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Amoebic Liver Abscess with Synchronous Colitis: Lessons Learnt in Recent Times

Shobna J Bhatia¹, Sridhar Sundaram²

Entamoeba histolytica is aptly named as it causes tissue-lysing that results in amoebic colitis and liver abscess. It is one of the most important enteropathogens worldwide accounting for 40 to 100 thousand deaths annually.1,2 The population prevalence of Entamoeba is high in our country due to crowding, poor sanitation, lower socioeconomic status, and unhygienic practices. In a study from North-East India, 13.7% of stool samples were positive for Entamoeba histolytica when tested using DNA dot blot technique.3 In another study from Vellore, 8.2% of all stool samples were positive for Entamoeba cysts or trophozoites.4

More than 95% of patients with Entamoeba in their stools are asymptomatic. Invasive amoebiasis accounts for only 1% of all amoebic infections.5 Amoebic liver abscess (ALA) in the most common extraintestinal presentation of invasive amoebiasis. Risk factors associated with disease severity and mortality6-7 include young age, alcoholism, and corticosteroid use. Amoebic colitis occurs in the same frequency in men and women. However, ALA is found more commonly among men (M:F ratio >10). Testosterone has been implicated in the increased ALA risk in men, which also explains middle aged men being the most commonly affected cohort.6 Hormonal factors and higher rates of iron deficiency anemia in women are likely protective against development of ALA.7 Alcohol consumption confers high risk of ALA leading to hepatocellular damage.

The life cycle of the Entamoeba histolytica has two stages (cyst and the trophozoite) and was first described in 1928 by Clifford Dobell.8 In most infections, the pathogenic trophozoites are restricted to the mucin layer in the intestine, where they produce new cysts. A few trophozoites invade the epithelium and lead to dissemination to extraintestinal sites like liver. The amoeba has cytolysic capabilities, creating liver abscesses with cellular debris, dead hepatocytes and liquefied cells. The lesion is surrounded by connective tissue, inflammatory cells and amoebic trophozoites. Most patients develop symptoms within 2-4 weeks of exposure.9 Although synchronous colonic lesions in patients with amoebic liver abscess are seen in over 50% patients, symptoms of diarrhea and bleeding are uncommon. The reasons for low incidence of preceding diarrhea in these patients is unclear. Jaundice is an uncommon manifestation. There are multiple theories for jaundice which include hepatic necrosis with pressure on biliary apparatus, biliovascular fistula leading to increased bilirubin and necrosis at the margins of the abscess.10

In the present issue of this Journal, Premkumar et al.11 present their findings on 52 patients with ALA; half of their patients had simultaneous colonic involvement at colonoscopy. Most patients with colonic involvement (20 of 28 patients) had large ileo-caecal ulcers. Of these patients, 16 patients had history of intermittent bleeding per rectum; the remaining 8 patients presented with liver abscess and anemia, and gave history of bleeding per rectum on enquiry. Also, almost all their patients were men (51/52). Significant alcohol intake was more common in patients with synchronous lesions.

The large number of patients with synchronous colonic involvement in this study appear surprising at first glance, but are actually in line with previous studies from India. In a previous Indian series of patients with amoebic liver abscess, colonic involvement was seen in 58% patients.12 Only 7% of patients had diarrhea and bleeding at presentation. The patients who had diarrhea had large confluent colonic ulcers. In another series of ALA, 77.5% patients had synchronous colonic involvement.13 Caecum was the most commonly affected site (70%) with colonic involvement seen more commonly in patients with multiple abscesses. Small ulcerations were seen in three-fourths of patients, while large ulcerations (>3 cm) were seen in half of them. Only a quarter of the patients in this study had diarrhea at presentation, and only 5% presented with jaundice. In another series by Misra et al.,14 colonic lesions were seen in 55%. However, patients who presented with diarrhea or had history of diarrhea in preceding 2 months (28%) had more propensity for colonic lesions (90%). Also large left sided ulcers were commonly seen in elderly and those with diarrhea as presenting symptom.

The rates of synchronicity remained similar in different series. In the present series, there was unusually high prevalence of patients with jaundice (75% in patients with synchronous colonic involvement), patients with intermittent bleeding per rectum and patients needing endotherapy (24/28 patients with colonic lesions). This suggests that sicker patients were included due to a referral bias to a tertiary hepatobiliary centre.

Treatment for the patients with invasive amoebiasis include use of metronidazole with a luminal amoebicide like diloxanide furate or paromomycin to eradicate Entamoeba cysts.15 The clinical implication of concomitant colonic infection would be to ensure that the cysts are eradicated in these patients to prevent further spread.

Therapeutic options for ALA range

¹Professor and Head, ²Assistant Professor, Department of Gastroenterology, Seth G.S Medical College and K.E.M Hospital Mumbai, Maharashtra
from simple pharmacotherapy to use of interventions like aspiration or catheter placement. In a previous study of 60 patients, 82% were managed conservatively and 18% needed intervention in form of aspiration and catheter placement. Larger size of abscess with deranged liver functions were predictive of need for intervention. Patients who underwent intervention had a longer stay at the hospital. On post hoc analysis, a size of >7.7 cm predicted need for intervention. Premkumar et al reported need for aspiration or catheter placement in 53% patients with concurrent colonic lesions and 41% patients without concurrent lesions.

In patients with ALA with amoebic colitis, management has remained the same over the last few decades. It is the researcher who continues to treat ALA with the same drugs and protocols used over the last few decades. It is the researcher who determines the strategy for prevention, including development of vaccines for amoebiasis.

In the colon, trophozoites of *E. histolytica* often reside together with resident microbial flora. In patients with diarrhea and amoebic abscess, Rani et al reported a reduction in *Lactobacillus* in patients with colonic infection. Also, *Bacteroides* and *Peptostreptococcus* were detected in ALA pus samples. They suggested that bacterial flora provides anaerobic conditions or low redox potential beneficial for amoebic growth. The microbiome in the colon may be altered by many causes, including alcohol and steroids; whether the increased risk of ALA in these patients can be explained by a change in microbiome is conjectural.

In conclusion, the clinician will continue to treat ALA with the same drugs and protocols used over the last few decades. It is the researcher who remains intrigued. In the near future we may find strategies for prevention, including development of vaccines for amoebiasis.

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Clinical and Endoscopic Management of Synchronous Amoebic Liver Abscess and Bleeding Colonic Ulcers

Shivani Dudha1, Madhumita Premkumar2, Devaraja Devurgowda2, Anand Kulkarni2, Yogendra Kumar Joshi3

Abstract
Background. Intestinal amebiasis is endemic in India, with myriad clinical presentations. The liver is the most common extra-intestinal organ to be involved in invasive amoebiasis up to 37% of cases. Synchronous presentation of hepatic and intestinal disease is unusual, and presentation as acute gastrointestinal bleed, or amoeboma even more atypical.

Goals: We aimed to assess the frequency of synchronous hepatic and colonic amebiasis and the efficacy of endoscopic management of colonic bleeding.

Results: We screened 52 consecutive patients with amebic liver abscess for synchronous intestinal amoebiasis and report the clinical course of 28 patients (mean age 48.3 years, all male) with amoebic liver abscesses (ALA), (mean size, 7.2 ± 2.8 cm) who presented to us with lower gastrointestinal bleed requiring endotherapy. Patients with synchronous infection had higher bilirubin, liver enzymes and prothrombin time. Most needed percutaneous drainage of the liver abscess, and had prolonged hospital stay. They had ileocaecal ulcers with active bleeding; ulcer with adherent clot in 10(50%), and visible vessel in 8(37.5%), or active ooze in 4(12.5%). One patient had an ulcerated rectal mass, which appeared malignant on endoscopy, which was later found to be an amoeboma on microscopy. Hemostasis was achieved with dilute epinephrine injection, one patient required argon plasma coagulation, and 4 subjects required haemoclip placement at the site to control ooze from a visible vessel.

Conclusion: Synchronous hepatic and intestinal amoebiasis is not uncommon, and often requires endoscopic haemostasis in case of gastrointestinal bleeding due to colonic disease. We report the successful endoscopic control of bleeding amoebic ulcers in all 24 patients.

Introduction
Intestinal amebiasis is endemic in India, but has been reported worldwide.1 The liver is the most common extra-intestinal organ to be involved in invasive amoebiasis up to 37% of cases.2,3 Conversely, two studies from India reported that colonic ulcers have been associated with the liver abscess, even in asymptomatic subjects in 55% of patients with ALA.4,5 These ulcers are more common in patients with both active or those with resolving or quiescent diarrhoea.6 Formation of an amoeboma has been reported in only about 1.5% of all cases.6 Although there have been recent reports dealing with the problem of bleeding in amoebic ulcers, the synchronous presentation of complicated liver abscesses and colonic bleeding is rare. An amoeboma is a rare complication of amoebic colitis, which presents as a mass or growth on colonoscopy.7 On histology, it is seen as a mass of granulation tissue in the bowel wall with peripheral fibrosis with a mixed inflammatory infiltrate secondary to chronic amoebic infection.8 The initial presentations are usually obstruction and gastrointestinal bleeding. The most common sites are the ascending colon and the caecum, followed by the sigmoido-rectum.9,10 In view of better availability of diagnostic facilities like ultrasonography, an increasing number of patients are being diagnosed early and found to have synchronous intestinal and liver amoebiasis.11

Patients and Methods
We screened consecutive patients with liver abscess who presented at the out-patient hepatology clinic at the Institute of Liver and Biliary Sciences (ILBS) between July 2016 and January 2017, for evidence of synchronous intestinal amebiasis. All patients were enrolled with written informed consent for this observational study in accordance with the Declaration of Helsinki, and approval was taken from the Institutional Ethics Committee. The diagnosis of amoebic liver abscess was determined on the basis of the clinical presentation with fever, right upper abdominal pain, tender hepatomegaly, with typical imaging findings of a single or multiple hypoechoic lesion(s) in the liver and antiamebic IgG titre >1: 160 in serum using immunofluorescent assay. They underwent ultrasound examination of the liver and basic blood investigations including tests like complete blood count, coagulation profile, liver function tests, and serologies for amoebiasis and echinococcosis, iron profile, serum ferritin, and other relevant tests. All patients underwent a colonoscopic examination with targeted biopsies for histopathological examination. In patients with large liver abscesses with impending rupture, interventional radiology opinion was taken regarding the need for drainage and percutaneous drains would be
Table 1: Comparison between synchronous hepatic and intestinal amoebiasis patients and the control group with amebic liver abscess alone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case: Synchronous Liver + Colonic Disease (N=28)</th>
<th>Control: Liver abscess alone (N=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.3 ± 4.2</td>
<td>46.5 ± 13.7</td>
<td>0.498</td>
</tr>
<tr>
<td>Males</td>
<td>100%</td>
<td>95.8%</td>
<td>0.554</td>
</tr>
<tr>
<td>Haemoglobin g/l</td>
<td>8.5 ± 2.8</td>
<td>10.4 ± 2.2</td>
<td>0.032*</td>
</tr>
<tr>
<td>Total leucocyte count x10⁹/l</td>
<td>17.8 ± 4.8</td>
<td>12.5 ± 7.7</td>
<td>0.078</td>
</tr>
<tr>
<td>Platelet count x10⁹/l</td>
<td>172.5 ± 78.3</td>
<td>439.3 ± 78.6</td>
<td>0.044*</td>
</tr>
<tr>
<td>Total bilirubin mg/dl</td>
<td>7.1 ± 5.6</td>
<td>3.7 ± 6.6</td>
<td>0.041*</td>
</tr>
<tr>
<td>Aspartate transaminase (AST; IU/l)</td>
<td>149.7 ± 73.4</td>
<td>121.1 ± 42.3</td>
<td>0.006*</td>
</tr>
<tr>
<td>Alanine transaminase (ALT; IU/l)</td>
<td>96 ± 25.5</td>
<td>43.3 ± 23.6</td>
<td>0.036*</td>
</tr>
<tr>
<td>Alkaline phosphatase (SAP; IU/l)</td>
<td>326.8 ± 54.6</td>
<td>233 ± 59.1</td>
<td>0.074</td>
</tr>
<tr>
<td>INR</td>
<td>1.8 ± 0.34</td>
<td>1.36 ± 0.69</td>
<td>0.546</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>1.9 ± 0.69</td>
<td>2.12 ± 0.54</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.89 ± 0.9</td>
<td>1.2 ± 0.48</td>
<td>0.229</td>
</tr>
<tr>
<td>Need for percutaneous drainage (n,%)</td>
<td>15 (53.3%)</td>
<td>10 (41.6%)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>9.6 ± 2.6 days</td>
<td>2.4 ± 2.7 days</td>
<td>0.076</td>
</tr>
<tr>
<td>Shock (n,%)</td>
<td>5 (17.8%)</td>
<td>0</td>
<td>0.036</td>
</tr>
<tr>
<td>Acute kidney injury (n,%)</td>
<td>4 (14.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SOFA score</td>
<td>3.9 ± 3.6</td>
<td>2.1 ± 1.4</td>
<td>0.078</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>12.8 ± 4.3</td>
<td>5.4 ± 3.6</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Abbreviations: SOFA, sequential organ failure score; APACHE II, acute physiology and chronic health evaluation score; INR, international normalized ratio.

Statistical analysis

We used SPSS v.12 by IBM for Windows to perform all of the statistical calculations. For each variable, we calculated the normality, means and standard deviations. The Student’s t-test was used to compare the two groups, with normal distribution. The Wilcoxon-rank sum test was applied for data with a non normal distribution. Results were considered significant if the P value <0.05.

Results

We report a series of 52 consecutive patients with amoebic liver abscess (ALA), of which 28 male patients had concomitant intestinal disease, and 24 had ALA alone. Thus synchronous disease was noted in up to 53.8% of all patients. Twenty (71.4%) of patients with synchronous amoebiasis had large ileocecal ulcers, which resulted in intermittent fresh bleeding per rectum in 16 (80.0%), requiring transfusion and also endoscopic intervention. One patient had an ulcerated rectal mass, which appeared malignant on endoscopy, which was later found to be an amoeboma on histopathological examination. In addition, six patients had sigmoidorectal ulcers, which also presented with fresh bleeding per rectum. The mean age of these patients was 48.3 ± 4.2 years (range 24 to 48 years). These 20 patients presented with active bleeding as the primary symptom and were incidentally found to have liver abscesses. Conversely, 8 patients presented with a liver abscess and severe anemia, and on questioning admitted to fresh bleeding per rectum. As demonstrated in Table 1, these patients had higher AST, ALT and bilirubin as compared with liver abscess alone. They also had a tendency to develop acute kidney injury due to volume depletion, increased transfusion requirements and electrolyte imbalances. All of them were found to have ileocecal ulcers with active bleeding; ulcer with adherent clot in 10 (50%), and visible vessel in 8 (37.5%), or active ooze in 4 (12.5%). All 28 patients with synchronous hepatic and intestinal amoebiasis reported fever, nausea, and weight loss, and significant alcohol intake, with only one patient noting diarrhoea in the last three months. Contrary to conventional teaching, we noted jaundice in 21 (75%) subjects suggesting severe disease.

Investigations

Laboratory investigations revealed anemia (75%), leukocytosis (100%), raised creatinine (50%), hypoalbuminaemia (100%) and mild elevation of liver enzymes (75%). Ultrasound findings showed a single liver abscess in 10 (35.7%) patients, and multiple abscesses in the other 18 (64.2%) (Figure 1). Ten patients also had peri-hepatic fluid, and pleural effusion (33.3%) on the ultrasound. Doppler ultrasound revealed an eccentric right hepatic vein thrombus in 6 (21.4%) subjects but no evidence of hepatic vein outflow tract obstruction was noted. The mean size of the largest abscess was 7.2 ± 2.8 cm. Contained rupture was seen in 4 (12.5%) patients only. Computed tomography (CT) scan confirmed the findings on ultrasound. In the typical case, arterial-phase contrast-enhanced CT scan showed a hypo-attenuating lesion with enhancing thickened walls due to hyperaemia (the double target sign) (Figure 2). Stool microscopy was positive in 10 (35.7%) for trophozoites or cysts of E histolytica. Serology was positive in all 28 subjects. When these subjects developed bleeding per rectum, all were noted to have fresh blood mixed with stools with passage of mucus. Five patients developed hemodynamic instability secondary to the colonic bleed, and required transient ionotropic support and blood transfusion with packed red blood cells. These 2 patients also had a prolonged prothrombin time and required thromboelastography based coagulopathy correction with fresh frozen plasma and cryoprecipitate. Percutaneous aspiration was done in 15 (53.5) subjects, and percutaneous drains were placed using ultrasound guidance, for 14 patients with multiple abscesses, which showed the characteristic anchovy sauce appearance, but did not reveal any active trophozoites. We cultured Klebsiella pneumoniae and E coli from the pus aspirate in 2 patients each as secondary infections.
In contrast, the patients who had only hepatic amoebiasis, had a much more favourable course requiring single time aspiration in 10 cases only. The sequential organ failure assessment score, (SOFA; 3.9 ± 3.6 vs. 2.1 ± 1.4, p=0.07), and the Acute Physiology and Chronic Health Evaluation (APACHE II; 12.8 ± 4.3 vs. 5.4 ± 3.6, p=0.046) were higher in those with synchronous disease than those with ALA alone. Up to 17.8% and 14.2 % of patients with synchronous amebic liver and intestinal involvement had acute kidney injury and shock respectively, reflecting systemic sepsis. Three patients who presented with shock met criteria for toxic colitis, but were managed successfully with medical treatment or drainage of the liver abscess alone.

**Endoscopic and pathological evaluation**

On colonoscopy, ulcers were noted in the ileoecal area in 21 patients and sigmoido-rectal area in 3 patients. The ileal ulcers were serpiginous, with distinct raised, thickened, often undermined edges and erythematous indurated margins, haemopurulent exudates, and necrotic slough. Four had an adherent clot, which on washing revealed a visible vessel in the base of the ulcer. Active bleeding was noted in 18 patients, which was controlled initially with dilute epinephrine injection (1:1000). In cases with a visible vessel, we placed haemoclips at the site to control ooze (Figure 3). For patients with ooze from the ulcer margins, with used argon plasma coagulation (APC) to control the bleed. Sometimes two sessions were required to control bleeding, but all were managed successfully by endoscopic therapy alone. One patient had sigmoidorectal ulcers, which had ooze from the ulcer margins, and underwent a single session of APC to control the bleeding. As mentioned earlier, one patient had a large ulceroproliferative growth in the rectum with friable overlying mucosa, and superficial bleeding which appeared to be a malignant lesion on colonoscopic evaluation (Figure 4). The mass was biopsied and sections showed a base formed by fibrin and few degenerating cells. Beneath it there was granulation tissue composed of few blood vessels and mild inflammation. A few trophozoites of *E histolytica* were observed in the ulcer base, and showed haemophagocytosis

**Differential Diagnosis**

- Tuberculosis
- Inflammatory bowel disease
- Colonic carcinoma with liver metastases.
- Pyogenic liver abscess
- Infected hydatid cyst
Treatment

All subjects received 2 weeks of oral or intravenous metronidazole in a dose of 2.4 gm per day in 3 divided doses. In addition, iv ceftriaxone or cefepime in a dose of 4 gm per day in two divided doses were given for ten days, for treatment of secondary infections as all the patients presented in a toxic state with complicated abscesses. The rectal mass due to the amoeboma disappeared after treatment with metronidazole for 2 weeks. Repeat colonoscopy did not reveal any abnormality in the 28 patients with ileocaecal ulcers and only residual erythema in the patient with the rectal amoeboma. Aspiration improved symptoms like fever, pain and breathlessness, but did not shorten the duration of hospital stay or duration of antibiotic therapy. The ALA resolved completely in all 28 cases. Colonic ulcer bleeds were controlled endoscopically, and a repeat colonoscopy 3 months hence showed a complete resolution of the ulcers (Figure 5).

Discussion

It is generally considered that amoeboma formation occurs due to untreated or partially treated amoebic colitis and occurs in patients with chronic persistent infection. However, in the present report, only one patient had a prior history of symptoms or had received anti-amoebic treatment in the past. Moreover, all of them had evidence of ALA at the time when they were found to have colonic ulcers, suggesting that amoeboma formation can occur even in the acute phase of infection with simultaneous liver and bowel inflammation. Nevertheless, up to 50% of patients have been found to exhibit colonic ulceration on colonoscopy. Jaundice is noted in just 24% cases, as hepatic function remains largely unaffected in the majority of cases with ALA. Signs of liver cell failure such as jaundice, hypoalbuminemia and encephalopathy are caused by loss of viable hepatic parenchyma due to necrosis by the amoebae, and therefore are only seen in patients with large abscess volume or multiple abscesses.

Radiological imaging in amebiasis

On ultrasonography, an ALA is visualised as a a focal hepatic lesion, which is single in 60% of cases and is most commonly located in the posterior superior part of the right lobe of the liver, classically involving segment VIII of the liver. The abscess is usually hypoechoic as compared with the normal liver parenchyma with fuzzy margins. In the center of the ALA, hyperechoic content may be seen. After completion of treatment with metronidazole or related compounds, the lesion tends to become more hypoechoic, and the margins become clearer due to walling off of the inflammation. Computed tomographic (CT) findings of Caecal amoeboma with and other colonic presentations has also been described as a mimicker of colonic malignancy. The ileocaecal valve is classically indurated with involvement of the mesentry and enlarged loco regional lymph nodes in the pericolonic area. The differential diagnoses for this clinical scenario include tuberculosis, lymphoma, actinomycosis, inflammatory bowel disease or even colonic cancer. Therefore a diagnosis of ameboma can only be one of exclusion, after eliminating more sinister diseases on histological examination of multiple biopsies obtained during colonoscopy. In a recent series, Misra et al reported that 55% of patients with ALA had colonic ulcers, including 90% of cases with and 41% in cases without diarrhoea at presentation. Although in the present series, we encountered a bleeding rectal amoeboma, the more common site for this lesion is the caecum. The frequency of colonic ulcers is clearly higher in patients with active diarrhea at presentation, as this would imply concurrent infection in the liver and intestine with shedding of amoebae (trophozoite or cyst forms) in the stools. Dysentery is rare in such cases, and the patients may well be asymptomatic cyst passers. In a meta-analysis of 310 patients with ALA, needle aspiration + metronidazole versus drug therapy alone produced similar benefit. Therefore there is little evidence to support or refute the practice of aspiration in order to hasten clinical recovery. This has to be done in cases with severe progressive or high risk disease, such as a subcapsular location with possibility of pericardial or peritoneal rupture, large left lobe abscess, secondary sepsis or in the case of non response to drugs alone. Risk factors for mortality include volume of abscess > 500ml, and signs of liver cell failure like encephalopathy, deepening jaundice (serum bilirubin >3.5 mg/dl) or hypoalbuminemia (serum albumin <2 gm/dl).

Endoscopic and intervention radiological management of bleeding colonic ulcers

Endoscopic management of bleeding colonic ulcers is tricky as the exact site may be difficult to localize in the presence of clots and slough. The armamentarium of endoscopic techniques include, epinephrine injection (1:10,000 dilution), application of haemoclips, heat cautery, and argon plasma coagulation (APC), alone or in combination. Hemostatic clip placement offers the advantage of less injury to the mucosa and adjacent tissues compared to coagulation therapy, but in case of active bleeding and no visible vessel, APC may help provide superficial hemostasis. If an arterial source is suspected, urgent angiography and coil embolization is indicated to control massive bleeding, as this is difficult to control endoscopically. The feeder vessel is identified on computed tomographic angiography or digital subtraction angiography as an arterial blush at the site of the bleed. The vessel is selectively cannulated and microcoils or gelooam are deployed to embolize the vessel. Severe lower gastrointestinal bleed is defined as:

- Continued bleeding within the first 24 hours of hospitalization,
- Transfusion requirement of at least 2 units of packed red cells
- Decrease in the haematocrit value of 20% or more
- Recurrent bleeding after 24 hours of stability
- Need for multiple blood transfusion to maintain hemoglobin level despite adequate endotherapy

Toxic colitis is a rare and severe complication. It is defined by (1) radiographic evidence of colonic dilatation; (2) Three or more of the following clinical findings: fever (>38.6°C), tachycardia (>100 beats/min), leukocytosis (>10.5 × 10^9 cells/µL) or anaemia; and (3) any of the following symptoms: dehydration, encephalopathy, electrolyte abnormalities, or refractory shock.

In refractory cases emergency hemicolectomy is still necessary, but the procedure still has high mortality.
risk. The current indications for emergency surgery include:
- A poor response to medical treatment with overwhelming sepsis
- Perforation of the colonic ulcers
- Intra-abdominal abscess or collection not responding to catheter drainage, and
- Presence of peritonitis

Usually, the clinical prognosis for amoebic toxic colitis is dismal with a mortality rate of nearly 40 to 70% in various reported series. Ishida et al reported that conservative surgery (e.g. colostomy or ileostomy without resection) leads to a mortality rate of around 80%, while radical surgery (e.g. hemicolectomy or total colectomy) reduces the mortality rate to 55.

**Conclusion**

The clinical presentation of amoebiasis is varied, and remains a clinically conundrum in the present era. The synchronous presentation of amoebic liver abscess and intestinal disease has been described in our series with emphasis on medical treatment with timely antibiotics, effective radiological intervention, and most importantly judicious endoscopic management of bleeding in colonic disease to avert the need for emergency surgery. Thus we are able to report excellent results even in what would be considered fulminant colitis. In our patients, the most common manifestations were fever, jaundice, diarrhea or hematochezia. Evaluation reveals synchronous hepatic and intestinal disease in 53% of patients with amebiasis.

**Take home message**

- There are four clinical forms of invasive intestinal amoebiasis, all of which are generally acute: dysentery or diarrhoea, fulminant colitis, and localised proliferative growth known as ameboma of the colon.
- Synchronous amebic liver abscess and colonic ulcers are more common than reported, as these are frequently asymptomatic.
- Endoscopic management of bleeding colonic ulcers is challenging and requires a combination of techniques such as epinephrine injection, application of haemoclips, heat cautery, or argon plasma coagulation (APC).
- In case of endoscopic failure, microcoil embolisation of the feeding vessel or even emergency surgery is necessary.

**References**

Trichosporon–Blood Stream Infection

Meera Challapilla¹, Kinjal Patel²*, Bhargav Patel³, Rajeev Soman⁴, Camilla Rodrigues⁵, Anjali Shetty⁶

Abstract

Aim: Trichosporon species are the major emerging opportunistic pathogen in immunocompromised patients. Its diverse refractoriness to conventional antifungal drugs and association with high mortality rate is worrisome. The present study aims to determine the risk factors, treatment outcome and antifungal susceptibility pattern of Trichosporon species in blood stream infections.

Material and Methods: All patients with blood culture positive for Trichosporon species from January 2012 to August 2016 at PD Hinduja National Hospital and research centre were evaluated retrospectively. Species identification and antifungal susceptibility by broth microdilution method for various drugs was determined using Vitek2 compact automated system.

Results: 12 patients were found to have Trichosporon blood stream infection. 9 isolates that were speciated all were T. asahii. All patients had central venous catheter and received prior antibiotics. Overall mortality rate was 50%.

Conclusion: Higher mortality was associated with central venous catheter and voriconazole should be used as drug of choice for treatment. Identification of Trichosporon species along with its sensitivity and proper treatment of patients is of utmost importance.

Introduction

Trichosporon species are known to be inhabitants of soil and may colonize human skin, upper respiratory tract and gastrointestinal tract.¹ Over the past few decades, Trichosporon species have emerged as an important opportunistic pathogen especially in immunocompromised patients.²

Previously, all pathogenic members of the genus Trichosporon were referred as a single species, T. beigelli.³ Biochemical and morphologic differences within the genus had led to new nomenclature of T. beigelli into 9 distinct species, amongst them Trichosporon asahii is the most common cause of disseminated disease.⁴ Phenotypic identification of Trichosporon species usually gives very inconsistent results, so molecular methods are required for accurate identification, but they are still expensive and not suitable for most laboratories.⁵,⁶

In the past, amphotericin B was recommended for treatment but response was poor and failure rate was high. Even MICs of echinocandins are very high and multiple incidences of breakthrough infections have been reported. Trichosporon species are usually susceptible to azoles thus, treatment should be done using one of these azoles.⁷,⁸ Considering the diverse refractoriness to conventional antifungal drugs and association with high mortality rate, present retrospective study was conducted to determine the risk factors, treatment outcome and antifungal susceptibility pattern of Trichosporon species in blood stream infections.

Material and Methods

All patients with blood culture positive for Trichosporon species from January 2012 to August 2016 at PD Hinduja National Hospital and research centre were evaluated retrospectively. Medical records of all patients were reviewed. According to the consensus statement of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group of the National Institute of Allergy and Infectious Diseases, patients that met the criteria for proven invasive fungal infections were taken.⁹ Risk factors, treatment regimens and outcome of each patient were recorded.

Trichosporon species were identified by phenotypic method. An automated Vitek2 compact system was used to identify them up to species level and for antifungal susceptibility testing. MICs of amphotericin B (AMB), 5 flucytosine, fluconazole (FLU), itraconazole (ITR) and voriconazole (VOR) were determined using broth microdilution method for antifungal susceptibility testing of yeasts described in the Clinical Laboratory and Standards Institute (CLSI) M27-S4, Volume 32.¹⁰ Candida albicans ATCC 14053, Candida parapsilosis ATCC 22019, and Candida krusei ATCC 6258 were used as quality-control strains.

Results

Total 12 patients were found to have Trichosporon blood stream infection. 9 were T. asahii and 3 were not speciated. All of these isolates were primarily grown on Sabouraud’s Dextrose Agar that showed dry, wrinkled cream coloured colonies (Figure 1). Lactophenol Cotton Blue (LCB) mount showed septate hyphae with arthroconidia formation along with lateral blastoconidia (Figure 2). These isolates were further confirmed by positive urease test (Figure 3). Clinical and microbiological data of 12 patients are summarized in Table 1. All 12 patients had central venous catheter
and received prior antibiotics. Amongst them, 8(66%) patients were admitted in ICU and 6(50%) patients had CKD and were on maintenance hemodialysis. Overall mortality rate was 50%. The MIC values of *Trichosporon* isolates are shown in Table 2.

**Discussion**

Most common risk factors for *Trichosporon* spp. are acute leukaemia, neutropenia, on chemotherapy or high doses of corticosteroids, solid tumors, transplants, peritoneal dialysis and human immunodeficiency virus. Apart from host factors, previous or current use of antibiotics and use of central venous catheter (CVC) are also predisposing factors for trichosporonosis. In the present study, out of 12, 6(50%) were on maintenance hemodialysis due to chronic kidney disease and all (100%) the patients had central venous catheters.

Previous studies showed that voriconazole and posaconazole were the best *in vitro* antifungal drugs. However, MICs were higher for Amphotericin B. Even echinocandins are not recommended as they have little or no activity against *Trichosporon* spp.

Breakthrough *Trichosporon* infections have been reported in patients treated with echinocandins. ESCMID guidelines recommends voriconazole as the preferred agent because it displays good in vitro activity. In the present study, according to the MIC values observed, voriconazole should be used as treatment of choice. But, literature showed that despite appropriate treatment with antifungals, outcome was always poor and failure rate was very high. In the present study too, mortality rate was 50%.

The Infectious Diseases Society of America (IDSA) guidelines recommends

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**Table 1: Clinical and microbiological data of patients that grew *Trichosporon* spp. from blood culture**

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Current diagnosis</th>
<th>ICU stay</th>
<th>CVC/HD catheter</th>
<th>Bacteremia</th>
<th><em>Trichosporon</em> spp</th>
<th>Antifungal drug given</th>
<th>Catheter removal</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>69/M</td>
<td>Liver cirrhosis, DM</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>T. spp</td>
<td>Fluconazole, Anidulafungin, Voriconazole</td>
<td>Yes</td>
<td>Expired</td>
</tr>
<tr>
<td>54/F</td>
<td>CKD, on MHD</td>
<td>Yes</td>
<td>Yes</td>
<td>S. maltophila, P. aeruginosa</td>
<td>T. spp</td>
<td>Voriconazole</td>
<td>Yes</td>
<td>Discharged</td>
</tr>
<tr>
<td>34/M</td>
<td>Chronic pancreatitis</td>
<td>Yes</td>
<td>Yes</td>
<td>E. agglomerans</td>
<td>T. asahii</td>
<td>Fluconazole</td>
<td>Yes</td>
<td>Expired</td>
</tr>
<tr>
<td>54/F</td>
<td>CKD, on MHD</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>T. spp</td>
<td>Not received</td>
<td>Not done</td>
<td>Discharged</td>
</tr>
<tr>
<td>63/F</td>
<td>CKD, on MHD, ESRD</td>
<td>Yes</td>
<td>Yes</td>
<td>S. maltophila</td>
<td>T. asahii</td>
<td>Voriconazole, Fluconazole</td>
<td>Yes</td>
<td>Expired</td>
</tr>
<tr>
<td>76/M</td>
<td>CKD, on MHD</td>
<td>No</td>
<td>Yes</td>
<td>E. coli</td>
<td>T. asahii</td>
<td>Not received</td>
<td>Yes</td>
<td>Discharged</td>
</tr>
<tr>
<td>12/F</td>
<td>Osteosarcoma with chickenpox</td>
<td>Yes</td>
<td>Yes</td>
<td>Gram positive cocci</td>
<td>T. asahii</td>
<td>Fluconazole</td>
<td>Not done</td>
<td>Discharged</td>
</tr>
<tr>
<td>85/M</td>
<td>DM, TB meningitis, Lt. pyelonephritis</td>
<td>Yes</td>
<td>Yes</td>
<td>P. aeruginosa</td>
<td>T. asahii</td>
<td>Voriconazole</td>
<td>Yes</td>
<td>Expired</td>
</tr>
<tr>
<td>91/F</td>
<td>CKD, not on MHD, TKR, Fracture humerus</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>T. asahii</td>
<td>Fluconazole</td>
<td>Yes</td>
<td>Discharged</td>
</tr>
<tr>
<td>64/M</td>
<td>Fracture supracondylar humerus</td>
<td>Yes</td>
<td>Yes</td>
<td>Enterobacter, Klebsiella</td>
<td>T. asahii</td>
<td>Fluconazole, Anidulafungin, Caspofungin</td>
<td>Not done</td>
<td>Expired</td>
</tr>
<tr>
<td>66/M</td>
<td>Myelodysplastic syndrome</td>
<td>Yes</td>
<td>Yes</td>
<td>CONS</td>
<td>T. asahii</td>
<td>Fluconazole, Voriconazole</td>
<td>Yes</td>
<td>Discharged</td>
</tr>
</tbody>
</table>

**Table 2: Antifungal susceptibility pattern of *Trichosporon* species by microbroth dilution method**

<table>
<thead>
<tr>
<th>MICs*</th>
<th>pt 1</th>
<th>pt 2**</th>
<th>pt 3</th>
<th>pt 4**</th>
<th>pt 5</th>
<th>pt 6**</th>
<th>pt 7</th>
<th>pt 8**</th>
<th>pt 9</th>
<th>pt 10</th>
<th>pt 11</th>
<th>pt 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FC</td>
<td>≤ 4</td>
<td>-</td>
<td>&lt; 4</td>
<td>-</td>
<td>&lt; 4</td>
<td>-</td>
<td>8</td>
<td>-</td>
<td>16</td>
<td>&lt; 1</td>
<td>2</td>
<td>≤ 1</td>
</tr>
<tr>
<td>AMB</td>
<td>0.5</td>
<td>-</td>
<td>&lt; 5</td>
<td>-</td>
<td>&lt; 5</td>
<td>-</td>
<td>≥ 16</td>
<td>-</td>
<td>&lt; 5</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>FLU</td>
<td>1</td>
<td>32</td>
<td>-</td>
<td>2</td>
<td>≥ 64</td>
<td>-</td>
<td>16</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ITR</td>
<td>0.125</td>
<td>-</td>
<td>0.25</td>
<td>-</td>
<td>0.25</td>
<td>-</td>
<td>-</td>
<td>&lt; 0.12</td>
<td>&lt; 0.12</td>
<td>0.12</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Minimum Inhibitory Concentration of 5FC- 5 Fluycytosine, AMB-Amphotericin B, FLU-Fluconazole, ITR-Itraconazole, VOR-Voriconazole; **Antifungal susceptibility testing not done.
that, CVC should be removed in all patients with a CRBSI caused by Candida species.\textsuperscript{18} Raad et al\textsuperscript{19} (2004) and Nucci et al\textsuperscript{20} (2005) also reported that CVC should be removed in all patients with Trichosporon CRBSIs. In the present study, severity of primary condition with CVC should be removed in all patients with invasive medical devices. Higher mortality rate was observed because of its refractoriness to conventional antifungal drugs. Voriconazole should be used as drug of choice for treatment.

**References**


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Clinical Manifestations and Complications of Scrub Typhus: A Hospital-based Study from North Andhra

Nrushen Peesapati1*, Rohit L1, Sunitha S2, Sivaram PV3

Abstract
Aims and Objectives: To describe the diversity of clinical manifestations, laboratory findings and outcome of scrub typhus in hospitalised patients of Tirumala Hospital, Vizianagaram during 2014-2015.

Material and Methods: All the cases of acute febrile illness diagnosed as scrub typhus were analysed. Diagnosis was based on clinical and serological data.

Observations and Results: A total of 60 patients were studied. All of them presented with fever; the other major symptoms were headache, cough, dyspnoea and myalgia. On examination, Eschar was seen in 10 cases and common sites was trunk and axilla. Patients had hepatosplenomegaly, lymphadenopathy and eschar. On investigation elevated SGOT, SGPT with normal or elevated bilirubin levels were the most common findings. Other laboratory findings were thrombocytopenia and deranged renal function tests. Other complications were MODS, ARDS, hypotension and meningoencephalitis. There was a dramatic response to doxycycline in nearly all the patients.

Conclusion: Scrub typhus though prevalent is under-reported in our country. It should be considered as an important differential diagnosis in a febrile patient with thrombocytopenia, deranged liver or renal functions. Early diagnosis and appropriate treatment is rewarding and prevents morbidity and mortality.

