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COVID 19 and the Liver

Akash Shukla¹,², Ravi Mohanka²

The novel corona virus infection named as Corona virus Disease 2019 (COVID-19) affects multiple organs including the liver. The main receptor for COVID 19, angiotensin-converting enzyme 2 (ACE2) is highly expressed in the endothelial layer of small blood vessels and cholangiocytes (59.7%), less in hepatocytes (2.6%) and none in the sinusoidal endothelium of the liver.¹ The association of COVID-19 with liver encompasses

Impact of COVID-19 on liver

Pre-existing liver disease as a risk factor for COVID-19 infection

Considerations of liver disease on choice of therapy for COVID-19

Care of patients after liver transplant

Impact of COVID-19 on liver

Despite the cholangiocyte predominant distribution pattern of ACE2 expression in the liver, the usual form of liver injury, due to COVID 19, is raised transaminases rather than cholestasis. This suggests that the liver injury is likely to be mediated by the cytokines rather than direct effects of the virus, a phenomenon referred to as “by-stander hepatitis”.

The spectrum of injury in patients without pre-existing liver disease can vary from mild biochemical changes to acute liver failure.²³ In a recent meta-analysis of 45 studies, of which the author was also a part, any abnormal liver biochemical abnormality at admission was seen in 27.2% patients. The common abnormalities were increased ALT (20.4%), AST(21.8%), GGT (35.8%) and low ALB 39.8%. Less common abnormalities are increased ALP (4.7%) and BIL (8.8%). Abnormal liver biochemical indicator any time during hospitalization was 36%. Severe COVID 19 infections had a significantly higher incidence of abnormal AST at admission (RR = 2.91). Rarely, acute liver failure presumably due to cover 19 has been reported in the absence of any other identifiable etiology, although this causality is not yet beyond doubt.

Liver biopsy in these patients have revealed microvesicular steatosis, macrosteatosis and inflammatory infiltrates in the hepatic lobule and portal tract.⁴

Pre-existing liver disease as a risk factor for COVID-19 infection

There have been concerns whether patients with chronic liver disease will develop a more severe form of COVID-19, and will COVID-19 worsen the course of their liver disease and induce liver-related mortality. The evidence available so far suggests that patients with chronic liver disease are at the same risk of acquiring the infection as individuals in the general population. Patients with hepatocellular carcinoma are at higher risk of contracting SARS-CoV-2 infection, developing severe illness and higher risk of mortality.⁵

COVID-19 related complications are more common in cirrhotics than patients of liver diseases without cirrhosis; respiratory failure (23.2% versus 8.6%, p < 0.001), acute kidney injury (18.6% versus 5.4%, p < 0.001) and hypotension (14% versus 3.8%, p < 0.001).⁶ While patients without cirrhosis do not appear to have a severe worsening of liver disease, cirrhotics may develop acute-on-chronic liver failure or acute decompensation. Liver related complications increase with severity of cirrhosis and a Child-Turcotte Pugh score of 9 or more at presentation predicts high mortality.⁷

Considerations of liver disease on choice of therapy for COVID-19

Hepatic side effects of some of the drugs used in treatment of COVID 19 mandates caution while using in patients with cirrhosis. Remdesivir is known to cause elevated transaminases and bilirubin even in patients without underlying liver disease.⁷ Regular monitoring of liver biochemistries should be performed in all hospitalized COVID-19 patients, particularly those treated with remdesivir or tocilizumab, regardless of baseline values. Remdesivir should not be initiated in patients with ALT ≥5xULN at baseline and discontinued if on therapy ALT ≥5xULN or ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR. It should be used with extreme caution in patients with cirrhosis. Corticosteroids may be associated with increased risk of infections and concomitant antibiotic prophylaxis is warranted in cirrhosis. The other potential complication, one has to be wary of, is gastrointestinal bleeding. Tocilizumab should not be given to patients with decompensated cirrhosis and used cautiously while treating patients with hepatitis B, due to risk of flare.⁷

Care of patients after liver transplant

Patients who have undergone liver transplant are at higher risk of infection since they are on immunosuppressants. The mortality rates are not higher than those observed in general population. One should be cautious in using azithromycin as it has significant interactions with Cyclosporine, Tacrolimus, Sirolimus and Everolimus. The choice of immunosuppression during the infection will depend upon the time from transplant, status of graft function and use of corticosteroids for COVID 19 related systemic inflammation. Mycophenolate may increase the risk of severe Covid-19 in a dose dependent-manner. Calcineurin inhibitors and everolimus are not deleterious for Covid-19 and need

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not be stopped. In fact, calcineurin inhibitors, have been shown to inhibit the replication of coronaviruses. In a recent study from Spain, the outcomes of patients with COVID 19 after liver transplant were found to be better than the general population. In general, immunosuppressive drugs need to be continued but may be modified. Excessive lowering of immunosuppression may trigger rejection which may be difficult and complicated to evaluate and manage.

To summarize, liver abnormalities are mild and transient in patients with COVID 19 infection and rarely of major clinical consequence. Patients with liver cirrhosis may develop acute on chronic liver failure, acute decompensation or rapid deterioration of liver function due to Covid 19 infection, resulting in increased risk of mortality. Remdesivir should be used with caution in cirrhosis and Tocilizumab avoided in decompensated cirrhosis. In liver transplant recipients, Covid 19 related mortality appears to be low and immunosuppression should be continued but anti-metabolite therapy may be temporarily stopped.

References

Seroprevalence of COVID-19 Amongst Health Care Workers in a Tertiary Care Hospital of a Metropolitan City from India

Mahesh Goenka1*, Shivaraj Afzalpurkar2, Usha Goenka3, Sudipta Sekhar Das4, Mohuya Mukherjee5, Surabhi Jajodia6, Bhavik Bharat Shah7, Vikram Uttam Patil2, Gajanan Rodge2, Ujjwalyini Khan8, Syamasis Bandyopadhyay9

Abstract

Background: Seroprevalence studies for COVID-19 evaluate the extent of undetected transmission in a defined community, with special significance among health care workers (HCW) owing to their greater exposure and potential to transmit.

Methods: A total of 1122 HCW (approximately 25% of the employees) of a large tertiary care hospital in India were recruited for this cross-sectional study. COVID PCR-positive HCW were excluded. Based on their risk-assessment, participants were grouped into three categories. A questionnaire was administered and they were tested for SARS-CoV-2-IgG antibodies using the chemiluminescence.

Results: The overall seroprevalence among workers was 11.94%, which included 19.85% in COVID units, 11.09% in non-COVID units, and 8% in administrative workers (p=0.007). Antibody prevalence was highest in the department of gastroenterology (11.94%), followed by oncology (10.53%), pathology (10.26%), emergency medicine (7.84%) and critical care medicine (7%). Housekeeping staff, food and beverage staff, lab assistants and technicians had higher seroprevalence rate than doctors and nurses (p < 0.0001). HCW with a history of BCG vaccination in childhood and those who received an adequate prophylactic dose of hydroxychloroquine (HCQ) had a lower seroprevalence as compared to those who did not (7.31% vs. 16.8% and 1.30% vs. 11.25% respectively).

Conclusion: BCG vaccination, HCQ prophylaxis, and the job profile influence the seroprevalence rate in HCW. Seroprevalence rate and follow-up evaluation of its durability may help hospitals to triage their staff at risk, rationalize their placement, prioritize the use of PPE, thereby potentially reducing the risk.

