticoagulants are double edged weapons and clinicians must master judicious & properly individualised usage. Having a safe & effective antidote always ready at hand would allow clinicians to use these newer anticoagulants with easy mind.

References


Cognitive Effect of Standardized Group Education Programme in Diabetes Population

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Sir,

Diabetes is most challenging public health problem of 21st century. Indian diabetes federation had mentioned 69.1 million cases of diabetes in India in 2015 with prevalence of 8.7% that will be doubling in near future.1 Indians have a peculiar genetic composition that predisposes them to have higher propensity to metabolic syndrome, diabetes mellitus and coronary artery disease. Epidemiological transition, economic boom, physical inactivity, trendy dietary patterns and environmental factors also add to this risk. Indian healthcare professionals and patients in India face a number of challenges such as clinical inertia in achieving glycemic control, inadequate follow-up and lack of disease awareness.2

Self-care deficit exist when self-care demand is not met. We cannot expect the patient to follow the regimen when they lack basic understanding on rationale, procedure and requirements of their regimen. Patient education is the needed solution for self-care deficit and fostering patient compliance and adherence.

The American Diabetes Association recommends assessment of self-management skills and knowledge of diabetes at least annually, and provision or encouragement of continuing diabetes education.3 High prevalence of diabetes in India and lesser doctor population ratio makes it difficult to give one to one education. We thereby designed a standardized group education programme including following topic with two sessions 15 days apart.3

• Basics of diabetes
• Deal with physical symptoms
• Healthy eating and nutrition: Meal plan was prepared by dietician
• Appropriate use of medications
• Relaxation Techniques, Physical exercises
• Preventing or delaying complications
• Communicating effectively with friends, family, and medical team

Two hundred patient were exposed to the group education and was found to be highly effective in improving the cognition of patient regarding diabetes. Average learning gain was 77.98 + 23.27 % after the group education. Sixty-four percent of participants demonstrated more than 75 % of learning gain. Changes in BMI, glycaemic control needs around 6 months to exhibit, so only change in knowledge score is unveiled in this study, long term benefit study is going on. Patients felt free to ask question and express opinion regarding their socio-cultural and psychological issues. Sharing each other’s experiences on coping with the diabetes was appreciated by participants as it gave them platform to discuss their psycho-social problems. Also such programme helped them to have an open dialogue with health care providers.

With the growing burden of diabetes and out of pocket expenditure to individual, achieving the therapeutic goal and preventing the complications is of utmost importance. Diabetes education plays an important role in management of diabetes. This Group education programme was found to be feasible, effective and acceptable to patients which can be implemented on routine basis for all diabetic patient annually.

References

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