Introduction

Scrub typhus is a Rickettsial infection caused by Orientia tsutsugamushi transmitted through bite of chiggers (larval stage of trombiculid mite). In India, epidemics of scrub typhus have been reported from Pondicherry, Goa, and Andhra Pradesh in South India, Uttarakhand, and Southeastern states in North India. Although the disease is endemic in our country, it grossly remains underdiagnosed owing to the nonspecific clinical presentation, lack of access to the specific diagnostic facility, and low index of suspicion by the clinician. It is a common observation that when the diseases of acute febrile illness such as malaria, typhoid, leptospirosis and fever due to localized causes were excluded, a good percentage of cases among the patients with acute febrile illness were ultimately diagnosed to have scrub typhus. Complication associated with scrub typhus is not uncommon and sometimes proved to be fatal. Common complications associated with scrub typhus are acute kidney injury, hepatitis, acute respiratory distress syndrome (ARDS), meningoencephalitis, myocarditis, and septic shock. Though effective treatment in the form of doxycycline and azithromycin is available a large number of patients develop complication with high mortality mostly because of delay in the diagnosis and late initiation of specific treatment. The public health importance of this disease is underestimated because of difficulties with clinical diagnosis and lack of laboratory methods in many areas.

Scrub typhus, though endemic in India; yet is under reported. During the months of November to April of 2014-2015, we encountered a spurt in cases of fever with serology negative for dengue, malaria parasite. On further evaluation, Scrub typhus serology emerged positive in all these patients. Keeping this clinical scenario in mind effort has been made to conduct an observational prospective study on scrub typhus among the adult patients admitted in the department of general medicine and critical care in our hospital.

Aims and Objectives
The aim is to study the different clinical manifestation and complications associated with scrub typhus.

Material and Methods
All patients admitted with acute febrile illness in our hospital were evaluated. Patients were included in the study group whose scrub typhus IgM serology was positive. Detailed history and clinical examination were followed with a meticulous search for the presence of eschar. Basic laboratory evaluation included complete blood count, peripheral blood smear, blood sugar, liver and renal function tests, and chest Xray. Special investigations such as rapid antigen test for malaria parasite, dengue serology (IgM and IgG), Widal test, blood culture, polymerase chain reaction for H1N1, and serology for leptospirosis were done to exclude alternative diagnosis and concurrent infections. Other tests such as cerebrospinal fluid analysis, magnetic resonance imaging brain were performed as indicated.

For the diagnosis of scrub typhus, serological test was performed by Weil–Felix test (PROGEN, Tulip Diagnostics (P) Ltd.) and lateral flow format immunochromatographic test for the detection of O. tsutsugamushi, IgM.
IgG, and Ig antibodies (SD Bioline Tsutsugamushi, Standard Diagnostic, Inc., Korea), which has good sensitivity.

Results and Observation

Total 60 patients were diagnosed to have scrub typhus in the present study. Most of the patients were reported from the month of January to March although the cases were reported throughout the year. As shown in female patients 35(58.3%) are more than male patients 25(41.7%) that include one pregnant woman.

Majority of the patients were belong to age group 11-30 years (41%) and 31-50 years (31%) were younger than 11 yrs. and 10% more than 50yrs. Patients with acute febrile illness were only included in the present study. As shown in (Table 1), the most common presentation was fever (100%) with headache (70%). Other common sign and symptoms (Table 2) on presentation include lymphadenopathy, cough, dyspnea, eschar, altered sensorium, jaundice, hepatomegaly, splenomegaly and oliguria. Distribution of lymphadenopathy was painful in most of the instances mostly in inguinal region. Eschars found were mostly of subcentimeter in size having firm adherent black scab with red margin. Eschars were mostly found in trunk almost all patients and is single (Figure 1). Uncommon presentations in the present study include hemoptyis, epistaxis, rash, and neck rigidity. Others include seizure and cholangitis with cholecystitis in 1 (1.67%) and 1 (1.67%) patient, respectively. Investigation report has been shown in (Table 3). Hemoglobin <11 g/dl was present in 28 (46.6%), leukocytosis in 26 (43.3%), leukopenia in 15 (25%), and platelet count <150,000/cumm in 20 (33.33%) number of patients. Deranged liver function were present in 15(20%) and deranged renal function in 7 (11.6%) of patients respectively associated complications found were hepatitis and acute renal failure others include pancreatitis, ARDS, MODS, and meningoencephalitis as shown in Table 2. Two patients expired with a mortality rate of 3.33% in the present study.

Discussion

Scrub typhus is a wellknown miteborne disease. In Andhra Pradesh, it is less studied though it has on and off outbreaks. In the present study, most of the cases were seen between January and March although cases were reported in other months also. Most of the cases in the present study were involved in outdoor activity, particularly agriculture activities or collecting firewood from the agency.

Patients usually present with fever, headache, malaise, suffused face, lymphadenopathy, and eschar. It is so characteristic for scrub typhus that in the present study, doxycycline was started empirically. In our study, the most common presentation was an acute febrile illness with headache (70%), which is dull aching in character although some other studies reported headache (1-16) in only 14.3% of cases. Lymphadenopathy, usually painful, is a common finding in scrub typhus reported in 13–18% of patients; in the present study, lymphadenopathy was present in 6% of cases. Cervical lymphadenopathy (22.03%) is most common. Although rash was reported in many studies as a common finding, but in our study only one patient (1.69%) had rash on presentation. A necrotic eschar which is considered most useful diagnostic clues for scrub typhus was present in 6 (10%) cases of our study population although it was reported as high as 86.3% in some studies while some studies from India reported of eschar in as less as 5.56% of patients. In the present study, the most common site for eschar was trunk. Hepatomegaly was present in 8.3% of cases and splenomegaly in 8.3% of patients though hepatosplenomegaly was reported to be a very common finding, especially in children.

In contrast to other case series, elevated serum glutamicoxaloacetic transaminase (8.3%) and serum glutamic pyruvic transaminase (8.3%) was present in less number of cases. Raised bilirubin was present in 15 (25%) and raised serum creatinine in 7 (11.6%) of patients. Leukocytosis was noted in 43.3% patients, but leukocytopenia was also present in 25% of patients. Platelet count of <150,000/cumm was present in 33% cases. MODS and meningoencephalitis are the common complications associated with scrub typhus as is the ARDS with high mortality rate. In our study, MODS was present in 8.3%, meningoencephalitis in 3.3%, and ARDS in 6.6% patients although other studies reported meningoencephalitis as a more common complication (26%) and ARDS as...
(11.1%). Pancreatitis and disseminated intravascular coagulopathy (DIC) are uncommon complications with few case reports; however, in the present study, no case of pancreatitis or DIC was reported. The case fatality rate for admitted patients, mortality is expected is hospital based which includes only those who had a high index of suspicion is required. The study highlights the clustering of cases during September to November. The study also shows the response of treatment with doxycycline.

**Conclusion**

The study shows a wide variety of clinical manifestations and complications of scrub typhus, a well-known mite-borne disease in India. Due to the varied presentation and high mortality due to complications, a high index of suspicion is required. The study highlights the clustering of cases during September to November. The study also shows the response of treatment with doxycycline.

**References**


**Table 3: Lab parameters**

<table>
<thead>
<tr>
<th>Investigations</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB &lt;11</td>
<td>28</td>
<td>46.66%</td>
</tr>
<tr>
<td>HB &gt;11</td>
<td>32</td>
<td>53.33%</td>
</tr>
<tr>
<td>Leucocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4000</td>
<td>15</td>
<td>25%</td>
</tr>
<tr>
<td>4000-11000</td>
<td>19</td>
<td>31.66%</td>
</tr>
<tr>
<td>&gt; 11000</td>
<td>26</td>
<td>43.33%</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5000</td>
<td>4</td>
<td>6.66%</td>
</tr>
<tr>
<td>5000-10000</td>
<td>11</td>
<td>18.33%</td>
</tr>
<tr>
<td>&lt; 150000</td>
<td>5</td>
<td>8.33%</td>
</tr>
<tr>
<td>SGOT</td>
<td>5</td>
<td>8.33%</td>
</tr>
<tr>
<td>SGPT</td>
<td>5</td>
<td>8.33%</td>
</tr>
<tr>
<td>ALK</td>
<td>6</td>
<td>10%</td>
</tr>
<tr>
<td>Serum creatinine &gt; 1.0</td>
<td>7</td>
<td>11.66%</td>
</tr>
<tr>
<td>SBT &gt; 1</td>
<td>15</td>
<td>25%</td>
</tr>
<tr>
<td>Elevated ESR</td>
<td>6</td>
<td>10%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>6</td>
<td>10%</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td>16</td>
<td>26.66%</td>
</tr>
<tr>
<td>Polymorphocytosis</td>
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<td>16.66%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9</td>
<td>15%</td>
</tr>
<tr>
<td>Erythropenia &lt;3.8</td>
<td>12</td>
<td>20%</td>
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**Table 4: Duration of stay**

<table>
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<tr>
<th>Days of stay</th>
<th>Recovered</th>
<th>Referred</th>
<th>Ventilatory support</th>
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</thead>
<tbody>
<tr>
<td>&lt; 5 days</td>
<td>41</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>6-10 days</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 days</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 5: Prognosis**

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Recovered</th>
<th>Referred</th>
<th>Ventilatory support</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Obituary**

“Professor JS Bajaj passed away on 8th January, 2019. With that, an era of academic giants at AIIMS is coming to an end. He was an exceptionally gifted scholar and statesman, who sailed academic seas with equal ease in India and abroad. He was among the first to have widespread Global recognition. He was equally adept in internal medicine, diabetes, pathology, anatomy, pharmacology and any other branch of medicine (I remember his impromptu discourse on arthrogryposis multiplex congenita at 10 PM in ward D2). Interestingly he mastered finance and economics in about two weeks time when he joined planning commission, and subsequently engaged in discussion with top economists in India. Once he was giving lecture in Sweden, and his bag (with plastic slides at that time) had not arrived, he gave his oration for 60 minutes on two remaining slides that he had, and received a standing ovation.

I and many other colleagues of mine have been fortunate to be taught by him. I have been mentored by him. I am, what I am today, is largely because of him.

This is my appreciation for a larger than life personality. A taller man who walked among many tall men/women.”

Shashank R Joshi

Endocrinologist, Joshi Clinic, Lilavati Hospital, Apollo Sugar Clinic & Bhatia Hospital
In Hypertension,

Zilarbi™
Azilsartan Medoxomil 40/80 mg Tablets

Drop in BP, as it should be...

In newly diagnosed T2DM patients

Right from the start

Glipsov
Teneligliptin 20 mg Tablets

Morning to...Morning control

In Hypertension & Angina

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

For any medical query, please write to us on emquest@emcure.co.in
To report any adverse event or product complaint, please write to Pv.R&D@emcure.co.in

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Early Clinical Suspicion and Early Use of Doxycycline Reduces Scrub Typhus Associated Complications

Jatinder Mokta¹, Asha Ranjan²³, Kiran Mokta³

Abstract
Background: Scrub typhus has emerged as an important cause of febrile illness in this Himalayan region of the country. However, it is under considered in the differential diagnoses of febrile illnesses and is not treated and thus, patients often land up with complications in this tertiary care hospital.

Methodology: It was a retrospective observational study done in department of Medicine from August 2013 to October 2013. All the patients more than or equal to 18 yrs of age admitted during this period with scrub typhus were analysed and their outcome followed. S. ELISA was used to detect scrub typhus.

Results: Total of 106 patients were observed out of which only 10 patients had received anti scrub antibiotics (doxycycline or azithromycin) prior to admission. Seven patients died (6.6%) and none had received anti scrub antibiotics prior to hospitalisation and presented late with average duration of illness of 9.2 days and had more severe form of complications at presentation. Those patients who had received prior anti scrub treatment had fewer and mild complications and none died among that group.

Conclusion: Doxycycline or azithromycin (pregnancy or in child <8 years) should be included in the initial empirical antimicrobial therapy in febrile patients during tick season to treat scrub typhus. The goal is to begin anti-scrub therapy early to reduce the morbidity and mortality associated with this illness.

Introduction

Recently scrub typhus has emerged as an important cause of febrile illness in this Himalayan region of the country. However, it is under considered in the differential diagnoses of febrile illnesses and is not treated and thus, patients often land up with complications in this tertiary care hospital. It is a mite borne rickettsial disease caused by Orientia tsutsugamushi leading to widespread vasculitis and consequently organ dysfunction. Its early clinical manifestations are nonspecific and are characterized by fever, chills, headache, and myalgia. These are easily overlooked and consequently patients often present with severe complications which otherwise can be prevented with early clinical diagnosis and treatment. Severe complications of scrub typhus reported; includes interstitial pneumonia, acute renal failure, meningoencephalitis, gastrointestinal bleeding, and multiple organ failures. Patients often die because of these complications. During the pre-antibiotic era, the overall mortality was 50%. As the effective antibiotics came, the mortality and morbidity has decreased. For various reasons effective treatment is often delayed, prominent of which is failure to suspect scrub typhus as a cause of febrile illness by the primary care physician. Consequently, patients presents with complications. Therefore, this study was conducted to assess the failure of the primary care doctor to consider scrub typhus as a cause of pyrexia and delay in appropriate treatment as a factor for increased morbidity and mortality among patients with scrub typhus.

Methodology

It was a retrospective observational study done in department of Medicine from August 2013 to October 2013. All the patients more than or equal to 18 yrs of age admitted during this period with scrub typhus were analysed and their outcome followed. Scrub typhus was defined as the patient presenting with fever, myalgias, headache with or without eschar with positive IgM titre against O. tsutsugamushi done by ELISA method. Other causes of acute febrile illness were excluded with appropriate investigations. History and relevant general physical and systemic examination were recorded and complete haemogram, biochemical parameters and relevant radiological investigations were conducted. Complications documented and data was analysed.

Results and Discussion

We analysed total of 106 patients; out of which 64 were females (60.37%) and 42 (39.62%) were males. Maximum number of patients; 56 patients (52.83%) were from Shimla district followed by 20 patients (18.86%) from Mandi and 12 patients (11.3%) from Bilaspur. The epidemiological and clinical observations shown in Table 1.

Mean age of presentation was 39.68 ± 3.12 yrs for females and 42.78 ± 4.23 yrs for males. Maximum number of patients (37.73%) presented in the age 40 to 60yrs; followed by age group 20-40 (36.79%). 60.37% patients were female in our study as females are mostly engaged in farming and other outdoor activities in this tiny hilly state and hence exposed to mites causing scrub typhus. Our demographic profile is similar to studies conducted in other
had received anti scrub antibiotics (doxycycline or azithromycin) and rest 52 patients received some non-specific therapy in the form of cephalosporin, anti-stryptococcal and multi-vitamins. 44 patients did not receive any treatment before presentation at this institution. Out of the total patients; seven died (6.6%) and rest all (93.39%) improved with the in hospital treatment. This mortality rate is similar (7.8%) to studies conducted by Varghese et al,\(^6\) less (12.2%) that that found by Kim et al.\(^6\) Complications rates observed were also high with 67 patients (63.2%) developing hepatic dysfunction with raised bilirubin and aminotransferase, 48 patients (45.28%) developing renal dysfunction and 14 patients requiring renal support, 23 patients (21.69%) having CNS manifestations, 14 patients (13.2%) having shock and 32 patients (30.1%) having either acute respiratory distress syndrome or acute lung injury. These rates of complications were in accordance with other studies.\(^{7,9,11}\)

Seven patients who died none had received anti scrub antibiotics prior to hospitalisation and presented late with average duration of illness of 9.2 days and had more severe form of complications at presentation. Those patients who had received prior anti scrub treatment had fewer and mild complications (hepatic and renal dysfunction) and none died among that group (Table 2). Patients who survived despite not receiving anti scrub treatment before hospitalisation presented early with average duration of illness of 6.8 days and had only mild form of renal, hepatic, nervous system and lung dysfunction (ALI).

**Conclusion**

Scrub typhus is a serious febrile disease in this part of the country with nonspecific symptoms but high mortality and complication rates. Failure to receive doxycycline in early course of disease leads to prolonged disease course, increased complications and mortality and increased expenditure on treatment. Because of unavailability of laboratory facilities in the peripheral health institutions, the diagnosis of scrub typhus should be based on high index of clinical suspicion and careful clinical examination; especially during the rainy season of the year when scrub typhus is rampant. Doxycycline or azithromycin (pregnancy or in child <8 years) should be included in the initial empirical antimicrobial therapy in febrile patients during tick season to treat scrub typhus. The goal is to begin anti-scrub therapy early to reduce the morbidity and mortality associated with this illness. Health education is also of paramount importance to spread awareness among health care providers and public not only about how to prevent and control scrub typhus but also about early use of doxycycline in febrile patients during scrub season to reduce the complications.

**Table 1: Profile of patients**

<table>
<thead>
<tr>
<th>Area</th>
<th>Total (n)</th>
<th>(%)</th>
<th>males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shimla</td>
<td>56 (52.8)</td>
<td>25</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Solan</td>
<td>8 (7.5)</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Mandi</td>
<td>20 (18.9)</td>
<td>4</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Kullu</td>
<td>5 (4.7)</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bilaspur</td>
<td>12 (11.3)</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>5 (4.7)</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>106</td>
<td>42</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Outcome and complications in patients receiving prior doxycycline vs no treatment**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Total Recieved doxycycline</th>
<th>No treatment or doxycycline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>106</td>
<td>96 (90.6%)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>7</td>
<td>7 (6.6%)</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>67</td>
<td>3 (2.8%)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>48</td>
<td>4 (3.7%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>23</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>ARDS/ALI</td>
<td>32</td>
<td>32 (30.1)</td>
</tr>
<tr>
<td>Shock</td>
<td>14</td>
<td>14 (13.2%)</td>
</tr>
</tbody>
</table>

**References**

Effect of Pulmonary Rehabilitation (PR) Programme in patients with Interstitial Lung Disease (ILD)—Indian scenario

Poorvi Devani¹, Nicole Pinto¹, Priyanka Jain², Pralhad Prabhudesai³*, Abha Pandey⁴

Abstract

Introduction: Interstitial Lung diseases (ILD) are group of disorders wherein due to varied etiologies, interstitium goes into progressive inflammation or fibrosis. Although, the awareness has improved but the therapy is still facing challenges. Pulmonary Rehabilitation (PR) is a worthy modality, which not only supports but also imparts evident benefits in these patients.

Material and Methods: The study is a retrospective observational study conducted over a period of 2 years at Pulmonary Rehabilitation center, a private clinic setup on patients with different restrictive lung diseases like interstitial lung diseases, neuromuscular disorders and post-surgical patients. A total of 100 patients were enrolled, out of which 21 patients were lost to follow up. The study population included 34% males and 66 % females with a mean age of 56.3 ± 14.2 years. 24 patients required oxygen support (where SpO2< 90% at baseline). Outcome measures were assessed in these patients at the time of enrollment into the program (0 week) and at the end of the program (8 weeks). Effect of PR programme was then analyzed with appropriate statistical methods.

Results: Overall, statistically significant benefits were noted in 6 Minute walk distance (6MWD), muscle strength, dyspnea and Quality of life with 8 weeks. The mean 6 MWTD was 297.9 meters pre PR, which improved to 359.7 meters at the completion of 8 weeks post PR. Mean difference was 61.8 meters, which was found to be statistically significant (p value<0.001) Improvement in muscle strength of different upper and lower limb muscle groups were noted. Also, significant improvement in comprehensive score of Chronic Respiratory Diseases Questionnaire (CRDQ) scores was documented. Statistically significant improvement was found in the dyspnea, fatigue and emotional components. However, mastery components did not show statistically significant change.

Conclusion: PR has proven to be a very useful modality in the management of restrictive lung diseases, especially with the known limitations of pharmacological options to treat this disabling chronic lung diseases, even with those with evident type I respiratory failure at the beginning.

Introduction

Interstitial lung disease (ILD) is a group of diffuse parenchymal lung disease characterized by varied etiologies, clinical features and radiological appearance, with a rising morbidity and mortality. It is characterized by acute or chronic inflammation of lung parenchyma leading to fibrosis. Under this broad term of ILD we have major contributions from hypersensitivity pneumonitis, Idiopathic Pulmonary Fibrosis(IPF), connective tissue diseases related ILD, Sarcoidosis and many other miscellaneous forms. Interestingly, heterogeneity lies in all the aspects related to ILD. Exercise limitation has been a common point or rather a hallmark of all the varied forms of ILD. Interplay of multiple contributors has been discovered such as gas exchange limitation due to architectural distortion of capillary bed, circulatory limitation, and reduced diffusion capacity due to thickened alveolar capillary membrane or pulmonary capillary bed destruction. Also, peripheral dysfunction adds to the ongoing embarrassment: Thereby, leading to marked oxy hemoglobin desaturation while exercise. This capillary bed destruction in addition to pulmonary vasoconstriction may lead to pulmonary hypertension. All these mentioned factors play role to limit their exercise capacity pushing them into a so called vicious cycle, where the disabled state leads to exercise limitation and exercise limitation in turn leads to deconditioning. Patients with greater degree of interstitial fibrosis in IPF have more severe diffusion limitation at rest and also show greater oxy hemoglobin desaturation during exercise than those patients with less fibrosing ILD patterns like Sarcoidosis or asbestosis. Typically, patients’ present with progressive exertional breathlessness, dry cough and easy fatigability. These symptoms knowingly or unknowingly withdraw them from their daily activities. Despite a growing understanding of this disease, therapeutic modalities to offer are quite disheartening as yet, in terms of survival benefit. From the era of observation to pharmacological tools in terms of corticosteroids, N acetyl cysteine, azathioprine and then anti-fibrogenic agents, the struggle to herald the fibrosis continues. Where pharmacology is still under evolution, non-pharmacological support in form of Pulmonary Rehabilitation (PR) has shown to benefit these patients. The American Thoracic Society (ATS)/ European Respiratory Society (ERS) statement on PR from 2013 defined pulmonary rehabilitation (PR) as a comprehensive intervention based on a

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Received: 10.07.2017; Accepted: 25.09.2018
thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors. PR is recommended in all patients with chronic respiratory disease and there has been ample evidence that shows its benefits in these patients. The evidence of PR has been well consolidated in patients with Chronic Obstructive Pulmonary Disease (COPD). However, for patients with ILD, PR holds a weak recommendation only. PR programme is a wholesome platter where therapy gets individualized as per patients’ capabilities and requirements. In totality, it recruits all the peripheral muscle functioning, enhances endurance of various groups of muscles, helps with coping strategies, breathing techniques and provides with psychological and nutritional support. Thereby, allowing the patients to participate better in their activities around and improving their quality of life. Our study focuses upon the various beneficial aspects of an 8 weeks PR program on patients with ILD.

Methods

Study design

Our study is a retrospective observational study comprising of 100 patients suffering from restrictive lung diseases, who attended the PR programme over duration of 8 weeks, at an outpatient clinic setup over a period of 2 years. Flow of events are shown in Figure 1.

Setting

Prathibha Prabhakar Pulmonary Rehabilitation center, a private outpatient setup at Goregaon, Mumbai

Methodology

A total of 137 patients with restrictive lung disease were referred for pulmonary rehabilitation to Prathibha Prabhakar Pulmonary Rehabilitation Centre over a period of 2 years. Out of these, 100 patients were enrolled into the program. Patients with restrictive lung disease namely nonspecific interstitial lung disease (NSIP), Idiopathic Pulmonary fibrosis (IPF), unclassified interstitial lung disease (U-ILD) and other restrictive lung conditions (structural and post-surgery cases) were included in the study. The diagnosis of restrictive lung diseases, was made based on a complete pulmonary function test (PFT) and high-resolution computed tomography (HRCT) supported with a detailed history. Where possible and indicated, lung biopsy (transbronchial lung biopsy and VATS guided lung biopsy) was performed. A subset of patients also underwent bronchoscopy to rule out infection, as per clinical indications. As a pre requisite to enrollment, all patients underwent a detailed assessment of clinical history, investigation and comorbidity status assessment (diabetes mellitus, hypertension any orthopedic and psychological conditions) by a pulmonologist and by other fraternity physicians where needed. All baseline routine blood investigations along with their cardiac function parameters with an electrocardiogram (ECG) and 2D ECHO were documented. A written informed consent was obtained. The study population included 34% males and 66% females with a mean age of 56.3 ± 14.2 years. Thereafter, all the patients referred for the PR programme were primed about the program in terms of utility, schedule, components and realistic benefits. Outcome measures namely aerobic capacity (6MWT), muscle strength and Quality of life (CRDQ) were assessed in these patients when they enrolled into the program (0 week) and at the end of the program (8 weeks).

Aerobic capacity: 6 minute walk test

The aerobic capacity was evaluated using the 6-minute walk test (6MWT) and the distance (6MWT) was documented. The test was performed according to the American Thoracic Society (ATS) guidelines. The heart rate (HR), blood pressure (BP), oxygen saturation (SpO2), respiratory rate (RR) and rate of perceived exertion (RPE) were assessed pre, post and 3 minutes after the test (10). Patients whose basal SpO2 was less than 90%, and who were on who were on long term oxygen therapy; 6MWT was done with supplemental oxygen. 6MWT walked by the patient was calculated, documented and analyzed.

Muscle Strength

The muscle strength was assessed using the submaximal 10 repetitions maximum (10RM) method. The lung foundation of Australia recommends using the 10 RM method instead of the 1RM method in pulmonary patients to assess muscle strength as there may be concerns regarding joints, ligaments and bone density in many of these patients. In addition, it is a safer method as it avoids unnecessary muscle soreness and injury in an already weak muscle. Upper limb muscles namely biceps, triceps, shoulder flexors, shoulder abductors and lower
limb muscles namely hamstrings and quadriceps were assessed. The strength of these muscles were assessed by repeating the specific muscle action 10 times at a given load with the help of dumbbells and weight cuffs. This strength of the muscle i.e. the maximum load lifted by the patient was documented as the 10 RM of the patient. This weight corresponds to 75% of the muscle’s 1 RM.

Quality of Life

The quality of life was assessed using the chronic respiratory disease questionnaire (CRDQ). It is a validated, reliable test used to measure the effect of the disease on the activities of daily living of the patient. The 4 components assessed were dyspnea, fatigue, emotional aspect and mastery. The assessing therapist interviewed the patients with the questions of the CRDQ. The scores of the individual domains and the total score was calculated and analyzed.

The PR program

Patients were subjected to a structured program, which was individually tailored to each patient according to their level of functional impairment, severity of ILD (e.g. hypoxemia), presence of comorbid disease and any other potential factors that could limit intensity or safety of exercise. Patients mandatorily exercised for 45-60 minutes, thrice a week for 8 weeks. The program comprehensively offered breathing training, exercise training and patient education. Breathing training comprised of breathing techniques (pursed-lipped, diaphragmatic breathing, intercostal and segmental breathing), pacing and energy conservation. Exercise training involved aerobic (level walking, treadmill and stationary bicycle) and resistance training (light weights, resistance bands, and dumbbells). Intensity and duration of PR were gradually increased to build tolerance and confidence with the goal of reaching maximum tolerated workload during each exercise period. Supplemental oxygen was given to maintain minimum oxygen saturation of 90%, in patients whom desaturation was observed at rest and during the 6MWT. Regular educational sessions were conducted aiming at promoting coping strategies, management of infections and exacerbations, dyspnea, use of oxygen, return to activities of daily living, and maintaining and improving physical function. In addition, advice on nutrition was provided by dietician. Patients also received psychosocial support.

Statistical analysis

Data was entered in Microsoft Excel and analyzed using Stata Version 13. For linear variables, mean, medians, standard deviation and Inter Quartile Ranges (IQR) were calculated and for categorical variables, proportions were used. Paired t-test was used to compare mean between two groups (pre-and post-means respectively). Distribution of continuous variables across multiple groups, were assessed using the Kruskal Wallis test. A value of less than 0.05 was considered to be statistically significant.

Results

A total of 137 patients were referred for pulmonary rehabilitation program over a period of 2 years at our center. Of these, 100 patients got enrolled in the study. Study population included 34(34%) males and 66(66%) females, with a mean age of 56.3 ± 14.2 years. Most common diagnosis was Idiopathic Lung Fibrosis (IPF) found in 28(28%) followed by other restrictive lung diseases in 25(25%), hypersensitivity pneumonitis in 20(20%), other patterns of restrictive lung disease in 14(14%) and Non-specific interstitial pneumonitis (NSIP) pattern of ILD in 13(13%). We found that Pulmonary Rehabilitation had beneficial effects on patients, both subjectively and objectively. The end of 8 weeks as depicted in Table no.1. On comparison, patients when performed 6-MWT, the mean 6 MWT was 297.9 meters pre PR, which improved to 359.7 meters at the completion of 8 weeks post PR. Mean difference was 61.8 meters, which was found to be statistically significant (p value<0.001) and more than the Minimal clinically important distance (MCID) value in ILD. In subgroup analysis of patients with IPF, mean 6MWD was 276 meters pre PR, which improved to 335 meters at the end of PR. Thus, a significant gain of 59 meters was evident (Figure 2). In our study, 24 patients were given oxygen support (where SpO2< 90% at baseline) and eventually at the end of 8 weeks 6 were lost to follow up.

Exercising capacity of muscles was analyzed by measuring the muscle strength of both upper limb and lower limb muscles by 10RM method. There was statistically significant improvement in different muscle group namely biceps, triceps, shoulder flexors, shoulder adductors, hamstring and quadriceps group, as depicted in Figure 3 when measured at the end of 8 weeks PR program as compared to that at beginning. Similar results were appreciated in patients with IPF also. Importantly, we studied Quality of life in all the patients with the help of chronic respiratory disease questionnaire (CRDQ). The questionnaire comprises of dyspnea, fatigue, emotional status and mastery. On comparison of parameters pre an post PR, statistically significant improvement was found in 3 variables of CRDQ namely dyspnea, fatigue and emotional status when assessed individually and also in global rating as shown in Figure 4. However, when mastery was analyzed separately, there was improvement perceived clinically but was not statistically significant. Again, similar results were noted in IPF subset as well.

Interestingly, when patients were analyzed depending upon the total duration of their restrictive lung disease, calculated from the time of enrollment to PR program in years, none of the measured variables i.e. 6MWT, aerobic capacity and quality of life, could show statistically significant difference, pre and post PR program as depicted in Table 2. Around 79% of patient could successfully finish 8 weeks of PR program and 21% patients were lost to follow during the study duration, reasons of which were not analyzed as a part of this study.

Discussion

Our study data supported the handful of studies that have been done on effects of PR in ILD patients till date. Improved functional exercise capacity, symptoms and quality of life were clearly demonstrated following a structured outpatient exercise training programme for 8 weeks, using a standard pulmonary rehabilitation training protocol. As in our study, most of the studies evaluated effects of PR in an outpatient setup only.

Pulmonary Rehabilitation is a science, which has evolved over past 40 years till date. It was established as a beneficial modality to aidtherapy
for those struggling with chronic lung diseases. Despite the understanding as to how and why PR could help these patients, the concerns have been the quantum and longevity of benefits. PR was never meant to be the primary therapy for chronic lung disease patients. Instead, the goal had always been to help them attain the highest possible level of independence to pursue ordinary activities of daily living. It was devised as an adjunct to ongoing therapies to alleviate symptoms, optimize the functional capacity of patients and to inculcate coping strategies in them. Majorities of research have happened in the COPD patients. However, PR has been successfully helpful to patients with other diseases as well such as interstitial diseases, cystic fibrosis, bronchiectasis and thoracic-cage abnormalities.

A prospective study done by Huppmann and colleagues over 11 years, including 402 individuals with ILD showed that pulmonary rehabilitation definitely has benefits on patients with ILD. The most common ILD worldwide is Idiopathic Pulmonary Fibrosis (IPF). In the recent management guidelines published in 2011, PR has got a weak recommendation in IPF as well. Point to be understood here is that there has been a moderate quality of evidence for improvement in functional status and patient-oriented outcomes, dilemma still hovers over duration of benefits. These statements do not dilute the favorable impact of PR, but insist on more of research before consolidating the spectrum and extent of benefits of PR in this domain of chronic lung disease.

**6 minute walk test (6 MWT)**

Following 8 weeks of PR programme, we found a significant improvement in 6MWD of 359.7± (76.6) m, which was 20.8% of the baseline value (Figure 5). The mean difference in distance covered pre and post PR was 61.8 meters, which was clearly more than minimal clinically important distance (MCID) in not only ILD but also COPD patients across the world. When IPF patients were analyzed separately, with 8 weeks PR programme 59 m of gain was noted. However, we lack a clear cut off value of MCID in ILD patients as yet but for COPD patients 54 m is accepted as significant. When results were compared among the different groups of restrictive lung disease, we did not observe any significant difference in improvements in 6MWD before and after PR.

Across the world when literature on ILD patients was analyzed, our findings matched with almost all the available work in this area. Holland et al in 2008 observed a mean increase in the 6MWD of 35 m in ILD patients and of 25 m in a subgroup analysis of 34 patients with IPF. Nishiyama et al observed a PR effect of 46 m in 6MWD. In 2009, Ferreira et al reported a mean increase of 61 m in 6MWD in their study of 21 IPF patients. Swigris et al documented an improvement of 61 m in 6MWD in their study of 21 IPF patients.

Our results were in concordance with most of them with some variability in the amount of increment in the distance covered, walked post PR as depicted in table 5. 6 MWT has been taken as a surrogate marker of functional exercising capacity of patients with ILD, which uncovers de compensation when patients are made to walk at their own pace. Improvement

**Table 1: Effect of PR program on patients’ parameters**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre PR Mean ± (SD)</th>
<th>Post PR Mean ± (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWTD</td>
<td>297.9 ± (78.9)</td>
<td>359.7 ± (76.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Muscle Strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps</td>
<td>1.54 (0.71)</td>
<td>2.39 (0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triceps</td>
<td>0.88 (0.47)</td>
<td>1.90 (0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shoulder Flexors</td>
<td>1.32 (0.71)</td>
<td>2.27 (0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shoulder abductors</td>
<td>1.26 (0.68)</td>
<td>2.23 (0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quadriceps</td>
<td>1.41 (0.74)</td>
<td>2.40 (1.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>1.11 (0.56)</td>
<td>2.36 (1.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRDQ Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.02 (1.19)</td>
<td>4.30 (1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.66 (1.03)</td>
<td>4.81 (0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mastery</td>
<td>4.53 (0.85)</td>
<td>4.47 (0.75)</td>
<td>0.57</td>
</tr>
<tr>
<td>Emotional</td>
<td>4.09 (0.93)</td>
<td>4.93 (0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total CRDQ Score</td>
<td>14.27 (2.56)</td>
<td>18.40 (2.44)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 2: Comparison of variables depending upon the duration of diagnosis at the time of initiation of PR program**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Within 1 year of diagnosis</th>
<th>Between 1-5 yrs of diagnosis</th>
<th>More than 5 yrs of diagnosis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>33 (33)</td>
<td>44 (44)</td>
<td>23 (23)</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>6 (18)</td>
<td>11 (25)</td>
<td>4 (17)</td>
<td>0.68</td>
</tr>
<tr>
<td>Outcome measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWTD</td>
<td>64 (48, 104)</td>
<td>56 (32, 96)</td>
<td>56 (24, 80)</td>
<td>0.20</td>
</tr>
<tr>
<td>Muscle Strength</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps</td>
<td>0.5 (0.5, 1)</td>
<td>1 (0.5, 1.25)</td>
<td>0.5 (0.5, 1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Triceps</td>
<td>1 (0.5, 1.5)</td>
<td>1 (0.5, 1)</td>
<td>1 (1, 1.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>Shoulder Flexors</td>
<td>1 (0.5, 1)</td>
<td>1 (0.5, 1.5)</td>
<td>1 (0.5, 1)</td>
<td>0.59</td>
</tr>
<tr>
<td>Shoulder abductors</td>
<td>1 (0.5, 1)</td>
<td>1 (1, 1.5)</td>
<td>1 (0.5, 1)</td>
<td>0.16</td>
</tr>
<tr>
<td>Quadriceps</td>
<td>1 (0.5, 1)</td>
<td>1 (0.5, 1.5)</td>
<td>1 (0.5, 1)</td>
<td>0.32</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>1 (1, 1.5)</td>
<td>1 (0.5, 2)</td>
<td>1 (1, 1)</td>
<td>0.47</td>
</tr>
<tr>
<td>CRDQ Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (1.4, 3.6)</td>
<td>2.3 (1.4, 3.1)</td>
<td>2.6 (2, 4)</td>
<td>0.71</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (0.5, 1.75)</td>
<td>1.5 (0.5, 2.0)</td>
<td>1 (0.25, 1.25)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mastery</td>
<td>-0.25 (-0.75, 0.25)</td>
<td>0 (-0.5, 0.25)</td>
<td>-0.25 (-0.75, 0.75)</td>
<td>0.65</td>
</tr>
<tr>
<td>Emotional</td>
<td>0.86 (0, 1.43)</td>
<td>0.57 (0, 1.29)</td>
<td>1.14 (0.43, 1.86)</td>
<td>0.21</td>
</tr>
</tbody>
</table>
Peripheral muscle dysfunction has been a contributor in poor exercise tolerance in ILD too. R kozu et al demonstrated that in patients with IPF, those who had more dyspnea (MMRC grade 4 and grade 5) had greater impairment of quadriceps force and handgrip. This skeletal muscle worsening could have eventually contributed in reduced 6MWD in them. In 2013, ATS/ ERS statement on PR clearly stated that peripheral dysfunction contributes to exercise limitation and can be benefitted with PR. This effect can be due to mere physical deconditioning or as side effect of steroids in some. Effects of PR in ILD patients were definitely appreciated although in lesser magnitude and were short-lived up to 6 months duration. To the best of our knowledge, this is the first study in India, analyzing the effect of PR on muscle strength of ILD patients and eventually displaying promising results too.

**Conclusion**

Pulmonary Rehabilitation is a scientifically endorsed modality for patients with chronic lung diseases. We found distinct betterment in bothersome symptoms like fatigue and dyspnea in patients at the end of 8 weeks of PR. We documented improvement in muscle strength, which is a less read parameter. With lesser symptoms and improved muscle strength their participation in activity of daily living improved. Overall, the quality of life showed satisfactory improvement too. It’s no more all about a comfort zone that patient gets, it has rather emerged as a measure that imparts statistically significant enhancements in patient care in terms of both subjective and objective parameters. The assets are better defined and extensively studied in COPD patients and need more research in the remaining chronic lung diseases like ILD with common targets dyspnea, deconditioning and exercise limitation. This study adds asset to the ongoing research on PR with evident lacuna from not only our country but also from majority of the world.