Introduction

COVID-19 (Coronavirus disease 2019) was declared a pandemic illness on 11th March 2020 and is still evolving. Clinical presentation of the disease varies from mild upper respiratory tract symptoms to severe pneumonia and acute respiratory distress syndrome. It is difficult to predict the exact number of individuals being infected, since many of them may be asymptomatic carriers for several weeks.1-4 The current data suggest that the pre-symptomatic and asymptomatic patients can be potential source of infection, though the extent of transmission of infection via asymptomatic individuals is unclear.5,6

Health care workers (HCW) are subjected to a greater risk of contracting the infection due to their direct contact with the infected patients. An infected HCW poses a risk to other patients under his or her care as well as to a fellow HCW.7 It is, therefore, vital to understand the true prevalence rates of COVID-19 infection among the HCW. There is a sparse data on the seroprevalence of SARS-CoV-2 infection among HCW, with only a few published studies.7-19 Since no data is available for the COVID-19 infection in HCW in India or the adjoining geographical areas, this research attempted to study the seroprevalence of anti- SARS-CoV2 antibodies in HCW from a tertiary care hospital in India.

Methods

A. Study design: It is a cross-sectional study extending over 6 weeks starting from 12th July 2020. A survey was conducted using an online questionnaire followed by antibody testing using chemiluminescence. The study was approved by the internal ethical committee of the institute.

B. Sample selection: A list of hospital employees was obtained from the human resource department. Subjects who were COVID RT-PCR positive either before or during the study were excluded. Subjects were divided into three groups based on the risk of exposure to the COVID positive patients:

1. Category A: High risk
   • Working/ have worked in a COVID ward/Intensive Care Unit
   • Regularly involved in the testing or investigating a COVID-19 patients
2. Category B: Intermediate risk
   • Those not belonging to category A or category C i.e., HCW who are managing patients or performing procedures on patients not diagnosed/ suspected to be having COVID. These included but were not limited to, staff working in emergency, aerosol-
generating facilities, and outpatient services.

3. Category C: Low risk
   • No direct contact with the patients or their belongings, for example, staff belonging to the administrative office, human resource department, and marketing.

A systematic random sampling method was applied to recruit participants. As categorized above, every third employee in each category was selected and was offered to participate in the study. A total of 1122 (out of a total of 4656) HCW participated in the study. Written informed consent was obtained from each participant who agreed.

C. Procedure: A questionnaire was formulated after discussion with scientific committee. The same in Google Forms was sent to the participants, either through a registered phone number or email address to collect demographic and clinical data. The form had twenty-six questions with multiple-choice option answers, requiring either a single or multiple replies. Survey questions were divided into the following three categories:

1. Demographic details of the study participants
2. Details of participant’s job profile and working pattern
3. Relevant medical history.

D. COVID antibody testing:
Antibodies to COVID-19 were tested using the enhanced chemiluminescence method (Vitros ECi, Ortho Clinical Diagnostics, New Jersey, US). It involves a ‘signal generating’ reaction using a luminol derivative in the presence of peroxide. Horseradish peroxidase (HRP) provides electrons from peroxide to luminol to produce light. The enhancer, 3-chloro 4-hydroxy acetanilide, acts as a catalyst for the luminal reaction. It accelerates electron transfer and increases the oxidation of luminol by HRP almost 1000 times maintaining the signal ~20min (Figure 1). The signal is read by a luminometer 16 times in 1.6 seconds in ‘Glow’ type chemiluminescence.

Statistical Analysis
All statistical tests were performed using SPSS version 20.0. Categorical variables were expressed as frequency and percentage of patients. These were analyzed using Pearson’s Chi-Square
Test for Independence of Attributes/Fisher’s Exact Test as appropriate. We also used Univariate and Multivariate logistic regression analysis. In all cases, statistical significance was set at a p-value of less than 0.05.

Results

Clinical Profile

A total of 1122 HCW (approximately 25% of the employees), categorized into three categories based on their risk assessment were recruited for this study. Figure 2 shows the study flow chart with distribution in the three categories and reasons for exclusion. A majority of participants belonged to 30-50 year age group (n = 665, 59.26%), with a male preponderance (n = 734, 65.42%). The clinical profile of these HCW is shown in Table 1. Figure 3 shows the distribution of participants in terms of their job profile. Doctors (n = 255, 22.72%) formed the most common group, followed by housekeeping staffs (26.11%), followed by dieticians/food and beverage staff (18.37%), lab assistants/pharmacists (15.28%), nurses (9.38%), administrators (8%), ward executives (7.04%) and doctors (3.92%).

Table 1: Demography and medical history of study group and seropositivity rate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Total number</th>
<th>Positivity, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>734</td>
<td>101 (13.76%)†</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>388</td>
<td>33 (8.51%)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;30 years</td>
<td>364</td>
<td>43 (11.81%)‡</td>
</tr>
<tr>
<td></td>
<td>30-50 years</td>
<td>665</td>
<td>88 (13.23%)</td>
</tr>
<tr>
<td></td>
<td>&gt;50 years</td>
<td>93</td>
<td>3 (3.23%)</td>
</tr>
<tr>
<td>Diet</td>
<td>Vegetarian</td>
<td>60</td>
<td>4 (6.67%)†</td>
</tr>
<tr>
<td></td>
<td>Non vegetarian</td>
<td>1062</td>
<td>130 (12.4%)</td>
</tr>
<tr>
<td>Blood group</td>
<td>A group</td>
<td>210</td>
<td>21 (10.00%)</td>
</tr>
<tr>
<td></td>
<td>Non A group</td>
<td>832</td>
<td>88 (10.58%)</td>
</tr>
<tr>
<td>Rh factor</td>
<td>Rh Positive</td>
<td>1005</td>
<td>105 (10.45%)</td>
</tr>
<tr>
<td></td>
<td>Rh Negative</td>
<td>37</td>
<td>4 (10.81%)‡</td>
</tr>
<tr>
<td>Job profile</td>
<td>Administration</td>
<td>75</td>
<td>6 (8.00%)‡</td>
</tr>
<tr>
<td></td>
<td>Doctor</td>
<td>255</td>
<td>10 (3.92%)</td>
</tr>
<tr>
<td></td>
<td>Ward executives</td>
<td>71</td>
<td>5 (7.04%)</td>
</tr>
<tr>
<td></td>
<td>Nurses</td>
<td>224</td>
<td>21 (9.28%)</td>
</tr>
<tr>
<td></td>
<td>Housekeeping</td>
<td>226</td>
<td>59 (26.11%)</td>
</tr>
<tr>
<td></td>
<td>Dietician/FB</td>
<td>49</td>
<td>9 (18.37%)</td>
</tr>
<tr>
<td></td>
<td>Lab assistants/pharmacists</td>
<td>72</td>
<td>11 (15.28%)</td>
</tr>
<tr>
<td></td>
<td>Technicians</td>
<td>99</td>
<td>12 (12.12%)</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>51</td>
<td>1 (1.96%)</td>
</tr>
<tr>
<td>Mode of transport</td>
<td>Walking</td>
<td>91</td>
<td>18 (19.78%)†</td>
</tr>
<tr>
<td></td>
<td>Personal Vehicle</td>
<td>545</td>
<td>49 (9.99%)</td>
</tr>
<tr>
<td></td>
<td>Public transport</td>
<td>451</td>
<td>56 (12.42%)</td>
</tr>
<tr>
<td>Residence in containment zone</td>
<td>Yes</td>
<td>293</td>
<td>31 (10.58%)†</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>656</td>
<td>73 (11.13%)</td>
</tr>
<tr>
<td>Place of residence</td>
<td>Metropolitan</td>
<td>501</td>
<td>46 (9.18%)†</td>
</tr>
<tr>
<td></td>
<td>Suburbs</td>
<td>621</td>
<td>88 (14.17%)</td>
</tr>
<tr>
<td>Number of persons in room</td>
<td>1 to 2</td>
<td>537</td>
<td>49 (9.12%)‡</td>
</tr>
<tr>
<td></td>
<td>3 to 5</td>
<td>435</td>
<td>58 (13.33%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 5</td>
<td>91</td>
<td>22 (24.18%)</td>
</tr>
<tr>
<td>Time spent in hospital in a week</td>
<td>&lt; 48 hours</td>
<td>731</td>
<td>102 (13.95%)</td>
</tr>
<tr>
<td></td>
<td>48 hours or more</td>
<td>373</td>
<td>29 (7.77%)</td>
</tr>
<tr>
<td>BCG vaccine</td>
<td>Received</td>
<td>561</td>
<td>41 (7.31%)‡</td>
</tr>
<tr>
<td></td>
<td>Not Received</td>
<td>77</td>
<td>13 (16.88%)</td>
</tr>
<tr>
<td>MMR vaccine</td>
<td>Received</td>
<td>336</td>
<td>29 (8.63%)‡</td>
</tr>
<tr>
<td></td>
<td>Not received</td>
<td>303</td>
<td>25 (8.25%)</td>
</tr>
<tr>
<td>HCQ prophylaxis</td>
<td>Not received</td>
<td>885</td>
<td>115 (12.29%)</td>
</tr>
<tr>
<td></td>
<td>Inadequate dose</td>
<td>160</td>
<td>18 (11.25%)</td>
</tr>
<tr>
<td></td>
<td>Adequate dose</td>
<td>77</td>
<td>1 (1.30%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Diabetes</td>
<td>65</td>
<td>6 (9.23%)</td>
</tr>
<tr>
<td></td>
<td>Hypertension / CAD</td>
<td>107</td>
<td>5 (4.67%)</td>
</tr>
<tr>
<td></td>
<td>Lung disease</td>
<td>31</td>
<td>3 (9.68%)</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>919</td>
<td>120 (13.06%)</td>
</tr>
</tbody>
</table>