**Limitation of study**

Individual groups were not studied separately for delineating if one had different amount of improvement than rest. ILD is a heterogeneous group of diseases where the progression may vary individually. We could not

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**Table 3: Comparative analysis of our results with similar studies**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Holland et al</th>
<th>Nishiyama et al</th>
<th>Ferreira et al</th>
<th>Swigirs et al</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication year</td>
<td>2008</td>
<td>2008</td>
<td>2009</td>
<td>2011</td>
<td>2017</td>
</tr>
<tr>
<td>Sample size</td>
<td>57</td>
<td>28</td>
<td>99</td>
<td>21</td>
<td>100</td>
</tr>
<tr>
<td>PR Setup</td>
<td>Outpatient</td>
<td>Outpatient</td>
<td>Outpatient</td>
<td>Outpatient</td>
<td>Outpatient</td>
</tr>
<tr>
<td>ILD group</td>
<td>ILD</td>
<td>IPF only</td>
<td>ILD</td>
<td>IPF</td>
<td>Restrictive lung ds</td>
</tr>
<tr>
<td>Age in years</td>
<td>67</td>
<td>68±9</td>
<td>66</td>
<td>71.5±7.4</td>
<td>56.3±14.2</td>
</tr>
<tr>
<td>Duration of PR</td>
<td>8 weeks</td>
<td>8 weeks</td>
<td>8 weeks</td>
<td>8 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>35</td>
<td>46</td>
<td>56</td>
<td>61±4.1</td>
<td>61.8</td>
</tr>
<tr>
<td>LTOT</td>
<td>NA</td>
<td>CI</td>
<td>6</td>
<td>NA</td>
<td>24</td>
</tr>
</tbody>
</table>

Key: LTOT: long term oxygen therapy; 6MWD: change in 6 minute walk distance; NA: not applicable; CI: contraindication
perform a subgroup analysis as to establish if there was any difference in the effect of PR. Pulmonary Function test was not included in the study. So effect of PR on lung function wasn’t analyzed, though the effects have been meager as yet. Reasons for drop out were not included as a part of this study. Follow up of these patients has not been included in this study, to establish the longevity of favorable effects. Also, ongoing pharmacological treatment for various restrictive lung diseases was not documented.

Acknowledgement

The authors wish to acknowledge the contribution of Dr. Maninder Sethia, for the statistical analysis of our data. Use of the Chronic Respiratory Disease Questionnaire (CRQ)™, authored by Gordon Guyatt, Holger Schünemann, Marie Townsend, Stewart Pugsley and Larry Chambers, was made under license from McMaster University, Hamilton, Canada.

References

Association of Genetic Non-alcoholic Fatty Liver Disease with Insulin Resistance-Are we Different?

Ritu Karoli1, Jalees Fatima2, Prem Shanker Singh3, Zeba Siddiqi4, Shishir Varshney5, Mohd. Sameer Beg5, Mohsin Ali Khan6

Abstract

Introduction: Metabolic risk factors such as obesity, insulin resistance, type 2 diabetes mellitus and dyslipidemia are associated with non-alcoholic fatty liver disease (NAFLD). In the development and progression of NAFLD genetic mutations also play a significant role. NAFLD associated with the rs 738409 polymorphism of patatin-like phospholipase domain containing 3 gene (PNPLA3) G allele does not feature the typical metabolic abnormalities of NAFLD, including insulin resistance. In the light of rising epidemic of obesity in our population this study aimed to evaluate the relation of PNPLA3 polymorphism with insulin resistance.

Methods: In this case control hospital based study, 100 patients of NAFLD were recruited based on ultrasound findings of hepatic steatosis. Healthy subjects age and gender matched (n = 100) from the institute who volunteered to be part of the study were recruited as controls based on the sole criteria of the absence of fatty liver on ultrasonography and normal alanine and aspartate transaminases (ALT and AST) levels. Anthropometry, biochemical profiles and insulin resistance by homeostatic model assessment of insulin resistance (HOMA-IR) were assessed.

Results: A higher frequency of CG and GG genotypes of rs738409 polymorphism of PNPLA3 was observed in patients with NAFLD than controls. These patients with G allele had increased ALT, dyslipidemia and insulin resistance. The polymorphism had positive correlation with severity of hepatic steatosis.

Conclusion: The presence of the PNPLA3 G allele is associated with a risk of NAFLD. Our study shows that subjects with variant PNPLA3 are not only at increased risk for the development and progression of NAFLD, but also have increased insulin resistance.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as hepatic fat accumulation (steatosis) exceeding 5% in the absence of excessive ethanol consumption, drugs, toxins, infectious diseases or any other specific etiologic factors of liver disease.1 NAFLD embraces a morphological spectrum ranging from non alcoholic fatty liver (NAFL) to non alcoholic steatohepatitis (NASH) in which hepatic inflammation and fibrosis co-exist and NASH can progress towards cirrhosis and even hepatocellular carcinoma.2 NAFLD has been recognized as the leading cause of chronic liver disease, with a prevalence up to 20%-30% in the general population.3

NAFLD shares common pathophysiology and frequently associated with features of the metabolic syndrome that predisposes individuals to type 2 diabetes and cardiovascular disease (CVD) or to NASH and cirrhosis.4 Genetic and environmental factors have important roles in the development of NAFLD.5,6

According to genome-wide association study of NAFLD a single nucleotide polymorphism (rs738409, encoding I148M) in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene on chromosome 22 conferred susceptibility to NAFLD in a population that included Hispanic, African-American and European-American individuals.7,8 Another systematic review showed that rs738409 GG genotype was associated not only with liver fat accumulation but also with susceptibility to more aggressive disease.9

NAFLD often coexists with metabolic syndrome has been incriminated as a risk factor of future cardiovascular events [10] but the common genetic forms of NAFLD, especially those associated with variation in the genes PNPLA3 are not associated with insulin resistance, features of the metabolic syndrome or an increased risk of type 2 diabetes or CVD.11,12

In view of rising epidemic of obesity and metabolic syndrome in our country, which are the root causes of NAFLD, we need to study the genetic aspects of this common disease in our own population and to also assess its propensity towards cirrhosis or metabolic syndrome. In the present study we aimed to find out prevalence of PNPLA3 I148M variant in patients with NAFLD and its association with insulin resistance and other metabolic traits.

Material and Methods

The present study was carried out in a medical college hospital situated in North India as a case

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Received: 06.05.2018; Accepted: 03.10.2018
Table 1: Baseline characteristics of patients with NAFLD and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with NAFLD (n=100)</th>
<th>Controls (n=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45±8.2</td>
<td>46±7</td>
<td>0.4</td>
</tr>
<tr>
<td>Male Gender</td>
<td>46(46%)</td>
<td>47(47%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>93±12</td>
<td>81±14</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32(32%)</td>
<td>12(12%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>21(21%)</td>
<td>11(11%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>12(12%)</td>
<td>6(6%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data is expressed as n(%) or mean±SD

Table 2: Frequency of genotypes among study participants

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients with NAFLD (n=100)</th>
<th>Controls (n=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>20</td>
<td>51</td>
<td>0.03</td>
</tr>
<tr>
<td>CG</td>
<td>55</td>
<td>32</td>
<td>0.001</td>
</tr>
<tr>
<td>GG</td>
<td>25</td>
<td>17</td>
<td>0.01</td>
</tr>
</tbody>
</table>

and their relatives. The study protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from all study participants.

Determination of PNPLA3 genotype

PNPLA3 rs738409 was genotyped by the TaqMan SNP genotyping assay (Applied Biosystems, Foster City, CA, USA). Five milliliters of peripheral blood were collected from all the subjects in 0.5M EDTA tubes. Genomic DNA was isolated from whole blood using the standard phenol-chloroform extraction method. The quantity and quality of DNA was checked by spectrophotometry and gel electrophoresis. DNA was stored at -20°C. A simple PCR-RFLP based method was used for the assay of PNPLA3 rs738409. The sequence of sense primer is 5’- TGGGCCTGAAGTCCGAGGGT-3’ and that of anti sense primer was 5’- CCGACACCAGTGCCTGAGCAG-3’. PCR mixture consist of 1X PCR buffer (Tris-HCl 10 mM, KCl 50 mM, MgCl2 2 mM), 0.2 mM each dNTP, 1 mM each primer, 100 ng genomic DNA and 1.5 U Taq DNA polymerase in a total volume of 50 μL. The amplification program was as follow: Initial denaturation at 94°C for 2 min, denaturation at 94°C for 30 sec, annealing at 66°C for 30 sec and synthesis at 72°C for 30 sec. Final synthesis was carried out at 72°C for 5 min. PCR product was digested with 4U of BtsCI (Biolabs inc., New England, U.S.) at 50°C for 4 hr. Digested PCR product was electrophoresed in 2% agarose gel and visualized on a UV transilluminator. A detailed history, thorough physical examination was performed, and anthropometric measurements were recorded. The metabolic syndrome was defined according to International Diabetes Federation (IDF) criteria. 

Biochemical parameters including liver transaminases, alanine transaminase (ALT), and aspartate transaminase (AST) fasting blood glucose, lipid profile and insulin levels were measured. Homeostasis model assessment (HOMA) method for insulin resistance was calculated by the formula: Fasting serum insulin(microunits/ml)x fasting serum glucose(millimoles per litre)/22.5. [15]

Statistical analysis

The Statistical Package for the Social Sciences version17 (SPSS, Inc., Chicago, IL USA) was used for data analysis. To ensure the normal distribution of variables, Kolmogorov-Smirnov test was applied. Nonparametric tests (chi-squared test, Fischer exact probability test, and Mann-Whitney U test) were used to compare the characteristics of the groups.

We used Pearson’s correlation coefficient to assess the relationships and P < 0.05 was considered statistically significant.

Results

The present study was conducted to investigate association of PNPLA3 gene polymorphism with insulin resistance in patients with nonalcoholic fatty liver disease. Hundred patients fulfilling the inclusion criteria for NAFLD were enrolled in the study as cases and equal number of (n=100) age and gender matched healthy individuals were recruited as Controls having ultrasonographically normal liver echogenicity and normal liver function tests. Table 1 is showing base line characteristics of cases and controls. Age of subjects ranged from 20-70 years and mean age was 45±8.2 years and 46±7 years. The anthropometric parameters including waist circumference, waist-hip ratio and BMI were higher in patients with NAFLD than controls. Significantly higher proportion of patients with NAFLD as compared to controls had dyslipidemia, hypertension and prediabetes as shown in Table 2.

PNPLA3 rs738409 genotype assay was performed and genotype frequencies were summarized according to 3 possible genotypes (CC, CG and GG) among study participants.

It was observed that PNPLA3 rs738409 polymorphism occurred at a higher frequency in patients with NAFLD than controls as described in Table 3. G allele containing genotypes(CG and GG) were present in 64% in patients with NAFLD and 37% in controls.

Anthropometric parameters

control study, which was conducted between January 2015 to June 2016. All consecutive patients >18 years old with hepatomegaly detected on clinical and/or ultrasonographic examination attending the outpatient department or admitted in medical wards of the Era’s Lucknow Medical College and diagnosed to have hepatic steatosis were included after screening of inclusion criteria. The patients were diagnosed to have NAFLD on the basis of presence of hepatic steatosis as bright/echogenic liver on abdominal ultrasound. Ultrasonography was performed by a high resolution B-mode scanner of General Electric Logic 5 with a 3.5 MHz convex-array probe. Hepatic steatosis was defined as diffuse increase in fine echoes in liver parenchyma with impaired visualization of intrahepatic vessels and the diaphragm. Exclusion Criteria comprised of pregnancy, alcohol consumption (> 20 gm/day), Positive hepatic markers of viral hepatitis, autoimmune hepatitis, Wilson’s disease, Hemochromatosis, drugs known to cause fatty liver (methotrexate, estrogens amiodarone, tamoxifen).

NAFLD was defined as the presence of an ultrasonographic pattern consistent with the following criteria: liver-kidney echo discrepancy, attenuated echo penetration, visibility of diaphragm, and obscure hepatic vessel structures. The aforementioned ultrasonographic pattern was scored as described by Chan et al.13 The subjects were categorized to have mild, moderate, or severe steatosis if the overall score was 1–3, 4–6, or 7–9, respectively.

The controls were age and sex matched healthy individuals who had ultrasonographically normal liver echogenicity and normal liver function tests enrolled from the hospital staff.
including waist circumference and waist-hip ratio were significantly higher in patients with GG allele. Similarly, a significantly higher proportion of subjects with genotype CC and CG as compared to GG had raised triglycerides and LDL although total cholesterol, HDL and VLDL levels of subjects with CC, CG & GG genotypes were not different as depicted in Table 4. Raised transaminase levels were found among significantly higher proportion of subjects with CG and GG genotypes as compared to CC genotype. HOMA-IR of subjects with CC & GG genotypes was significantly higher as compared to CC genotype (3.31±0.53 vs 2.98±0.67, p=0.002).

We analysed the association of components of metabolic syndrome with the presence of CC, CG & GG genotypes and it was observed that triglycerides and fasting glucose levels were significantly higher in GG genotype. They also had higher HOMA-IR than CC genotype.

Table 5 has shown the impact of genotypes on grades of hepatic steatosis. The presence of G allele was associated with severity of NAFLD. Majority of subjects of CC genotype had mild hepatic steatosis while majority of subjects with CG and GG genotypes had moderate to severe steatosis.

In the present study it was observed that there was positive correlation of GG genotype with HOMA – IR (r = 0.56, P=0.001), fasting insulin (r = 0.43, P =0.01) and fasting glucose levels (r = 0.38, P =0.01) as depicted in Table 6.

### Discussion

NAFLD is the most common chronic liver disease whose prevalence has reached global epidemic proportions. Although the disease is relatively benign in the early stages, but may progress to severe forms, including cirrhosis and even hepatocellular carcinoma. A growing body of evidence indicates that NAFLD develops from a complex process in which many factors, including genetic susceptibility and environmental insults, are involved.

The prevalence of NAFLD in the Indian population is estimated to be around 25%-30%. In NAFLD, the hepatic manifestation of metabolic syndrome and is associated with obesity, dyslipidemia hypertension, insulin resistance and cardiovascular disease. Associated with the PNPLA3 G allele is characterized by an increase in hepatic fat and does not feature the typical metabolic abnormalities of NAFLD, or inflammation in adipose tissue and may be a cause of increased incidence of lean NAFLD.

The present study did not show any gender predisposition for NAFLD. On comparing the anthropometric and clinical profile of NAFLD patients with controls, we found a significant difference between two groups with respect to hypertension, obesity and lipid levels. All these factors are metabolic implications of NAFLD.

In the present study we observed higher frequency of the GG genotype of PNPLA3 gene polymorphism in NAFLD patients than controls. Similar to the findings of present study, Lin et al in a set of obese population with and without NAFLD also found prevalence of G allele to be 44.8% in NAFLD patients as compared to 33.6% in controls. Many studies of this polymorphism have been reported. In addition, the rs738409-GG genotype was associated with a higher risk of liver fibrosis, cirrhosis, and HCC.

In present study, we also assessed the metabolic traits including anthropometric parameters of central obesity, lipid profile and liver transaminase levels in patients with NAFLD and controls and found that those with presence of genotype GG and CC, had significantly higher waist circumference, waist-hip ratio, triglycerides and ALT levels. They were more insulin resistant.

In an Indian study by Alam et al, frequency of G allele was significantly higher (62.6%) in NAFLD than in healthy controls. The GG genotype had 6.53 times odds of having NASH. Regression analysis revealed that G allele odds of having cirrhosis was 3.9 times compared to C. The G allele was also significantly associated with steatosis, lobular inflammation, NAFLD activity score, and fibrosis. Patients with NASH had higher HOMA-IR levels.

In another Indian study by Bhatt et al a higher frequency of CC and GG genotypes of the rs738409 polymorphism was

---

**Table 3: Association of Genotypes with metabolic parameters**

<table>
<thead>
<tr>
<th>Variables</th>
<th>CC (n=71)</th>
<th>CG (n=87)</th>
<th>GG (n=42)</th>
<th>F</th>
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</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Waist Circumference</td>
<td>24.43 ± 2.85</td>
<td>26.64 ± 3.3</td>
<td>25.50 ± 3.42</td>
<td>9.993</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>110.96 ± 18.37</td>
<td>135.07 ± 28.22</td>
<td>127.33 ± 21.85</td>
<td>20.326</td>
</tr>
<tr>
<td>Fasting Insulin (IU/L)</td>
<td>5.08 ± 2.28</td>
<td>6.85 ± 2.84</td>
<td>6.50 ± 2.38</td>
<td>9.826</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dl)</td>
<td>119.68 ± 23.66</td>
<td>135.02 ± 24.04</td>
<td>136.81 ± 25.48</td>
<td>9.985</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dl)</td>
<td>40.43 ± 4.96</td>
<td>40.20 ± 4.86</td>
<td>39.34 ± 3.93</td>
<td>0.732</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>113.48 ± 20.40</td>
<td>160.07 ± 24.98</td>
<td>136.50 ± 22.92</td>
<td>80.341</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>117.37 ± 19.73</td>
<td>155.37 ± 17.90</td>
<td>148.63 ± 15.99</td>
<td>90.527</td>
</tr>
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<td>Fasting Insulin (IU/L)</td>
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<td>148.63 ± 15.99</td>
<td>90.527</td>
</tr>
</tbody>
</table>

P value: 0.02

**Table 4: Association of G allele genotypes with components of metabolic syndrome**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (N=200)</th>
<th>CC (n=71)</th>
<th>CG (n=87)</th>
<th>GG (n=42)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Blood glucose</td>
<td>110.96 ± 18.37</td>
<td>135.07 ± 28.22</td>
<td>127.33 ± 21.85</td>
<td>20.326</td>
<td></td>
</tr>
<tr>
<td>Insulin (IU/L)</td>
<td>5.08 ± 2.28</td>
<td>6.85 ± 2.84</td>
<td>6.50 ± 2.38</td>
<td>9.826</td>
<td></td>
</tr>
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<td>HDL Cholesterol (mg/dl)</td>
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<td>9.985</td>
<td></td>
</tr>
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<td>39.34 ± 3.93</td>
<td>0.732</td>
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</tr>
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<td>136.50 ± 22.92</td>
<td>80.341</td>
<td></td>
</tr>
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<td>155.37 ± 17.90</td>
<td>148.63 ± 15.99</td>
<td>90.527</td>
<td></td>
</tr>
</tbody>
</table>

P value: 0.02

**Table 5: Association of genotypes and severity of hepatic steatosis (n=100)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total (N=100)</th>
<th>CC (n=20)</th>
<th>CG (n=55)</th>
<th>GG (n=25)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>51</td>
<td>19 (95)</td>
<td>22 (40)</td>
<td>10 (40)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>38</td>
<td>1 (5)</td>
<td>24 (43.6)</td>
<td>13 (52)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>0</td>
<td>9 (16.4)</td>
<td>2 (8)</td>
<td></td>
</tr>
</tbody>
</table>

p = 0.001

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obtained in cases as compared to controls. In this study, the G allele was associated with significantly higher fasting insulin HOMA-IR, ALT and AST values in cases than controls. However, other studies from different populations did not confirm our results. A study by Peng et al on evaluating the association of CG/GG genotype with obesity, lipids and raised plasma glucose levels, did not find any significant association for any of the variables. In concordance with our study, though s also found higher AST and ALT levels in CG and GG genotypes as compared to that in CC genotype. This shows a possible deviation dependent on the ethnic variability. Role of ethnic differences affecting the genotypic distribution and their impact on prevalence of anthropometry, liver functions and lipid levels for PNPLA3 variants have also been reported in a study by Bale et al. comparing South Indian and north-East Indian population.

The present study also indicated a significant association between GG/CG polymorphism with grades of fatty liver disease. Kantartzis et al in their study showed a significant difference in total liver fat in different polymorphic forms of PNPLA3 variant rs738409. Akuta et al similar to present study also derived a similar significant association between stage of fatty liver disease and rs738409 polymorphism with higher prevalence of those with CG/GG genotype as compared to those having CC genotype. In previous studies PNPLA3 polymorphisms have been shown to have strong association with the risk for and severity of NAFLD, cirrhosis and hepatocellular carcinoma. In present study, we observed that it had strong relation with not only the severity of grades of NAFLD but carries a higher risk of dyslipidemia, obesity and insulin resistance. So there is a possibility that it can play an evolving role in diagnosis and treatment decisions in patients who have NAFLD.

In the present study our aim was to look for the association of PNPLA3 I148M variant and with insulin resistance in patients with NAFLD. The patients with genetic susceptibility of NAFLD have increased the risk of advanced liver disease but our study showed that they had association with insulin resistance as well.

Considering the high prevalence of carriers PNPLA3 I148M variant and the obesity epidemic, many of our young patients and might develop early onset and severe NAFLD. In these patients, the progression from simple steatosis to steatohepatitis seems to be accelerated and will also be contributed by degree of insulin resistance. Our patients have ‘double trouble’, i.e. carry both a genetic risk factor and have the metabolic syndrome though larger prospective studies in our population are needed to validate our results.

Limitations of our study were small sample size. Although liver biopsy is considered to be the gold standard for identifying NAFLD and NASH, absence of indication for asymptomatic individuals, the costs involved, risk of complications and ethical concerns were major deterrents. We did not follow the patients to observe the outcome in form of cirrhosis or cardio vascular events. Another major limitation was that patients were not subjected for liver biopsy or fibro scan to assess the severity of fibrosis.

We recognize the fact that our study should be considered exploratory and that the findings should be interpreted with caution because a larger study would be required to be more conclusive. In future, the PNPLA3 gene may be a potential target for therapy in NAFLD. Prospective data with large number of patients are now needed to further understand the association of PNPLA3 polymorphisms and insulin resistance particularly related to metabolic traits of NAFLD and for prediction of final outcome in form of end stage liver disease or cardiovascular disease.

Conclusion

The presence of the PNPLA3 G allele is associated with a risk of NAFLD. Our study shows that subjects with variant PNPLA3 are not only at increased risk for the development and progression of NAFLD, but also have increased insulin resistance. Therefore it is very important to identify individuals with genetic susceptibility of hepatic steatosis at an early stage so that appropriate interventions can be planned to curtail progression to higher stages.

References

10. Yki-Jarvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol 2014; 2:901-910.
21. Lin YC, Chang PF, Hu FC, et al. A common variant in the PNPLA3 gene is a risk factor for non-alcoholic fatty liver
Mortality in H1N1: A comparison of patient attributes in outbreaks due to A/California/7/2009 and A/Michigan/45/2015 strains

CL Nawal¹, Sujata Agarwal²*, Abhishek Agrawal¹, Ravi Prakash³, Pradeep Mital⁴, Aradhana Singh⁵, Radhey Shyam Chejara²

Abstract

Introduction: The resurgence of epidemic of Influenza A (H1N1) pdm 09 was phenomenal in 2015 and has become an annual phenomenon. Antigenic drift and reassortment is the rule rather than exception, conferring survival benefit to the virus. As this disease has high mortality, we compared the clinico-epidemiological profile of patients expired in the year 2015 due to “A/California/7/2009” strain with those of expired in the year 2018 due to “A/Michigan/45/2015” strain.

Material and Method: We collected data of all expired patients in our institute in the year 2015 from 1st January to 30th May as well as 2018 in the same time period. The data of 116 patients who expired in 2015 due to “A/California/7/2009” H1N1 strain were compared with similar data of 30 patients expired in 2018 due to “A/Michigan/45/2015” strain of H1N1. Patients of pneumonia, having age >18 years, positive for H1N1 by real-time reverse-transcriptase–polymerase chain-reaction (RT-PCR) and died in our hospital were included in this study. Clinical features and laboratory data were obtained from the hospital records of the patients. Data analysis was done using SPSS software.

Result: In 2015 total number of hospitalized patients due to “A/California/7/2009” strain were 571 and 116(20.31%) out of them died, in 2018 those due to “A/Michigan/45/2015” total admission were 177 and 30(16.94%) out of them died (p-0.032). Though it was not statistically significant but it is lesser than in 2015 despite the fact that more patients with co-morbidities were affected in 2018.

Duration in ICU was significantly longer in 2018 (MS) group [5(1-7)] compared to 2015 (CS) group [3(1-17)] with p value of 0.017 (i.e. < 0.05). But both groups were not different in terms of duration on mechanical ventilator. (p-0.257).

The 2015 (CS) group had 74.1% with other co-morbidities versus 96.7% of those in 2018 (MS) group (p<0.015). This implies that the mortality with “A/Michigan/45/2015” infection was mainly seen in the patients who already had one or more co-morbidities unlike “A/California/7/2009” infection.

The 2018 (MS) group had significantly higher proportion (60%) of patients with acute kidney injury compared to 34.5% in 2015 (CS) (p=0.019). 50% of dead patients in 2018 (MS) had anemia compared to 11.2% in 2015 (CS) (p<0.001). Deranged liver function test was seen in 46.7% patients in 2018 (MS) compared to only 15.5% patients in 2014 (CS) (p<0.001).

The only reverse trend was shown in case of diabetes, “A/California/7/2009” strain affected 27% diabetics compared with 6.7% affected by “A/Michigan/45/2015” strain (p=0.030) (Table 5).

Conclusion: The study showed that though “A/Michigan/45/2015” affected higher number of patients with co-morbidities compared to “A/California/7/2009” but had slightly lesser mortality.

Introduction


case which started in Mexico in 2009 and managed to spread across most part of the world within short span of time leading to significant mortality and morbidity over the years. A similar outbreak occurred in 2015 in western parts of India due to Influenza A(H1N1) pdm09, claiming many lives.

After a quiescence of 2-3 years, in 2018 there was again a rise in H1N1 cases. Meanwhile, the Indian Council of Medical Research (ICMR) bulletin has stated that a new strain of novel human influenza virus (H1N1) “A/Michigan/45/2015” also called Michigan strain (MS) was circulating in India since September 2016. As compared to the previous strain “A/California/7/2009” (CS) which was in circulation since 2009.

As India is the most densely populated country of the world, it is notorious for its reputation for rapid spread of various communicable diseases. The double whammy being the new strain of H1N1 “A/Michigan/45/2015” is reported to be active in summer season also unlike the previous one “A/California/7/2009”.

As Indian climate ranges from tropical in the southern part to temperate in north and alpine in Himalayas, we got prolonged heat wave and summer season, this was previously considered season of quiescence for influenza virus related illnesses. Many studies have confirmed that the most common population affected by H1N1 was young people, and the cause of death in majority of them was pneumonia, ARDS along with rapidly developing hypoxic respiratory failure.

This study was carried out to compare the clinico epidemiological profile of patients expired in 2015(CS) with those of 2018(MS), in a tertiary care hospital of north India i.e. Sawai Mansingh Hospital, Jaipur.

### Material and Methods

This cross sectional and analytical study was conducted at a tertiary care Medical College Hospital among swine influenza H1N1 positive patients. We collected exhaustive data of all expired patients in our institute in the year 2015 from 1st January to 30th May as well as 2018 in the same time period. The data of 116 patients who expired in 2015 due to “A/California/7/2009” H1N1 strain were compared with similar data of 30 patients expired in 2018 due to “A/Michigan/45/2015” strain of H1N1. The presented data was collected over four year duration. All patients with radiographic evidence of pneumonia, having age >18 years, positive for H1N1 by RT-PCR and died in our hospital were included in this study.

During the H1N1 outbreak the nasopharyngeal-swab samples were collected from all study subjects at the time of hospitalization and were subjected to analysis by RT-PCR assay. Radiography, hematology and routine biochemistry serum examination were performed in all the patients. Other specific investigation e.g. ABG, serum sodium, 2-D echocardiography, abdominal ultrasound were performed as indicated on the discretion of the clinician. Incomplete record was excluded from the study.

### Statistical Analysis

Microsoft Excel® and SPSS® 17.0 for Windows® was used for data storage and analysis. The continuous variables were expressed as mean ± standard deviation. Student’s t test and chi-Square test were applied to determine statistical difference between variables.

### Results

The patients died during 2015 epidemic were assigned 2015 (CS) group while the patients died during 2018 were assigned 2018(MS) group.

The age distribution of the expired patients were similar 42.34 ± 15.03 in 2015 (CS) group and 44.17 ± 17.07 in 2018 (MS) group with p value of 0.606. Gender distribution was also similar with 58.6% females in 2015(CS) versus 36.7% in 2018(MS) (Table 1).

In 2015 total number of hospitalized patients due to H1N1 were 571 and 116(20.31%) out of them died, likewise in 2018 total admission were 177 and 30(16.94%) out of them died (p=0.032). Though it was not statistically significant but it is lesser than in 2015 despite the fact that more patients with co morbidities were affected in 2018.

Time lag between onset of symptoms and hospitalization had median and range of 5 days (1-30) in 2015(CS) versus 6.5 days (6.5-30) in 2018(MS) group. Its P value was non-significant (0.244) (Table 1).

Time lag between onset of symptom and initiation of Oseltamivir was also similar in both the groups (p=0.156) (Table 1).

Duration in ICU was significantly longer in MS group [6±(1-7)] compared to CS group [3±(1-17)] with p value of 0.017 (i.e. < 0.05). But both groups were not different in terms of duration on mechanical ventilator which had p=0.257 (Table 1).

Pregnancy and post-partum patients presented in comparable number in both CS and MS group (p=0.498).

ARDS was present in 65 (56%) patients in 2015 (CS) group compared to 10 (33.3%) patients in 2018 (MS) group. This was not significant statistically. (p=0.092). Lung involvement was also

### Table 1: Factors associated with swine flu deaths during 2015 and 2018

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>2015</th>
<th>2018</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean ± SD</td>
<td>42.38 ± 15.03</td>
<td>44.17 ± 17.07</td>
<td>0.606</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Female 68 (58.6%)</td>
<td>11 (36.7%)</td>
<td>0.052</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male 48 (41.4%)</td>
<td>19 (63.3%)</td>
<td></td>
</tr>
<tr>
<td>Time lag between symptoms onset and hospitalization</td>
<td>Median (range) days</td>
<td>5 (1 – 30)</td>
<td>6.5 (6.5 – 30)</td>
<td>0.244</td>
</tr>
<tr>
<td>Time lag between symptoms onset and oseltamivir</td>
<td>Median (range) days</td>
<td>5 (0 – 30)</td>
<td>6.5 (2 – 30)</td>
<td>0.156</td>
</tr>
<tr>
<td>Duration of Hospitalization</td>
<td>Median (range) days</td>
<td>4 (&lt;1 – 22)</td>
<td>6 (&lt;1 – 18)</td>
<td>0.126</td>
</tr>
<tr>
<td>Duration of ICU stay</td>
<td>Median (range) days</td>
<td>5 (0 – 21)</td>
<td>5 (1 – 17)</td>
<td>0.017</td>
</tr>
<tr>
<td>Duration on ventilator</td>
<td>Median (range) days</td>
<td>2 (&lt;1 – 16)</td>
<td>3 (&lt;1 – 12)</td>
<td>0.257</td>
</tr>
<tr>
<td>Pregnancy/ postpartum/IUD</td>
<td>N (%)</td>
<td>22 (19%)</td>
<td>8 (26.7%)</td>
<td>0.498</td>
</tr>
<tr>
<td>ARDS</td>
<td>N (%)</td>
<td>65 (56%)</td>
<td>10 (33.3%)</td>
<td>0.092</td>
</tr>
<tr>
<td>Lung involvement (%)</td>
<td>Median (range) days</td>
<td>60 (10 – 100%)</td>
<td>50 (20 – 70%)</td>
<td>0.198</td>
</tr>
</tbody>
</table>

### Table 2: Severity at presentation among H1N1 deaths

<table>
<thead>
<tr>
<th>Severity at presentation*</th>
<th>2015</th>
<th>2018</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category B</td>
<td>5</td>
<td>4.3</td>
<td>0</td>
</tr>
<tr>
<td>Category C</td>
<td>109</td>
<td>94.0</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>100</td>
<td>30</td>
</tr>
</tbody>
</table>

Chi-square = 0.369 with 1 degree of freedom; P = 0.544 (S); *None of the deaths had Category A at presentation

Statistical significance was set at P value ≤ 0.05. P value of ≤ 0.005 was labeled as highly significant.
similar in both the groups (p=0.198) (Table 1).

Time lag between hospitalization and death i.e. duration of hospitalization was also comparable between both the groups (Table 1).

Severity of disease as per Ministry of Health and Family Welfare, clinical categorization \(^6\) at presentation among patients who died was similar illness in 2015(CS) (cat-B 4.3%, cat-C 94.0%) and 2018(MS) (cat-B 5%, cat-C 100%) with p value 0.544(NS). None of the expired patients in either group had category A clinical status on presentation (Table.2). This may be due to the fact that we studied hospitalized patients only and category A patients don’t require hospitalization.

It was observed that 83.6% patients were admitted in ICU at the time of death in 2015(CS) compared to 100% in 2018 (MS) which is statically significant with P value of <0.05 % (Table 3).

The 2015(CS) group had 74.1% with other co-morbidities versus 96.7% of those in 2018(MS) group which was statistically significant with p value of 0.015. This implies that the mortality with "A/Michigan/45/2015" infection was mainly seen in the patients who already had one or more co-morbidities unlike “A/California/7/2009” which fatally infected the relatively healthy population (Table 4).

Another significant observation was that A/California/7/2009 affected 27% diabetics compared with 6.7% affected by A/Michigan/45/2015 (p=0.030) (Table 5).

The 2018 (MS) group had significantly higher proportion (60%) of patients with acute kidney injury compared to 34.5% in 2015 (CS) p=0.019. 50% of dead patients in 2018 (MS) had anemia compared to 11.2% in 2015 (CS). This was highly significant (p<0.001). Deranged liver function test was seen in 46.7% patients in 2018 (MS) compared to only 15.5% patients in 2014 (CS) (p<0.001).

### Table 3: ICU admission among study subjects

<table>
<thead>
<tr>
<th>ICU admission</th>
<th>2015</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>97</td>
<td>30</td>
</tr>
<tr>
<td>No</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>100</td>
</tr>
</tbody>
</table>

Chi-square = 4.295 with 1 degree of freedom; P = 0.038 (S)

### Table 4: Co-morbidities among H1N1 subjects

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>2015 (N=116)</th>
<th>2018 (N=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>3</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>CAD</td>
<td>5</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>RHD</td>
<td>2</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>SABE</td>
<td>2</td>
<td>1</td>
<td>0.0</td>
</tr>
<tr>
<td>CCF</td>
<td>7</td>
<td>6</td>
<td>10.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>13</td>
<td>13.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32</td>
<td>27</td>
<td>6.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>15</td>
<td>50.0</td>
</tr>
<tr>
<td>Asthma</td>
<td>12</td>
<td>11</td>
<td>13.3</td>
</tr>
<tr>
<td>COPD</td>
<td>16</td>
<td>13</td>
<td>11.7</td>
</tr>
<tr>
<td>K chest</td>
<td>16</td>
<td>10</td>
<td>13.3</td>
</tr>
<tr>
<td>ILD</td>
<td>17</td>
<td>11</td>
<td>13.3</td>
</tr>
<tr>
<td>Liver disease</td>
<td>17</td>
<td>11</td>
<td>13.3</td>
</tr>
<tr>
<td>Renal failure</td>
<td>11</td>
<td>9</td>
<td>13.3</td>
</tr>
<tr>
<td>AKI</td>
<td>13</td>
<td>12</td>
<td>11.2</td>
</tr>
<tr>
<td>Pregnancy/Postpartum/IUD</td>
<td>22</td>
<td>19</td>
<td>26.7</td>
</tr>
<tr>
<td>Obesity</td>
<td>11</td>
<td>12</td>
<td>11.2</td>
</tr>
<tr>
<td>Anaemia</td>
<td>13</td>
<td>12</td>
<td>11.2</td>
</tr>
<tr>
<td>Any one or more co-morbidity</td>
<td>86</td>
<td>74</td>
<td>67.7</td>
</tr>
</tbody>
</table>

The most common complications and causes of death among the expired patients were septicemia, acute respiratory distress syndrome (ARDS) and shock (Figure 1). The latter two were not different among both the groups but septicemia was found in 56% of 2015(CS) group compared to 33.3% in 2018 (MS) group. P=0.044 (Table 4).

### Discussion

The result of the cross sectional analytical study is being presented in this study. From 2009 till early 2016 the strain of H1N1 that was circulating all over the world was “A/California/7/2009” strain\(^5,7\), since the CDC confirmed the first case of “A/Michigan/45/2015”\(^8\), there are confirmation from various bodies regarding the change in strain of H1N1.\(^9\)

**Diversity of antigenic mutations of influenza A(H1N1)pdm09 is confirmed in various studies.**\(^1\)

We did a head to head comparison of demographic, clinical and laboratory data of patients who have expired in 2015 outbreak (1st January to 30th May) in our institute probably due to “A/California/7/2009” strain (number of patients expired in 2015 -16) with those expired in 2018(1st January to 30th May) presumably due to “A/Michigan/45/2015” strain (number of patients expired in 2018-30). The preliminary results of this study are presented here.

We found the study subjects had similar age and gender distribution implying that both outbreaks affected similar population.

Time lag between onset of symptoms and hospitalization as well as between hospitalization and death was also comparable in both the groups, suggesting similar behavior of both strains of virus. The time lag between onset of symptoms and start of antiviral Oseltamivir was similar in both CS and MS group. Though the duration of ICU stay was found to be more in MS group (p<0.05), but the duration of patient on ventilator was akin. This may be explained as 2015(CS) patients were more sick and died early after admission to ICU.

We also inferred that the number of pregnant and postpartum patient was alike in both CS and MS group. This was significant as H1N1 during pregnancy and puerperal period causes higher morbidity and mortality.\(^1,12\)

It was observed that the case fatality characteristics were similar in respect to severity of disease as most of expired patients were of category C (94.0% in 2015 and 100% in 2018) and some were of category B (4.3% in 2015 and 5% in 2018).

It was observed that none of the dead patients had category A on presentation reinforcing the previous conviction that category A patients can be managed at home to prevent them from spreading the disease as much as possible.\(^6\)

Lesser percentage (83.6%) of patients expired in ICU in 2015 compared to 2018 (100%) with p value <0.05, implying ICU care could not be offered to some seriously ill patients. This happened as overwhelmingly large population of patients were affected with H1N1 pneumonia in 2015 causing large scale influx of patient in our hospital.

The most interesting observation of
Fig. 1:  Complications among patients who expired due to H1N1 infection

this study was that the patients expired in 2015(CS) had lesser co morbidities compared to those of 2018(MS), (p= 0.015). This means that the “A/California/7/2009” attacked healthier population causing greater devastation compared to “A/Michigan/45/2015”.

Talking of individual complication, 60% of 2018(MS) group had acute kidney injury compared to 34.5% 2015 (CS) group (p value-0.019). This implies that newer stains has higher affinity to renal tissue. However the type of renal injury could not be established due to lack of autopsy data.

50% of expired patients of 2018 (MS) group had anemia compared to only 11.2% of 2015(CS) group, (ph<0.001), so were deranged liver function i.e. 46.7% in 2018 versus 15.5% in 2015.

Type 2 diabetes mellitus was the only co morbidity showing significant inverse trend, 2015(CS) group had 27.6% versus only 6.7% in 2018 (MS) (p-0.03).

Septicemia, ARDS and shock were overall the most common cause of death, but septicemia was more prevalent (56%) in 2015 (CS) group compared to (33.3%) 2018(MS) group.

During literature search the authors could not find any other study where head to head comparison between the clinical virulence of two strains of swine flu was done. This could be considered as a first of its kind study.

Limitations

Our study had some limitations. As the study was done at a tertiary care centre and we recruited only admitted patients. Thus the nature of the comparison and the results may not reflect the trends in general population. As this was a cross sectional study temporality could not be established between some parameters like LFT and AKI.

Another limitation was that due to lack of resources to isolate the virus the presence of Michigan stain could not be established specifically in our patients. The presence of Michigan stain was presumed as it was demonstrated from other samples from across the country in reference laboratory.

Conclusion

The study showed that though “A/Michigan/45/2015” affected higher number of patients with co morbidities compared to “A/California/7/2009” but had slightly lesser mortality.

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8. Joint Information Center 888-EMD-TODAY (888-363-8632) SOM - CDC Confirms First Michigan Case of Influenza A (H1N1). https://www.michigan.gov/som/0,4669,7-192-34773-213792--00.html
High Prevalence of Vitamin D Deficiency in HIV Infected on Antiretroviral Therapy in a Cohort of Indian Patients

Rajesh Deshwal1*, Sumit Arora2

Abstract

Objectives: The main aim of this study was to assess vitamin D [25(OH)D] levels in an HIV infected adult population and to define HIV and antiretroviral-related factors associated with vitamin D deficiency.

Methods: This observational analytical study was conducted on 475 adult patients on follow up at Apex Immunodeficiency Center of Base Hospital, Delhi Cantt. We estimated the prevalence of vitamin D insufficiency/deficiency (<30 ng/ml). Age, gender, BMI, CD4 count, plasma viral load, HBV/HCV coinfection, smoking status, time since diagnosis of HIV infection and selected liver enzymes were recorded. Antiretroviral therapy regimen was taken into account and its relationship with vitamin D levels were noted.

Results: Vitamin D insufficiency/deficiency was noted in 92.63% of patients out of which 65.68 % were males. Median age of vitamin D sufficient group was slightly higher(52.11 vs 49.95). Patients with higher body mass index (BMI) had a slightly higher rates of vitamin D insufficiency(24.2 vs 22.3). More the time interval from the date of diagnosis higher were the chances of deficiency/insufficiency. Co-infected patients with hepatitis B and C had sufficient vitamin D levels in 71.92% patients. Efavirenz(66.93%), nevirapine(79.02%), tenofovir(64.84%) and ritonavir(84.90%) containing regimens had consistently low levels of vitamin D. Abnormal liver enzymes viz alanine aminotransferase, alkaline phosphatase and gamma glutamyl transferase were associated with higher rates of deficient vitamin D levels.

Conclusions: Vitamin D deficiency is very high in HIV patients on antiretroviral therapy. Efavirenz (EFV), Nevirapine (NVP), Tenofovir (TDF) and Protease Inhibitors (PI’s) were associated with high levels of deficiency/insufficiency of vitamin D levels. Vitamin D supplementation as a global strategy in all HIV positive patients on antiretroviral therapy is advocated.

Introduction

Vitamin D is vital for calcium homeostasis and bone metabolism. Vitamin D deficiency is linked with a number of comorbidities, including hypertension, cardiovascular disease, insulin resistance, diabetes, dyslipidemia, impaired immune function, decreased neurocognitive function, and malignancies. The primary determinant of vitamin D status is exposure to sunlight. With increasing urbanization and sunscreen use, vitamin D deficiency has become highly prevalent among the general population.

Middle-aged persons with human immunodeficiency virus (HIV) infection are at risk for numerous comorbidities typically seen in older aging populations, including frailty, metabolic syndrome, osteoporosis and fragility fractures, insulin resistance, diabetes, cardiovascular disease, and cognitive impairment. Many of which have also been associated with vitamin D deficiency. Recently, low vitamin D levels have been associated with HIV disease progression and HIV-related complications. Therefore, the role of vitamin D in preventing or mitigating these complications of HIV is of particular interest. Low vitamin D levels among HIV-infected persons have been described; however, these reports were either case series or studies from small cohorts of HIV-infected persons. HIV infection and exposure to certain antiretrovirals might contribute to altered levels of 25-hydroxy vitamin D (25(OH)D).

The preferred and most commonly used parameter for assessment of vitamin D status is serum 25(OH)D concentration. 25(OH)D is the major circulating metabolite of vitamin D and reflects the vitamin D inputs from cutaneous synthesis and dietary intake. Several studies in general population have shown a high prevalence (50-97%) of vitamin D deficiency in tropical and subtropical regions of India and other South Asian countries, despite abundant sunlight.

This study aimed at assessing vitamin D status and its relationship with CD4 count, viral load, antiretroviral therapy and selected liver enzymes.

Methods

This observational analytical study was carried out at Apex Immunodeficiency Center, Base Hospital, Delhi Cantt. The study included 475 patients who were on antiretroviral therapy (ART) for at least more than a year. Approval of the hospital ethics committee was obtained prior to commencement of the study. Patients receiving Vitamin D supplementation, treatment for osteoporosis, on renal dialysis and patients with creatinine >2 mg/dl were excluded. Patients on antitubercular therapy, statins, antihypertensives,
Table 1: Baseline parameters (n=475)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. (%) of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (BMI)</td>
<td></td>
</tr>
<tr>
<td>Less than 25 Kg/m²</td>
<td>371 (78.10)</td>
</tr>
<tr>
<td>25.1 - 30 Kg/m²</td>
<td>65 (13.68)</td>
</tr>
<tr>
<td>30.1Kg/m² and higher</td>
<td>39 (8.21)</td>
</tr>
<tr>
<td>Baseline CD4 T-cell count</td>
<td></td>
</tr>
<tr>
<td>&gt;350 cells/mm³</td>
<td>248 (52.21)</td>
</tr>
<tr>
<td>200 – 350 cells/mm³</td>
<td>164 (34.52)</td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>63 (13.26)</td>
</tr>
<tr>
<td>Lowest CD4 T-cell count</td>
<td></td>
</tr>
<tr>
<td>&gt;350 cells/mm³</td>
<td>19 (4.0)</td>
</tr>
<tr>
<td>200 – 350 cells/mm³</td>
<td>167 (35.15)</td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>289 (60.84)</td>
</tr>
<tr>
<td>Plasma viral load, copies/ml</td>
<td></td>
</tr>
<tr>
<td>&lt; 50 copies/ml</td>
<td>233 (49.05)</td>
</tr>
<tr>
<td>≥ 50 copies/ml</td>
<td>242 (50.94)</td>
</tr>
<tr>
<td>Co-infection, n (%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>84 (17.77)</td>
</tr>
<tr>
<td>Yes</td>
<td>371 (78.10)</td>
</tr>
<tr>
<td>Time since diagnosis, median (years)</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Table 2: Baseline parameters and clinical factors associated with Vitamin D deficiency or Insufficiency

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Insufficient or deficient (&lt;30 ng/ml)</td>
</tr>
<tr>
<td>Sex</td>
<td>No (%) of patients</td>
</tr>
<tr>
<td>Male</td>
<td>288 (92.30)</td>
</tr>
<tr>
<td>Female</td>
<td>152 (93.25)</td>
</tr>
<tr>
<td>Median age, years (IQR)</td>
<td>49 (33-72)</td>
</tr>
<tr>
<td>Body Mass Index, median (IQR), Kg/m²</td>
<td>24.2 (21.3-32.4)</td>
</tr>
<tr>
<td>Time since diagnosis, median (IQR), years</td>
<td>8.18 (1.0-25.0)</td>
</tr>
<tr>
<td>Base line CD4 T-cell count</td>
<td></td>
</tr>
<tr>
<td>&gt;350 cells/mm³</td>
<td>186 (92.07)</td>
</tr>
<tr>
<td>200 – 350 cells/mm³</td>
<td>228 (93.44)</td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>26 (89.65)</td>
</tr>
<tr>
<td>Lowest CD4 T-cell count</td>
<td></td>
</tr>
<tr>
<td>&gt;350 cells/mm³</td>
<td>81 (94.18)</td>
</tr>
<tr>
<td>200 – 350 cells/mm³</td>
<td>106 (92.17)</td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>253 (92.33)</td>
</tr>
<tr>
<td>Co-infection (HBV/HCV)</td>
<td>16 (28.07)</td>
</tr>
</tbody>
</table>

Table 3: Baseline parameters and clinical factors associated with vitamin D levels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Insufficient or deficient (&lt;30 ng/ml)</td>
</tr>
<tr>
<td>Regimen containing</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>166 (66.93)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>113 (79.02)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>166 (64.84)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>45 (84.90)</td>
</tr>
<tr>
<td>Liver enzymes (U/L)</td>
<td></td>
</tr>
<tr>
<td>ALT Normal</td>
<td>312 (87.88)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>43 (12.11)</td>
</tr>
<tr>
<td>ALP Normal</td>
<td>338 (95.21)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>17 (4.78)</td>
</tr>
<tr>
<td>GGTV Normal</td>
<td>286 (80.56)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>69 (19.43)</td>
</tr>
</tbody>
</table>

This single center study included 475 patients who met the inclusion and exclusion criteria. Males comprised the majority (65.68%), 226(47.57%) of the patients were in 41-50 years age bracket. Mode of transmission was predominantly heterosexual (80.42%), no risk could be identified in 56(11.78%) of the patients. Baseline patient parameters are shown in Table 1.

248 (52.21%) patients had a baseline CD4 T-cell count of more than 350 cells/mm³, while 63(13.26%) had a count of <200 cells/mm³. Nadir CD4 T-cell count of < 200 cells/mm³ was seen in 289 (60.84%) of patients. Plasma viral load showed <50 copies/ml in approximately half of the patients. Co-infection with hepatitis B virus and hepatitis C virus was noticed in 12% of all patients.

Median time after HIV diagnosis was around 8.1 years. About 1/3 of all patients were currently smoking.

440/475 (92.63%) patients were found to be either having insufficient or deficient levels of vitamin D out of which about 34.54 % were females. Vitamin D levels of more than 30 ng/ml were found in 35 (7.36%) patients. Median age of vitamin D sufficient group was slightly higher (52.11 vs 49.95). Patients with higher body mass index (BMI) had a slightly higher rates of Vitamin D insufficiency (24.2 vs 22.3). More the time interval from the date of diagnosis higher were the chances of deficiency/insufficiency. Baseline characteristics and clinical factors associated with vitamin D deficiency/insufficiency and sufficiency are enumerated in Tables 2 and 3.

Co-infected patients with hepatitis B and C had sufficient vitamin D levels in 71.92% patients. Efavirenz (66.93%), nevirapine (79.02%), tenofovir (64.84%) and ritonavir (84.90%) containing regimens had consistently low levels of vitamin D. Abnormal liver enzymes viz alanine aminotransferase, alkaline phosphatase and gamma glutamyl transferase were associated with higher rates of deficient vitamin D levels.

Statistical analysis

Characteristics of the patients and the prevalence of vitamin D deficiency are presented for all patients on ART. Variables were described using the median and IQR for quantitative variables and proportions for qualitative variables.

Discussion

This study documents the high prevalence of vitamin D insufficiency and deficiency in an Indian cohort...
of HIV- infected adult subjects. In all around 92.63% of all patients had vitamin D deficiency or insufficiency. Out of which about 34.54% were females. A large US prospective cohort study (SUN study) assessed the prevalence of hypovitaminosis D in 672 HIV-positive subjects, demonstrating that 70.3% of them had 25(OH)D levels below 30 ng/ml19. In a cross-sectional study evaluating vitamin D status in HIV-infected postmenopausal women living in New York, Stein et al23 found that 74% out of 89 HIV-positive women had 25(OH)D levels < 30 ng/ml; the prevalence rate was similar, however, in HIV-negative controls. They also found no differences in 1,25(OH)2D levels, which were normal in both groups. Data coming from EuroSIDA study, a prospective, observational work on a large cohort of HIV positive subjects across 31 European countries, Israel and Argentina, confirmed hypovitaminosis D to be very common among HIV-positive individuals:21 23.7% out of 1985 patients had indeed 25OHD below 10 ng/ml, 65.3% between 10 and 30 ng/ml and only 11% above 30 ng/ml. Conflicting data are available about the impact of body mass index (BMI) on 25OHD levels. As in the general population, some Authors22,23 have found a negative correlation between 25OHD serum levels and BMI, possibly because of vitamin D storage in adipose tissue.24 By contrast, others have associated hypovitaminosis D with low BMI25 or have related vitamin D insufficiency with a higher risk of wasting, defined as BMI<18 kg/m². Our study has shown a median BMI of 24.2 kg/m² in vitamin D insufficient/deficient group as compared to 22.3 kg/m² in sufficient one.

The relationship between 25OHD levels and CD4+ T-cell count is not clear cut. Some studies8,30,36 have described a positive correlation, some others19,22,29,30,32 have failed to demonstrate a significant association. Our study could not link 25(OH)D levels with CD4 + T-cell count as there was hardly any change in Vitamin D levels between nadir and basal CD4+ T-cell count.

Both protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been associated with the impairment of vitamin D metabolic pathways. PIs have been shown to inhibit vitamin D 1α- and 25α-hydroxylation in hepatocyte and monocyte cultures33 reduced conversion of 25OHD to its active metabolites may potentially explain the increased 25OHD levels found by some Authors in subjects with low 1,25(OH)2D.19 As refers to NNRTIs, there is an increasing amount of data associating efavirenz (EFV) with compromised vitamin D homeostasis. EFV has been described indeed to increase 25OHD catabolism, through the induction of CYP2434 and reduced transcription of CYP2R1, a 25-hydroxylase.35,36 Welz et al37 found current EFV, but not nevirapine (NVP) use, to be associated with severe vitamin D deficiency (odds ratio (OR) 2 (CI 1.5-2.7), p < 0.001). In a recent report38, NNRTIs current use correlated with lower 25OHD levels: Pasquet et al found indeed an association between hypovitaminosis D and exposure to NNRTIs (p = 0.05), but not to EFV and NVP, probably because of a lack of statistical power of their analysis. However, considering the crude and adjusted coefficients for EFV and NVP in their regression models, the authors suggested a NNRTI class effect, rather than a specific EFV impact, on vitamin D levels. Our study showed that both EFV and NVP use are associated with higher rates of vitamin D deficiency and insufficiency rather than EFV alone and it is possibly a NNRTI class effect. Tenofovir (TDF) assumption has been associated with low BMD, because of its capability to induce proximal renal tubular dysfunction, which may cause in turn renal phosphate wasting and finally BMD loss.39 Patients starting a TDF-based regimen have a greater BMD loss in comparison with those treated with other antiretrovirals.40,41 In addition, higher PTH levels have been described in subjects receiving TDF with suboptimal 25OHD levels.42-44 Though parathyroid hormone (PTH) measurement was not part of our study, lower levels of vitamin D were demonstrated in around 65% of patients on TDF.

C. W. Gichuhi et al45 showed that sufficient vitamin D levels in serum associate with high incidence of normal enzymes while deficient levels of vitamin D were observed to strongly associate with abnormal levels of these enzymes in serum oh HIV patients not on ART. However, this trend was not observed for patients on ART with relatively lower percentages of patients with abnormal levels of these enzymes being observed in this group of patients. Our study also corroborates these findings. This may be explained by the involvement of the liver in vitamin D metabolism given that hydroxylation of vitamin D occurs in the liver and damage to the liver during HIV infection may result in low levels of vitamin D.

**Limitations**

This study had several limitations. Firstly this study was conducted in a single center and these result may not be generalized to other HIV infected populations and therefore a study including other centers should be conducted to confirm these results. Secondly 25(OH)D was measured at a single time point and we are unable to determine whether deficient vitamin D levels at a single time point or long term deficiency is biologically relevant. Thirdly neither the daily intake of vitamin D and calcium nor other lifestyle factors which could affect vitamin D levels were assessed. Fourthly some patients were on Tenofovir and NNRTI’s/PI’s, hence the confounding effect of these two drugs on 25(OH)D levels could not be assessed.

**Conclusions**

Our study confirms very high levels of vitamin D deficiency in patients on antiretroviral therapy. It would be extremely difficult to separate HIV related factors including antiretroviral related factors from the confounding risk factors, which are over represented in the HIV infected population. Efavirenz (EFV), Nevirapine (NVP), Tenofovir (TDF) and Protease Inhibitors (PI’s) were associated with high levels of deficiency/insufficiency of vitamin D levels, whether this can be attributed to these drugs alone or is part of large scale deficiency/insufficiency in general population is not very clear. Future studies are needed to verify potential alterations in vitamin D metabolism caused by the exposure to antiretrovirals and their duration of use. It would be prudent to advocate vitamin D supplementation as a global strategy in all HIV positive patients on antiretroviral therapy. More studies are required to assess the effects of vitamin D supplementation in these patients.
References

Role of 3T MRI in Evaluation of Bone Marrow Changes in Spine in Various Diseases

Anagha Joshi¹, Sukhada Kulkarni², Tilak Dedhia², Aakash Vaswani²

Abstract
Multiplanar MR imaging provides excellent spatial and contrast resolution necessary to differentiate the signal intensities of fatty (yellow) marrow elements from hematopoietic (red) marrow elements and hence it is useful for evaluation of various pathologies of bone marrow. Utilization of typical imaging features on conventional MR imaging techniques and other newer imaging techniques, such as diffusion-weighted imaging (DWI) and in- and out-of-phase MRI, for better characterisation of bone marrow pathologies has been highlighted.

Aims and Objectives
1. To determine the prevalence of various bone marrow pathologies in spine.
2. To study the MRI signal changes of bone marrow in various lesions such as anaemia, leukaemia, lymphomas and various bone marrow disorders.

Materials and Methods: A total of 100 patients who were investigated between November 2012 and October 2014 were included. MRI spine studies were done on a 3.0 Tesla Philips Achieva Medical Systems.

Observations and Results: In our study, out of 100 cases studied for various spinal pathologies, 48 patients were male and 52 were female indicating almost equal male to female distribution. Maximum cases were degenerative with most common site of involvement being lumbar followed by cervical region. There were only 3 cases of depletion disorder and no case with deposition disorder. The mean age group was 45.37 years, with the range being 9 years to 72 years. Maximum patients (n = 67) were found in the age group of 41-60.

Conclusion: Various bone marrow disorders were classified and evaluated separately. A systematic approach to its evaluation by categorization is essential with prudent use of both conventional and problem-solving techniques, such as CSI and DWI, for accurate diagnosis and appropriate patient management.

Conventional radiology depicts changes of an altered bony matrix while MRI displays changes at a cellular level and is well suited for imaging the bone marrow. MRI serves as a screening method in bone marrow disorders and the diagnosis is established in context with the clinical findings or by biopsy.

Introduction

Normal Bone Marrow
Bone marrow is divided into two main constituents, yellow and red marrow. “Yellow marrow” is considered as hematopoietically inactive and is mainly composed of fat cells while “Red marrow” in contrast, is characterized by a rich sinusoidal system and contains approximately 60% hematopoietic cells and 40% fat cells. During growth, conversion of red to yellow marrow occurs following a predictable and orderly pattern until a balanced distribution pattern is reached by the age of 25. The exact pattern of marrow changes depend on many factors like sex, age and the health of the individual. With age trabecular bone is also decomposed and replaced by fat cells, hence the increase in fatty marrow with age is greater than the reduction in volume of red marrow. Sometime reconversion of yellow to red marrow takes place if a sudden rise in the demand for haematopoiesis occurs.

Disorders that affect bone marrow can be divided into following categories: Reconversion due to hyperplasia, Marrow infiltration or replacement disorders, Depletion of hematopoietic marrow, Depletion of myeloid elements with fibrosis and Deposition of metabolic products. This article reviews MRI protocols, including routine and non-routine pulse sequences such as diffusion-weighted imaging (DWI) and in- and out-of-phase MRI and outlines a systematic approach and typical imaging features of various pathologies based on available literature.

Materials and Methods
A total of 100 patients who were investigated between November 2012 and October 2014 were included. MRI spine studies were done on a 3.0 Tesla Philips Achieva Medical Systems.

Indications
A prospective study of 100 patients who presented to the OPD or Emergency department or admitted with clinically suspected pathology involving the axial skeleton underwent MRI of spine on an elective basis. Standard tests (history taking, physical examination, relevant blood investigations) were directed to all patients, whereas, the mode of additional imaging (x-ray spine or x-ray/CT chest and abdomen in patient with primary at other known location) was also carried out.

Inclusion Criteria
Clinical suspected pathology involving the axial skeleton.

Biochemical examination suggestive
of deranged haematological profile / Ineffective haematopoiesis (like in cases of thalassemia)

In patients with known primary malignancy presented with backache.

In patients with backache radiating to extremities without any previous significant past history.

In patients with hyperparathyroidism.

**Exclusion Criteria**

Patients not consenting for the study

 Intracranial aneurysm clips (Unless the referring physician is certain that it is made of non-ferromagnetic material such as titanium)

 Intra-orbital metal fragments

 Any electrically, magnetically or mechanically activated implants

1. Including cardiac pacemakers, biostimulators, neurostimulators,

2. Cochlear implants and hearing aids.

 Pregnancy (Risk Vs benefit ratio to be assessed).

 Known h/o contrast allergy.

 Other implanted medical devices (eg. Swan Ganz catheter).

 Metal shrapnel or bullet.

 For use of MR contrast (gadolinium):

1. Lactating women

2. Patients with moderate to severe renal insufficiency (i.e. with GFR<30ml/min or a S. creatinine> 2mg/dl)

**Imaging Technique**

The MRI appearance of the bone marrow depends on the pulse sequence used for its evaluation as well as on the relative amount of water, fat, protein and cells within the bone marrow. Among these the major determinants of the MR appearance of bone marrow are the fat and water content.

The routine spine evaluation on MRI typically includes T1-weighted, T2-weighted, and Short Tau Inversion Recovery (STIR) sequences. Post-contrast (intravenous gadolinium) fat-suppressed T1W imaging should always include pre-contrast baseline fat-suppressed T1W imaging in at least one plane. Several non-routine MRI sequences include T1 FLAIR Imaging, Diffusion-weighted imaging (DWI), in- and out-of-phase MRI, MR spectroscopy (MRS), and dynamic contrast enhanced MRI (DCE-MRI). These aid in enhancing contrast and visualize changes in the bone marrow at a molecular level.

**Observation and Results**

**Prevalence of various bone marrow disorders**

Out of 100 patient studied following diagnoses were made. Diagnosis and relative frequency of occurrence of various bone marrow disorders has been given below (Table 1).

**Age distribution**

The patients were divided on the basis of age group. Maximum patients (n = 67) were found in the age group of 41-60. Otherwise an equal distribution was seen in all age groups. The mean age group was 45.37 years, with the range being 9 to 68 years. Age distribution of the bone marrow disorders has been given below (Table 2).

**Degenerative disorder**

In our study of various spinal pathologies, there were 60 cases (60%) of degenerative changes of spine on MRI - Disc degeneration, Disc bulge, Disc herniation, Modic changes, Canal stenosis/Nerve root compression. Various types of degenerative changes and their frequency of distribution has been given below (Table 3).

**Classification of Infiltrative / Replacement diseases**

In our study of various spinal pathologies, there were 16 cases (16 %) of infiltrative / replacement disorders of spine, of which most common pathology was metastasis found in 11 cases (68.7%). Marrow can be replaced by either neoplastic disorders or non-neoplastic disorders. Various neoplastic diseases include metastatic disease, lymphoma, leukemia, and multiple myeloma. These cases were confirmed pathologically with bone biopsy. Various types of infiltrative / replacement disorders and their frequency of distribution has been given below (Table 4).

**Classification of Reconversion disorder**

Reconversion disorders can be classified in to the chronic anemia, hyperparathyroidism and miscellaneous conditions (Heavy smoking, increase oxygen requirements), there were total 11 (11%) cases of reconversion disorders of spine in our study, of which most common was chronic anaemia due to thalassemia accounting for approximately 45.5% (5 cases) of all reconversion disorders. Cases of thalassemia and sickle cell disease were proven clinically and with blood parameters and Hb electrophoresis. Cases of hyperparathyroidism were proven clinically and with blood parameters viz S. PTH, calcium and phosphate levels. Various types of reconversion disorders and their frequency of distribution has been given below (Table 5).

**Classification of Depletion disorders**

In our study, there were 3 (3%) cases of depletion disorders. Various depletion disorders can be classified in to depletion disorders secondary to radiotherapy, chemotherapy, idiopathic and depletion disorders with fibrosis (myelofibrosis), aplastic anaemia and tabulated below. Various types of depletion disorders and their frequency of distribution has been given below (Table 6). Bone biopsy was performed for confirmation.
on many MRI scans in asymptomatic subjects, thus questioning its specificity.

**Prevalence of bone marrow pathologies**

In our study of 100 patients of various spinal pathologies, around 60% were degenerative disorders. Among the various bone marrow pathologies, after excluding degenerative changes, most common pathology was infiltration/replacement disorder (16%) of which most common was metastasis. Second most common pathology was reconversion disorder (11%) followed by focal disorders of bone marrow (10%). Least common pathologies were Depletion disorders and Deposition disorders. Vogler et al, have grouped the bone marrow pathologies into reconversion disorder, infiltration disorders, depletion disorders, bone marrow edema and bone marrow ischemia.4

**Age Distribution**

In our study patients were found in all age groups with the mean age group being 45.3 years, with the range being 9 years to 68 years. The mean age group of above 45 is expected considering that a major cause of various marrow pathologies are degenerative and infiltrative / replacement disorder of which most common is metastasis, which tend to occur in elderly population.

**Discussion**

The role of diagnostic imaging is to provide accurate anatomic information and to affect the management decision making.1 This cross-sectional hospital based study used MRI to diagnose various bone marrow pathologies in spine as it has better tissue differentiation and it can show bone marrow changes at an early stage as compared to other imaging techniques (such as CT Scan and radiographs). Other advantages of MRI include a) no known side effects or morbidity, b) no radiation exposure and is c) non-invasive.2,3 Despite its high sensitivity, few of the marrow changes are observed

### Table 4: Various types of infiltrative / replacement disorders and frequency of distribution.

<table>
<thead>
<tr>
<th>Infiltrative / replacement disorders</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>11 (68.7%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Non-neoplastic disorders</td>
<td>3 (18.8%)</td>
</tr>
</tbody>
</table>

### Table 5: Various types of reconversion disorders and frequency of distribution.

<table>
<thead>
<tr>
<th>Reconversion disorders</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic anaemia : Sickle cell anaemia</td>
<td>1 (9.09%)</td>
</tr>
<tr>
<td>Chronic anaemia : Thalassemia</td>
<td>5 (45.4%)</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>2 (18.1%)</td>
</tr>
<tr>
<td>Others (Heavy smoking, increase Oxygen requirements)</td>
<td>3 (27.2%)</td>
</tr>
</tbody>
</table>

### Table 6: Various types of depletion disorders and frequency of distribution.

<table>
<thead>
<tr>
<th>Depletion disorders</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown cause</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>Aplastic anaemia</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>Secondary to chemo or radiotherapy</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

### Table 7: Various types of focal disorders and frequency of distribution.

<table>
<thead>
<tr>
<th>Focal disorders of bone marrow</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal edema(Infection)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>4 (40%)</td>
</tr>
</tbody>
</table>
Dual-FFE sequence was done in only 5 patients with metastasis; increased signal was noted in all the 5 patients on out phase (Figure 2 A, B).

**Lymphoma**

When lymphoma involves the spine, it is more commonly found isolated to the epidural space as a result of secondary spread. Tumour location within the epidural space can vary, but there is a proclivity for the thoracic levels. 12,13

On MRI, Spinal lymphoma is typically hypointense on T1 and in homogenously hyperintense on T2W. 14 In our study, in patients with lymphoma, lesions were hypointense on T1 and hyperintense on T2. There was no significant post contrast enhancement in either of the patients.

**Reconversion Disorder**

11 cases of reconversion disorders of spine seen in our study, of which most common was chronic anaemia due to thalassemia followed in order were hyperparathyroidism and sickle cell anaemia and other causes like increase oxygen requirements and heavy smoking.

**Hemolytic Anaemia-Thalassemia**

Signal characteristics of marrow were compared with those of surrounding muscle and fat. Fatty marrow (isointense with subcutaneous fat) was compared with red marrow (hypointense to fat and slightly hyperintense to muscle). Marrow hypointense to muscle was identified as iron deposition within red marrow.

There are only a few studies addressing marrow SI in transfusion-dependent patients with thalassemia 15,16 and sickle cell anaemia 17,18 by using T1- and T2-w SE sequences. They report the presence of hypointense bone marrow in both T1- and T2-w images as attributed to iron deposition. 15-18 In our study, we found that 3 out of 5 patients (60%) with thalassemia had diffuse bone marrow hypointensity in all MR sequences (Figure 3 A, B). 2 out of 5 patients (40%) had hypointensity on the T2*-W GRE sequence alone without any significant post contrast enhancement. Hence, findings were almost consistent with previous data.

Fig. 2: In this k/c/o carcinoma prostate, multiple hyperintense lesions are seen scattered throughout the dorsal vertebral bodies and appear hyperintense in in-phase sequence (A) and do not suppress on out-phase sequence (B) s/o infiltrative disorder

Fig. 3: In this k/c/o Thalassemia major patient, vertebral bodies show diffuse hypointensity on T1 W (A), T2 weighted (B) sequences compared to intervertebral disc s/o Marrow Reconversion

their high water content. Metastases often (but not consistently) have a rim of bright T2 signal around them (a halo sign). 11 The halo sign and diffuse signal hyperintensity were shown to be a strong indicator of metastatic disease. In our study, all patients with metastasis had hypo to isointense signal on T1 and heterogeneously hyperintense signal on T2 with 4 out of 11 were showing halo sign and 6 out 11 were showing the post contrast enhancement. Hence, findings were almost consistent with previous data.
and lumbar vertebral bodies\(^9\). In our study there was diffuse T1 and T2 hypointensity noted in all patients with depletion disorders (Figure 4 A, B).

### Focal Disorders of Bone Marrow

#### Trauma

In our study, out of 4 patients with trauma to spine, 3 patients had injury and associated vertebral fracture involving cervical vertebra while rest 1 had fracture involving the thoracic region.

In study conducted by us, there were 4 patients of benign traumatic fractures; all had diffusely hypointense signal on T1-weighted images and hyperintense signal on FSE T2-weighted fat-suppressed images and contrast given to 1 patient showed contrast enhancement (Figure 5 A, B).

#### Infection (Tuberculous spondylitis)

Thoracolumbar spine is most common site of involvement in Tuberculous Spondylitis (50% of patients). Each of cervical spine and lumbar spine are involved in 25% of patients.\(^{20}\) In our study, there were 6 patients of Tuberculous Spondylitis out of which 5 had thoracolumbar spine involvement (i.e. 83.33%) and 1 had multiple level diffuse involvement (16.67%).

### Conclusion

Bone marrow lesion can be seen as a non-specific finding in a variety of conditions. A systematic approach to its evaluation by categorization is essential with prudent use of both conventional and problem-solving techniques, such as CSI and DWI, for accurate diagnosis and appropriate patient management.

Conventional radiology depicts changes of an altered bony matrix while MRI displays changes at a cellular level and is well suited for imaging the bone marrow. It is very sensitive, although the specificity of MRI findings is not always without fallacies. Hence MRI serves as a screening method in bone marrow disorders and the diagnosis is established in context with the clinical findings or by biopsy.

In Hodgkin’s lymphoma marrow involvement is detected more often with MR than with marrow biopsy. In low-grade NHL the involvement is diffuse and biopsy is superior. In high-grade lymphomas the involvement is more focal and MRI is more efficient. Also, the nodular nature of

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*Fig. 4: There is diffuse hypointensity noted on both T1 W (A) and T2 weighted (B) sequences involving the vertebral bodies compared to intervertebral disc resulting in a “black marrow”*

*Fig. 5: Fracture line appears hypointense on T1 W (A), T2 weighted (B) sequences and hyperintense signal of marrow on T2 weighted sequence indicating marrow edema*
Correlation of Thyroid Function Test with Severity of Liver Dysfunction in Cirrhosis of Liver

Nilesh Kumar Patira1, Nirali Salgiya2, Deepak Agrawal3*

Abstract

Aims and Objectives: To evaluate the Thyroid functions in patients with cirrhosis of liver and to assess the severity of liver dysfunction in relation with interpretation of thyroid functions.

Material and Methods: The present study was undertaken at Maharana Bhopal Govt. Hospital, attached to R.N.T. Medical College, Udaipur (Raj.). Study included total 50 patients admitted at Maharana Bhopal Govt. Hospital, attached to R.N.T. Medical College Udaipur (Raj.) with clinical, biochemical, and radiological evidence of cirrhosis of liver. All patients were subjected to medical examination as per the fixed Performa.

Observations and Conclusion: Prevalence of subclinical hypothyroidism with cirrhosis was 62%. 31 out of 50 patients had subclinical hypothyroidism. The study showed that prevalence of hypothyroidism in cirrhosis patients increases as the severity of cirrhosis increases and findings were statistically significant (p value 0.00). This study found association between serum T3 and severity of liver disease. As the severity of cirrhosis increases which is indicated by Child Pugh A to C, serum level of T3 reduces and findings were statistically significant (p value 0.00). All 50 patients of cirrhosis had their serum T3 level within normal or below normal value and findings were statistically significant (p value 0.00). This study found association between serum FT3 and severity of liver disease. As the severity of cirrhosis increases which is indicated by Child Pugh A to C, serum level of FT3 reduces. All patients of Child Pugh C had low FT3 level and the findings were statistically significant (p value 0.00). This study showed that serum bilirubin, prothrombin time, INR, TSH level increases and serum albumin level, T3, FT3, and FT4 level reduces as the severity of cirrhosis increases.

According to this study all cirrhotic patients should undergo thyroid function evaluation as these patients are definitely associated with development of hypothyroidism. There is significant inverse correlation between serum level of T3, FT3, and FT4 with severity of cirrhosis. These parameters can be used as markers to indicate the severity of cirrhosis.

References


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Assistant Professor, Department of Medicine, American International Institute of Medical Sciences, Udaipur, Rajasthan; **Senior Demonstrator, Department of Biochemistry, R.N.T. Medical College, Udaipur, Rajasthan; †ADMO, Central Hospital, North Western Railway, Jaipur, Rajasthan; Received: 30.06.2016; Revised: 01.02.2017; Accepted: 06.10.2018
Introduction

The liver plays the dominant role in the metabolism of thyroid hormones. It is here that 5’deiodinase enzyme act to convert part of T4 to T3. There are eight further circulating iodothyronines. The rT3, mainly derived from T4, appear to be a major inhibitor of T4 and T3. Thus if rT3 increases, the metabolic effect of T3 and T4 decreases. In the course of some chronic systemic disease (hepatic cirrhosis) rT3 increases simultaneously with the decrease of T3 level. Therefore one can describe particular alteration of thyroid pattern of chronic liver disease; low T3 syndrome, low T3 and T4 syndrome or high T4 syndrome mixed form.

T3 and T4 diminish due to inefficient hepatic deiodinization and defective hepatic cellular uptake. T4 level decreases, most likely because of an inefficient production of thyroid binding globulin or due to the action of peripheral binding inhibitors. During acute liver disease and primary biliary cirrhosis one can observe an increase of T4 and TBG together with an increase of the acute phase proteins. Such complex hormonal mechanisms are not influenced by TSH, which appear normal or inhibited, as the TRH stimulation test is normal. The explanation can be found in an enhanced conversion of T4 to T3 in the pituitary gland.

The biological and clinical significance of these mechanisms might be that of creating a “protective” state of an organ in a catabolic state by reducing the circulating thyroid hormone T3. A relation has been found between circulating hormone level particularly the T3, rT3, and rT3/ T3 ratio, and the hepatic functional insufficiency. In different types of liver diseases, similar processes may occur to those seen in the sick euthyroid syndrome, but in addition a number of changes specific to the type or stage of liver disease is also found.

The most consistent thyroid hormone profile in patients with cirrhosis are a low total and free T3 and an elevated rT3, probably reflecting a reduced deiodinase type 1 activity resulting in reduced conversion of T4 to T3. This results in an increase in conversion of T4 to rT3 by the deiodinase type 3 system and an increase in the rT3 to T3 ratio.

The plasma T3/rT3 ratio has a negative correlation with the severity of cirrhosis when assessed in non-alcoholic cirrhotic. Since T3 and rT3 bind to the same plasma proteins, the T3/rT3 ratio provides a parameter of liver function that is largely independent of protein binding. Both the T3/rT3 ratio and free T3 levels in plasma thus provide a correlation of liver function in cirrhosis, and are of prognostic value, albeit seldom used.

In cirrhosis of liver several hormones may be affected, including insulin and glucagon due to deamination defects, glucocorticoid and gonadal steroids due to a conjugation defects, and thyroid hormone due to an iodination defect.

Numerous clinicians have reported a sub clinical hypothyroidism in patients with chronic liver disease. Although studies in different populations vary in their findings with respect to the type and degree of thyroid dysfunction in cirrhosis, but found to have consistently low FT3 in the face of a normal TSH and a clinical euthyroidism. Not only the free hormone level has been delineated as an indicator of thyroid dysfunction, but FT3 level has also been correlated with the degree of liver dysfunction.

Material and Methods

The present study entitled “Correlation of Thyroid Function Test with Severity of Liver Dysfunction in Cirrhosis of Liver” was undertaken at Maharana Bhupal Govt. Hospital, attached to R.N.T. Medical College, Udaipur (Raj.).

Patients

This study included total 50 patients admitted in Maharana Bhupal Govt. Hospital, attached to R.N.T. Medical College Udaipur (Raj.) with clinical, biochemical, and radiological evidence of cirrhosis of liver.

All patients were subjected to medical examination as per the fixed Performa.

Inclusion criteria

Patients with clinical, biochemical, and radiological evidence of cirrhosis of liver.

Patients who himself or his/her relatives gave consent.

Exclusion criteria

Patients with diabetes. Pregnant subjects.

Patient with prior h/o thyroid disease.