Abbreviations: FB—food and beverage, BCG—Bacille Calmette-Guerin, MMR—Measles Mumps Rubella, HCQ—Hydroxychloroquine, CAD—coronary artery disease. *Inadequate dose was defined as 400 mg once a week for <6 weeks. †Adequate dose was defined as 400 mg once a week for >6 weeks; Note: some of the participants did not respond to certain parameters; ‡p<0.05; *p<0.005

Fig. 3: Distribution of antibody reactivity among the health care workers based on their job profile. The seroprevalence rate was highest among housekeeping staffs (26.11%) followed by dieticians/food and beverage staff (18.37%), lab assistants/pharmacists (15.28%), nurses (9.38%), administrators (8%), ward executives (7.04%) and doctors (3.92%).
Table 2: HCW category according to the risk assessment and their seropositivity rate

<table>
<thead>
<tr>
<th>Category</th>
<th>Total, n (%)</th>
<th>Reactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>136 (12.12%)</td>
<td>27 (19.85%)</td>
</tr>
<tr>
<td>B</td>
<td>911 (81.19%)</td>
<td>101 (11.09%)</td>
</tr>
<tr>
<td>C</td>
<td>75 (6.68%)</td>
<td>6 (8.00%)</td>
</tr>
<tr>
<td>Total</td>
<td>1122 (100%)</td>
<td>134 (11.94%)</td>
</tr>
</tbody>
</table>

Category A: High risk; Category B: Intermediate risk; Category C: Low risk (details in text)

Of the 1122 HCW evaluated in our study, 134 tested positive for IgG antibodies, giving a seroprevalence rate of 11.94% (Table 2). While most (n = 803, 71.6%) of these individuals were asymptomatic in the past three months, 28.4% (n = 319) had mild or non-specific symptoms including headache, runny nose, and generalized body ache.

The seropositivity rate was significantly higher in category A (n = 27, 19.85%) in comparison to category B (n = 101, 11.09%) and C (n = 56, 8.00%) with a P value of 0.007 (Table 2). On comparing the individual categories with one another, the positivity rate was significantly lower among category C compared to category A (p = 0.023), while the rate of B vs C (p = 0.491) and A vs B (p = 0.106) were not statistically significant.

2. Prevalence according to the department: As shown in figure 4, among the various medical departments of the hospital, the antibody prevalence was highest in the gastroenterology department (11.94%), followed by oncology (10.53%), pathology (10.26%), emergency medicine (7.84%), critical care medicine (7%), orthopaedics (5.26%), radiology (4%) and cardiology (3.57%).

3. Prevalence as per demography and medical history: Table 1 shows the clinical profile, demography, and medical history of the study population and the related seroprevalence rate. Male HCW had a significantly higher prevalence rate as compared to females (13.76% vs. 8.51) and the younger population had a higher prevalence compared to those above 50 years. There was no statistically significant difference in relation to diet (vegetarian vs non-vegetarian) or blood group (A vs non-A or Rh factor positive vs negative). Regarding the job profile, the seroprevalence rate was highest among housekeeping staffs (26.11%) followed by dieticians/food and beverage staff (18.37%), lab assistants/pharmacists (15.28%), nurses (9.38%), administrators (8%), ward executives (7.04%) and doctors (3.92%). Mode of transport to the hospital or time spent in the hospital did not influence seropositivity (p = 0.094 and 0.201 respectively). HCW staying in the metropolis had a lower prevalence in comparison to those staying in suburbs i.e. traveling from down-town (9.18% vs. 14.17%). Those staying in a crowded residence (>5 inhabitants/room) had a higher prevalence rate (24.18%).

HCW with a history of BCG (Bacille Calmette-Guerrin) vaccination in childhood had a lower seroprevalence rate than those without (7.31% vs. 16.8%, p = 0.004). The positivity rate was significantly lower with adequate (>6 weeks) hydroxychloroquine (HCQ) prophylaxis (1.30%), in comparison to inadequate or no prophylaxis (11.25% and 12.99% respectively, p = 0.009). Diabetes mellitus did not influence IgG antibody positivity, while patients with cardiac ailments (hypertension, ischemic heart disease, and others) had a lower seroprevalence rate (4.67%) as compared to those without any morbidity (13.06%).

Table 3 shows the univariate and multivariate analysis of demography and relevant medical history. As shown, male gender, younger age, job profile (housekeeping, food and beverage staff, lab assistant/PhD student, technician, and nurses), staying in downtown, crowded inhabitation, administration of BCG vaccine were significant influencing parameters during univariate analysis.

On multivariate analysis, however, job profile (housekeeping, food and beverage staff), crowded inhabitation, history of receiving BCG vaccination, and adequate HCQ prophylaxis were significant.

Discussion

The seroprevalence in HCW in the concerned tertiary-care hospital was at 11.94%. Similar studies from other countries show a rate of as low as 0% in Malaysia, 4% in Denmark, 1.06% - 13.7% in the United States of America, 6.4% in Belgium, 9.3% in Spain, 10.6% in the United Kingdom (UK) to as high as 17.14% in China. This difference may be related to the period of study, the prevalence in the local community, and hospital policy in terms of triage, social distancing, hand sanitization, use of PPE. It is worthwhile to mention that the tertiary care hospital in this study is a Joint Commission Accreditation approved facility with proper workforce education, patient triage, and strict PPE usage policy.

It is critical for any seroprevalence study to use an optimal test, both in terms of the nature of the antibody (IgG, IgM, or both) as well as the test technique. Iversen et al. and Pallett et al, both have used a point of care testing for antibody, which has a lower sensitivity of 82.5%, 8.15 IgM antibody tests have lower sensitivity and specificity, shorter duration, and heterogeneity in results. We have therefore used the IgG antibody for our seroprevalence study. The antibody tests can target the Spike-protein S1 antigen, Spike-protein S2 antigen, nucleocapsid antigen, or a combination. The assay which we used in this study was Vitros anti-SARS-COV-2 IgG, which targets the S1 spike protein. As compared to other coronaviruses, S1 protein is more specific and unique to COVID-19. In SARS-CoV-2 infection SI is, therefore, more specific than S2 or nucleocapsid (N) protein. Woon et al have used the test to detect the IgG antibody against nucleocapsid. The test kit used in the present study has a sensitivity of more than 90% and specificity of nearly 100%.