Patient receiving drugs that may interfere with thyroid hormone metabolism and function.

Patient with any other chronic illness (except liver cirrhosis).

Sample analysis

Fasting morning blood sample was collected.

The samples of blood were allowed to stand to clot. Serum was separated by centrifugation and analyzed by following methods.

Thyroid function test was measured with the COBAS e 411 analyser which is an automated random-access; multi-channel analyzer for immunological assay (Roche Diagnostic Ltd.). It is designed for both qualitative and quantitative in vitro determination of a wide range of chemicals by use of electro-chemiluminescence technology.

Estimation of T3, T4, and TSH by electro-chemiluminescence immunoassay (ECLIJA)

Estimation of T3 & T4

The principle & procedure for estimation of FT3 & FT4 are similar.

Principle: (Competition principle). The T3 and T4 assay employs a competitive test principle with polyclonal antibodies specially directed against T3 and T4. Endogenous T3 and T4 released by the ion of 8 anilino-1-naphthalene sulphonic Acid (ANS) competes with the added biotinylated T3 and T4 derivative for the binding sites on the antibodies labeled with the ruthenium complex.

Procedure: Total duration of assay 18 min.

1st incubation: 30 micro liter sample

2nd incubation: After addition of streptavidin-coated micro particles and biotinylated T3, the still free binding sites of the labeled antibody become occupied with formation of an antibody-hapten complex. The entire complex bounds to the solid phase via interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the
micro particles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with procell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photo multiplier.

Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

Reagents
Streptavidin-coated micro particles contain 0.72 mg/ml in preservative.
Anti T3-Ab & Anti T4-Ab (separate for both) contains polyclonal Anti-T3 & Anti T4 antibody (sheep) labeled with ruthenium complex 75 ng/ml for T3 & 1 mg/ml for T4; phosphate buffer 100 mmol/l pH 7.4; preservative for both.

T3 or T4 — biotin: Contains biotinylated T3 3 ng/ml & biotinylated T4 3 ng/ml & phosphate buffer 100 mmol/l pH 7.2 in preservative.

Estimation of TSH

Principle: (Sandwich principle)
The TSH assay employs monoclonal antibody specifically directed against human TSH. The antibodies labeled with ruthenium complex consist of chimeric construct from human & mouse specific components. As a result interfering effects due to HAMA (human anti -mouse antibodies) are largely eliminated.

Procedure: Total duration, 18 min.
1st incubation: 50 µl of sample, a biotinylated monoclonal TSH specific antibody and a monoclonal TSH specific antibody labeled with a ruthenium complex react to form a sandwich complex.
2nd incubation: After addition of streptavidin coated micro particles, the complex becomes bound to the solid phase via interactions of biotin & streptavidin.

The reaction mixture is aspirated into the measuring cell where the voltage to the electrode then induces chemiluminescent emission which is measured by photomultiplier.

Results are determined via calibration curve which is instrument-specifically generated by 2 point calibration and a master curve provided via the reagent barcode.

Reagents
Streptavidin-coated micro particles contain 0.7 mg/ml in preservative.
Anti-TSH-Ab Contains monoclonal anti-TSH antibody (mouse/human) labeled with ruthenium complex 1-2 mg/l; phosphate buffer 100 mmol/l pH 7.2 in preservative.

Results
A total of 50 patients with cirrhosis of liver were selected. Majority of patients 36 (72%) belonged to age group 41-60 yrs., 9 (18%) patients were below 40 yrs. of age and 5 (10%) patients were above 60 yrs. of age. 39 (78%) patients were male, and 11 (22%) were female. 26 (52%) patients were from rural areas and 24 (48%) patients were from urban areas. Most common etiology of liver cirrhosis was Alcoholism which comprised 35 (70%) patients, 13 (26%) patients had HBV related cirrhosis, and 2 (4%) patients had HCV related cirrhosis. 37 (74%) patients had serum Free T3 level more than 3.10 pmol/L and 13 (26%) patients had serum Free T3 level below 3.10 pmol/L. Normal Free T3 Level is 3.10-6.80 pmol/L. 45(90%) patients had serum Free T4 level more than 12 pmol/L and 5(10%) patients had serum Free T4 level below 12 pmol/L.

Table 1: Distribution of patients according to FT3 levels

<table>
<thead>
<tr>
<th>FT3 levels (pmol/L)</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3.10</td>
<td>37</td>
<td>74.00</td>
</tr>
<tr>
<td>&lt; 3.10</td>
<td>13</td>
<td>26.00</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100</td>
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</tbody>
</table>

Table 2: Distribution of patients according to FT4 levels

<table>
<thead>
<tr>
<th>FT4 levels (pmol/L)</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 12</td>
<td>45</td>
<td>90.0</td>
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<tr>
<td>&lt; 12</td>
<td>5</td>
<td>10.0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3: Distribution of patients according to TSH levels

<table>
<thead>
<tr>
<th>TSH levels (µIU/ml)</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.27</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.27-4.20</td>
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</tr>
<tr>
<td>&gt; 4.20</td>
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<td>62.0</td>
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<tr>
<td>Total</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4: Distribution of patients according to child pugh score

<table>
<thead>
<tr>
<th>Child pugh score</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (5-6)</td>
<td>13</td>
<td>26.0</td>
</tr>
<tr>
<td>B (7-9)</td>
<td>26</td>
<td>52.0</td>
</tr>
<tr>
<td>C (10-15)</td>
<td>11</td>
<td>22.0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100</td>
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</table>

Table 5: Comparison of child pugh score with FT3 levels

<table>
<thead>
<tr>
<th>FT3 levels (pmol/L)</th>
<th>Child Pugh score</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>7-9</td>
<td>10-15</td>
</tr>
<tr>
<td>&gt; 3.10</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>&lt; 3.10</td>
<td>0</td>
<td>0</td>
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Table 6: Comparison of child pugh score with FT4 levels

<table>
<thead>
<tr>
<th>FT4 levels (pmol/L)</th>
<th>Child Pugh score</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>5-6</td>
<td>7-9</td>
<td>10-15</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>&lt; 12</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 7: Comparison of child pugh score with TSH levels

<table>
<thead>
<tr>
<th>TSH levels (µIU/ml)</th>
<th>Child Pugh score</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>7-9</td>
<td>10-15</td>
</tr>
<tr>
<td>&lt; 0.27</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.27-4.20</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 4.20</td>
<td>2</td>
<td>18</td>
</tr>
</tbody>
</table>
who were categorized in Child Pugh A, out of them 11 patients had normal serum TSH level and 2 patients had TSH level more than 4.20 μIU/ml. 26 (52%) patients who were included in Child Pugh B, out of them 8 patients had normal TSH level and 18 patients had TSH level more than 4.20 μIU/ml. 11 (22%) patients who were categorized in Child Pugh C, all of them had TSH level more than 4.20 μIU/ml. Study demonstrated that as the severity of cirrhosis increased from Child- Pugh A to C serum level of TSH started to rise above normal level (p value 0.00).

Discussion

In this cross sectional study it was seen that prevalence of hypothyroidism in cirrhosis patient was 62% i.e. 31 out of 50 cirrhotic patients had increased TSH level. The prevalence of hypothyroidism increases as the severity of liver cirrhosis increases. All 31 patients did not have clinical signs of hypothyroidism and there TSH level was also in subclinical range of hypothyroidism. 23(46%) out of 31 patients with hypothyroidism were male indicating that hypothyroidism is more common in male cirrhotic.

Regarding the etiology of cirrhosis in those with hypothyroidism our study found alcoholic cirrhosis to be the most common etiology. Our study showed that as the severity of liver disease increases indicated by Child Pugh grade A to C the prevalence of reduced serum FT3 level increases (p value<0.00). This study was supported by Agha F et al study which confirms the presence of abnormalities in serum thyroid hormone levels in cirrhosis of liver. Alteration in serum T3 and FT3 levels correlate well with the disease severity and may be useful in assessing the course and prognosis in cirrhotic patients.

Conclusion

According to this study all cirrhotic patients should undergo thyroid function evaluation as these patients are definitely associated with development of hypothyroidism. As the study suggest significant inverse correlation between serum level of FT3, FT4 and TSH with severity of cirrhosis. These parameters can be used as markers of severity of cirrhosis.

References

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To Evaluate the Association of Neck Circumference with Metabolic Syndrome and Cardiovascular Risk Factors

Rajesh Kumar Bochaliya¹, Aradhna Sharma²*, Puneet Saxena³, GD Ramchandani⁴, Girish Mathur⁵

Abstract

Background: It is accepted that metabolic syndrome increases the relative risk of cardiovascular disease and visceral adiposity lies at root of the cardio-metabolic risk. Upper body fat distribution has long been recognized as associated with metabolic syndrome and increased cardiovascular risk; hence the present study was conducted with the objective to evaluate the association of neck circumference with metabolic syndrome and cardiovascular risk factors.

Material and Methods: The present study was a hospital-based observational, Descriptive and comparative analysis, conducted at Department of General Medicine at a tertiary care centre of west India after Ethical clearance from the institute’s ethical committee and written informed consent. A total of 405 subjects aged 18 – 60 years were selected consecutively after inclusion and exclusion criteria. Subjects were evaluated for metabolic syndrome components and cardiovascular risk factors. Neck circumference of ≥ 37 cm in males and ≥ 34 cm in females was considered abnormal.

Results: Metabolic syndrome was seen in 189 (46.7%) subjects. Raised triglyceride level was the most common (52.8%) component. Neck circumference was found to be statistically significant associated with metabolic syndrome (p<0.001) as well as cardiovascular risk factors like BMI, Waist circumference, Hypertension, Fasting blood sugar, TG and HDL were also found to be statistically significant associated with neck circumference.

Conclusion: Neck Circumference can be used as a sensitive tool for metabolic syndrome and cardiovascular risk factors. Patients with abnormal Neck circumference should be screened for cardiovascular risk factors to detect abnormality for early and appropriate intervention.

Introduction

Metabolic syndrome is defined as a set of risk factors that includes insulin resistance, dyslipidemia, abdominal obesity and high blood pressure, increases the risk of cardiovascular diseases and diabetes.1,2 Globally, the prevalence of metabolic syndrome may range from 8 to 13% in men and 2 to 18% in women depending on the population and definitions used.3,4 In India, studies have reported prevalence varying upto 24.9% in northern India and 41% in Southern India using different definitions.5,6

Upper body obesity have been found to be more strongly associated with glucose intolerance, hyperinsulinemia, diabetes, hypertriglycerideremia and has long been recognized as related to increased cardiovascular disease risk, and neck skin fold7,8 or neck circumference (NC) has been used as its index.8,9 NC has been reported to be a simple and time-saving screening measure to identify high risk overweight and obese individuals. It has been shown that men with a NC < 37 cm and women with a NC < 34 cm probably have a less chance of developing metabolic syndrome.10 Evidence regarding clinical significance of Neck Circumference in cardio-metabolic syndrome is limited and needs to be further clarified hence present study aimed to investigate the independent contribution of NC to cardio-metabolic risks. This study could present a novel approach for screening cardio-metabolic risks.

Material and Methods

The present study was a hospital-based observational, Descriptive and comparative analysis, conducted at Department of General Medicine at a tertiary care centre of west India after Ethical clearance from the institute’s ethical committee and written informed consent. A total of 405 subjects aged 18 – 60 years were selected consecutively after inclusion and exclusion criteria, from patients attending Medicine Out Patient Department. Sample size was calculated at α-error 0.05 and study power 80% and was adequate to assess an expected proportion of neck circumference abnormality among metabolic syndrome and normal patients to be 60% and 38.6% respectively.11

Subjects taking antihypertensive, antilipid, anti diabetic drugs, weight reduction drugs and those who had undergone neck or abdominal surgery and those with h/o malignancy or thyroid disease were excluded from study. Detailed medical history, General and physical examination, Anthropometric indices, Neck Circumference, Waist Circumference, FBS and Lipid profile were measured as per standard methods. NC was measured with plastic tap calibrated to one millimeter with head positioned in horizontal plane and superior border of plastic tap placed just below the laryngeal prominence and applied...
perpendicular to the long axis of the neck. Neck circumference of ≥ 37 cm in males and ≥ 34 cm in females was considered abnormal.

Statistical analysis

Qualitative data was presented as number and proportions and associated between qualitative variables was analyzed using Chi square test or Fischer exact test as applicable. Quantitative data was presented as mean and standard deviation. A p value less than 0.05 were taken as statistically significant.

Results

The mean age of study subjects was 44.7 ± 18.3 years. There were 211 (52.1%) female and 194 (47.9%) males in the study population. The mean BMI of the study population was 27.51 ± 4.53 Kg/m². Based on the IDF criteria, 189 (46.7%) subjects were found to have metabolic syndrome.

Metabolic syndrome was seen in 189 (46.7%) subjects. Raised triglyceride level was the most common (52.8%) individual component of metabolic syndrome followed by abnormal waist circumference seen in 50.86% (Table 1 and Figure 1). Overall, the mean neck circumference was 39.08 ± 2.315 cm. Among the males the mean neck circumference was 38.91 ± 1.956 cm and in females it was 39.23 ± 2.597 cm.

Neck circumference was found to be significantly associated with metabolic syndrome (p<0.001). Individual components like BMI, waist circumference, Hypertension, Fasting blood sugar TG and HDL were also found to be significantly associated with neck circumference (Table 2 and Figure 2).

Discussion

Present study was undertaken to evaluate the relationship of NC with metabolic syndrome and cardiovascular risk factors. Studies like that by Ravikiran M et al have
showed that metabolic syndrome and cardiovascular risk in Asian Indians/South Asians are increased by their relative increase in body fat mass, truncal subcutaneous fat mass, intra-abdominal fat mass, and also by ectopic fat deposition like neck region.

In the present study, significant association was found between neck circumference and metabolic syndrome (P<0.001) and its individual components. All subjects with metabolic syndrome had abnormal neck circumference using age specific criteria. Kumar S et al\textsuperscript{13} had hypothesized that NC could be a predictor of obesity and overweight in rural Indian population and that higher tertile of neck circumference may be associated with higher prevalence of cardiovascular risk factors like hypertension and diabetes. Ben-Noun L et al\textsuperscript{14-16} have also indicated that neck circumference may be an independent correlate of metabolic risk factors above and beyond BMI and waist circumference.

In a study to identify overweight patients by measuring neck circumference Ben-Noun L et al\textsuperscript{16} in 2001, reported that Men with NC <37 cm and women with NC <34 cm may not be considered overweight. It was found that NC >37 cm for men and >34 cm for women were the best cutoff levels for determining the subjects with higher BMI of >25.0 kg/m\textsuperscript{2}.

The Fat Redistribution and Metabolic study had showed that increased levels of upper-body Subcutaneous fat were positively associated with LDL cholesterol and inversely associated with HDL cholesterol levels, after adjustment for demographic and lifestyle factors.\textsuperscript{17} Systemic free fatty acid concentrations are known to be primarily determined by upper-body subcutaneous fat, suggesting that this fat depot may play an important role in risk factor pathogenesis. Elevated free fatty acid concentrations have been associated with insulin resistance, increased VLDL cholesterol production, and endothelial cell dysfunction.\textsuperscript{18}

In present study, abnormal neck circumference was also found in many individuals without metabolic syndrome. These false positives results could be because abnormalities in components of metabolic syndrome were present in these patients but criteria were not fulfilled as a whole metabolic syndrome.

Another study done in Israel reported a strong correlation between NC, BMI and other upper-body obesity indexes (WC and waist-to-hip ratio). NC also strongly correlated with SBP, DBP, total cholesterol, LDL-cholesterol, triglycerides, fasting glucose, and uric acid levels.\textsuperscript{19} No significant correlation was found between NC and HDL-cholesterol levels, which were similar with present study results.

These novel findings presumably reflect NC is an indicator of central obesity and other cardio-metabolic risk factors and metabolic syndrome as a whole. Evaluation of NC based on single measurements might be considered a minor limitation.

**Conclusion**

Upper-body fat distribution has long been recognized as related to increased cardiovascular disease risk and Neck Circumference could be used as an index. NC can be use as a sensitive marker for metabolic syndrome although not specific. Patients with abnormal Neck circumference should be screened for cardiovascular risk factors and followed up at regular intervals to detect abnormality at earliest for prevention of cardiovascular disease.

**References**


Pattern of Poisoning in a Tertiary Care Center with Special Reference to Odollam Poisoning

Renymol B¹, Suma TK²

Abstract

Introduction: Suicide is a major public health challenge in Kerala. Majority of adult poisoning is intentional. Most of those who attempt ‘deliberate self harm’ are young adults and many a time the reason is trivial.

Objectives: To find out the pattern of poisoning, prognostic factors in different type of poisoning, precipitating factors for deliberate self harm and to suggest preventive measures

Methodology: This was a prospective observational study conducted among patients admitted with history of poisoning in a tertiary care centre in Kerala. Detailed history, physical examination, relevant lab investigations were done in all the patients. Psychiatric assessment and counselling was done in all survivors.

Results: A total of 195 patients were included in this study-109 males and 86 females. The intention of poisoning was suicidal in 98.82% of cases. The mortality rate was 13.33%. Common poisons consumed were odollam, drugs, pesticides and rodenticides. Majority of deaths were due to organophosphorous compounds (42.31%) followed by odollam (38.46%). The common precipitating factors were family problems, personal stressors and marital discord in both sexes. Psychiatric assessment showed adjustment disorder as the commonest problem followed by impulsive act.

Conclusion: The common poisons ingested are organophosphorous compounds, drugs and odollam. Organophosphorous and odollam carries higher mortality. Pesticide regulation, use of less toxic pesticides in agriculture, early management and quick referral to well equipped hospitals will help in reducing mortality. Suicide prevention programmes like psychosocial support and counselling, raising public awareness about deliberate self harm and alcohol de-addiction programmes will help in reducing the incidence of deliberate self harm.

Introduction

Over 800,000 people commit suicide every year and there are many more who attempt suicide.¹ In 2012, suicide was the second leading cause of death among 15-29 year olds globally.¹ WHO estimated that nearly 1,70,000 people commit suicide every year in India.²³ Of these, 29.10% of suicides were due to poisoning (NCRB 2014 report).⁴ The common methods adopted by the patients include ingestion of organophosphorous compounds, rodenticides, drug overdose, vegetable poisons etc.

Suicide is a major public health challenge in Kerala. The suicide rate in Kerala (23.9 out of every 1,00,000 population) is much higher compared to the National rate of 10.6 out of every 1,00,000 population in 2014.⁴ Attempted suicides tend to occur 8 to 20 times more frequently than completed suicides.⁵

Poisoning constitute an important cause of admission to the casualty departments of hospitals. Such admissions carry significant mortality also. Majority of adult poisoning are intentional. Most of those who attempt ‘deliberate self harm’ are young adults. Psychological analysis of these patients has revealed that many a time the reason is trivial. Hence, there is definitely a case for prevention of such incidents. In this study we tried to find out the pattern of poisoning in adults admitted to Govt T. D. Medical College, Alappuzha over a period of one year with special reference to the substance used, socio-demographic factors, precipitating factors, prognostic factors and management measures to be adopted.

Objectives

To find out the pattern of poisoning among patients admitted to Medical College, Alappuzha over a period of One year.

To look for prognostic factors in different poisoning cases.

To find out any specific precipitating factors for deliberate self harm and also to suggest preventive measures.

Methodology

This prospective observational study was done at Govt T.D. Medical College, Alappuzha from March 2012 to October 2012. All patients admitted with history of alleged consumption of poison were included in the study after obtaining written, informed consent. The protocol for the study was approved by the Institutional Ethics Committee of Govt. TD Medical College, Alappuzha.

Detailed history was gathered including the nature of poison, time of ingestion, quantity of poison ingested, precipitating causes, past and family history of DSH or psychiatric illness, co-ingestion with alcohol, addictions etc. Further, Socio-demographic factors like education, occupation etc were also recorded. Detailed physical examination was also carried out along with all relevant investigations to look for organ dysfunction based on the type of poison. Psychiatric assessment was done in all the survivors and

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²Received: 22.10.2016; Revised: 29.09.2018; Accepted: 16.10.2018
**Results**

A total of 195 patients were included in the study. Out of this 109 were males and 86 were females with mean age of 37.74 in males and 28.04 in females. Commonest age group was between 21-40 yrs. The intention of poisoning was suicidal in 98.82% of patients. The mortality rate was 13.33% (males-15.59%, females-10.46%).

The common poisons consumed were Odollam (30.77%), Drugs (28.21%), Pesticides (25.13%) and Rodenticides (10.77%). There was only one case of Aluminium Phoshphide poisoning and the patient expired. In males pesticides (organophosphorus, organochlorides and carbamates) were the commonest (33.94%) followed by Odollam (27.52%), whereas as in females drugs and Odollam were the commonest (34.88%).

Majority of deaths were due to Organophosphates (42.31%) followed by Odollam (38.46%).

Organophosphorus compounds exhibited the highest mortality rate – 30.56%, followed by Odollam – 16.67%. It is seen that the mortality rate of Organophosphorus is nearly double that of Odollam (Table 2).

Among males Labourers, students and skilled workers were common whereas females were predominated by homemakers and students:

The common precipitating factors were family problems, personal stressors and marital discord, in both sexes. Personal stressors were the commonest reason in males (29.55%), whereas females cited family problems as the commonest reason (40.26%).

Psychiatric assessment showed Adjustment disorder (44.97%) as the commonest problem followed by Impulsive act (21.89%), Depression (15.38%) and Alcohol related problems (10.06%) (Table 3).

The common findings observed in Organophosphorous poisoning were vomiting, diarrhoea, smell of kerosene, sweating, bronchoconstriction, miosis, fasciculations and frothing from mouth.

Nausea, vomiting, abdominal pain, bradycardia, irregular pulse, hypotension were the common features in odollam poisoning. ECG changes commonly observed were sinus bradycardia and different degrees of heart blocks. Atrial fibrillation with complete heart block and ventricular tachycardia were observed in two patients.

In Odollam poisoning the incidence of Bradycardia, Hypotension, ECG changes and Hyperkalemia were observed more in those who succumbed. 7 out 10 deceased patients had taken more than 2 kernels of Odollam. 5 patients had complete heart block and 3 patients had second degree heart block. One each had first degree heart block and atrial fibrillation. 9 out of 50 survivors needed Temporary pacing.

**Discussion**

Poisoning accounts for about a third of all suicides that occur in India. Nearly half of these are attributed to insecticides. During our study, common poisons consumed by the patients were found to be Odollam, Drugs, Pesticides and Rodenticides.

In our study pesticides were the most common poison consumed by males. Many other studies have also reported similar findings. In developing countries use of pesticides is poorly regulated. This easy availability without restrictions makes them a popular method of self harm. As observed in other studies also, pesticides were less common in females compared to males. Pesticides are more easily accessible to men which explain the higher usage by males. Many male patients had taken the poison along with alcohol and they sought medical care late and in some cases the symptoms were initially mistakenly attributed to alcohol by the relatives. This also might have contributed to the high mortality. However, compared to studies from North India much lower use of Aluminium phosphide was found in our study.

Compared to other studies from India and other countries we had a higher proportion of patients who had consumed Odollam. We noticed higher incidence of Odollam poisoning even compared to studies from other parts of South India and Kerala. This could be due to abundance of Odollam around the wetlands of Alappuzha. Young adults were involved in maximum cases, similar to many other studies. Although, adolescents constituted a sizeable group in females, no mortality was reported in this group indicating less lethal poisons were used.

In our study, adjustment disorder and Impulsive acts were most common. Many western studies have reported...
high prevalence of psychiatric disorders (92%) and personality disorders in DSH patients. But, in our study psychiatric disorders were less common.

One significant finding in our study was the high incidence of Odollam poisoning. It was the commonest method employed by females. The mortality observed in Odollam was 16.67%. Globally plants are an uncommon source of poisoning. However, in some parts of the developing world it is a major clinical problem.

Cerbera Odollam ‘suicide tree’ belongs to Apocynaceae family, which is found in many parts of South Asia. This plant is abundantly seen in Alappuzha. It is the green fruit of the plant which is poisonous and it looks like mango. The seeds of Odollam contain Cerberin, cerebrosides –cardiotoxins. Odollam is responsible for about 50% of plant poisoning cases and 10% of total poisoning cases in Kerala. It is used mainly for suicidal purpose. The kernel is mashed and taken along with sugar or jiggery as it is very bitter. As this tree is very commonly seen near many houses, the majority of the victims are women. It’s easy availability and high lethality makes it a very common suicidal agent even in patients who take it impulsively without any suicidal intention.

In Odollam poisoning, patients usually present with nausea, vomiting, abdominal pain etc. The major effect is the cardio toxicity which includes bradycardia, and various types of heart blocks and arrhythmias. Hypotension is a bad sign and usually indicates myocardial depression. Hypokalemia is common. These patients are managed with atropine, meperidine, and keeping under watch of persons. This study was funded by the State Board of Medical Research, Kerala.

References
1. World Health Organisation, Suicide Data [access on 19th April 2016]
4. National Crime Records Bureau, New Delhi, Accidental Deaths and Suicides in India 2014
Serum Alanine Aminotransferase Elevations in HIV Positive Patients on Antiretroviral Therapy in India

Rajesh Deshwal¹, Sumit Arora²

Abstract

Background: Alanine aminotransferase (ALT) is commonly used to measure liver injury in resource limited settings. Elevations in ALT are predictive of increased mortality from liver disease and may be influenced by antiretroviral drugs and concomitant hepatitis B infection.

Methods: A cross-sectional analysis of the prevalence and predictors of elevated ALT (defined as > 40 IU/L) on HIV patients on antiretroviral therapy (ART) was conducted. Baseline ALT levels and at two weeks, six weeks, twelve weeks, twenty four weeks and one year were recorded for 320 patients on ART. Hepatitis B surface antigen was also recorded at baseline.

Results: Out of the total 320 patients, 249 were males and 71 females. A total of 252 patient records were used as controls who were not on ART. The mean ALT record before initiating ART was 30.6 IU/L. Peak rise in ALT was observed at twenty four weeks of therapy with mean ALT levels of 54.42 IU/L. Total toxicity was almost similar between the two regimes, nevirapine based being 17.62% and efavirenz based being 16.16%. Toxicity grades were lesser in Hepatitis B positive patients as compared with hepatitis B negative patients overall.

Conclusions: This study concludes that elevated ALT levels are seen in patients on antiretroviral therapy and persist throughout the course of first year, though maximum levels are seen at around twenty four weeks of therapy. Total hepatotoxicity was found to be 16.89%. Longer follow up of patients is required to assess the effect of ALT elevations on morbidity and mortality of patients and a close monitoring of ALT is required in patients on ART and other hepatotoxic therapies.

Introduction

India has the third largest HIV epidemic in the world. In 2016, HIV prevalence in India was an estimated 0.3%. This figure is small compared to most other middle-income countries but because of India’s huge population (1.2 billion) this equates to 2.1 million people living with HIV. In the same year, an estimated 68,000 people died from AIDS-related illnesses and 43% adults are on antiretroviral treatment (ART). Overall, India’s HIV epidemic is slowing down, with a 19% decline in new HIV infections (130,000 in 2013), and a 38% decline in AIDS-related deaths between 2005 and 2013. Despite, this 51% of deaths in Asia are in India. HIV prevalence in India varies geographically. The five states with the highest HIV prevalence (Nagaland, Mizoram, Manipur, Andhra Pradesh and Karnataka) are in the south or east of the country. Some states in the north and northeast of the country, report rising HIV prevalence.

Since the introduction of antiretroviral drugs, Human Immunodeficiency Virus (HIV) infection management has become more complex. HIV positive patients are receiving an array of drugs to treat and prevent opportunistic infection. With the increased availability of antiretroviral therapy, more people are now surviving with HIV but more are presenting with increasing liver disease. Alanine aminotransferase (ALT) is a liver enzyme commonly used to measure liver disease in resource-limited settings. Elevated ALT is a highly specific indicator for liver injury and has been shown to be associated with deaths from liver disease in non-HIV infected populations. Since it is often the only marker used to monitor liver disease in HIV infected individuals in resource-limited settings, understanding the prevalence and risks associated with elevations in ALT in these settings is important. Liver enzyme elevation is common in HIV patients in Sub-Saharan Africa and various risk factors have been described mainly in Europe and North America including: male sex, HIV itself, viral hepatitis, most antiretrovirals, anti-tuberculosis and lipid lowering drugs; alcohol, and metabolic syndrome.

Certain antiretroviral (ARVs) drugs have well known documented toxicity. Although almost all drugs can cause toxicity, those found to cause liver toxicity include nevirapine, efavirenz, abacavir and lamivudine. Previous studies have indicated liver toxicity ranging from 13-18%. A retrospective cohort study that determined the incidence of NNRTI hepatotoxicity in a group of HIV-infected patients in New York City practice found that grade 3 - 4 elevations in ALT and/or AST levels occurred in 3 (1.1%) of 272 patients. Another study in the US concluded that severe hepatotoxicity occurred throughout the course of NNRTI-based therapy and was more common among patients prescribed with NVP (occurring in 15.6%) than those prescribed with efavirenz (8.0%). However, it is likely that co-infection with viral hepatitis was a contributing factor.

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In a Switzerland cohort of 2365 HIV-infected individuals not co-infected with either HBV or HCV, 385 (16%) had chronically elevated ALT (defined as > 2 × upper limit of normal). A post-mortem study of 86 HIV-infected individuals undergoing autopsy in rural South Africa demonstrated that 10% had liver related conditions at the time of death. Liver toxicity particularly is one of the many side effects of ART. Certain factors have been associated with the development of liver toxicity such as hepatitis co-infection, numerous other liver diseases, including alcohol-related injuries, drug-induced hepatotoxicity, metabolic fatty liver, vascular and autoimmune diseases, infectious diseases and hepatobiliary malignancies. These conditions can affect the clinical management and prognosis of HIV infection. The severity of liver toxicity ranges from transient elevations in transaminases to hepatic failure and death. Drug toxicity is graded according to serum ALT results as follows: Grade 0 (< 1.25 × Upper Limit of Normal [ULN]); Grade 1 (1.25 - 2.5× ULN); Grade 2 (2.6 - 5×ULN); Grade 3 (5.1 - 10× ULN) and Grade 4 (>10× ULN).

No published data exists on prevalence of elevated liver enzymes in HIV positive patients on ART in India. Therefore this study aims at prevalence of elevated liver enzymes in HIV patients on ART in New Delhi.

**Methods**

This retrospective study was done at Apex Immunodeficiency Center (AIDC), Base Hospital, Delhi Cantt in which 320 adult patients records were used for data collection. Prior ethical clearance was obtained from the hospital ethics committee. Patient clearance was not required as the data was collected from the AIDC records and the patients identity was concealed. Base line ALT was recorded and then after two weeks, six weeks, twelve weeks, twenty four weeks and one year. Hepatitis B surface antigen was recorded at baseline only. Patients were being screened for CD4 count and HIV RNA (Quantitative) every six months.

**Inclusion criteria**

Patients who initiated ART during 2014-16 were included in the study.

Patients who started first line ART during the study period were included.

**Exclusion criteria**

Patients not having baseline ALT records.

Patients transferred in from other centers.

Poorly adherent patients on ART.

Patients having any evidence of clinical, immunological or virological failure.

Patients on other drugs with hepatotoxic potential.

Patients with serum creatinine of more than 2 mg%.

The liver enzymes ALT and AST were measured using COBAS Integra Chemistry Analyzer, Roche Diagnostics, Mannheim, Germany. CD4 counts were determined with a FACS counter (Becton and Dickinson, Immunocytometry Systems, San Jose, CA). Hepatitis B virus surface antigen tests were analysed using the Architect analyser (Abbott, Illinois, USA).

**Statistical analysis**

Data was analysed using the Statistical Package for Social Sciences (SPSS) version 22.0. The Pearson Chi-square p value was used to determine whether a statistically significant association existed between variables. Using a 95% confidence level, a P value of less than or equal to 0.05 (P ≤ 0.05), was considered to be statistically significant. The paired t-test was used to compare the monitoring periods ALT means to the initial ALT and determine whether the difference was significant or not. The independent t-test was used to compare the initial ALT mean and the one year ALT mean of the patients with Hepatitis B co-infection or otherwise.

**Results**

Out of the total 320 patients, 249 were males and 71 females. The period of study extended from July 2014 through August 2016. Age of the patients ranged from 26 to 81 years. Adherence counseling and avoidance of substance abuse is routinely done in all our patients on ART at our center. Out of the total patients, 208 patients were on Tenofovir (TDF), Lamivudine (3TC) and Efavirenz (EFV), 166 being males and 42 females. Rest 112 patients were on Tenofovir (TDF), Lamivudine (3TC) and Nevirapine (NPV), 83 being males and 29 females.

The baseline ALT levels were used as the control group which indicated the levels of ALT in HIV positive patients who were not on treatment. A total of 252 patient records were used as controls who were not on ART. Out of these 252 controls, 161 were males and 91 females. The mean ALT record before initiating ART was 30.6 IU/L. ALT was recorded at two, six, twelve, twenty four weeks and one year from starting ART. Table 1 depicts mean ALT values at different monitoring periods. Fifty eight patients (18.12%) had elevated ALT levels before initiation of ART.

Peak rise in ALT was observed at twenty four weeks of therapy with mean ALT levels of 54.42 IU/L (Figure 1). Mean ALT levels at initiation and two weeks after therapy were statically insignificant (P= 0.091) though it was significant during latter part of therapy as compared to baseline.

Toxicity was observed in both nevirapine as well as efavirenz based regimes. Toxicity in nevirapine based regimes remained almost static from two weeks till about twelve weeks of therapy (14.1 – 14.5%) reaching a maximum at twenty four weeks (22.9%). Toxicity in efavirenz based regimes remained higher than nevirapine based group reaching at 22.6% at twenty four weeks and dropping down to 6.4% at
Table 1: Toxicity grades at varying intervals in treatment regimens

<table>
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<tr>
<th>Monitoring ART periods</th>
<th>(n)</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Cumulative toxicity (%/n)</th>
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<tr>
<td>Two weeks</td>
<td>78</td>
<td>14.2</td>
<td>0.3</td>
<td>0.0</td>
<td>0.0</td>
<td>14.5/11</td>
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<tr>
<td>Efavirenz based</td>
<td>178</td>
<td>14.8</td>
<td>0.2</td>
<td>1.2</td>
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<td>16.2/29</td>
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<tr>
<td>Six weeks</td>
<td>57</td>
<td>11.3</td>
<td>2.3</td>
<td>0.6</td>
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<td>14.4/8</td>
</tr>
<tr>
<td>Nevirapine based</td>
<td>134</td>
<td>18.7</td>
<td>1.4</td>
<td>0.0</td>
<td>0.0</td>
<td>20.1/27</td>
</tr>
<tr>
<td>Twelve weeks</td>
<td>62</td>
<td>9.2</td>
<td>3.2</td>
<td>1.7</td>
<td>0.0</td>
<td>14.9/11</td>
</tr>
<tr>
<td>Efavirenz based</td>
<td>146</td>
<td>11.6</td>
<td>3.9</td>
<td>0.0</td>
<td>0.0</td>
<td>15.5/23</td>
</tr>
<tr>
<td>Twenty weeks</td>
<td>63</td>
<td>19.4</td>
<td>3.5</td>
<td>0.0</td>
<td>0.0</td>
<td>22.9/14</td>
</tr>
<tr>
<td>Nevirapine based</td>
<td>187</td>
<td>21.5</td>
<td>0.9</td>
<td>0.2</td>
<td>0.0</td>
<td>22.6/42</td>
</tr>
<tr>
<td>Four weeks</td>
<td>61</td>
<td>17.2</td>
<td>5.2</td>
<td>0.0</td>
<td>0.0</td>
<td>22.4/14</td>
</tr>
<tr>
<td>Efavirenz based</td>
<td>165</td>
<td>4.3</td>
<td>2.1</td>
<td>0.0</td>
<td>0.0</td>
<td>6.4/11</td>
</tr>
</tbody>
</table>

Table 2: Cumulative toxicity in treatment regimens

<table>
<thead>
<tr>
<th>Type of regimen</th>
<th>Mild toxicity</th>
<th>Severe toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1 (%)</td>
<td>Grade 2 (%)</td>
</tr>
<tr>
<td>Nevirapine based</td>
<td>14.26</td>
<td>2.9</td>
</tr>
<tr>
<td>Total</td>
<td>15.88</td>
<td>0.28</td>
</tr>
</tbody>
</table>

P value = 0.95

Discussion

Mean ALT levels were always higher during two, six, twelve, twenty four weeks and one year as compared to baseline levels. Elevated ALT levels were noted throughout the treatment period for the patients on ART. Though other causes like viral hepatitis, kidney failure and alcoholism can cause rise in ALT levels, antiretroviral therapy has an effect on liver. The nonnucleoside reverse transcriptase inhibitors (NNRTIs) typically cause either hypersensitivity reactions or direct drug toxicity and therefore have 2 peaks of onset, within days to weeks or several months after initiation. Nevirapine (NVP) is the NNRTI most associated with hepatotoxicity, although hypersensitivity reactions resulting in liver failure have been reported with the newer NNRTI etravirine. Efavirenz can also cause hepatotoxicity but does so less frequently than NVP or etravirine. In our study toxicity due to efavirenz was higher than nevirapine in the initial half of the study but then declined over the next half to less than nevirapine, although cumulative toxicity of efavirenz was lesser than nevirapine. The maximum toxicity was observed at two weeks, 22.9% for nevirapine and 22.6% for efavirenz in our study. Shanyengana LP et al documented a maximum toxicity of 26.5 and 28.2 % for nevirapine and efavirenz respectively. Other similar studies from Tanzania and Ethiopia have documented a prevalence of 13 and 32% respectively. The difference could be due to different risk factors, alcohol abuse, co-infection, different treatment regimens, pretreatment ALT elevations and duration of treatment.

Severe hepatotoxicity (grades 3 and 4) was higher among patients on nevirapine based regimens (0.46vs 0.28%). These results are in sync with a US based study which concluded that severe hepatotoxicity was more common among patients prescribed with nevirapine (15.6%) than those prescribed with efavirenz (8.0%) based regimens and are different from a Namibian study which observed that severe hepatotoxicity was higher (1.6%) in patients who were enrolled on efavirenz based regimens than patients who were enrolled on nevirapine based regimens (1.1%). Similarly, other studies conducted in Botswana and Nigeria found that 3.4% and 16% of nevirapine and 0.9% and 8.0% of efavirenz treated patients developed hepatotoxicity respectively. Our study demonstrated higher prevalence of milder toxicity (17.16 % and 15.88 %) and a very low prevalence of severe toxicity (0.46 and 0.28%). The results of our study are similar to the results of a study done in Ethiopia which showed higher mild toxicity levels (22.3% grade 1 toxicity levels, 7.8% grade 2 toxicity levels) and lower severe toxicity levels (1.1% and 0.74% for grade 3 and 4 toxicity respectively). A study done in New York City, USA had similar results to our findings with mild toxicity (grade 1 and 2) of 16.7% and severe toxicity (grade 3 and 4) of 1.4%. Lower results were also found in a study conducted in Tanzania which found 0.3% severe hepatotoxicity.

Hepatitis B has been shown to be contributing factor in patients on ART for liver injury in South Africa and Switzerland. Our study showed Hepatitis B related toxicity at two and twelve weeks only and at other times it was much lower as compared to Hepatitis B negative patients.

Limitations of study

This study had few limitations. Firstly, data on alcohol and illicit drugs, which could have caused elevated ALT, was not available. Secondly, the effect
of Lamivudine in causing a rise in ALT could not be made out, though both the groups had lamivudine as part of therapy.

Conclusions

This study concludes that elevated ALT levels are seen in patients on antiretroviral therapy and persist throughout the course of first year, though maximum levels are seen at around twenty four weeks of therapy. Total hepatotoxicity was found to be 16.89%. Slightly higher toxicity was observed in nevirapine based regime as compared to efavirenz based regime. Hepatitis B co-infected patients showed a higher toxicity levels at two and twelve weeks of therapy, at other times it was lower than hepatitis B uninfected. Longer follow up of patients is required to assess the effect of ALT elevations on morbidity and mortality of patients and a close monitoring of ALT is required in patients on ART and other hepatotoxic therapies.

References


A Concurrent Comparison of the Epidemiology and Clinical Presentation of Patients Hospitalized with Pandemic 2009 (H1N1) Influenza and Seasonal Influenza-A in Sub-himalayan Region of Himachal Pradesh

Thakur C1*, Singh DV2, Sharma A, Kumar V1, Kanga A2

Abstract

Background: Pandemic influenza (H1N1) 2009 emerged in April 2009 and spread widely in India. Although an unprecedented number of cases required intensive care, comparative community-based studies with seasonal influenza strains have not shown any significant differences in clinical symptoms or severity.

Methods: The authors performed active surveillance on confirmed influenza-related admissions and compared the clinical profile of patients with pandemic (H1N1) 2009 influenza and patients with seasonal influenza at a tertiary care hospital in Shimla, Himalach Pradesh.

Results: A total of 309 patients with flu like illness (category-C) admitted at IGMC were tested for influenza A infection and 58 (18.77%) patients had laboratory confirmed influenza A infection. Out of 58 patients, 22 with pandemic A (H1N1) and 36 with seasonal influenza A infection were compared. Compared with seasonal influenza, pandemic A (H1N1) patients were more likely to have sore throat (68.2% vs 16.7%, p<0.001), g.i.t symptoms (63.6% vs 16.7%, p<0.001), myalgia (36.4% vs 13.9%, p<0.047), radiologically confirmed pneumonia (81.8% vs 55.6%, p=0.042), multifocal changes on CXRs (72.7% vs 36.1%, p=0.012) and

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hypothyroidism as a risk factor (22.7% v 0%, p= 0.002) Patients with pandemic A (H1N1) were more likely to receive oseltamivir (91.3% vs 40.2%, p=0.002). ARDS was the major reason for intensive care unit admission in both the groups. There were no statistical significant differences in the other clinical features, comorbidities, rate of intensive care unit admission and mortality.

Conclusions: The clinical features and outcomes of pandemic (H1N1) 2009 influenza and current circulating seasonal influenza A strains were comparable in hospitalised patients. However, since both seasonal and pandemic influenza can lead to significant morbidity and mortality, the impact of pre-existing seasonal influenza should not be underestimated during the pandemic period.

Introduction

In late March and early April 2009, an outbreak of H1N1 influenza A virus infection was detected in Mexico with subsequent cases observed in many other countries including India and the USA.1 WHO declared H1N1 as a pandemic on 11th June, 2009. In India first case was seen in Gujarat on July 6th, 2009.

The pandemic 2009 (H1N1) influenza A virus is a novel reassortant virus comprising two swine strains (North American and Eurasian swine viruses lineages), one human strain and one avian strain of influenza A. On the basis of early estimates from Mexico, pandemic 2009 (H1N1) appeared to have higher transmissibility than seasonal influenza but lower clinical severity than the 1918 influenza pandemic. Transmission is mainly person-to-person by droplet infection or droplet nuclei created by sneezing, coughing or talking.

According to other studies, there are some points that differentiate H1N1 2009 from seasonal influenza A like more virulence younger age distribution,2,3 young age as principal mortality risk factor, novel risk factors such as obesity,1,4 new symptoms previously not frequently associated with influenza infection, such as diarrhea and vomiting,3-5 and more hospitalization without coexisting medical conditions.6 Other reports found similarities between 2009 H1N1 and seasonal influenza with regard to rates of viral shedding and transmissibility7, basic reproduction number, range of severity, clinical symptoms of hospitalized patients, and risk factors for severe disease. The most common risk factors associated with complications in both 2009 H1N1 and seasonal influenza patients were chronic pulmonary, cardiovascular, hepatic, renal, metabolic disorders, neurological diseases, chronic smoking, pregnancy and underlying immune compromise. Confirmation of pandemic 2009 (H1N1) virus infection can be made with rRT-PCR, viral culture or four-fold rise in virus specific neutralizing antibodies.1

There are little data directly comparing confirmed pandemic (H1N1) 2009 with contemporaneous seasonal influenza over the same influenza season. The purpose of the study was to compare the epidemiology, clinical features, and outcome of hospitalized patients with pandemic and seasonal influenza A over the same influenza season.

Methods

This prospective study was conducted in a tertiary care Indira Gandhi Medical College and Hospital (IGMC), Shimla, HP in Category-C patients with flu-like symptoms hospitalized in IGMC, Shimla.

Table 1: Demographic characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>2009 H1N1 n=22 (%)</th>
<th>Seasonal influenza n=36 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.) &lt;18</td>
<td>2 (9.1%)</td>
<td>5 (13.9%)</td>
</tr>
<tr>
<td>18-40</td>
<td>8 (36.4%)</td>
<td>19 (52.8%)</td>
</tr>
<tr>
<td>41-60</td>
<td>8 (36.4%)</td>
<td>7 (19.4%)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>4 (18.2%)</td>
<td>5 (13.9%)</td>
</tr>
<tr>
<td>Mean (Range in years)</td>
<td>41.88 (0.5-74)</td>
<td>35.29 (0.5-73)</td>
</tr>
</tbody>
</table>

| Sex | Female | 11 (50%) | 15 (41.7%) |
|     | Male   | 11 (50%) | 21 (58.3%) |
| Nosocomial | 00 | 5 (13.9%) |

Table 2: Interval between onset of symptoms and admission

<table>
<thead>
<tr>
<th>Interval (Days)</th>
<th>2009 H1N1 n=22 (%)</th>
<th>Seasonal influenza n=36 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>7 (31.8%)</td>
<td>17 (47.2%)</td>
</tr>
<tr>
<td>5-9</td>
<td>15 (68.2%)</td>
<td>18 (50%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>00</td>
<td>1 (2.8%)</td>
</tr>
</tbody>
</table>

All the enrolled patients for this study were categorized as per the recommendations of Ministry of Health and Family Welfare, Government of India. Appropriate clinical specimens (nasopharyngeal or throat swabs, broncho-alveolar lavage, tracheal aspirates and nasopharyngeal or oropharyngeal aspirates as washes) were collected in a viral transport medium, as per the guidelines of the Centers for Disease Control and Prevention (CDC), Atlanta. All the collected clinical specimens were subjected to real-time polymerase chain reaction (rRT-PCR) analysis as per CDC protocol for the detection of the pandemic H1N1-2009 virus.

Pandemic influenza case was defined as PCR-confirmed pandemic (H1N1) 2009 influenza infection and seasonal influenza case was defined as any PCR-confirmed influenza A infection for which infection with pandemic (H1N1) 2009 virus had been excluded. All the positive cases were followed up in their respective wards and their demographic characteristics, clinical profile and outcome was noted.

Statistical analysis were performed using Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and SPSS student version 16.0 (SPSS Inc, Chicago, USA). Univariate analyses were performed to compare patients with pandemic influenza with those with seasonal influenza with respect to reported symptoms, underlying medical conditions, and treatment. A p value < 0.05 was considered significant.

Results

During the study period, a total of 309 patients with flu like illness (category-C) admitted at IGMC were tested for influenza A infection. A total of 58 (18.77%) patients had laboratory confirmed influenza A infection and 251 (81.23%) patients did not have influenza A infection. Out of these 58 patients, a total of 22 (37.93%) patients had 2009 H1N1 infection and 36 (62.07%) patients had seasonal influenza A infection.

The number of males (32) were more than the females (26) with the male to female ratio of 1.23:1 in the influenza A positive cases (Table 1). For 2009 H1N1 positive cases (n=22) the number of males was equal to the number
of females (11 each) and in seasonal influenza A positive cases (n=36), the number of males (n=21) were more than the number of females (n=15). Most of the pandemic and seasonal influenza patients in the study were male but the proportion of male patients among the seasonal influenza patients was greater than that among patients with pandemic influenza, 58.3% and 50%, respectively (p=0.139).

In this study the minimum age group for seasonal influenza A was 5 months while the maximum was 73 years. The percentage of the patients with seasonal influenza (72.7% v 36.1%, respectively) was significantly more common in patients with seasonal influenza as compared with pandemic influenza (81.8% v 55.6%, respectively; p=.012), whereas the proportion of male patients among pandemic influenza was 58.3% and 50%, greater than that among patients with seasonal influenza.

No nosocomial infection was detected in 5 (13.9%) cases in the seasonal influenza group and no case was detected in 2009 H1N1 influenza group.

The percentage of the patients with pandemic influenza who got admitted within 5 to 9 days of onset of symptoms was 68.2% as compared with 50% of patients with seasonal influenza (Table 2).

**Clinical and Diagnostic Features**

The most common symptoms in pandemic influenza cases were fever (100%), cough (95.5%) and dyspnoea (90.9%) followed by sore throat (68.2%), g.i.t symptoms (63.6%), cyanosis (50%), rhinorrhea (36.4%), myalgia (36.4%) and conjunctivitis (22.7%) and in seasonal influenza the most common symptoms were cough (94.4%), fever (91.7%), and dyspnoea (77.8%) followed by rhinorrhea (38.9%), cyanosis (25%), chest pain (16.7%), g.i.t symptoms (16.7%) and sore throat (16.7%) (Table 3). Sore throat, myalgia and g.i.t symptoms (diarrhoea and vomiting) were significantly more common in patients with pandemic influenza than seasonal influenza (p=.0001, p=.047 and p=.0001, respectively).

Overall 31.8% of patients with pandemic influenza and 38.9% of patients with seasonal influenza had leucocytosis and none of the patient in both groups had leucopenia. Only 9.1% of patients with pandemic influenza and 11.1% of patients with seasonal influenza had lymphopenia and none of the patient in both groups had lymphopothy. Pneumonia was reported in significantly higher proportion of patients with pandemic influenza as compared with seasonal influenza (81.8% v 55.6%, respectively; p=.042).

Chest X-rays (CXR) were taken in all the patients in the study and normal CXR was significantly more common in patients with pandemic influenza as compared with seasonal influenza (41.7% v 18.2%, respectively; p=.012). In CXRs with abnormal findings, multifocal changes were significantly more common in patients with pandemic influenza as compared with seasonal influenza (72.7% v 36.1%, respectively; p=.012), whereas the
unifocal changes and pleural effusion were more common in patients with seasonal influenza. Blood and sputum culture were taken in all the patients with pneumonia. Blood cultures were taken in 18 patients with pandemic influenza and only in one patient, S. aureus was isolated and out of 20 seasonal influenza patients only in four patients significant pathogen was isolated (S. aureus 2, K pneumoniae 1, CoNS 1). Sputum cultures were positive in two patients with pandemic influenza (S pneumoniae 2) and in three patients with seasonal influenza pneumonia (S pneumoniae 2, K pneumoniae 1).

**Risk Factors**

The most common risk factors/ underlying medical disorders (Table 4) in pandemic influenza cases were smoking (40.9%), COPD (27.3%), cardiac disorders (27.3%), and thyroid dysfunction (22.7%). The most common risk factors/underlying medical disorders in seasonal influenza cases were smoking (41.7%), COPD (27.8%), other concurrent infections (27.8%) and cardiac disorders (19.9%). Univariate analysis showed that thyroid dysfunction as a risk factor was significantly more common for pandemic influenza patients (p=0.002). Other concurrent infections were reported in three pandemic influenza patients (HV 1, pulmonary tuberculosis 2) and in ten seasonal influenza patients (tuberculosis-4, Scrub typhus-2, purpureal sepsis-2, K pneumoniae septicemia-1, SABE with CoNS 1). Obesity was reported more commonly in patients with pandemic influenza as compared with seasonal influenza (18.2% vs 5.6%), though not statistically significant (p=0.13).

**Management and Outcome**

The proportion of patients treated with oseltamivir (Table 5) was significantly higher in pandemic influenza as compared with seasonal influenza (100% v 66.7%, respectively; p=0.002). The mean lag time between illness onset and starting antiviral treatment was 5.3 days for patients with pandemic influenza and 5.9 days for patients with seasonal influenza (p = 0.39). Similar proportion of patients in both groups were treated with antibiotics and oral steroids. The median duration of hospitalization was 7 days for patients with pandemic influenza and 5 days for those with seasonal influenza (p = 0.13). Although the findings were not significant, a trend toward longer hospital stays did appear for those with pandemic (H1N1) 2009 versus seasonal illness, based on the proportion of patients hospitalized an additional ≥7 days (54.5% vs. 44.4%, respectively). Similar proportion of patients in both groups had ARDS and required ICU admission. Patients with radiologically confirmed pneumonia commonly required admission to ICU; 23.6% of patients with pneumonia (9/38) were admitted to ICU- four with pandemic and five with seasonal influenza. The mortality was higher in pandemic influenza patients than in seasonal influenza patients (18.2% vs. 11.1%, respectively), though statistically not significant (p=0.779). Out of eight patients in both the groups(four each) who expired, five (62.5%) had ≥1 underlying risk factor/comorbidities. One pandemic influenza patient and two seasonal influenza patients expired without any underlying risk factor/comorbidities.

**Discussion**

This study compares the demographic characteristics, clinical profile and outcome of hospitalised patients with pandemic H1N12009 influenza with the other seasonal influenza A strains infection. A major strength of our study was that the cases of seasonal and pandemic H1N12009 influenza occurred concurrently, which allowed us to make a direct comparison.

Our study shows that there was significant co-circulation of other seasonal A viruses in India during the current pandemic also shown in a study by Chudasama et al done in Gujarat. This study showed that pandemic and seasonal influenza affected all age groups and the mean age of pandemic influenza cases was higher than the seasonal influenza cases (41.8 years vs. 35.3 years). However, less number of cases with pandemic influenza was observed in > 55 years of age. Similar findings were reported by 6% (49/871) of the study participants with pandemic influenza were >55 years Carcione et al only 3.15% were older than 60 years Chang et al 9.2% positive cases were reported in 2015 in a age group of >65 years in a recent study from Rajasthan by Sharma et al. The relative sparing of adults in this age group is presumably due to the exposure of persons in this age group to antigenically related influenza viruses earlier in life resulting in the development of cross-protective antibodies.

We observed that there was no difference in terms of sex distribution of the cases similar to other studies. Maximum number of patients in both the groups in our study got admitted within mean time of 5 days which is similar to that reported by Chudasama et al and comparable to mean of 4 days reported by Chang et al.

In our study, the most common symptoms in both the groups (pandemic influenza and seasonal influenza) were fever, cough and dyspnea similar to common clinical features, fever (100%), cough (90-7%), sore throat (85-7%) as reported in a recent study done by Gurav et al but sore throat, myalgia and g.i.t symptoms (diarrhoea and vomiting) were significantly more common in patients with pandemic influenza than seasonal influenza, p=.0001, p=.047 and p=.0001, respectively.

There was no difference between the two groups in the mean total white blood cell count and lymphocyte count. Positive blood cultures were observed more commonly in seasonal than in pandemic influenza cases (20% vs. 5.5%). This is consistent with other studies suggesting that bacterial pneumonia following H1N1/09 influenza is less common than viral pneumonitis. Pneumonia (radiologically confirmed) was reported in significantly higher proportion of patients with pandemic influenza as compared with seasonal influenza (81.8% v 55.6%, respectively; p=.042). Abnormal chest radiographs and multifocal changes were also significantly more common in pandemic influenza group (p=0.012).

We observed that smoking and COPD were the most common risk factors/underlying medical disorders in both the groups also reported by Carcione et al, Cheng et al and Murata et al.

In our study thyroid dysfunction (hypothyroidism) as a risk factor was found to be significantly more common for pandemic influenza patients (p=0.002). Obesity was reported more commonly in patients with pandemic influenza in this study, though not statistically significant (p=0.13) and
also by Bautista et al., To et al., Cui et al. and Cheng et al. This is similar to the previous study of Morgan et al. The complication-rate in patients with respiratory co-morbid conditions was significantly higher as compared to those without.

In our study the proportion of patients treated with oseltamivir was significantly higher in pandemic influenza as compared to seasonal influenza (p<.002) probably due to the perceived higher risk of complications in this group of patients. All other similar studies done by Carcione et al., Chang et al., Cheng et al. and To et al. have reported the same. Most studies of oseltamivir were performed in patients with seasonal influenza, and it was shown that treatment with an antiviral reduced the mortality rate in hospitalised patients with seasonal influenza.

The median duration of hospitalization in both the groups was not statistically significant in this study and also in studies by Chang et al., Cheng et al. and Carcione et al.

Similar proportion of patients in both groups had ARDS and required ICU admission in our study, in contrast to higher proportion of pandemic influenza cases reported by Chang et al. and Cheng et al. All the patients in both the groups admitted to ICU had multifocal changes in their chest X-rays and our finding highlights the importance of lower respiratory tract involvement, regardless of strain, as a marker of severity of disease and admission to intensive care. The mortality was higher in pandemic influenza patients in our study, though it was not found to be statistically significant. Six out of the eight deaths in the study were due to ARDS.

Conclusion

During the study period it was found that patients hospitalized with symptoms of flu like illness were predominantly suffering from seasonal influenza A infection as compared to pandemic 2009 (H1N1) infection. Our findings show that the clinical profile and outcome of the patients with pandemic 2009 (H1N1) influenza infection is comparable to those with seasonal influenza A infection in terms of sex distribution, symptomatology, total white blood cell count and lymphocyte count, blood and sputum culture positivity for bacterial infections, common risk factors, treatment with antibiotics and oral steroids, duration of hospitalization, ARDS and ICU admission, mortality and mode of death. However, pandemic influenza patients reported sore throat, myalgia, g.i.t symptoms, hypothyroidism, multifocal changes on chest radiographs, pneumonia and treatment with oseltamivir significantly more commonly than seasonal influenza patients. We must not lose sight of the fact that influenza remains an important cause of illness and death. Therefore, influenza vaccination should be advised to all the high risk groups, which currently is not being done in our setting.

References


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Cefixime-ofloxacin Combination in the Management of Uncomplicated Typhoid Fever in the Indian Community Setting

Mangesh Tiwaskar

Abstract

Antimicrobial resistance is a global problem and is definitely a cause of concern in India too, in the context of typhoid fever. It is becoming clearer that monotherapy is not effective for typhoid fever and the option to be considered is combination therapy. There are very few antibiotic combinations that are approved and backed by clinical evidence, available in India for the treatment of typhoid fever. Cefixime-ofloxacin combination is approved by Indian Regulatory Authority and has a good body of clinical evidence in the current Indian context. In-silico studies have demonstrated positive rationale of combining these two drugs, while in-vitro studies have substantiated the same by showing a strain specific synergistic and or additive activity between the two drugs against S. typhi. Clinical studies in Indian patients have shown multiple benefits of using this combination in typhoid fever such as a quick time to defervescence (~3 days), complete clinical cure in ~7 days, effective symptomatic relief, efficacy in relapse cases and a reduced need for hospitalization. The drug combination also demonstrates a very good tolerability profile. Recommendations of the Association of physicians of India also back this combination in typhoid fever. Thus, in the current era of emerging antibiotic resistance, cefixime-ofloxacin is a safe, effective and reliable treatment option for clinicians to treat uncomplicated typhoid in the Indian community setting.

Introduction and Relevance in the Current Indian Context

Antimicrobial resistance is a burning problem and is definitely a cause of concern in India too, in the context of typhoid fever. The 2016 -National treatment guidelines for antimicrobial use in infectious diseases issued by the national centre for disease control (DGHS, MOHFW – Govt of India) indicate that majority of the strains of bacteria causing enteric fever are nalidixic acid resistant.1 In 2017, ICMR released ‘Treatment Guidelines for Antimicrobial Use in Common Syndromes’ document. This report once again highlights that quinolone resistance is increasing and is as high as 69% for Salmonella typhi and 23% for S. Paratyphi A.2

It is becoming clearer that monotherapy is not effective for typhoid fever and the best option is considered to be combination therapy.3 The 2015, Association of Physicians of India (API) recommendations for the management of typhoid fever highlight the fact that, a number of physicians currently use fixed-dose combinations in typhoid.4 In a recent (2016) knowledge, attitude, practices study with general practitioners in India for typhoid fever, the investigators reported that in 38% of typhoid cases combination therapy is used.5 This is in line with reports of Butler et al 2011, suggesting that the use of a combination of cephalosporin and fluoroquinolone is very common in the United states of America. WHO also supports the use of combination therapy for the treatment of typhoid fever.6

Of relevance, here, the NCDC Indian guidelines cited above suggest, that combination antimicrobial therapy can be considered in conditions1

i. Where synergism of antimicrobials established

ii. When there is a need to extend the antimicrobial spectrum beyond a use of a single agent (treatment of poly microbial infections)

iii. Where treatment is initiated for pan-resistant organisms and to prevent emergence of resistance

iv. Where monotherapy is not recommended

As seen in the detailed review in subsequent sections, in the Indian context of enteric fever and the above recommendations for use of combination therapy, the combination of cefixime-ofloxacin ticks all the requirements of use of combination therapy i.e., it has a demonstrable synergistic and or additive effects against S. typhi, can extend the anti-microbial spectrum to fluoroquinolone non-susceptible S. typhi strains, has a role in preventing emergence of drug resistance and is also recommended by Association of Physicians of India (API) guidelines where fluoroquinolone monotherapy fails. There is also a good body of Indian evidence supporting the efficacy and tolerability of cefixime-ofloxacin combination in the management of typhoid fever. The combination has been approved the drug regulators in India for the treatment of typhoid fever.

In this backdrop, this review aims to elaborately present the following aspects related to cefixime-ofloxacin combination, with respect to typhoid fever in the Indian context:

1. Rationale for the combination.

2. Evidence for use of cefixime-ofloxacin combination in typhoid fever:

   I. In-silico evidence
   II. In-vitro evidence

3. Clinical study evidence

IV. Drug utilization patterns study evidence

3. Regulatory status in India

4. Guideline recommendations in the Indian context

5. Clinical evidence in the Indian context

6. Physician usage and prescription

Consultant Physician and Diabetologist, Asian Heart Institute, Mumbai, Maharashtra
Received: 14.12.2018; Accepted: 28.12.2018
1. Rationale for the combination:

a. The auto dock binding energies between PBP2 and cefixime was found to be -5.95 kcal/mol with the inhibitory constant of 43.69 uM.

b. The auto dock binding energies between DNA gyrase subunit A and DNA topoisomerase IV subunit A with ofloxacin were found to be -5.8 kcal/mol and -6.8 kcal/mol, with the inhibitory constants of 49.94 uM and 103.3 uM respectively.

c. Also, cefixime forms three hydrogen bonds with amino acid residues (LYS554, TYR559, and ASN556) and Ofloxacin forms two hydrogen bonds (ILE264 and PRO218). Comparatively highest numbers of hydrogen bonds (6 hydrogen bonds) were found to be involved in the interaction.

2. Evidence for use of cefixime-ofloxacin combination in typhoid fever:

i. In-Silico evidence: The testing of drug toxicity on the animals are constrained by ethical consideration, cost and time. To reduce this burden, the involvement of computing technology in drug discovery has become a better alternative. Bhaktavachalam et al, 2017 reported the results of an in-silico approach of study to understand the drug-drug interaction, toxicity, docking with receptors for binding affinity and energy, for cefixime-ofloxacin combination.

   The auto dock binding energies between DNA gyrase subunit A (gyrA), DNA topoisomerase IV subunit A (parC) and DNA topoisomerase 2-alpha (TOP2A).

   - The auto dock binding energies between PBP2 and cefixime was found to be -5.95 kcal/mol with the inhibitory constant of 43.69 uM.
   - The auto dock binding energies between DNA gyrase subunit A and DNA topoisomerase IV subunit A with ofloxacin were found to be -5.8 kcal/mol and -6.8 kcal/mol, with the inhibitory constants of 49.94 uM and 103.3 uM respectively.
   - Also, cefixime forms three hydrogen bonds with amino acid residues (LYS554, TYR559, and ASN556) and Ofloxacin forms two hydrogen bonds (ILE264 and PRO218). Comparatively highest numbers of hydrogen bonds (6 hydrogen bonds) were found to be involved in the interaction.

   - The investigators used a checkerboard assay to evaluate the antimicrobial properties of the cefixime-ofloxacin combination. They suggested that cefixime-ofloxacin combination, demonstrates a strain specific, synergistic or additive activity against S. typhi bacterium. This observation was based on the results which showed that in all isolates which were non-susceptible to fluoroquinolones, cefixime-ofloxacin combination demonstrated either an ‘additive’ inhibitory activity (89% isolates) and ‘synergistic’ (11% isolates) against S. typhi. There were no isolates where the combination showed an ‘antagonistic’ activity.

   - The investigators also used a time-kill assay (TKA) to demonstrate the additive / synergistic properties and bactericidal effects of cefixime-ofloxacin combination as compared to the individual components, i.e. cefixime and ofloxacin. The TKA was performed for three types of isolates –

   i. cefixime-resistant and ofloxacin resistant isolates

   ii. cefixime susceptible and ofloxacin moderately susceptible isolates.

3. Conclusion

The parameters studied and final observations for cefixime-ofloxacin combination are summarized in Table 1.

Table 1: Key findings of the study

<table>
<thead>
<tr>
<th>Investigation details</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-target identification</td>
<td>BalezaWeb server / MetaPocket server</td>
<td>Network analysis showed that the target of cefixime was found to be PBP2, and the targets of ofloxacin were found to be DNA gyrase subunit A (gyrA), DNA topoisomerase IV subunit A (parC) and DNA topoisomerase 2-alpha (TOP2A).</td>
</tr>
<tr>
<td>Drug-target interaction</td>
<td>AutoDock 4.2 / PyMOL</td>
<td>The auto dock binding energies between PBP2 and cefixime was found to be -5.95 kcal/mol with the inhibitory constant of 43.69 uM. The auto dock binding energies between DNA gyrase subunit A and DNA topoisomerase IV subunit A with ofloxacin were found to be -5.8 kcal/mol and -6.8 kcal/mol, with the inhibitory constants of 49.94 uM and 103.3 uM respectively. Also, cefixime forms three hydrogen bonds with amino acid residues (LYS554, TYR559, and ASN556) and Ofloxacin forms two hydrogen bonds (ILE264 and PRO218). Comparatively highest numbers of hydrogen bonds (6 hydrogen bonds) were found to be involved in the interaction.</td>
</tr>
<tr>
<td>Drug-drug interaction</td>
<td>RsList server</td>
<td>No direct interaction between cefixime and ofloxacin</td>
</tr>
<tr>
<td>ADMET analysis</td>
<td>pkCSM server</td>
<td>Overall good distribution activity. The distribution property of the drug in the body, showed a lower value -1.737 and -0.028 log L/kg for cefixime and ofloxacin respectively. Both cefixime and ofloxacin do not have a substrate or inhibitor activity for any of the CYP family of proteins.</td>
</tr>
<tr>
<td>Absorption</td>
<td>Water solubility / Caco2 permeability</td>
<td>Overall, there was good absorption activity shown by both the drugs. Water solubility was -2.523 mol/L and -3.179 mol/L for cefixime and ofloxacin respectively. Caco2 permeability was observed to be -0.585 X 10-6 cm/s and 1.365 X 10-6 cm/s for cefixime and ofloxacin respectively.</td>
</tr>
<tr>
<td>Distribution</td>
<td>VDss (human)</td>
<td>Overall good distribution activity. The distribution property of the drug in the body, showed a lower value -1.737 and -0.028 log L/kg for cefixime and ofloxacin respectively. The cefixime and ofloxacin showed fraction unbound of 0.527 and 0.577 Fu.</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP interaction</td>
<td>Both cefixime and ofloxacin do not have a substrate or inhibitor activity for any of the CYP family of proteins.</td>
</tr>
<tr>
<td>Excretion</td>
<td>Total clearance and Renal OCT2 substrate activity</td>
<td>Overall good excretion. Total clearance activity of 0.85 log ml/min/kg for cefixime and 0.414 log ml/min/kg for ofloxacin showed an ‘antagonistic’ activity. No renal OCT2 substrate activity for both the drugs was seen.</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Series toxicity assay</td>
<td>No AMES toxicity, hERG I inhibitor, hERG II inhibitor toxicity and skin sensitisation.</td>
</tr>
</tbody>
</table>

4. Availability in India

The study used a non-duplicate isolates collected from blood culture, between 2012 -2014 from a tertiary hospital in south India. The study used a checkerboard assay to evaluate the antimicrobial properties of the cefixime-ofloxacin combination. The investigators suggested that cefixime-ofloxacin combination, demonstrates a strain specific, synergistic or additive activity against S. typhi bacterium. This observation was based on the results which showed that in all isolates which were non-susceptible to fluoroquinolones, cefixime-ofloxacin combination demonstrated either an ‘additive’ inhibitory activity (89% isolates) and ‘synergistic’ (11% isolates) against S. typhi. There were no isolates where the combination showed an ‘antagonistic’ activity.

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i. cefixime-resistant and ofloxacin resistant isolates

ii. cefixime susceptible and ofloxacin moderately susceptible isolates.
iii. cefixime susceptible and ofloxacin resistant isolates.

For the cefixime susceptible, ofloxacin moderately susceptible isolate, the cefixime-ofloxacin combination showed synergy in the time-kill assay and highest bactericidal activity at 24 hrs compared to cefixime or ofloxacin alone. In the cefixime-resistant, ofloxacin resistant as well as cefixime susceptible and ofloxacin resistant isolate, cefixime-ofloxacin combination showed additive activity in the time-kill assay, but however a bactericidal effect was not reported in 24hrs.

Sawant C et al, 2015 reported

i. A total of 53.4% (n=625) patients were afebrile on day 3 itself and this number increased to 93.1% (n=1089) on day 5 and finally all patients were afebrile by day 14.

ii. The mean defervescence time reported in the study was 4.9 days.

iii. The hepatomegaly, splenomegaly and other symptom scores were also reduced significantly (p<0.05) on days 3, 5, 7 and 14 as compared to the baseline. The mean hepatomegaly score reduced from 0.67 at baseline to 0.38 on day 3, 0.22 on day 5, and 0.04 on day 14. Similarly, the splenomegaly score was 0.54 at baseline which came down to 0.32 on day 3, 0.17 on day 5 and 0.04 on day 14. Lastly, the mean abdominal pain score reduced from 0.88 at baseline to 0.37 on day 3, 0.20 on day 5, and 0.02 on day 14.

iv. Other symptoms:

1. Coated Tongue: (~57%) patients had a coated tongue at baseline, which came down 47.0% (~41%) patients on day 3 and finally 33.7% (~29%) patients on day 14.

2. Constipation: 713 (~61%) patients had constipation at baseline, which came down 477 (~41%) patients on day 10 and finally 382 (~33%) patients on day 14.

3. Diarrhoea: 682 (~58%) patients had diarrhoea at baseline, which came down 507 (~43%) patients on day 3, 475 (~41%) patients on day 5, 399 (~34%) patients on day 7 and finally 220 (~19%) patients on day 14.

v. Other symptoms:

1. A reduction in body temperature of 101.0°F at baseline to 98.12°F on day 3, (p<0.0001) and to 96.18°F on day 14.

2. Diarrhoea (~2%), Vomiting (~2%), Abdominal pain (~10%), Abdominal pain (~3%), Headache (~1%).

The investigators thus concluded that the fixed dose combination of cefixime 200mg – Ofloxacin 200mg is effective and safe in the management of uncomplicated typhoid fever.

2. Naik et al [Aug 2010] conducted a post marketing clinical study to evaluate the clinical efficacy and tolerability of the fixed dose combination of cefixime 200mg-ofloxacin 200mg in typhoid patients with respiratory abnormalities. The study was designed as an open label, prospective, non-comparative, multicentric, observational, post marketing study conducted across hospitals and clinics in India. The study enrolled 386 patients (age between 18 – 75 years) across 72 centres, who had a respiratory abnormality like bronchial asthma or infection. The patients were administered a fixed dose combination of cefixime 200mg-ofloxacin 200mg, twice daily for 10-14 days. The patients were evaluated at baseline and days 2, 3, 5, 7, 10 and 14 (if required). The study results analysing data from 365 patients revealed –

i. A reduction in body temperature of 101.70°F at baseline to 98.30°F on day 3, (p<0.0001) and completely normalized day 5 onwards.

ii. A total of 89.9% (n=328) patients were afebrile on day 3 itself and this number increased to 94.5% (n=345) on day 5 and finally all patients were afebrile by day 14.

iii. The mean defervescence time reported in the study was 3.2 days.

iv. The hepatomegaly, splenomegaly and other symptom scores were also reduced significantly (p<0.05) on days 3,5,7 and 14 as compared to the baseline. The mean hepatomegaly score reduced from 0.67 at baseline to 0.38 on day 3, 0.22 on day 5, and 0.04 on day 14. Similarly, the splenomegaly score was 0.54 at baseline which came down to 0.32 on day 3, 0.17 on day 5 and 0.04 on day 14. Lastly, the mean abdominal pain score reduced from 0.88 at baseline to 0.37 on day 3, 0.20 on day 5, and 0.02 on day 14.

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V. Other symptoms:

1. Coated Tongue: 279 (~76%) patients had a coated tongue at baseline, which came down to 166 (~46%) patients on day 3 and finally 70 (~19%) patients on day 7 and only 14 (~3.8%) patients on day 14.

2. Constipation: 235 (~64%) patients had constipation at baseline, which came down to 213 (~58%) patients on day 10 and finally 201 (~51%) patients on day 14.

3. Diarrhoea: 88 (~24%) patients had diarrhoea at baseline, which came down to 53 (~15%) patients on day 3, 24 (~7%) patients on day 5, 22 (~7%) patients on day 7 and finally 10 (~3%) patients on day 14.

The following adverse events (all mild to moderate in intensity) were reported in the study – nausea (~9%), Abdominal pain (~5%), Diarrhoea (~2%), Vomiting (~2%), Constipation (~1%) and headache (1%).

The investigators thus concluded that the fixed dose combination of cefixime 200mg – Ofloxacin 200mg is effective and safe in the management of uncomplicated typhoid fever patients with respiratory abnormalities.

vi. Faruqui et al 2012, studied the efficacy and tolerability of the fixed dose combination of cefixime 200mg & ofloxacin 200mg in a post marketing surveillance study in Indian patients. The study was conducted as a nonrandomized, open label, non-comparative, multicentric trial (5 centres), enrolling thirty patients aged 18-72 years suffering from typhoid fever. The patients were administered the study drug every 12 hours, for 10 – 14 days. Patients were assessed at baseline, day 3, 7, and 14 after enrolling into the study.

For the primary outcomes evaluated included the results were as follows:

i. Reduction in body temperature on 3rd, 7th, and 14th day from baseline – All patients reported fever on the first day of treatment. Body temperature was significantly reduced from baseline (mean ± SD) value 101.5± 0.8 °F to 98.34± 1.42°F, 97.26 ± 2.03°F and 97.06 ± 2.03°F on the 3rd, 7th and 14th days of treatment respectively. This reduction in body temperature was statistically significant (p< 0.0001) from baseline to 3rd day and onwards.

ii. Time to defervescence (i.e. normalization of body temperature to ≤ 98.40°F) during the study period - The time taken to achieve the normal body temperature was 2.93 ± 0.23 days.

iii. Interference in sleep patterns of the patients – At baseline, there was frequent nocturnal awakening (3.06 ± 0.88). Nocturnal awakening came down on day 3 (2.27± 0.70) and further down on day 7 (1.41± 0.73). On 14th day there were no or few cases of nocturnal awakening and the mean value was 0.44 ± 0.57. Thus, there was a significant reduction in the nocturnal awakening from the baseline on 3rd day of treatment and onward 7th and 14th day of treatment (P<0.001).

For the secondary outcome measures the results were as follows:

i. Global assessment of efficacy by investigator – ~97% reported ‘Good to Excellent’ efficacy.

ii. Global assessment of tolerability by investigator – ~93% reported ‘Good to Excellent’ tolerability.

Overall, only mild to moderate adverse events that did not require discontinuation of study drug like nausea, headache and epigastric pain were reported in ~13% patients. The investigators concluded that the fixed dose combination of cefixime and ofloxacin therapy is effective and achieves rapid clinical cure in typhoid fever, with excellent tolerability & safety.

b. Prospective prescription event monitoring study

Kadhe et al, 2012 conducted a post marketing prescription event monitoring study to evaluate the efficacy and safety of the fixed dose combination of cefixime 200mg – ofloxacin 200mg in Indian patients with typhoid fever. A total of 225 doctors enrolled 1029 patients suffering from typhoid fever in this prospective, open label, multicentric, post marketing prescription event monitoring study. The treatment given was cefixime-ofloxacin (200mg/200mg), twice daily for 14 days. Results were based on the analysis of data from physician recorded patient responses, on a pre-designed prescription event monitoring questionnaire.