During our study, 207 out of 4656 (4.44%) HCW from the hospital were diagnosed to have COVID by a PCR test just before or during our study period. This would mean an estimated 16.38% of HCW in the hospital had evidence of an active or recent COVID-19 infection. These figures are similar to study from Spain (11.2%) and the UK (18%).

In univariate analysis of our study, males and younger HCW had a higher seroprevalence rate. Brant-Zawadzki et al also noted a lower mean age in seropositive HCW compared to antibody-negative HCW. Iversen et al noted seropositivity to be higher in male HCW compared to females. In contrast, Basteiro et al found no difference between the two genders. Our multivariate analysis showed no significant difference in age and gender.
Table 3: Univariate and multivariate analysis of demography and medical history of study group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tr>
<td></td>
<td>OR</td>
<td>95% Confidence interval</td>
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<tr>
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<td>Upper bound</td>
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<tr>
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<tr>
<td>A</td>
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<tr>
<td>B</td>
<td>1.43</td>
<td>0.61</td>
</tr>
<tr>
<td>C</td>
<td>-58</td>
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<td>Nurse</td>
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<td></td>
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<td></td>
<td>Others</td>
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<td>3-5</td>
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<td>-52</td>
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<tr>
<td></td>
<td>≤48 hours</td>
<td>-52</td>
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<td></td>
<td>Lung disease</td>
<td>-71</td>
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Abbreviations: FB: food and beverage, BCG: Bacille Calmette-Guerin, MMR: Measles Mumps Rubella, HCQ: Hydroxychloroquin, CAD: coronary artery disease. *Adequate dose was defined as 400 mg once a week for >6 weeks. **Inadequate dose was defined as 400 mg once a week for >6 weeks.

Our lack of significant difference in seroprevalence rate for HCW performing duty in the COVID unit and non-COVID unit could be related to the strict use of personal protective equipment by individuals entering the COVID units. Moreover, among non-administrative staff, the housekeeping, food and beverage staff, lab assistants/pharmacists and technicians, had a higher rate of seroprevalence, while doctors (3.92%) and nurses (9.38%) had a lower rate. One explanation could be that those with higher rates were moving in and out of different hospital areas, whereas nurses and doctors were working in the well-defined designated location. Higher awareness and better implementation of hospital protocols could also be responsible for a lower rate among doctors and nurses. Among various medical departments gastroenterology (11.94%), oncology (10.53%), pathology (10.26%) and emergency services (7.84%) had relatively higher seroprevalence. This could be attributed to exposure to aerosol-generating procedures (gastroenterology), handling immunosuppressed patients who carry silent infections (oncology), lab sample handling (pathology), or exposure to a mixed patient population during triaging (emergency). However, due to the lack of available data on such a correlation, contrasting findings, like a Spanish study which did not find any relation between working in COVID unit or professional category with seropositivity, become difficult to explain. We noted significantly higher antibody positivity in those staying in suburbs (compared to those in the metropolis) and with crowded housing. This may be due to the lower socioeconomic status of these individuals.

An interesting finding in the present study was a significantly lower prevalence in HCW who had received BCG vaccination in childhood and also in those receiving adequate HCQ prophylaxis in the recent past. While the protective role of BCG vaccination and HCQ in the occurrence of COVID-19 is still debatable, there is literature supporting the role of both these interventions in either disease prevention or progression. Sharma et al have reported that the rate of confirmed cases and mortality is lower and recovery rate is higher in those countries who have BCG vaccination in their universal health program, in comparison to countries where BCG vaccination is not implemented.

Strengths and Limitations

The strength of the present study includes a well-defined cohort and the inclusion of only asymptomatic or mildly symptomatic individuals. The hospital HCW were classified into three categories with an intent to have a realistic and representative sample for analysis. Also, a standardized sensitive, and specific immunoassay was used. The authors also plan to follow up and retest the cohort with a positive antibody to understand the dynamics and durability of these antibodies. Limitations of the study include...
include a moderate sample size for any seroprevalence study. However, 33% of the total HCW were enrolled and ultimately 25% of the total eligible hospital staff could be included, which is fairly representative. The study period was 6 weeks which is too long for evaluating a dynamically changing pandemic. However, this could not be avoided due to frequent lockdown in the geographical area during the study. Also, a clear seroprevalence data from the general community to compare with was not available. Such comparison would have helped us to study the difference, if any, between HCW and the general population.15

Conclusions

This study gives a fair idea about the existing seroprevalence among HCW of similar large hospitals in the country. Obtaining data about seroprevalence and subsequent follow up evaluation of durability and protective nature of this antibody may help hospitals to triage the staff at risk, rationalize their placement, prioritize the use of PPE and potentially reduce the risk of transmission.

References


Dermatomyositis during COVID-19 Pandemic (A Case Series): Is there a Cause Effect Relationship?

Yojana Gokhale¹, Aditi Patankar², Usha Holla³, Mrinal Shilke⁴, Lalana Kalekar⁴, Niteen D Karnik⁵, Kushal Bidichandani⁶, Sujata Baveja⁷, Anagha Joshi⁸

**Abstract**

Viruses have been shown to modify the clinical picture of several autoimmune diseases, including type 1 diabetes, systemic lupus erythematosus (SLE), rheumatoid arthritis and multiple sclerosis. Viral infections have also been considered as a possible trigger for autoimmune disorders like myositis through myositis specific antibodies. Dermatomyositis is an acquired inflammatory myopathy which is relatively rare with incidence of 9.3 per 1 million persons. Usually we come across 1-2 patients of dermatomyositis per year, amongst 800–1000 new patients in our tertiary care rheumatology services. A surge in the incidence was noted this year during the months of April-August of 2020, the period coinciding with the occurrence of corona virus (COVID-19) pandemic in the city of Mumbai, the total number of cases encountered being five in a span of six months. The following case series includes five such cases with review of available literature on virus-triggered autoimmunity with special reference to SARS-CoV-2 and the challenges of immunosuppression during this pandemic.

**Case series**

**Case 1**

On April 16, 2020, a 64-year-old male presented with erythematous rash on the back, neck, chest (shawls sign), periorbital area (heliotrope rash) (Figure 1), cheeks and nasal bridge along with proximal muscle weakness of both upper and lower limbs for 30 days. Patient had difficulty in swallowing and in lifting his head. He had low-grade fever, productive cough and breathlessness. On examination, pulse rate was 120/min, blood pressure of 100/70 mmHg, respiratory rate of 34/min with an oxygen saturation of 100/70 mmHg, respiratory rate of 12/minute (normal-30/minute). Creatinine phosphokinase (CPK) was 990IU/L (normal range 38-174IU/L). Erythrocyte sedimented rate (ESR) was 72mm/hr and C-reactive protein (CRP) was 242mg/dl (normal range 0-5). Serological tests performed included Antinuclear antibody (ANA) by Immunofluorescence which was positive in a homogenous pattern with a titre of 1:320. Anti-ds-DNA and Anti Smith were negative. Myositis specific antibodies were negative for Anti M1-2, Jo-1, PM-SCL 75, PM SCL 100 and Anti MDA-5. Magnetic resolution imaging (MRI) of muscles was suggestive of myositis in bilateral shoulder girdles, triceps, erector spinae, psoas iliacus, gluteal muscles, thighs, calves. Nasopharyngeal swab RT-PCR sent in view of breathlessness, cough, fever and hypoxia was positive for SARS-CoV-2 virus. High resolution CT chest (HRCT) had multifocal bilateral ground glass opacities, most likely to be COVID-19 pneumonia with CT severity index of 8/25 (Figure 2). Muscle biopsy and electromyography (EMG) could not be performed as all elective procedures were stopped during initial period of COVID-19 pandemic. Patient was started on IV antibiotics, hydroxychloroquine and ivermectin for COVID-19 pneumonia. Due to nonavailability of Remdesivir at that time, it was not used. He was started on intravenous immunoglobulin (IVIG) at a dose of 2g/kg body weight given over 5 days in view of bulbar involvement and fear of worsening of pneumonia while being immunosuppressed. He was put on a maintenance dose of Prednisolone 1mg/kg, mycophenolate mofetil (MMF) 1.5 gm daily. The patient drastically improved symptomatically in terms of respiratory distress as well as muscular weakness within 7 days.
of starting IVIG. His repeat COVID RT-PCR was found negative by day 14 of hospitalization. His power on 3 monthly follow up was 5/5 in all groups and skin rash had dramatically improved. Repeat creatinine kinase was 150 IU/L.