For the study end points the following results were reported:

i. Time to defervescence was 4.36±2.53 days in 86% patients (n=883). However, noteworthy was the finding that the cefixime-ofloxacin combination showed a significant reduction in the body temperature after the first dose itself.

ii. Time to provide symptomatic relief was 4.76±3.62 days in 89% patients (n=917).

iii. Time to complete cure was 7.12±3.38 days in 87% patients (n=891).

iv. Reduction in need for hospitalization was seen in 86% patients (n=929).

v. Global assessment of treatment efficacy compared to standard treatment was reported as ‘Good’ in ~16.58%, ‘Very Good’ in 42.71% and ‘Excellent’ in 40.71% cases.

Overall, 92.4% investigators affirmed that they would recommend this combination for the treatment of enteric fever.

Of the 942 patients who reported adverse effects, ~85% (~802) patients indicated that the adverse effects were not distressing and or disturbing their daily routine, while ~15% (~140) patients considered the side effects as distressing or disturbing their daily routine.

The investigators thus concluded that cefixime-ofloxacin combination is efficacious, safe, offers quick symptomatic relief and a lesser need for hospitalization in patients with typhoid fever.

c. Retrospective Observational Survey Study

Patil et al, 2015, studied the efficacy of cefixime-ofloxacin 400mg sustained release tablets in the treatment of enteric fever in community settings of India. The study was designed on a retrospective, questionnaire based survey methodology, involving 78 family physicians across the country. A total of 881 patient data forms were analysed, of which cefixime-ofloxacin 400mg SR tablet was prescribed in 580 patients. The duration of therapy ranged from 5 days to 14 days, depending on
the clinician’s judgement. Fever clearance on the 7th day was reported in 97% cases (n=565) treated with cefixime-ofloxacin SR tablets. A further sub-analysis of high risk cases, i.e. relapse/ recurrence, showed equally good response to the combination as cases without defervescence on day 7 were only 1.3%. The study results also included cases with co-morbid conditions like diabetes (n=97), hypertension (n=106), others (n=41). Thus overall, the investigators concluded that cefixime-ofloxacin 400mg SR tablets as an optimal choice in the management of typhoid fever, including cases with co-morbidities like diabetes and hypertension.

IV. Drug utilization pattern study

Rajaram et al, 2016 analysed the drug utilization patterns in primary health centres from a semi-urban area in south India. General practitioner’s prescription data from 500 patients was collected and analysed. The results showed that in general, the doctors mainly used combination therapy (92%) for the patients. Cefixime-ofloxacin was the most commonly recommended antibiotic combination, i.e., 30% patients and the 2nd most commonly recommended antibiotic, behind only cefixime monotherapy, which was recommended to 36% patients.

3. Regulatory Status in India: Cefixime-Ofloxacin combination is approved by the Indian Regulatory Authority. The Indian Regulatory Authority website shows approvals for six formulations of cefixime-ofloxacin combination as listed in Table 3.

In the recent years, many FDCs were re-evaluated by the Indian regulatory authorities for their rationality and continuance of manufacturing and marketing in India. Cefixime-ofloxacin combinations also feature in the list FDCs permitted for continued manufacturing and marketing in respect of the applicants under 18 months’ policy decision (as on 21.02.2017) published by Indian Regulatory Authority website (Table 3).

Apart from cefixime-ofloxacin combination, combinations of cefpodoxime and ofloxacin in various formulations / strengths are approved by Indian Regulatory Authority. There do not seem to be any other antibiotic combinations in the list of approvals on the Indian Regulatory Authority website for typhoid fever.

4. Guideline Recommendation in the Indian context: It is becoming clearer that monotherapy is not effective for typhoid fever, the best is considered to be combination therapy. The 2015, Association of Physicians of India (API) recommendations for the management of typhoid fever highlight the fact that, a number of physicians currently use fixed-dose combinations in typhoid.

In a recent (2016) knowledge, attitude, practices study with general practitioners in India for typhoid fever, the investigators reported that in 38% of typhoid cases combination therapy is used. This is in line with reports of Butler et al 2011, suggesting that the use of a combination of cephalosporin and fluoroquinolone is very common in the United states of America. WHO (also supports the use of combination therapy for the treatment of typhoid fever).

The 2015 API recommendations for the management of typhoid fever, cite the lack of clear guidelines for the use of monotherapy and combination therapy in typhoid fever. However, API also recommends the use of combination therapy (Cefixime + Fluoroquinolone like ciprofloxacin and ofloxacin), but still reserves its use to cases where response to monotherapy is inadequate or unresponsive. Of special relevance here is the specific recommendation by API for cefixime in the context of combination therapy with fluoroquinolones, further reinforcing the advocacy for cefixime-ofloxacin combination in the treatment of typhoid fever.

Also, both cefixime and ofloxacin individually figure as 1st line therapy in the recommendations of API for treating typhoid fever.

5. Clinical Evidence in the Indian context: The in-silico studies, in-vitro studies, clinical studies (retrospective, post marketing observational / surveillance, prescription event monitoring, interventional studies) have all been done in the Indian setting, i.e., with Indian strains of typhoid pathogens, patients and treatment facilities and have all been done between 2010 – 2017, and hence can be considered convincingly relevant to the Indian typhoid landscape. Also, the combination of cefixime-ofloxacin seems to be the only combination backed by multiple research initiatives and robust Indian data for typhoid fever. The available clinical evidence in this context has already been reviewed in detail in the earlier sections.

6. Physician usage and prescription trends in the Indian Context: As mentioned earlier, clinicians currently use combination therapy often in their practice. Mukherjee et al reported the usage data for various antibiotics, including cefixime-ofloxacin combination in the Indian context, as of September 2015. The data quite interestingly suggests that there are 142 branded generics of cefixime 200mg -ofloxacin 200mg combination and it is the 7th most prescribed antibiotic amongst all antibiotics in the Indian market, despite being available for use only since 2010. A closer look at the data reveals that, cefixime 200mg -ofloxacin200mg combination is the number one prescribed antibiotic combination by the Indian healthcare practitioners.

Antimicrobial resistance is a global problem and is definitely a cause of concern in India too, in the context of typhoid fever. It is becoming clearer that monotherapy is not effective for typhoid fever and the option to be considered is combination therapy. The Global Antibiotic Research & Development Partnership (GARDP), a joint initiative of DNDi and the WHO, aims to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists. GARDP R&D priorities include in-vitro evaluation of combination therapies as well as evaluation of salvage regimens for multi-drug resistant typhoid fever.

In this context GARDP report highlights the following:

- Development of combination regimens for typhoid fever and invasive salmonella infections.
- Data to suggest that in other
In India, there are very few antibiotic combinations that are approved and backed by clinical evidence, for the treatment of typhoid fever. Cefixime-ofloxacin combination is approved by Indian Regulatory Authority and has a good body of clinical evidence in the current Indian context. The two drugs act on different sites of the pathogen, as well as have complementary actions i.e. cefixime acting on the extracellular pathogens, while ofloxacin acting on the intracellular pathogens. In-silico studies have demonstrated positive rationale of combining these two drugs, while in-vitro studies have substantiated the same by showing a strain specific synergistic and/or additive activity between the two drugs against S.typhi. Clinical studies in Indian patients have shown multiple benefits of using this combination in typhoid fever such as a quick time to defervescence (~3 days), complete clinical cure in ~7 days, effective symptomatic relief, efficacy in relapse cases and a reduced need for hospitalization. The drug combination also demonstrates a very good tolerability profile. Recommendations of the Association of physicians of India also back this combination in typhoid fever, where response to monotherapy is inadequate or unresponsive. Thus, in the current era of emerging antibiotic resistance, cefixime-ofloxacin is a safe, effective and reliable treatment option for clinicians to treat uncomplicated typhoid in the Indian community setting. Further studies evaluating the efficacy of this combination compared to monotherapy, in first time cases as well as relapse and non-responsive cases will help establish the role of the combination further in the treatment of uncomplicated typhoid fever.

References


Table 2: List of formulations approved by indian regulatory authority

<table>
<thead>
<tr>
<th>Formulation Details</th>
<th>Indication</th>
<th>Approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefixime 100 mg + Ofloxacin 100 mg</td>
<td>For the treatment of patients with typhoid fever and urinary tract infection in adults.</td>
<td>26.04.10</td>
</tr>
<tr>
<td>Tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefixime 200 mg + Ofloxacin 200 mg</td>
<td>For the treatment of patients with typhoid fever and urinary tract infection in adults.</td>
<td>26.04.10</td>
</tr>
<tr>
<td>Tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefixime SR 200mg + Ofloxacin 200 mg</td>
<td>(Additional Strength) For the treatment of patients with typhoid fever and urinary tract infection in adults.</td>
<td>31.08.10</td>
</tr>
<tr>
<td>Tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefixime Sr 400 mg + Ofloxacin 400 mg</td>
<td>(Additional Strength) For the treatment of patients with typhoid fever and urinary tract infection in adults.</td>
<td>31.08.10</td>
</tr>
<tr>
<td>Tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefixime Trihydrate IP Eq. to Anhydrous Cefixime 100 mg + Ofloxacin IP 100 mg/400mg Tablets</td>
<td>(Additional dosage form) For the treatment of patients with typhoid fever and urinary tract infection in adults.</td>
<td>20.04.11</td>
</tr>
<tr>
<td>Dispersible Tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefixime Trihydrate IP Eq. to Anhydrous Cefixime 200 mg + Ofloxacin IP 200mg Tablets</td>
<td>(Additional dosage form) For the treatment of patients with typhoid fever and urinary tract infection in adults.</td>
<td>20.04.11</td>
</tr>
<tr>
<td>Dispersible Tablet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Indian Regulatory Authority - FDCs permitted for continued manufacturing and marketing in respect of the applicants under 18 months policy decision (as on 21.02.2017)

<table>
<thead>
<tr>
<th>Formulation Details</th>
<th>Date of NOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefixime (as Trihydrate) IP Eq. to anhydrous Cefixime 50mg + Ofloxacin IP 50mg per 5ml of reconstituted suspension</td>
<td>17.07.15</td>
</tr>
<tr>
<td>Cefixime Trihydrate IP eq. to (anhydrous) Cefixime 50mg/100mg/200mg+Ofloxacin IP 50mg/100mg/200mg uncoated tablets</td>
<td>17.07.15</td>
</tr>
<tr>
<td>Cefixime 200mg/100mg+Ofloxacin 100mg/200mg tablets</td>
<td>17.07.15</td>
</tr>
<tr>
<td>Cefixime Trihydrate IP</td>
<td>17.07.15</td>
</tr>
<tr>
<td>Eq. to anhydrous Cefixime 200mg/400mg+Ofloxacin IP 200mg/400mg tablets</td>
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Essential Yet Neglected Role of Primary Care Physicians in Palliation Team

Neeti Rustagi¹, Puneet Pareek², Manoj Verma³, Pramod Kumar Sharma⁴

Abstract

Quality home-based care for patients with the end-stage disease is increasingly being preferred. Responding to disease associated symptoms and complications may pose an array of challenges in evolving palliative care systems, as no formal institutional mechanism exists to respond to patient and caregiver’s wishes. Family and primary care physicians can play an instrumental role in such scenarios by bridging the gaps between cancer specialists and patient and caregivers expectations.

Introduction

Palliative care, especially at end-stage, focusses primarily on maintaining comfort and quality of life. Home-based palliative care is preferred for receiving the end of life care and recognized as a cost-effective option.¹ National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke (NPCDCS) has introduced need of home-based palliative care team comprising of nurse and counsellor trained in identifying symptoms, pain management, communication, psychosocial and emotional care.² This is a quintessential step towards addressing nursing needs of terminally ill patients.

Field Experience

A 55-year-old female with 20 years’ history of tobacco chewing presented with a non-healing ulcer at the base of tongue for past 6 months associated with complaints of progressive speech disturbance and difficulty in swallowing and masticating food. Local examination revealed solitary midline ulcer of approximately 2cmx2cm size on the outer surface of the floor of the mouth. Mouth opening was restricted to three fingers and tongue appeared dry with white adherent patches observed in the buccal cavity. Caregivers reported three episodes of hematemesis in the past that resolved spontaneously.

A punch biopsy from the left lateral border of tongue revealed moderate to poorly differentiated squamous cell carcinoma. Magnetic resonance image of a face to the neck from the base of the skull to clavicle showed a poorly circumscribed large mass of intraoral tongue centered along the left lateral margin measuring 5.2 cm x 3.8 cm x 6.4 cm in size. Infiltration of intrinsic tongue muscles with contralateral extension across the lingual septum with a tumour extending to right lateral tongue margin was present. Posteriorly, the tumour extended into left retromolar trigone. Anteriorly, there was destructive involvement of body of the mandible in bilateral para-sagittal planes with tumoural extension in anterior subcutaneous soft tissue across mandible. On the coronal image, the floor of the mouth and myelohyoid sling appears infiltrated. No focal osseous metastatic lesion was visible (Figures 1 and 2). Diagnosis of Squamous cell cancer oral tongue Stage IV “Loco-regionally Advanced Tongue Cancer” was made by the oncologist. Malignancy was considered inoperable and management plan defined was to initiate palliative care with an emphasis on symptoms guided preventive and therapeutic measures.

Detailed treatment history revealed visits to multiple private and public practitioners including those from an alternative system of medicine and faith healers. A referral visits to neighbouring state Gujarat was made for palliative elective radiotherapy only to be discontinued a few weeks later due to financial constraints. Throughout the course of treatment and referral, both patient and caregivers were never prognosticated about life-limiting nature of the current illness and end-stage disease.

As part of the management plan, spouse and son of the patient were explained about poor prognosis and life-limiting nature of the disease. They were explained in detail regarding futility of running from one practitioner to another in search of a cure. Their approval was sought before explaining patient about the same. Patient and caregivers opted for the end of life care at home. A team of medical social worker and community physician trained in palliative care was constituted. The team actively established a good rapport with primary care physician and general practitioner in close vicinity to patient residence who were then explained about essence and their role in primary palliation. The team engaged both primary care physician and caregivers in providing home-based palliative care related to oral and general hygiene, relief of constipation, controlling episodes of pain and hematemesis and providing energy-dense food and water to the patient at frequent interval. Once in a week, telephonic communication was done with stakeholders and the fortnightly home visit was carried out to monitor patient condition. Female
members of the family were identified as the main care provider and were actively involved in the treatment plan. Over the duration of 2 weeks, patient weight improved from 46 kg to 47.3 kg. Improvement in hydration status and oral hygiene was observed. After initial one to two visits to the tertiary centre, the preference of family members shifted to primary care physicians for guidance and support regarding nasogastric feeding, achieving hemostasis during episodes of hematemesis, maintenance of oral and basic hygiene, physiotherapy and issues related to the general well-being of the patient. Patient oral intake and symptoms of pain and constipation reportedly improved in follow up visits. Finally, the patient expired in sleep after 3 months of institutionalizing home-based care. The caregivers conveyed a sense of satisfaction and emotional fulfilment regarding home-based care provided with the support of all stakeholders.

**Discussion**

Preference of oncologists for aggressive cancer care in form of surgery, adjuvant chemotherapy or radiation at cost of palliative care referral and services at end of life stage is reported. Visiting multiple practitioners in and around city reflects poor patient-physician communication and neglected sharing of prognosis as the patient was referred from one health facility to another with the hope of cure and not palliation. Ignored and ineffective communication by hospital-based clinicians is observed to cause false expectations, side effects and complications among patients “sick enough to die” and deprives them to prepare for their approaching death.

End-of-life care policy continues to promote dying at home, assuming that caregivers will be able and willing to provide care. The system approach to provide support to family caregivers for managing dying patient is segmented as informational, management and relational continuity of care. In the current case, establishing a communication network between cancer specialists, community physicians and family physicians provided necessary support to caregivers (management and relational continuity) in taking care of dying patient and prepared both patient and caregivers about approaching and accepting death (informational continuity).

The current case study highlights that communication network between specialist and primary physicians are effective in enabling family physicians or general practitioners in competently providing patient-centric care in the context of family and community and in addressing areas of grief, bereavement and other caregiver issues in terminal illness patients.

The burden of chronic disease including cancers continue to rise in India and other developing economies. Effective role of primary care providers in ensuring cancer care and lack of an integrated system where family physicians are involved in planning and providing services to cancer patients as noted in our set up is reported even in developed countries.

Lack of such collaborative networks in nations especially where palliative care systems are evolving lead to confusion regarding the organization of patient-centric care due to the poor orientation of primary care physicians. Necessary attention and resources to integrate primary physicians in palliative care teams is thus an effective strategy for ensuring continuity of care for cancer patients preferring to die at home.

**Conclusion**

Terminally ill patient and caregivers present with a diverse need, which extends beyond physical care and control of disease-related symptoms. The focus of healthcare providers on curative and life-prolonging treatment may jeopardize the quality of life of the patient. Institutionalizing care to patient terminal illness requires close coordination between cancer specialists and primary care providers to bridge the gap between demand and supply in establishing essential components of appropriate care.

**Learning points**

Health systems with evolving palliative care practices must recognize the role of collaborative networks with primary care and family physicians. This will provide a unique platform to establish coordinated cost-effective care of the patient in consultation with cancer specialists. It will also help in bridging gaps towards institutionalizing home-based palliative care. Primary physicians need to be equipped for managing the palliative care of end-stage disease patients. They are the one who can fulfill their role of effective communicator.
Non-transplant Options in Advanced Heart Failure: Emergent Need for Guidelines

Srilakshmi M Adhyapak¹, V Rao Parachuri²

Abstract

Advances in revascularization techniques along with its timeliness has significantly prolonged survival in Coronary Artery Disease. Progressive heart failure is one of the complications which persists in a large scale. The challenges of surgical revascularization in such patients with left ventricular dysfunction are daunting, necessitating short cross-clamp and cardio-pulmonary bypass times. Associated co-morbidities like renal dysfunction, low cardiac output state and pulmonary vascular obstructive disease are additional significant deterrents to surgical success. In the situation where transplant options are limited, viability of high-risk surgical revascularization may need radical re-thinking.

The burden of ischemic cardiomyopathy is increasing in large proportions particularly in South East Asia reflecting the population’s ethnic genotype. Most of these patients progress relentlessly to end-stage heart failure despite maximal tolerated medical therapy. Heart transplantation is limited by logistic constraints of donor in-availability and lack of funds, and is presently being carried out in less than 5% of patients.¹

The challenges of corrective surgery for these patients would require adequate myocardial protection with short cross-clamp and cardio-pulmonary bypass times. Associated co-morbidities like renal dysfunction, low cardiac output state, pulmonary vascular obstructive disease are significant deterrents to surgical success. In the situation where transplant options are limited, the viability of corrective high-risk surgeries may need radical re-thinking. The lack of focused guidelines targeting this population makes decision making even more difficult.

Although the mortality is slightly higher with CABG in patients LV dysfunction, the 30-day mortality being 5.6% versus 1.1% for patients with normal LV function, the benefits of revascularization far exceed the benefits of medical therapy alone.²

Clinical non-randomized studies on CABG in patients with LV dysfunction clearly demonstrate the need for viability testing. In patients with severe left ventricular dysfunction and evidence of relatively large areas of viable myocardium, improved long-term survival with revascularization as compared with medical therapy has been clearly demonstrated.²

However, the degree of LV remodeling seemed more important. Improvements in LV function after CABG occurred in patients with myocardial viability who had less severe LV remodeling, whereas functional recovery seemed less likely, despite viable myocardium, in patients with severe LV remodelling.² Re-analyzing the STICH database, it was noted that among patients with coronary artery disease and LV systolic dysfunction, lower LV end-systolic volume index did not identify patients in whom myocardial viability predicted better outcome with surgical relative to medical treatment.³ So, the question arises in the population with larger LV ESVI and larger proportions of non-viable myocardium, whether LVAD or cardiac transplantation are more viable options than revascularization.

All the observational studies on revascularization in LV dysfunction have studied patients with a wide range of LVEF ranging from 20% to 40%; representation of patients with LVEF≤20% being <3%. Patients with an ESVI> 120 ml, severe pulmonary hypertension; mean PAP > 25 mm Hg, VO2 max <14 ml and LVEF< 20% have not been included in these studies, as are patients in NYHA class III/IV. Patients in NYHA class III/ IV in these studies constitute < 2-4%. Therefore, it is difficult to extrapolate the findings of these studies to a population who are transplant or LVAD eligible.

Although the results of randomized controlled trials are often disappointing and difficult to interpret, there is a paucity of these trials in these patients. The STICH trial was a randomized study designed to determine the benefit of CABG in patients with

References

LV dysfunction due to ischemic cardiomyopathy. These patients were in NYHA class II/III with an LVEF ≤35% and did not qualify to be transplant or left ventricular assist device (LVAD) eligible. Also, most investigators believe that the high crossover rate from medical therapy to surgery in the first year after randomization significantly confounded the interpretation of the STICH study. The post hoc analysis examining treated patients revealed a significant benefit of surgical intervention with respect to overall mortality and freedom from repeat hospitalization. Patient selection was flawed by including patients with milder degrees of heart failure which does not allow interpretation of its results for patients with severe LV dysfunction.

Transplant eligible patients undergoing CABG are different from the patients with LV dysfunction in terms of longer duration of symptoms, presence of right heart failure, and a greater incidence of previous revascularization. Although the operative risk in the coronary bypass group with LV dysfunction was significantly higher for those with a greatly increased left ventricular end-diastolic pressure (LVEDP) (>24 mm Hg), a low preoperative cardiac output (<2.0 l/min/m²), NYHA class IV, there was no significant difference in hospital mortality in patients with LVEF between 10–20% versus those between 20–30%. Survival at six years was comparable between the two groups; 78.9% for the LV dysfunction versus 68.9% in the transplant group. Reinvestigation showed a significant decrease in mean pulmonary artery pressure from 28.2±4.7 mm Hg to 21.2±3.9 mm Hg (p<0.01), pulmonary capillary wedge pressure from 19.2±4.3 mm Hg to 13.1±2.8 mm Hg (p<0.01) and mean improvements in left ventricular ejection fraction from 0.24±0.03 to 0.39 ±0.06 (p<0.0001). Patients eligible for transplant had surprisingly favorable mid-term outcomes when subjected to high-risk corrective surgeries. However, these patients constituted a highly selected group with an LVEF <20% with a VO2 max <14 ml/min/m². None of these patients required inotropic support and were not on any support device. Even the transplant in-eligible patients had better outcomes although their outcomes were worse than those who were transplant eligible. The mortality associated with CABG alone was much lower than when CABG was performed with concomitant mitral valve repair or LV restoration (2.3% versus 14%). There was a significant improvement in NYHA class following CABG at mid-term. This demonstrates that patients with severe LV dysfunction due to ischemic etiology who are transplant eligible, with preserved renal function, no evidence of cardiogenic shock, and without concomitant mitral surgery have mortality benefits from CABG. This study did not address the benefits of corrective surgeries in patients who had undergone previous open-heart surgeries. These patients constitute a very difficult population and in our opinion may require LVAD or transplantation.

Although long-term evidence is lacking, high risk percutaneous coronary Intervention (HR-PCI) has shown benefits at 12 months in this population. In the PROTECT 2 trial, Impella provided superior hemodynamic support in comparison with IABP, and at 90 days a trend toward decreased events was observed in the intent-to-treat population (40.6% Impella vs. 49.3% IABP, p=0.066). A subsequent analysis redefining myocardial infarction as the development of new Q waves or CKMB more than eight times the upper limit of normal demonstrated lower rates of events in patients treated with Impella (composite event rate 37% vs. 49%, p = 0.014), respectively; and major adverse cardiac and cerebrovascular events 22% vs. 31%, p = 0.034). The potential mechanism for late benefit may relate to more stable procedural hemodynamics allowing for greater and more complete revascularization, including allowing for more complex PCI procedures such as rotational atherectomy.

Therefore, MCS may be considered for patients undergoing high-risk PCI, such as those requiring multivessel, left main, or last patent conduit interventions, particularly if the patient is inoperable or has severely decreased ejection fraction or elevated cardiac filling pressures.

Surgical ventricular restoration (SVR) based on Laplace’s law may well become a definitive solution in selected patients especially when transplant options are not available. The reasons for the decreasing numbers for SVR in developed countries may be the wide availability of timely revascularization, which is still scarce in most developing countries, making SVR applicable.

As the incidence of heart failure following an acute coronary event or chronic ischemic heart disease is increasing, high-risk revascularization and SVR need re-thinking. Although framing treatment guidelines for this population is fraught with difficulties, these may help in better management of this increasing malady.

References
Esophageal Scleroderma- Changes in Esophageal Manometry

Mayank Jain

Fig. 1: Manometry

Systemic sclerosis (scleroderma) commonly involves the esophagus. It mainly causes esophageal motility disturbances which lead to gastroesophageal reflux and its complications.1,2

A forty year old lady presented with history of gradually progressive dysphagia for solids and liquids for last one month. Upper gastrointestinal endoscopy done at an outside centre revealed reflux esophagitis (Los Angeles Classification-C). She was given proton pump inhibitors for 4 weeks with which she had excellent improvement. She returned three months later with worsening dysphagia. She had lost around 2 kgs and noted skin thickening. Her appetite remained good. On high resolution manometry (Figure 1), basal lower esophageal sphincter pressures were normal and mean integrated relaxation pressures was <15. There was absent contractility in the distal 2/3 of the esophagus (smooth muscle portion). The possibility of scleroderma was considered. Anti nuclear antibodies were positive. She was stared on high dose PPI with good relief in symptoms. Over a six month follow up, she noted Raynaud’s phenomenon and progressive skin tightening suggesting disease progression.

Progressive systemic sclerosis (PSS) causes smooth muscle atrophy and fibrosis of the distal two-thirds of the esophagus. Motility studies show reduced-amplitude or absent peristaltic contractions in this region and normal or decreased lower esophageal sphincter pressure. Patients complain of dysphagia, heartburn, and regurgitation due to reflux and dysmotility. Complications include strictures (17% - 29%) and Barrett esophagus (up to 37%). Symptoms correlate poorly with evidence of esophagitis or abnormal 24-hour pH recordings.3

References


Gallstone Pancreatitis and Extramedullary Paraspinal Hematopoiesis in Hb E/beta Thalassemia

Longjam Goldie1, Wangda Kinzang2, Gautam Thangjam3, Vaskarjeet Konsam4

Fig. 1: Chest x ray showing well-defined extra cardiac shadow

A 45 years old male with Hb E/beta thalassemia and past history of multiple blood transfusions presented with diffuse abdominal pain for 2 days. The physical examination revealed icterus, anemia and generalized tender abdomen with hypoactive bowel sounds. Laboratory studies showed hemoglobin of 8 gm/dl, elevated serum lipase 15000U/L (23-300) and amylase 1300U/L (30-110). Liver function test was deranged with total bilirubin of 10.8mg/dl, direct fraction comprising of 6.8mg/dl, SGOT 63 IU/L (17-46), SGPT 75 IU/L (13-69) and ALP 159U/L (38-129). Renal function test was normal. Abdominal ultrasound showed evidence of pancreatitis, cholelithiasis with mildly dilated CBD of 6mm and hepatosplenomegaly. The chest X-ray showed well circumscribed shadow behind the heart (Figure 1) and lobulated bilateral thoracic paraspinal mass extending from D8-12

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was seen on CECT thorax (Figure 2), from which FNAC was done. The histopathological report was consistent with extramedullary hematopoiesis (Figure 3). It is reported that paraspinal location for the hematopoietic tissue occurs in 11–15% of cases with EMH in thalassemia\(^1\) and more than 80% of the cases remain asymptomatic\(^2\) like in our case. MRCP ruled out choledocholithiasis (Figure 4). He was treated for mild acute biliary pancreatitis and was discharged after laparoscopic cholecystectomy.

References


Rare Cause of Pain Abdomen: Dorsal Pancreatic Agenesis

Divendu Bhushan\(^1\), Ramesh Kumar\(^2\)

A 24 yr old male with no addiction presented to Medicine OPD Paras HMRI, Patna with pain abdomen around umbilicus, burning type radiating to back. There was no tenderness in abdomen. Investigations including blood glucose, LFT and S. Amylase and lipase, Ultrasound abdomen UGI endoscopy were normal. CT abdomen which reveals agenesis of pancreatic body and tail, Pancreatic duct was not dilated (Figure 1).

Dorsal pancreatic agenesis is a very rare pancreatic developmental anomaly and only few case reports are found in literature. It may be sporadic or genetically transmitted (autosomal dominant or X linked dominant).\(^1\) Pancreas develops by 2 buds-ventral and dorsal. Ventral bud derives from hepatic diverticulum and form head of pancreas. Dorsal bud arises from dorsal mesogastrium and form body and tail of pancreas.

Mostly asymptomatic but patients may present with abdominal pain, hyperglycemia, bile duct obstruction and pancreatitis.\(^2\) It is critical to rule out pancreatic carcinoma with proximal atrophy, pancreas divisum, and pancreatic masses as these may resemble agenesis of the dorsal pancreas in imaging. Treatment is conservative including low fat diet and enzyme supplements.

References

Necrobiotic Xanthogranuloma as the Presenting Manifestation of Smouldering Myeloma

Nayani Makkar¹, Vettakkara Kandy Muhammed Niyas¹, Satish Swain¹, Prayas Sethi¹, Neeraj Nischal¹, Shipra Agarwal², M Ramam³, Naveet Wig¹

Abstract
Necrobiotic xanthogranuloma is a rare dermatological manifestation of underlying hematological malignancies, in particular, when associated with paraproteinemia. These patients who are clinically symptomatic with chronic papules, nodules or plaques which demonstrate a histopathological pattern suggestive of extensive and frequently confluent areas of necrobiosis with granulomatous infiltration, warrant evaluation for an underlying monoclonal gammopathy.

We present an unusual case of pyrexia of unknown origin. The patient, on evaluation, was found to have nodular lesions on his buttocks and thigh. Biopsy from these lesions demonstrated the histopathological findings of necrobiotic xanthogranuloma. Subsequent evaluation diagnosed the patient with smouldering myeloma. As the patient was not fulfilling the criteria for multiple myeloma and his symptoms were not debilitating it was decided to keep the patient under close follow up.

Necrobiotic xanthogranuloma (NXG) is a rare skin disorder grouped under non – Langerhans cell histiocytosis.¹ This condition is often associated with an underlying haematological disorder especially paraproteinemias. A monoclonal gammopathy is present in about 90% of cases of NXG.² We report an interesting case where in which a patient of smouldering myeloma presented as pyrexia of unknown origin and necrobiotic xanthogranuloma.

Case Report
A 50 year old male patient, a BSF Jawan from Rajasthan presented with complaints of recurrent fever and nodules in the buttocks and thigh for four years duration. The fever was episodic and with each episode of fever the patient noticed multiple nodules in the buttocks and thigh. The nodules were red and painful. The fever and swelling used to persist for around a week and subside without any treatment. The patient did not have any history of cough, breathlessness, bone pain or joint pain.

On examination the patient was conscious and oriented, pulse rate was 80/minute and blood pressure was 110/80 mm Hg. There was no pallor, lymphadenopathy or clubbing. There were multiple nodular swellings (2x2 cm) in the gluteal area and thigh which were tender on palpation. The skin surrounding these swelling were thick and indurated. Rest of the physical examination showed no abnormalities.

Blood investigations showed a Haemoglobin of 9.8 g/dL, a total leucocyte count of 8200/mm³ and a platelet count of 4, 47,000/mm³. His Erythrocyte sedimentation rate was 40mm in the first hour. Albumin level was 3.2g/dl and globulin level: 4.1 g/dl. Urine microscopy was normal and there was no proteinuria. Test for anti-nuclear antibodies by Immunofluorescence was negative. Rest of the investigations are summarised in Table 1.

A biopsy of the nodule from the gluteal area was done which showed a fragment of panniculus with septal thickening (Figure 1). The lobules showed many foamy macrophages and Touton giant cells with occasional polymorphs and eosinophils. These features were suggestive of xanthogranulomatous panniculitis which is a feature of necrobiotic xanthogranuloma.

In view of the biopsy finding and the reversed Albumin: Globulin ratio an underlying paraproteinemia was suspected. Serum electrophoresis showed a dense and narrow M band in the gamma region. Immunofixation studies showed the M Band to be IgG

Table 1: Laboratory investigations

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Lambda. A bone marrow study done showed 12% plasma cells (Figure 2). A serum Free Light Chain Assay showed a serum free Kappa light chains of 30.63 mg/L, free lambda light chains: 531.05 mg/L and a serum free kappa/lambda ratio of 0.05. PET scan done showed metabolically active ill-defined hypodense lesion in the region of left quadriceps muscle (Figure 3). There were no lytic bone lesions.

Patient was thus not fulfilling the criteria of Multiple Myeloma and was diagnosed as Smouldering Myeloma. He was decided to be kept under regular follow up.

Discussion
NXG is a rare skin disorder that occurs in patients with underlying haematological disorders especially paraproteinemia. NXG was first described by Kossard and Winkelman in 8 patients with underlying paraproteinemia. Currently this skin disorder is considered as a non-Langerhans cell histiocytosis.

Clinical presentation of NXG is in the form of chronic papules, nodules and plaques predominantly involving the face and periorbital areas. However the lesions can involve the trunk and extremities as well. Histopathological features include extensive areas of necrobiosis with a prominent granulomatous infiltrate in the dermis and subcutaneous tissue. Within the granulomas foreign body giant cells, Touton-type giant cells and foam cells are characteristically seen. Xanthogranulomatous panniculitis with Touton-type giant cells and palisading cholesterol clefts is a characteristic feature of NXG.

An underlying monoclonal gammopathy should always be investigated in a case of NXG. In a series of NXG patients, 86% had underlying paraproteinemia. 26% of patients in this series had an underlying hematologic malignancies at the time of NXG diagnosis or during followup. Multiple myeloma was present in 11% of the patients. In another series 71% had an underlying monoclonal gammopathy while 18% met the criteria for multiple myeloma.

Many peculiarities of our case mark it as a rather atypical clinical presentation. The first is the presentation of our patient as a case of pyrexia of unknown origin. He had presented to multiple health care facilities with the chief complaint of intermittent fever over the prior four years, with no evident cause on extensive evaluation including imaging. The systemic manifestation of pyrexia in the absence of overt systemic disease (while the patient demonstrated laboratory evidence for a plasma cell disorder, the absence of target organ damage led to the designation of a smouldering multiple myeloma) is an uncommon presentation not only of NXG but also of plasma cell dyscrasia.

The second is the unusual presentation of the dermatological disorder itself. The exclusive involvement of the lower limbs in the absence of facial or trunk lesions, while reported, is infrequent. Furthermore, the skin manifestations presented with a rather indolent course, marked by recurrent, spontaneously healing nodular swellings with no evidence of local infiltration or destruction, as well as no extracutaneous organ involvement over the four year symptomatic period.

Given the rarity of NXG, there exists no definite clinical guideline to direct management of the cutaneous manifestation. The treatment of the underlying plasma cell dyscrasia, hence takes precedence and the cutaneous manifestation has been seen to respond to treatment of multiple myeloma. Our patient, however, did not have significantly debilitating cutaneous manifestations or end organ manifestations from his plasma cell dyscrasia. On discussion with a panel of medical oncologists, physicians, dermatologists in conjunction with the patient, it was decided to continue close monitoring and regular follow-up with the subsequent initiation of therapy in the event of worsening of clinical and/or laboratory parameters.

References
Successful Pregnancy Outcome after Coiling of Ruptured Intracranial Aneurysm

Richa Vatsa¹, Jai Bhagwan Sharma², Rinchen Zangmo¹, Sunesh Kumar², Anshu Yadav³

Abstract
Rupture of intracranial aneurysm is a serious condition, prompt diagnosis and treatment may prevent potentially lethal complications in pregnancy and otherwise. Clipping and endovascular coiling are treatment modalities available. We accessed outcome of a pregnancy with ruptured intracranial aneurysm managed with endovascular coiling. We report a pregnant woman who suffered from SAH due to rupture of posterior cerebral artery aneurysm in third trimester. Endovascular coiling with Guglielmi detachable coil (GDC) followed by caesarean section done. She required coiling twice in pregnancy.

Introduction
Ruptured cerebral aneurysm, which can present as acute subarachnoid haemorrhage (SAH), is a rare cause of maternal morbidity and mortality. Approximately 2% of adult population have an intracranial aneurysm. Rupture is a serious complication of these aneurysms, which depends on the size, occurs in 0.1% if size < 10 mm and in 1% for those > 10 mm.¹ The incidence of aneurysmal subarachnoid haemorrhage (aSAH) for women in general is 11.5 per 100 000 person-years and increases with age. The incidence is similar in pregnancy. The risk being more in second half of pregnancy, only about 20% bleed in the first half, probably due to hemodynamic changes which are more pronounced in second half.

Endovascular surgery with Guglielmi detachable coil (GDC) is a minimally invasive method for treating aneurysm during pregnancy or otherwise. We report a pregnant woman who suffered from SAH due to rupture of posterior cerebral artery aneurysm, effectively managed by GDC followed by caesarean section.

Case Report
Mrs X, 25 year old primi gravida presented at 28 week pregnancy with sudden onset headache and recurrent vomiting. Her past history was not significant. MRI brain showed SAH. After presentation digital subtraction angiography (DSA) revealed 9x6 mm aneurysm of P3 segment of left posterior cerebral artery (PCA) with neck of 2.9 mm (Figure 1). Ultrasound showed normally growing fetus of 28 weeks. Through right femoral catheterisation, coiling of left PCA dissecting aneurysm pseudo lobule was done. Control angiogram showed complete occlusion of the aneurysm with patent parent artery lumen. She was discharged on 6th post-operative day with mild residual headache, normal motor function, without any cranial nerve deficit. Medicines continued after discharge were levitiracetam 500 mg BD and nimodipine 60 mg 4 hourly. She remained asymptomatic for around 1.5 months when she again presented with vomiting, seizure and altered sensorium for 1 day at 36 weeks and 4 days period of gestation. NCCT head done was suggestive of SAH. Digital subtraction angiography (DSA) done under general anaesthesia which showed dissecting aneurysm with pseudolobule (size 5.8 x 5 mm) of left distal PCA, just distal to the previously coiled aneurysm. The was occluded and didn’t show any recanalisation with mild medial shift probably due to new hematoma. Subsequently the parent aneurysm and the parent artery were coiled (Figure 2).

Patient remained intubated for the next 24 hrs. After stabilisation of patient’s condition, in consultation with neonatologist decision for caesarean section (CS) was taken. CS was performed under general anaesthesia and a healthy male baby weighing 3058 gm with apgar score 8/10 and 9/10 at 1 and 5 minute was delivered. She was...
extubated on day 2. Patient improved in post-operative period. Her headache subsided. She was discharged on day 9 in good general condition. Her baby was also doing well at discharge. Repeat angiography done after 6 months showed no residual aneurism of previously coiled left PCA but new bilateral small (3×2 mm) wide neck (3 mm) posterior communicating artery aneurysm. The patient is currently under follow up.

**Discussion**

Rupture of intracranial aneurysm is a serious condition, prompt diagnosis and treatment may prevent potentially lethal complications. The reported maternal case-fatality from a SAH during pregnancy or puerperium is comparable with the 50% case-fatality of SAH in general. The foetal case-fatality is approximately 17%.

Options for aneurysm repair, for both ruptured and un-ruptured, are clipping or endovascular coil placement, former being traditional and time tested modality of treatment. The most commonly raised concern with coiling in pregnancy is radiation exposure to fetus. Marshall et al reported an average effective dose equivalent to the patient of approximately 3.6 mSv in angiography, although no direct dosimetry for gravid uterus is available. Calculated dose to the uterus and fetus using the standard reference phantom was less than 0.1 mrad, far below the critical level outweighed by the benefits of the procedure to mother. Another problem with coiling is more chance of recanalisation compared to clipping. Nevertheless today coiling is an attractive option as it does not require opening of skull, less time taking and early recovery of patient, less procedural morbidity and mortality. According to AHA for patients with ruptured aneurysms judged to be technically amenable to both endovascular coiling and neurosurgical clipping, endovascular clipping should be considered. A meta-analyses of randomized trials comparing endovascular coiling and surgical clipping did not show a significant difference between endovascular treatment and neurosurgical clipping in mortality but former was associated with higher rates of re-bleeding. A follow up study of clipping versus coiling showed that the two groups were similar in rates of increased dependency alone but the probability of death or dependency was significantly greater in the neurosurgical group and re-bleeding was more likely after coiling. The choice of procedure depends on judgment of both experienced cerebrovascular surgeons and endovascular specialists based on characteristics of the patient and the aneurysm. Clipping is possible for much wider spectrum of aneurysms including almost all those which are manageable by coiling.

It seems reasonable that for women near term, caesarean delivery followed by either method is a consideration. It is unclear whether the risk of aSAH is increased during pregnancy, labour and puerperium. A study done by Andreas T et al showed that this risk is not increased. There appears to be no advantage to pregnancy termination unless there is associated preeclampsia. Vaginal delivery is safe if labour occurs remote from aneurysmal repair. The time period of “remote” is not defined, although some recommend 2 month, time required for complete healing is not known. Caesarean delivery is preferred if bleeding occur near term as in the present case and in unrepaird cases who survive aSAH as these are the patients who should avoid bearing down. Our patient required coiling twice during pregnancy with second coiling performed at 36 week 4 days.

**Conclusion**

Endovascular coiling is a minimally invasive treatment modality of ruptured or symptomatic un-ruptured intracranial aneurysm. This surgical modality has limited alteration in maternal- foetal physiology as compared to conventional neurosurgical procedure of clipping. Though less invasive, durability or long-term permanence of endovascular coiling is yet to be established.

**References**

Dengue Myocarditis Presenting as ST Segment Elevation MI

Rajesh Deshwal

Abstract
Dengue myocarditis masquerading as ST segment elevation myocardial infarction and was thrombolysed is being discussed.

Introduction
Dengue is the most common arthropod-borne viral (arboviral) illness in humans. Globally, 2.5-3 billion individuals live in approximately 112 countries that experience dengue transmission. Annually, approximately 50-100 million individuals are infected. The incidence has increased manifold in India due to unplanned urbanization and migration of population to urban areas. Although initially reported from urban locales, dengue is now being reported from urban and rural backgrounds alike. Clinically, a non-specific afebrile illness, a mild-form dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) are commonly encountered in dengue epidemics. Of note, a variety of cardiac complications have been reported in dengue-affected patients, which include atrioventricular conduction disorders, supraventricular arrhythmia, and myocarditis.

We report a case who presented with ST segment elevation myocardial infarction, was thrombolysed and latter diagnosed as dengue myocarditis.

Case Report
A 50 years old female presented to the emergency department of our hospital with history of left sided chest pain, epigastric pain and vomiting of 4 hours duration. Her pulse rate was 56/min, regular and BP was 70/40 mm Hg. Electrocardiogram done in casualty showed ST segment elevation in leads II, III and aVF (Figure 1). She was thrombolysed with alteplase and admitted to cardiac care unit. She was started on dopamine infusion to maintain her cardiac output and blood pressure. She was also prescribed antiplatelets and other supportive drugs. Her blood urea nitrogen and serum creatinine on admission were documented to be 34 mg/dl and 0.8 mg/dl, serum aspartate transaminase (AST) 339 U/L, serum alanine aminotransferase (ALT) 774 U/L. Her platelet count was 2,14,000/cumm. Troponin T was positive, creatinine kinase (MB fraction) was 42 μg/L (1.0–6.0 μg/L). Over the next 3 days her urine output dropped to 200 ml in 24 hours, she had azotemia (Serum creatinine 5.6 mg/dl). She was given hemodialysis after nephrologist’s advise. Echocardiography showed global hypokinesia and ejection fraction of 52%. Her platelet count had dropped to 81,000/cumm when she came out of cardiology unit to general ward.

A detailed and meticulous history elicited in the ward revealed that the patient had history of fever, headache, body ache and joint pains for 4 days prior to presentation to the hospital. She also divulged history of itching over palmar and plantar aspects of hands. She persistently complained of distension of abdomen. Clinical examination revealed a maculopapular erythematous rash over the face and the trunk. She also had facial puffiness, bilateral pedal edema, and ascites. Her chest radiographs revealed minimal pleural fluid bilaterally. Ultrasound abdomen had revealed moderate free fluid in peritoneal cavity, pericholecystic fluid, peri-hepatic fluid and gall bladder wall edema. Her IgM for dengue was sent and it was reported as positive.

History of fever, headache, bodyache, joint pains, erythematous rash over body, itching, thrombocytopenia, polyserositis, gall bladder wall edema and positive dengue serology clinched the diagnosis in favour of dengue infection. She had dengue induced myocarditis masquerading as acute inferior wall myocardial infarction and acute kidney failure. She was managed on lines of dengue, over next 4 days her urine output progressively improved and azotemia settled.

Discussion
Myocardial involvement in dengue may result either from direct viral invasion of cardiac muscles or cytokine-induced immune damage, or both. Increased levels of serum tumor necrosis factor-α, interleukins 6, 13 and 18, and cytotoxic factors in patients with dengue illness lead to increased vascular permeability and shock. Whether these cytokines play a role in the development of myocardial cell injury is uncertain. Cardiac involvement, although often mild, can be severe enough to result in progressive and intractable acute heart failure with global hypokinesia and acute cardiac dilatation. Lactic acidosis, which occurs as a result of the sluggish circulation, possibly contributes to myocardial depression in severe cases. Dengue virus subtype 2 (DENV2) is associated with unusual manifestations of dengue and asymptomatic myocarditis, and has also been shown to cause myocardial dysfunction in children who had dengue hemorrhagic syndrome (DHF) or dengue shock syndrome (DSS) in a series of 17 patients. Kularatne et al

Fig. 1: Electrocardiogram showing ST segment elevation in inferior leads
described three cases of myocarditis caused by DENV3 in Sri Lanka. Although there are no reports of cardiac involvement in DENV1 or DENV4, there is inadequate evidence to determine whether a particular serotype is preferentially associated with cardiac involvement. A diverse range of ECG abnormalities have been reported with dengue, including rate and rhythm abnormalities, heart block, wave form abnormalities, and voltage abnormalities. Reported rhythm abnormalities include relative bradycardia, sinoatrial block, disorders of atrioventricular conduction (junctional rhythm, second-degree and complete heart block, and monomorphic premature ventricular contractions on a background of heart block), atrial flutter, transient and persistent atrial fibrillation, self-limiting tachybrady arrhythmia, sinoatrial block, and uniform ventricular ectopics progressing to ventricular bigemini. Electrocardiographic features mimicking acute myocardial infarction as in our patient have also been reported. Clinical manifestations suggesting cardiac involvement in dengue are diverse and include chest pain, palpitations, pleurisy, irregularities of pulse, bradycardia, hypotension, pulmonary edema, and features of shock. Our case showed chest pain, bradycardia, hypotension and shock. Cardiac biomarkers may indicate the presence of cardiac involvement in dengue. A prospective study in Sri Lanka evaluated several cardiac biomarkers (myoglobin, creatine kinase-muscle brain-type, N-terminal pro-brain natriuretic peptide, heart-type fatty acid-binding protein, troponin T) in patients with dengue; 25% of patients had abnormal results in one or more biomarkers. However, the correlation between biomarkers and cardiac function has not been clearly demonstrated; troponin T was shown to correlate poorly with left ventricular function. Our patient was troponin T positive with 52% fraction. Constantine et al described echocardiographic features of myocarditis in 8 out of 37 adult and pediatric patients with dengue, and all of these patients belonged to the category of DHF. Reduced LVEF below 60% was noted only in four patients. Wali et al assessed cardiac function using echocardiography and radionuclide ventriculography in 17 patients with severe dengue. LVEF less than 40% was detected in 7 patients, and global hypokinesia in 12 patients.

Much of the evidence suggests that myocarditis is transient and self-limiting. A case of dramatic recovery following a single dose of intravenous methyl prednisolone in a 14-year-old with dengue complicated by myocarditis was reported by Premaratna et al. However, the current evidence base does not support the use of corticosteroids or immunoglobulins in treating severe dengue. Correction of serum calcium derangements to optimize cardiac status is usually carried out, especially in the presence of myocarditis. However, there is currently no evidence of its benefit.

The incidence of acute kidney injury (AKI) in dengue has ranged from 10.8% to 14.2% in various studies. AKI in our patient was part of multi organ dysfunction in dengue and was probably exacerbated by lack of appropriate hydration, restriction of fluids and use of inotropes in cardiac care unit.

**Conclusion**

Dengue myocarditis should be kept in mind in a patient, presenting with acute chest pain and electrocardiographic features suggestive of acute myocardial infarction, who has had the history and clinical features suggestive of dengue virus infection. Timely diagnosis can prevent an unnecessary cardiac intervention and results in a more favourable outcome.

**References**

Myelitis: A Rare Presentation of Epstein Barr Virus

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Abstract
EBV associated nervous system complications includes encephalitis, meningitis, cerebellitis, polyradiculomyelitis, transverse myelitis, cranial and peripheral neuropathies, and psychiatric abnormalities are usually more commonly seen in immunocompromised patients and rarely in immunocompetent patients. Here we are reporting a 13 years old boy developed headache, malaise, sore throat and low back pain with radiation to both lower limbs. Next day he felt numbness below umbilicus followed by acute onset weakness in both lower limbs and urinary retention. Motor exam revealed proximal muscle power MRC grade 4/5 and distal power 1/5 in right lower limb and proximal power 4-/5 and distal power 0/5 in left lower limb with normal power in both upper limbs. Deep tendon reflexes were bilaterally normal except absent ankle reflexes. Both plantars were mute. All the modalities of sensation including pain, touch, temperature, joint position and vibration were impaired below umbilicus. Routine investigations were normal. The magnetic resonance imaging (MRI) of thoracic spine showed intramedullary lesion in conus, which was iso-hyperintense on T1-weighted and hyperintense on T2- weighted images extending from D12thoracic level to L1 with cord expansion (Figures 1, 2). The MRI features were suggestive of conus myelitis. Cerebrospinal fluid (CSF) analysis revealed increased protein, normal cells, glucose and Chloride. CSF Polymerase chain reaction (PCR) was positive for Epstein Barr virus. The clinical and imaging findings were consistent with the diagnosis of myelitis and responded well to steroid plus acyclovir treatment. The clinicians should be aware of such uncommon etiology of a common disease.

Introduction

The Epstein-Barr virus (EBV) is a member of the her-pesviridae family associated with central nervous system (CNS) diseases (encephalitis and meningitis), but rarely cause myelitis.1 The EBV associated CNS infections usually have devastating consequence in immunocompromised patients of nasopharyngeal carcinoma, burkit lymphoma, Hodgkin’s disease and lymphoproliferative disease.2 The incidence of EBV related neurological complications is underestimated. It varies between 1-18 percent of individual with infectious mononucleosis and includes encephalitis, meningitis, cerebellitis, polyradiculomyelitis, transverse myelitis, cranial and peripheral neuropathies, and psychiatric abnormalities.3 The pathogenesis of EBV associated CNS complications is unknown but may be due to direct invasion of neuron, infiltration of EBV infected lymphocyte and deposition of immune complexes in the endothelium causing injury to neuronal parenchyma. Other possibilities of EBV infected B cells are actively attacked by EBV specific cytotoxic T cells causing injury to neuronal tissue.4 Here we are reporting EBV associated myelitis in an immunocompetent adolescent boy and response to steroid plus acyclovir treatment.

Case vignette

A 13 years old boy developed headache, malaise and sore throat. Over next 2 weeks he developed low back pain with radiation to both lower limbs initially right followed by left. Next day he felt numbness below umbilicus in form of inability to feel clothes and touching with his own hands. Few hours later he developed acute onset weakness in both lower limbs in form of inability to move his limbs in bed followed by difficulty in micturition leading to urinary retention. He required an indwelling catheter draining 800 ml urine on insertion. There was no h/o fever, loss of consciousness, visual blurring, seizure, upper limb weakness, trauma or tuberculosis. General physical and other systems examination was unremarkable. On neurological examination higher mental function, speech and cranial nerves including fundi were normal. Motor exam revealed proximal muscle power MRC grade 4/5 and distal power 1/5 in right lower limb and proximal power 4-/5 and distal power 0/5 in left lower limb with normal power in both upper limbs. Biceps, triceps supinator and knee deep tendon reflexes were bilaterally normal while ankle reflexes were absent. Both plantars were mute. Other superficial reflexes were absent. All the modalities of sensation including pain, touch, temperature, joint position and vibration were impaired below umbilicus. There were no meningeal or cerebellar signs. Examination of spine revealed local tenderness without gibbus below L1 vertebral level and SLR test was positive bilaterally.

Hemogram, biochemistry including liver functions, renal functions, thyroid function tests and serum vitamin B12 level, HIV and VDRL were normal. Erythrocyte sedimentation rate (ESR) was normal (15 in first hour). The magnetic resonance imaging (MRI) of thoracic spine showed intramedullary lesion in conus, which was iso-hyperintense on T1-weighted and hyperintense on T2-weighted images extending from D12thoracic level to L1 with cord expansion (Figures 1, 2). The MRI features were suggestive of conus myelitis. Computed tomography (CT) of chest and abdomen was normal. The markers for autoimmune and connective tissue disorders (ANA, Anti-ds DNA, Anti-nucleosome, Anti-histones, Anti-Sm, Anti SS-A, Anti RO, Anti Sc-I 70, Anti Rib-PProtein, Anti-JO, Anti-SS-B) were negative. Lumbar puncture showed normal intracranial pressure (140 mm H2O). Cerebrospinal fluid (CSF) analysis revealed increased protein, normal cells, glucose and Chloride. CSF acid-fast bacillus (AFB) stain was

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Fig. 1: The magnetic resonance imaging (MRI) of thoracic spine axial view showed normal → intramedullary lesion in conus, which was hyperintense on T2-weighted images extending from D12 thoracic vertebral level to L1

Fig. 2: The magnetic resonance imaging (MRI) of thoracic spine sagittal view showed intramedullary lesion in conus, which was iso to hyperintense on T1-weighted and hyperintense on T2-weighted images extending from D12 thoracic vertebral level to L1 with cord expansion

negative. Culture for Mycobacterium tuberculosis and other bacteria were negative. Polymerase chain reaction (PCR) was positive for Epstein Barr virus and negative for other viruses including Herpes simplex virus, Enterovirus and Cytomegalovirus. CSF anti-AQP4 antibody (NMO antibodies) and oligoclonal bands were negative. The clinical and imaging findings were consistent with the diagnosis of myelitis. The patient was treated with high dose intravenous methylprednisolone (1000 mg per day for 5 days) and antiviral drugs acyclovir 30mg/kg /day for 2 weeks. At the time of discharge, he showed moderate improvement in muscle power MRC grade 4/5 in both lower limbs with minimal left side foot drop during walking. He was discharged on supportive treatment and physiotherapy was advised.

Discussion

EBV myelitis is rare in immunocompetent individual. The clinical feature of myelitis and MRI findings of increased signal in conus part of spinal cord were similar to those described by Merelli et al. EBV DNA Virus is positive in CSF mainly in immunocompromised patients with CNS disease but our patient was immunocompetent. This CSF abnormality indicated that Acute EBV myelitis was an inflammatory disease process due to white matter involvement. There was transverse expansion of the spinal cord due to EBV infection, manifesting as asymmetric motor and sensory symptoms in immunocompromised patient. Our patient also presented with asymmetric motor and sensory symptoms but he was not immunocompromised. Steroid, immunoglobulin and antiviral had limited role in presenting disease progression described earlier in the literature but our patient responded well to steroid plus antiviral therapy. However, more studies are needed for consistent favorable response.

Conclusion

EBV associated nervous system complications are usually more commonly seen in immunocompromised patients and rarely in immunocompetent patients. Here we are reporting a 13 years old boy who was diagnosed as EBV associated conus myelitis and responded well to steroid plus acyclovir treatment. The clinicians should be aware of such uncommon
etiology of a common disease and ask for CSF studies for various viruses to differentially diagnose for precise underlying pathogens.

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Pruritus as Unusual Manifestation of Lupus Myelopathy

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Abstract
Lupus myelopathy is a relatively uncommon manifestation of SLE. Atypical presentation of this rare entity with neuropathic itch has never been reported. We report a young girl who presented with predominant symptom of refractory localized itching which after clinical localization and imaging was detected to have long segment patchy myelitis. Detailed evaluation led to a diagnosis of lupus myelopathy and the patient responded to immunosuppressive therapy with significant clinical and radiological improvement. Maintaining a high level of suspicion for neurological cause in a patient with refractory localized itching resistant to regular antiallergic treatment is important in the right clinical setting.

Introduction
The sensation of itch can only be perceived by a few tissues, specifically the skin and superficial mucous membranes. However, substantial numbers of patients who complain of disabling chronic itch have no apparent cause in the skin. Many of these patients have systemic or medical causes of itch such as drug reactions, metabolic or endocrine disorders, or kidney or liver dysfunction. There is recent interest in neurological disorders as an additional cause of focal or generalized pruritus.¹ Neuropathic itch is still under-recognized by most neurologists despite its localization value. Neuropathic itch is caused by diseased or malfunctioning pruritic neurons firing action potentials without pruritogenic stimuli in contrast to cutaneous or pruritoceptive itch which is caused by pruritogens activating cutaneous nerve endings bearing pruritogenic receptors. Various intramedullary lesions have been shown to cause pruritus in both humans and animals, attesting to the importance of the spinal cord as an itch modulating center.² We report a 20 yr old girl who presented initially with severe itching in localized distribution and did not respond to topical and antiallergic therapy and turned out to be lupus myelopathy on detailed work up and finally responded to immunosuppressive drugs. To best of our knowledge this is the first case report of lupus myelopathy presenting as neuropathic itch.

Case Report
20 yr old girl MK presented with history of paroxysmal itching in cape like distribution over bilateral upper limbs, neck and upper trunk of 2 months duration which was severe, uncontrollable, associated with forceful scratching and skin abrasion. Itching was associated with parasthesiae with similar distribution and was paroxysmal with variable location and duration and was mostly unpleasant/painful with burning, tingling and pins and needles sensation. She was treated at skin OPD with various topical and systemic drugs including emollients, antihistaminics, antifungals, antiseptics and steroids with minimal benefit and associated with periods of severe exacerbations interspersed with mild remissions. Detailed history further revealed symptom of fleeting joint pains, intermittently for last 3 yrs with occasional swelling. There was no history of fever, anorexia, weight loss, skin rash, constitutional symptoms, jaundice, edema, oliguria, nocturia. There was no history suggestive of dysthyroid state. There was no history suggestive of motor weakness, sensory deficits, band like sensation, bowel/bladder disturbance, cranial nerve deficits, visual disturbances. She denied history of any drug intake prior to the symptoms. On clinical examination she was afebrile, vital parameters were normal and there were

Fig. 1: Itchy areas with dermographism and skin abrasions

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no features suggestive of connective tissue disorder. Local examination revealed itching areas with erythema and dermographism with multiple excoriations and abrasions (Figure 1).

Neurological examination revealed normal bulk, tone, power in all four limbs with no sensory deficit. Deep tendon jerks were brisk in all four limbs (lower limb> upper limb) with normal plantar reflex. Other systemic examination was normal.

After clinical evaluation differential diagnosis of dermatological disorder/ hypersensitivity disorder, functional/psychogenic disorder, metabolic/endocrine disorder and Neurological disorder with cervical cord/ peripheral nerve lesions were sought. She was planned for detailed investigations and work up.

Investigations revealed normal complete blood count and liver/renal function tests. Urine routine/ microscopic examination and 24 hr urinary protein was normal. Serum electrolytes, prothrombin time, lipid profile, thyroid function test, chest X ray, USG abdomen were normal. HIV, HBsAg, Anti HCV was negative. ESR was 17 mm fall at 1 hr and CRP/ Rheumatoid factor was negative. MRI Brain was normal and MRI cervical spine revealed patchy long segment cervical myelitis (Figure 2 a, b, c).

At this stage an etiological diagnosis of Inflammatory CNS demyelinating disorders (MS, Neuromyelitis optica), Connective Tissue Disorders (SLE, Sjogrens Syndrome, Mixed connective tissue disorder) and Para/post infections were kept. To rule out possibility of Multiple sclerosis /Neuromyelitis Optica and other demyelinating disorder cerebrospinal fluid (CSF) study was done which revealed cells – 25/cumm, pred.- polymorphs, protein 85mg/dl, Sugar – 64mg% (random blood sugar – 102 mg%) staining/culture – neg, CSF Oligoclonal bands – negative, Serum and CSF NMO Ab(Anti AQP4) – negative. Detailed ocular examination revealed normal fundus with visual fields. Visual evoked potential was normal. Collagen profile (Qualitative) revealed positive ANA with antibodies positive for extractable nuclear antigens dsDNA, Nucleosome, PM- Scl. In view of ANA positivity with clinical and neuroimaging features suggestive of myelitis she was planned for quantitative autoimmune markers along with anti phospholipid antibody (APLA) work up which revealed ANA – 166.16 U (<20.00), Anti-ds DNA Ab – 675.46 IU/mL (<30.00), Anti-Cardiolipin Ab – IgG – 26.28 GPL (<15.00), IgM – 11.91 MPL (<12.50) MPL, Anti β2 Glycoprotein1 Ab – elevated with Complement – C3 – 82.5 mg/dL(<1.2), C4 – 14.5 mg/dl (Normal). With strong positive ANA, Anti dsDNA and antiphospholipid antibody with spinal cord involvement / musculoskeletal and cutaneous involvement, diagnosis of Systemic Lupus Erythematosus with Lupus Myelopathy and Secondary APLA syndrome was made. She was started on IV Methyl Prednisolone pulse – 1 gm IV OD x 5 days followed by oral prednisolone (1mg/kg bw), hydroxychloroquine, antithrombotic drug and other supportive measures. IV cyclophosphamide was not offered as induction agent in view of her age and fertility issues due to its significant gonadal toxicity. She was planned for rituximab as induction agent which was administered 500 mg IV infusion per week x 4 wks. Her itching and parasthesia/dysasthesia gradually subsided. Repeat MRI scan cervical spine 3 months after iv pulse steroid/ iv rituximab showed significant resolution of cervical cord lesions (Figure 3 a, b).

She was being planned for slow steroid taper with continuation of other supportive measures with close watch on recurrence/ relapse of disease and other systemic involvement.

**Discussion**

Involvement of the nervous system is common in patients with SLE. Depending on the accepted criteria it is estimated that symptoms of nervous system involvement are present in...
approximately 25–80% of patients. Myelopathy is one of the less common neuropsychiatric manifestations of SLE (1–3% of patients). The most common form is acute transverse myelitis (ATM). Longitudinal myelitis is less frequently observed. It has been recently recommended that all cases of myelitis – both transverse and longitudinal – in patients with SLE be referred to as lupus myelopathy. In the majority of cases, myelopathy occurs shortly after SLE is diagnosed, usually within the first 5 years from the onset of the disease. In nearly half of patients with lupus myelopathy ATM is the first clinical manifestation of SLE. The disease usually affects young and middle-aged females, although some males might be affected. Recurrence of myelitis within several months after the first episode of myelopathy is relatively frequently observed in patients with ATM in SLE. At least one recurrence of ATM in SLE is noted in 21–55% of patients. Episodes of recurrence were found mainly in untreated patients and in patients receiving long-term therapy with low or medium doses of glucocorticosteroids. Pruritic lesions may occur associated with collagen diseases and the diagnosis of SLE must be excluded in patients with chronic pruritus. In the index case patient had dominant disturbing symptoms of pruritus associated with paresthesia in a distribution pointing to the involvement of dorsal cervical cord. Patchy long segment spinal cord involvement along with other clinical and serological criteria including antiphospholipid antibody led us to definitive diagnosis of lupus myelitis after excluding multiple sclerosis and neuromyelitis optica. In general, the antiphospholipid antibodies may be detected in 30–50% of patients with systemic lupus erythematosus, while the incidence of antiphospholipid antibodies in systemic lupus erythematosus patients with transverse myelitis has been somewhat higher, to the tune of 55-64%. Because of low prevalence of myelitis there are no precise and unanimous recommendations for standard therapy of myelopathy in SLE. Currently, use of glucocorticosteroids and cyclophosphamide is a standard therapy of SLE involving the central nervous system, including myelopathy in SLE. In our case treatment with iv cyclophosphamide was not offered considering the patient being in reproductive age group and fertility related issues. She was administered iv rituximab as induction therapy. Use of rituximab as induction agent is solely based on case reports/case series from single centre and non-controlled studies. Rituximab rapidly improved refractory neuropsychiatric SLE as evident by improvement of various clinical signs and symptoms and resolution of radiographic findings. At present, there is no treatment strategy for patients with neuropsychiatric SLE who fail to respond to conventional therapies. In such patients some authors postulate repeated cycles of immunosuppression in therapy-resistant cases. However, duration and frequency of the repeated cycles have not been determined. Sole infusions of glucocorticosteroids were effective in some cases of lupus myelopathy. Few studies showed that rituximab is useful as a new treatment for such cases. Preliminary data indicated that rituximab could be beneficial in preventing permanent neurological damage in severe lupus myelopathy. The earlier immunosuppressive therapy is introduced and the more aggressive it is, the better the long-term prognosis is. Patients with inflammatory lesions visible in the MR of the spinal cord that resolve after the first intravenous immunosuppressive therapy have better prognosis. In present case patient has shown marked improvement both clinically and radiologically which indicates good prognosis. There are only few case reports of neuropathic itch secondary to spinal cord involvement but lupus myelopathy presenting as neuropathic itch has never been reported.

Conclusion

Pruritus and the long segment myelitis might be indicators of the lupus disease. Some of the refractory itches, currently attributed to psychiatric illness might be neuropathic instead. Itch can be a presenting symptom of a neurological problem that may require definitive treatment. Although dermatologists are increasingly aware of neuropathic causes of itch, early referral to neurologist could improve the diagnostic possibility in appropriate clinical setting.

References

Better performers have

Volibo

No indications for GI therapy

VoliboM

Diagram showing improvement in FT4, TSH, and T3/T4 ratios.

Diabetes control and β-cell function.

Preserves β-cell function.
Heparin is one of the earliest anticoagulant discovered by a second year medical student Jay Mclean (1890-1957) in 1916. However, it was not introduced in clinical practice till 1935. Mclean was working under Physiologist William H. Howell (1860-1945) at John Hopkins Medical College. He had asked for a problem which he could reasonably finish and publish in one academic year. Howell then was interested in blood coagulation and believed that in the body there was a balance between a clotting inhibitor (antithrombin), and a procoagulant called (thrombo-plastin). He had already isolated a substance cephalin from canine brain that had pro-coagulant activity. He had assigned the job to Mclean for examining the chemical purity of cephalin preparations, and to demonstrate that it was cephalin and not a contaminant in the preparation that produced procoagulant activity. Mclean had gathered knowledge from German chemistry literature and hence used ether-alcohol extract with which he could finish the work in a record time and proved that cephalin exhibited the anticipated thromboplastic effect and completed his assignment. He then started to isolate other substances produced in the heart (cuorin) and in the canine liver (heparphosphatid) by a process similar to the one he used for extracting cephalin. Both the compounds were fat soluble and had no pro-coagulant effect; instead they retarded coagulation. Heparphosphatid’s anticoagulant properties in vitro subsequently led to excessive bleeding in experimental animals.

When McLean reported his findings to Howell, he had great difficulty convincing him but ultimately succeeded. McLean did no further research on the phosphatides he had isolated. McLean’s work as a surgeon in private practice probably changed his focus. While he became obscure he was eventually honored as discoverer of heparin. Six years after his death he was given the credit for discovering heparin. The first human trials of heparin began in 1935. Best also demonstrated that heparin is produced by the mast cells.

Erik Jorpes (1894-1973) at Karolinska Institute published his research on the structure of heparin in 1935; he demonstrated it as a highly sulfated glycosaminoglycan, a mucolitain-polysulfuric acid. This made it possible for the Swedish company Vitrum to launch the first heparin product for intravenous use in 1936.

The term ‘heparin’ was coined by Howell from the Greek ‘hepar’, or liver. Howell introduced an aqueous extraction protocol for isolating heparin in 1926. This water soluble heparin was produced commercially by a local pharmaceutical company. However the preparation caused unacceptable side effects which precluded its use.

Between 1933 and 1936, Connaught Medical Research Laboratories- then a part of the University of Toronto, with the help of physiologist Charles Best (1898-1978) perfected a technique for producing safe, nontoxic heparin that could be administered to patients in a saline solution. The first human trials of heparin began in 1935. Best also demonstrated that heparin is produced by the mast cells.

Heparin acts by binding with co-factor antithrombin-III. The binding of heparin varies according to its molecular weight. Unfractionated heparin has a half-life of one to two hours after infusion, whereas LMWH (low molecular weight heparin) has a half-life of four to five hours. LMWH has now largely replaced conventional heparin.
Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus

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Cardiac Autonomic Neuropathy (CAN) is defined as the impairment of cardiovascular autonomic control in patients with established diabetes mellitus (DM) following the exclusion of other causes. The precise prevalence of CAN in DM ranges widely from 20-70% and it increases the mortality in Type 2 DM by 5 fold. This study was planned to look at the prevalence of CAN in Type 2 DM patients and its correlation with other complications and comorbidities associated with Type 2 DM.

Type 2 DM patients more than 18 years age with no other major comorbidities were included in the study. All patients had a detailed history and physical examination followed by evaluation of glycemic status, retinopathy, nephropathy, neuropathy and atherosclerotic vascular disease.

Cardiac dysautonomia was assessed by 5 standard non-invasive autonomic function tests - Valsalva manoeuvre, heart rate response to deep breathing, immediate heart rate response to standing, BP response to standing and BP response to sustained hand grip. A Sympathetic skin response (SSR) was done in addition. The first three reflect cardiac parasympathetic integrity, while the other three tests reflect sympathetic integrity.

Autonomic dysfunction was classified as normal, early, definite, severe and atypical according to Ewing and Clarke criteria.

Normal: All the tests are normal
Early: one of the three heart rate tests are abnormal
Definite: Two or more heart rate tests are abnormal
Severe: Two or more of the heart rate tests abnormal plus one or more of the blood pressure tests abnormal
Atypical: Any other combination of abnormal tests

A total of 67 Type 2 DM subjects were included in the study (31 females and 36 males). The mean age was 56.4 ± 10.6 years (range 33-77) and mean duration of diabetes was 12.64 ± 9.92 years (range 1-48). Mean HbA1c was 8.76 ± 1.94 (range 5.3-14.6).

The prevalence of CAN was 54/67 (80.6%). Only Parasympathetic dysfunction was seen in 26(48.1%) while only sympathetic dysfunction was seen in 1 (1.8%) and both together was seen in 27 (50%).

Details are given in Table 1

Prevalence of CAN had significant correlation only with diabetic retinopathy but with none of the complications or complications of diabetes like nephropathy, peripheral neuropathy, peripheral occlusive vascular disease, systemic hypertension or dyslipidemia. There was no correlation of CAN with age of the patient or with the level of glycemic control but there was significant correlation with the duration of diabetes; (p 0.05).

To summarise, this study, showed a very high prevalence of CAN of 80.6 % in Type 2 DM. Parasympathetic cardiac autonomic function tests were more sensitive for the detection of CAN than sympathetic cardiac autonomic function tests. Valsalva was the most sensitive parasympathetic function test and BP response to sustained hand grip was more sensitive to detect the sympathetic dysfunction.

Even though CAN increased with increasing duration of diabetes, there was significant number of patients with CAN even in short duration diabetes. Hence screening for CAN should be included along with screening for other microvascular complications of diabetes from the onset of Type 2 DM especially in those with diabetic retinopathy irrespective of the age or level of glycemic control.

References


Health Insurance and State Sponsored Health Scheme - Andhra Pradesh is a Role Model

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Sir,

Health is human right. There is progressively increasing cost of health care which is beyond the capacity of a common man in India. Even for a middle class man health care insurance can only can protect him from financial crisis during illness. Newer technology has made state of the art medicine almost impossible achievement for a common man.

Primary health care is the responsibility of the Government. Because of mushrooming costs of speciality state of the art care State Governments can have tie up with health insurance providers to provide speciality care for selective procedures both medical and surgical. Andhra Pradesh Government introduced Rajiv arogyasri scheme in 2007 and implementing successfully and it is renamed as NTR vaidya seva now. Under this scheme a total of 1044 procedures are covered for below poverty line people holding Arogyasri cards. Among them are included 873 surgical and 171 medical procedures. Amount of money to be distributed to the empanelled hospitals is decided by the expert committee. As per the Andhra Pradesh NTR vaidyaseva statistics of...
the 47000 beds available 61% of beds are in the private sector and 39% are in the public sector. Both speciality and super-speciality services are covered under the scheme. 273 corporate hospitals and 149 Government hospital are authorized to treat patients under the scheme.

A total of 15 million population is covered under the scheme since 2007 and an amount of 2,50,000 rupees is allotted to a family per year.

Predominant procedures utilized by the people belonged to Oncology, polytrauma, Cardiology and Cardiothoracic surgery and Nephrology. Similar services are extended to state Government employees and disabled population in Andhra Pradesh. These services can be extended to middle class population on payment of premium. Each person is provided a maximum of two and a half lakhs of rupees per year and the money is transferred to empanelled hospitals.

Vigilance is needed to prevent any fraudulent activities. Preauthorization is required in every case admitted under the scheme. For emergency procedures telephone pre-authorization services are provided. In Andhra Pradesh the whole scheme is run under the administration of NTR vaidyaseva trust. Stringent rules should be observed in recognizing specific hospitals for tertiary speciality care.

The Governments should take care of Primary medical care and health insurance like Andhra Pradesh model can help below poverty line population of India as a whole. The scheme is worth considering for expansion throughout India. Budget allotments have been generally low in many State Government budgets for health care. Government should allot enough budget for extensive primary care toward nutrition, immunization and other parameters of primary health care. Secondary health care can be covered under state sponsored health scheme by agreement with medical insurance companies and extra budget can be allotted by Governments for selective procedures which can cost more such as cardiac transplantation, renal transplantation and cancer surgeries in selective as decided by the expert panel.

Andhra Pradesh model is an ideal model worth expanding to the entire country.

References
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Effect of Magnesium Sulphate on Coagulation and Thromboelastographic Parameters in Chronic Liver Disease Patients

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Liver disease patients have deranged coagulation due to various factors (decreased production of coagulation factors, thrombocytopenia, gastrointestinal bleed and blood transfusion). Because patients with the chronic liver disease used to have hypomagnesemia due to various reasons and studies on coagulation have demonstrated variable results comparing the effect of magnesium.1 Thus, we evaluated the effects of intravenous magnesium sulphate on coagulation parameters in patients with chronic liver disease by thromboelastograph.

Hundred adult patients aged 18-65 years with chronic liver disease with hypomagnesemia were included in this study. The demographic profile and baseline thromboelastographic (R and K time, alpha angle maximum amplitude, G and LY 30) and laboratory parameters (serum magnesium, INR, aPTT, platelet count) were recorded. Patients were randomized in two groups (50 patients in each group): Intervention Group (Group M) and Control Group (Group N). In group M, 50 mg/kg magnesium sulphate in 100 ml of 0.9% saline and in group N, 100 ml of 0.9% saline was infused over 20 minutes. After 2 hours of intervention, serum magnesium levels and coagulation profile were repeated.

For discrete variables X2 test, for continuous variables Student’s t test and where the data was not normally distributed Mann-Whitney tests were used.

PT/INR, aPTT, platelet count was comparable in the two groups after magnesium supplementation. There was significant difference observed between the groups in term of TEG parameters after intervention. There was statistically significant decrease in K time (3.07 ± 1.02 Vs 3.95 ± 1.62 sec, P value <0.002) and LY 30 (1.79 ± 1.31 Vs 3.80 ± 2.19%, P Value <0.000) along with significant increase in MA (58.59 ± 8.6 Vs 53.89 ± 8.86 mm, P Value <0.008) and G value (8.98 ± 2.1 Vs 7.37 ± 1.49 Dyne/cm², P Value <0.000). There was improvement in R time and α angle but that did not reach statistical significance in Group M compared to Group N. Overall the CI did not differ in the two groups. CI in Group M and Group N was -1.46 ± 2.49 and -2.45±2.60 respectively (P value=0.18). Magnesium levels in Group M was statistically higher compared to Group N (1.82 ± 0.12 and 1.43 ± 0.17 mg/dl respectively) (P Value=0.000).

Conventional coagulation test PT and aPTT do not represent the balance between the pro- and anticoagulant proteins because the PT and aPTT are not sensitive to deficiencies of the anticoagulants. Coagulation in CLD is best assessed with viscoelastic measures of coagulation as it assesses all components of haemostasis. It is demonstrated that supplementing magnesium in liver transplant recipients leads to improvement in coagulation as measured by TEG.2 Our study demonstrated the improvement in all TEG parameters but without statistically significance for R time, α angle and coagulation index.

As supplementation of magnesium sulphate in chronic liver disease patients may lead to improvement in coagulation profile as measured by viscoelastic parameters on thromboelastograph. Studies with emphasis on change in ionized serum magnesium and its effect on viscoelastic coagulation parameter in patients with liver disease are warranted.

References
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