Case 2

Within 7 days of encountering our first case, on April 23, 2020, a 50-year-old female presented with proximal muscle weakness of upper and lower limbs along with diffuse erythematous rash over face, chest and back for 15 days. These symptoms were associated with low grade fever and dyspnoea on exertion. On examination, power was 4/5 at shoulder and hip joint. Bilateral basal crepitation was heard on auscultation with saturation of 95% on room air. ESR and CPK were 70mm/hr and 150IU respectively. Autoantibodies ANA and Anti smith were negative. Myositis specific antibodies Anti melanoma differentiation-associated protein 5 (MDA-5) and SAE-1 were found to be positive. HRCT was suggestive of cryptogenic organizing pneumonia (Figure 3). Magnetic resonance imaging of whole-body muscle showed myositis in right scapular and anterior thigh muscles (Figure 4). COVID-19 RT-PCR swab sent on admission in view of fever, breathlessness and hypoxia was negative on two occasions. She was started on Injectable methylprednisolone, injectable cyclophosphamide 1gm and methotrexate 15mg/ week for MDA-5 positive dermatomyositis related interstitial lung disease (ILD) taking all precautions (like use of N95 mask) to prevent COVID infection. With this her breathlessness subsided. However, she developed recurrence of breathlessness in subsequent week. Her third COVID RT-PCR done a week later was positive and she succumbed to COVID pneumonia.

Case 3

On May 12, 2020, 26-year-old female presented with complaints of erythematous skin rash, muscle weakness with power 4/5 at the shoulder and 3/5 at the hip joint, intermittent fever and loss of appetite for 2 months at private clinic of first author. Her investigations revealed a CPK of 8439 IU/L, ANA positivity with a titre of 1:100 and myositis specific antibody Mi-2 was positive. Myositis was proven on electromyography (EMG). Her HRCT chest was normal. However, she was unwilling to get tested for COVID-19. She was treated with methotrexate, prednisolone and hydroxychloroquine. Her power improved to 5/5 on follow up.

Case 4

One month later on June 23, 2020, a 46-year-old male was referred to private clinic of first author by a dermatologist for erythematous rash. On enquiry, patient had complaints of throat pain and low-grade fever in March 2020 for which he had consulted ENT specialist. On noticing redness of face, he was referred to a dermatologist. Suspecting dermatomyositis, his creatinine kinase was sent which was found to be 570 IU/L and a skin biopsy was done which was suggestive of interface dermatitis with an ANA titre of 1:320. With the above reports he was referred to us in June. At this time, patient had proximal muscle weakness with power of 4/5 at hip and shoulder joint. As interface dermatitis can occur both in dermatomyositis and SLE, he was further investigated. SLE was ruled out by negative Anti-ds DNA and Anti-Smith, normal complement levels and a normal urine routine examination. His myositis specific Anti-SAE Antibody was positive. Inflammatory muscle disease was proven on EMG and muscle MRI thus confirming the diagnosis of dermatomyositis. PET-CT for evidence of malignancy and HRCT chest for interstitial lung disease associated with dermatomyositis were done and found to be normal. We asked for COVID-19 related investigations as patient had throat pain and fever to begin with. After managing two dermatomyositis cases in April and one in May, we were having a doubt about COVID-19 triggering dermatomyositis and also, we wanted to be careful prior to starting immunosuppression. COVID-19 RT-PCR done in July 2020 was negative. The patient was started on hydroxychloroquine, mycophenolate mofetil and methotrexate. Patient agreed to test for Ig M and IgG COVID-19 Antibodies in October 2020 which were negative. His follow up examination in September showed a repeat CPK of 43 IU/L and improvement in power to 5/5.

Case 5

On 23 August 2020, a 50-year-old male with dermatomyositis (proven on EMG and MRI muscle with positive myositis specific antibody Mi-2 and PM-SCL) well controlled since 8 years on maintenance treatment of Tablet Prednisolone (5 mg OD) and Azathioprine (50mg BD) presented with complaints of proximal muscle weakness, erythematous rash, breathlessness and oxygen saturation of 88% on admission with PaO2 69mmHg and PCO2 44mmHg. He was found to have a muscle power of 1/5 at shoulder and hip joint and neck lag with single breath count of 10/minute. His creatinine kinase level was 1169. COVID RT-PCR which was sent in view of breathlessness and hypoxia was negative. But his COVID antibodies IgM and IgG were positive. He was treated with methotrexate, prednisolone and IVIG and his power improved to 3/5 in 2 weeks.

Summary of these 5 cases is shown in Table 1.

Discussion

Viral infections have been known to induce or protect from autoimmunity
COVID 19 related tests PCR - Positive

Duration of symptoms Age (years)/ sex 64/male 50/female 26/female 46/male 50 /Male

DM type 1 Rotavirus
DM type 1 Cosackie B
Systemic lupus erythematosus Dengue
Rheumatoid arthritis Ebstein barr virus
Multiple sclerosis Ebstein barr virus
Gullian Barre syndrome Zika virus
Herpetic stromal keratitis HSV

Autoimmune damage. In “bystander activation”, a non-specific, over-reactive antiviral immune response creates a localized pro-inflammatory environment along with the release of self-antigens from the damaged tissue. These self-antigens are subsequently taken up and presented by antigen presenting cells (APC) to stimulate auto reactive T cells in the vicinity triggering autoimmunity. Certain viruses like Ebstein Barr virus (EBV) may immortalise effector cells. Early antigen restricted (EA/R) EBV proteins are important in immune evasion and anti-apoptosis. Accordingly, this prevents both infected B cells and epithelial cells from apoptosis, and lead to a loss of tolerance and development of autoimmunity. Examples of viral infections that have been linked to autoimmune diseases in different organisms are discussed in Table 2.

Several reports linking COVID-19 with autoimmunity in children in the form of paediatric inflammatory multisystemic syndrome (PIMS; which includes Kawasaki disease, toxic shock syndrome, myocarditis and macrophage activation syndrome) are available. The clustering of cases of

### Table 1: Salient features of Dermatomyositis patients from April- August at our tertiary care centre and private clinic of first author

<table>
<thead>
<tr>
<th>Age (years) / sex</th>
<th>Duration of symptoms prior to hospitalisation</th>
<th>Clinical features</th>
<th>Respiratory findings</th>
<th>COVID 19 related tests</th>
<th>Myositis specific investigations</th>
<th>Treatment given</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>64/male</td>
<td>30 days</td>
<td>Erythematous rash, proximal muscle weakness, fever, difficulty in swallowing, breathlessness</td>
<td>Bilateral crepitations</td>
<td>PCR - Positive</td>
<td>CPK - K90</td>
<td>Prednisolone, IVIG</td>
<td>Power improved to 5/5, Pneumonia resolved</td>
</tr>
<tr>
<td>50/female</td>
<td>April 2020</td>
<td>Erythematous rash, proximal muscle weakness, fever, breathlessness</td>
<td>Bilateral crepitations</td>
<td>PCR – positive</td>
<td>CPK - 150</td>
<td>Methotrexate Prednisolone</td>
<td>Expired</td>
</tr>
<tr>
<td>26/female</td>
<td>April 2020</td>
<td>Skin rash, Fever on and off</td>
<td>HRCT- COVID pneumonia with CT severity</td>
<td>PCR – Positive</td>
<td>MRI muscle - myositis of right scapular and anterior thigh muscles</td>
<td>Prednisolone methotrexate cyclophosphamide</td>
<td>Power improved to 5/5</td>
</tr>
<tr>
<td>46/male</td>
<td>20 days</td>
<td>Low grade fever</td>
<td>PCR - Not willing</td>
<td>EMG NCV. generalised myopathy compatible with inflammatory myopathy</td>
<td>Anti SAE-1 - positive</td>
<td>Mofetil, Methotrexate</td>
<td>Power improved to 5/5</td>
</tr>
<tr>
<td>50/Male</td>
<td>August 2020</td>
<td>Difficulty in swallowing, Muscle weakness</td>
<td>PCR – negative</td>
<td>MRI muscle- N.A Autoantibodies- ANA - negative</td>
<td>Mi 2 – positive</td>
<td>Methotrexate</td>
<td>Power improved to 5/5</td>
</tr>
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### Table 2: Examples of viral infections that have been linked to autoimmune diseases in different organisms

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Virus implicated</th>
<th>Mechanism</th>
<th>Study</th>
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<tr>
<td>DM type 1</td>
<td>Rotavirus</td>
<td>Bystander mechanism</td>
<td>Pane et al., 2014</td>
</tr>
<tr>
<td>DM type 1</td>
<td>Cosackie B</td>
<td>Molecular mimicry</td>
<td>Laitinen et al., 2014*</td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>Dengue</td>
<td>Epitope spreading</td>
<td>Steed and Stappenbeck, 2014</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Ebstein barr virus</td>
<td>Epitope spreading</td>
<td>Dostal C et al., 1997</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Ebstein barr virus</td>
<td>Molecular mimicry</td>
<td>Guan et al., 2019</td>
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<tr>
<td>Gullian Barre syndrome</td>
<td>Zika virus</td>
<td>Molecular mimicry</td>
<td>Lucchese and Kanduc, 2016</td>
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<tr>
<td>Herpetic stromal keratitis</td>
<td>HSV</td>
<td>Molecular mimicry</td>
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In genetically susceptible population. Viral-induced autoimmunity can be activated through multiple mechanisms including molecular mimicry, epitope spreading, bystander activation, and immortalization of infected B cells. It was believed that viruses carry structurally similar antigens to self-antigens, which activate B and T cells. This causes cross-reactivity against both self- and non-self-antigens. This mechanism was known as “molecular mimicry”. It was one of the commonest mechanisms postulated in viral-induced autoimmunity. In a recent work by Kanduc et al., peptide sharing analysis of five common viruses (Borna disease virus, IAV, measles, mumps, and rubella) in comparison to human proteome revealed an unexpected
dermatomyositis coinciding with the peak of COVID-19 pandemic raises questions regarding an epidemiological link between the two. 

*Byedon et al* in “Myositis as a manifestation of SARS-CoV-2”, reported the first case of MRI proven myositis in a patient of COVID-19 in April 2020 in France. However, all myositis specific antibody tests were negative with only ANA being positive similar to Case 1. In the five cases of dermatomyositis that we have reported; Case 1 was nasopharyngeal RT-PCR positive on presentation for SARS-CoV-2 virus, Case 2 had two negative RT-PCR swabs with subsequent RT-PCR being positive. The sensitivity and specificity of COVID-19 RT-PCR is 70% and 95% respectively. Case 3 was unwilling to get tested. Case 4 was tested for RT-PCR 4 months after onset of his symptoms prior to starting immunosuppressants and antibodies were tested 7 months after the onset and both were found to be negative. IgM antibodies in SARS CoV-2 remain above the detection threshold for 14-21 days from symptom onset. IgG production starts rising around 14 days from symptom onset and continues to rise for 28-35 days. Case 5 had IgM/IgG antibodies for SARS CoV-2 virus positive proving possible causal association though the RT-PCR was negative.

Differentiating between interstitial lung disease due to dermatomyositis and acute respiratory distress syndrome due to COVID-19 pneumonia is a herculean task. Yukai et al has discussed the similarities and differences between severe COVID-19 pneumonia and anti-MDA-5 positive dermatomyositis- associated rapidly progressive interstitial lung diseases. Severe COVID pneumonia is seen in patients of older age group and those with comorbidities whereas high levels of Anti-MDA5 antibody and hyper ferritinemia contribute to Anti-MDA5 positive dermatomyositis related rapidly progressive ILD, treatment of which is immunosuppression.

Management of COVID pneumonia with immunosuppressants has not been established by clinical trials, however, Tocilizumab and Baricitinib have been shown to be beneficial in many observational studies. Clinical features, HRCT findings, raised blood cytokine levels and a good response to methyl prednisolone is seen in both the conditions. This supports the hypothesis of some common pathophysiological mechanism between the two.

Four out of the five cases had myositis specific antibodies with three cases having Anti Mi-2 antibodies and one case with Anti MDA-5 antibodies with additionally case 2 and 4 having Anti SAE positivity. The patient who had Anti MDA-5 antibodies succumbed. Patients with anti-MDA-5 antibody positive dermatomyositis are prone to present with life- threatening, rapidly progressive ILD. MDA-5 plays a critical role in the innate immune defence against viruses by driving the production of large amounts of type I Interferons. MDA-5 is a viral sensor and is activated by viral RNA. IFN induced with helicase C domain protein 1 (IFIH1) is a target of anti-MDA5 antibodies. IFIH1 is required for the normal immune response against coronavirus. It increases the production of cytokines such as IFN γ, TNF-α, IL-1β, IL-6 and IL-18 and stimulates TH1 cells and macrophages. In case of a defective anti-inflammatory counterbalance, the result is the development of a cytokine storm with the overexpression of pro-inflammatory mediators, sustaining rapidly progressive forms of interstitial lung disease. Pinel et al studied interferon signalling in dermatomyositis patients and found Interferon1 responsible for autoimmune trigger. In a study done by Megre mis et al in 2020, in dermatomyositis patients, he mapped six distinct epitopes with high sequence identity to human SARS-COV-2 virus. Of these, three linear epitopes of six amino acid length were highly specific for SARS-CoV-2. These epitopes map to SARS-CoV-2 2’-O- ribose methyltransferase, RNA-dependent RNA polymerase and 3’-to-5’ exonuclease proteins. This further consolidates the belief that latent exposure to the SARS COV-2 virus might contribute to musculoskeletal autoimmune disease development.

Treatment of dermatomyositis in COVID-19 is difficult given the risk of immunosuppression. Case 1 and case 5 were treated with pulse methyl prednisolone and intravenous immunoglobulin (IVIG). In severe myositis with bulbar involvement additional treatment options are IVIG and Rituximab. With the intent of treating autoimmunity along with some protection against COVID-19 pneumonia, we opted for IVIG over Rituximab. In case 2 due to the acute presentation of breathlessness and hypoxia, considering association of MDA-5 related dermatomyositis with severe form of interstitial lung disease, options for treatment were pulse cyclophosphamide and rituximab alone or in combination. In view of ongoing pandemic, we opted for pulse cyclophosphamide over rituximab due to short duration of action of former. Rituximab produces longer suppression of B cell function of 6 months with around 4% of patients documented to have B cell suppression for up to 3 years. Cases 3 and 4 which were mild to moderate were treated with methotrexate and prednisolone. Hydroxychloroquine was used in treatment of COVID pneumonia in all these cases due to its presumed immunomodulator action and protection against severe lung disease.

Out of the 5 cases included in the series, first 4 cases occurred during the first 2 months of the COVID pandemic in the city of Mumbai. COVID-19 infection was proven in 3 cases. The fourth case was not willing to get tested and the tests to prove COVID-19 in the fifth case were done beyond the testing window for COVID-19 infection.

**Conclusion**

The sudden spur in dermatomyositis cases coinciding with peak of COVID-19 pandemic points to an epidemiological cause and effect relationship between the two. Similarities between acute respiratory distress syndrome of COVID-19 pneumonia and Anti MDA 5 Positive dermatomyositis associated with rapidly progressive interstitial lung disease reinforces this observation which is supported by the role of MDA-5 in innate immunity against viruses. Five cases of dermatomyositis in six months during COVID-19 pandemic raises a possibility of COVID-19 triggered dermatomyositis which needs to be studied in detail.

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Demographic and Clinical Profile of Dengue Fever in a Tertiary Care Hospital of South India

Padmaprakash KV1, Vijoy Kumar Jha2*, Shashi Bhushan3, Deepkamal1, Sowmya Karantha C4

Abstract
Background: Dengue fever is the most common viral communicable disease caused by the bite of Aedes aegypti mosquito. Worldwide about 3.9 billion people are at the risk of this infection.

Materials and Methods: This prospective study was done in patients of dengue fever admitted in a service hospital in the coastal area of southern India from 01 Jan 2018 to 31 Dec 2018.

Results: 751 patients of confirmed dengue patients were admitted with 555 (73.9%) males and 196 (26.1%) females. The mean age was 30.6 (SD± 10.48) years, mean day of admission after the onset of illness was 3.4 days (SD±2.76). The most common presentation was fever (99.33%) followed by myalgia (77.62%), headache (67.24%), vomiting (35.41%), nausea (26.76%) and fatigue (9.05%). Bleeding diathesis was evident in 97 patients (12.91%). 306 (40.75%) patients presented with warning signs. The mean duration of hospitalization was 5.73 (SD± 2.75) days. Four patients died due to severe dengue (mortality rate-0.53%).

Conclusion: Intense monitoring, early detection, and management of complications can prevent mortality in dengue.

Introduction
Dengue is the commonest vector-borne viral disease. It is an emerging public health problem in tropical countries including India.2,3 The World Health Organisation (WHO) estimates an annual incidence of 50–100 million infections worldwide and the real numbers may be more than 390 million.4 The peak incidence of dengue cases occur during the period of July-November.4

Pathogen
Dengue viruses are RNA viruses belonging to the Flavivirus genus with 4 serotypes. Although the 4 dengue serotypes are serologically and genetically distinct,6 they also share several structural antigens. Laboratory
abnormalities may include leukopenia, thrombocytopenia, transaminitis. Atypical dengue presentations are increasingly seen. The diagnosis of dengue cases is possible by distinct clinical features, but they can present with atypical presentation also.

The present study was undertaken to assess the clinical manifestations along with the clinical features, complications, unusual features, and outcomes of cases admitted to a tertiary care hospital in Vishakapatnam, Andhra Pradesh.

Materials and Methods

This is a prospective observational study on patients diagnosed with dengue fever admitted to a tertiary care hospital in Visakhapatnam from 01 Jan 2018 to 31 Dec 2018. This study was done in the department of Medicine. The study was approved by the ethics committee of the hospital and informed consent was obtained from all the subjects. We included all the patients of dengue fever from 01 Jan 2018 to 31 Dec 2018.

Inclusion criteria

1. All the patients from 13 years or older who were admitted to the hospital were included in the study. All were confirmed dengue cases and were classified as per WHO guidelines 2009.
2. The cases were confirmed based on the presence of NS1 antigen and/or IgM antibody demonstration serological test by rapid ICT (Immunochromatographic test) and ELISA (Enzyme-linked immunosorbent assay).

Exclusion criteria

1. Coinfection with other confirmed cases of enteric fever, malaria, typhus, chikungunya, etc. was excluded from the study.
2. Unwillingness to participate in the study.

The relevant investigations were performed as per the clinical conditions of the patients. Data collected from the patients included demographic data, clinical profile of dengue patients, any coexisting conditions, complications, and outcomes. Clinical examination included hemodynamic parameters, general and systemic examinations. Haemoglobin, leukocyte count, platelets, hematocrit, and other relevant investigations were carried out regularly until discharge. Clinical fluid accumulation was considered when pleural effusion or ascites was detected on chest radiography or ultrasonography. Hemoconcentration was defined as a more than 20% increase in hematocrit from baseline. Leukocytosis was defined as a peripheral white blood cell count (WBC) more than 10000 cells/µL, and leukopenia as a peripheral WBC of less than 3000/µL.

Table 1: Demographic data of patients

<table>
<thead>
<tr>
<th>Season wise occurrence</th>
<th>Total No (n=751)</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan-Mar</td>
<td>27</td>
<td>3.6</td>
</tr>
<tr>
<td>Apr-Jun</td>
<td>110</td>
<td>14.6</td>
</tr>
<tr>
<td>Jul-Sep</td>
<td>499</td>
<td>66.5</td>
</tr>
<tr>
<td>Oct-Dec</td>
<td>115</td>
<td>15.3</td>
</tr>
</tbody>
</table>

Age & Sex wise distributions

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Total No (n=751)</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>30.67</td>
<td>SD=10.48</td>
</tr>
<tr>
<td>Median Age</td>
<td>28</td>
<td>Range 13-69</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Total No (n=751)</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-17</td>
<td>45</td>
<td>6</td>
</tr>
<tr>
<td>18-30</td>
<td>408</td>
<td>54.3</td>
</tr>
<tr>
<td>31-45</td>
<td>212</td>
<td>28.2</td>
</tr>
<tr>
<td>46-60</td>
<td>74</td>
<td>9.9</td>
</tr>
<tr>
<td>&gt;60</td>
<td>12</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Table 2: Clinical Details of Dengue cases (n=751).

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Number (Total n=751)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>746</td>
<td>99.33</td>
</tr>
<tr>
<td>Myalgia (body ache)</td>
<td>583</td>
<td>77.62</td>
</tr>
<tr>
<td>Backache</td>
<td>505</td>
<td>67.24</td>
</tr>
<tr>
<td>Headache</td>
<td>395</td>
<td>52.26</td>
</tr>
<tr>
<td>Nausea</td>
<td>201</td>
<td>26.76</td>
</tr>
<tr>
<td>Anorexia</td>
<td>80</td>
<td>10.65</td>
</tr>
<tr>
<td>Vomiting</td>
<td>266</td>
<td>35.41</td>
</tr>
<tr>
<td>Fatigue</td>
<td>68</td>
<td>9.05</td>
</tr>
<tr>
<td>Conjunctival suffusion</td>
<td>12</td>
<td>1.59</td>
</tr>
<tr>
<td>Retroorbital pain</td>
<td>10</td>
<td>1.33</td>
</tr>
<tr>
<td>Sore throat</td>
<td>33</td>
<td>4.39</td>
</tr>
<tr>
<td>Cough</td>
<td>39</td>
<td>5.19</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>11</td>
<td>1.46</td>
</tr>
<tr>
<td>Dysuria</td>
<td>87</td>
<td>1.15</td>
</tr>
<tr>
<td>Giddiness/Presyncope</td>
<td>46</td>
<td>6.13</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>37</td>
<td>4.92</td>
</tr>
<tr>
<td>Skin Rash</td>
<td>30</td>
<td>3.99</td>
</tr>
<tr>
<td>Coryza</td>
<td>3</td>
<td>0.39</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>01</td>
<td>0.13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>93</td>
<td>12.38</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>03</td>
<td>0.39</td>
</tr>
<tr>
<td>Seizure</td>
<td>01</td>
<td>0.13</td>
</tr>
<tr>
<td>Bleeding manifestations</td>
<td>97</td>
<td>12.91</td>
</tr>
<tr>
<td>Petechiae</td>
<td>48</td>
<td>6.39</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>02</td>
<td>0.26</td>
</tr>
<tr>
<td>Gum Bleeding</td>
<td>21</td>
<td>2.79</td>
</tr>
<tr>
<td>Melena</td>
<td>02</td>
<td>0.26</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>03</td>
<td>0.39</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>04</td>
<td>0.52</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>02</td>
<td>0.26</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12</td>
<td>1.59</td>
</tr>
<tr>
<td>ICH</td>
<td>03</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Exclusion criteria

1. Coinfection with other confirmed cases of enteric fever, malaria, typhus, chikungunya, etc. was excluded from the study.
2. Unwillingness to participate in the study.

The relevant investigations were performed as per the clinical conditions of the patients. Data collected from the patients included demographic data, clinical profile of dengue patients, any coexisting conditions, complications, and outcomes. Clinical examination included hemodynamic parameters, general and systemic examinations. Haemoglobin, leukocyte count, platelets, hematocrit, and other relevant investigations were carried out regularly until discharge. Clinical fluid accumulation was considered when pleural effusion or ascites was detected on chest radiography or ultrasonography. Hemoconcentration was defined as a more than 20% increase in hematocrit from baseline. Leukocytosis was defined as a peripheral white blood cell count (WBC) more than 10000 cells/µL, and leukopenia as a peripheral WBC of less than 3000/µL.

Severe hepatitis was defined as serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels more than 1000 U/L (reference value, 40 U/L). Minor gastrointestinal (GI) bleeding was defined as melena without affecting the hemodynamic status and hematocrit value. Severe GI bleeding was defined as any GI bleed associated with hemodynamic instability. Patients were diagnosed with AKI if their serum creatinine level increased by 0.3 mg/dL or more within 48 h or elevated to at least 1.5-fold from baseline. Hemophagocytosis

Table 3: Severity of Dengue cases (n=751).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number (Total n=751)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue without warning signs</td>
<td>445</td>
<td>59.25</td>
</tr>
<tr>
<td>Dengue with warning signs</td>
<td>306</td>
<td>40.75</td>
</tr>
<tr>
<td>Dengue with complications</td>
<td>80</td>
<td>10.65</td>
</tr>
<tr>
<td>Dengue with Severe Plasma leakage with Shock</td>
<td>70</td>
<td>9.33</td>
</tr>
<tr>
<td>Bleeding requiring transfusions</td>
<td>80</td>
<td>10.65</td>
</tr>
<tr>
<td>AKI</td>
<td>23</td>
<td>3.06</td>
</tr>
<tr>
<td>Severe Hepatitis</td>
<td>16</td>
<td>2.13</td>
</tr>
<tr>
<td>Lung/ARDS</td>
<td>17</td>
<td>2.26</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>08</td>
<td>1.06</td>
</tr>
<tr>
<td>Hemophagocytosis</td>
<td>01</td>
<td>0.13</td>
</tr>
<tr>
<td>Intravascular hemolysis</td>
<td>01</td>
<td>0.13</td>
</tr>
<tr>
<td>Encephalopathy/Impaired Consciousness</td>
<td>03</td>
<td>0.39</td>
</tr>
<tr>
<td>Cardiac Tamponade</td>
<td>01</td>
<td>0.13</td>
</tr>
<tr>
<td>Pulmonary thromboembolism</td>
<td>01</td>
<td>0.13</td>
</tr>
<tr>
<td>Cortical Venous thrombosis</td>
<td>01</td>
<td>0.13</td>
</tr>
<tr>
<td>Mortality</td>
<td>04</td>
<td>0.53</td>
</tr>
<tr>
<td>Causes of Mortality</td>
<td>01</td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>01</td>
<td></td>
</tr>
<tr>
<td>Myocarditis with Severe Plasma Leakage Refractory shock</td>
<td>01</td>
<td>0.13</td>
</tr>
<tr>
<td>Subarachnoid Hemorrhage and Severe Plasma Leakage with Refractory shock</td>
<td>01</td>
<td>0.13</td>
</tr>
<tr>
<td>Severe Plasma Leakage, Refractory shock, and ARDS</td>
<td>01</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Table 2: Clinical Details of Dengue cases (n=751).

<table>
<thead>
<tr>
<th>Admissions details of Dengue cases (n=751)</th>
<th>Mean days</th>
<th>SD(±)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of admission to hospital (Mean)</td>
<td>3.4 days</td>
<td>2.76</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>5.73</td>
<td>2.75</td>
</tr>
<tr>
<td>Minimum</td>
<td>01</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>
was defined as fever, splenomegaly, pancytopenia, hypertriglyceridemia, hyperferritinemiania, and demonstration of hemophagocytosis in the peripheral blood or bone marrow.\textsuperscript{14} Severe organ involvement included impaired consciousness, severe hepatitis, acute kidney injury, acute respiratory failure, rhabdomyolysis, disseminated intravascular coagulopathy, and hemophagocytosis.\textsuperscript{14} Severe dengue includes dengue infection with at least one of the following –severe plasma leakage leading to shock or fluid accumulation with respiratory distress; severe bleeding, severe organ involvement, impaired consciousness, and organ failure.\textsuperscript{3,14} Platelet concentrates were given to patients with thrombocytopenia who had significant bleeding. Secondary infections were treated appropriately.

### Statistical analysis

All the data was entered into the Microsoft Excel sheet and analyzed. P-value <0.05 was considered significant.

### Results

A total of 751 patients diagnosed with dengue fever were admitted during the study period from 01 Jan 2018 to 31 Dec 2018. Most cases occurred in the monsoon season from Jul-Sep quarter accounting for 66.5% (n=449) of all the cases followed by Oct-Dec quarter which accounted for 15.3% (n=115) cases (Table 1). Most patients were males with 66.4% (n=500) and 33.6% (196) were females. The commonest age group affected was from 18-30 years with 54.3 % (n=408) of all cases followed by age group from 31-45 years with 28.2% (n=212) of all cases. Dengue cases were rare beyond 60 years with 1.6% (n=12) (Table 1). The mean duration of admission after the onset of fever was 3.4 days (SD±2.76). The mean duration of hospitalization was 5.73 days (SD±2.75) with a range from 01 to 22 days (Table 2).

The most common manifestation was fever 746 (99.33%), followed by myalgia 583 (77.62%), headache 505 (67.24%), vomiting 266 (35.41%), nausea 201 (26.76%), diarrhea 93 (12.38%) and fatigue 68 (9.05%). Bleeding from different sites of the body was evident in 97 patients (12.91%). Petechiae 48 (6.39%) was the most common bleeding manifestation. Abdominal discomfort was seen in 37 (4.92%) patients (Table 2).

Out of 751 patients, 306 (40.75%) patients presented with warning signs (Table 3). Four patients died due to dengue (mortality rate-0.53%). The various complications encountered are enumerated in Table 3. Shock at admission and during hospitalization was seen in 80 (10.65%) patients. Bleeding diathesis with thrombocytopenia requiring platelet transfusions was seen in 97(12.91%) patients. In this study, 17 (9.45%) patients had respiratory complications/adult respiratory distress syndrome (ARDS), 8 (1.06%) had myocardiast, 3 had encephalopathy, 23 (3.06%) had AKI and one had cardiac tamponade. Severe hepatitis was seen in 16 patients (2.13%) (Table 4).

Persistent fever beyond seven days indicates a grave prognosis with multifold complications. One case of Hemophagocytic Lymphohistiocytosis was initially treated with IV immunoglobulin with no response and then successfully with high dose steroids. Secondary infections most commonly encountered were pneumonia and urinary tract infections. One case of pulmonary thromboembolism was diagnosed requiring anticoagulation. Another patient aged 31 years with persistent headache had cortical venous thrombosis. One patient had intravascular hemolysis on day 3 of fever and subsequently, capillary leak syndrome which was managed with supportive therapy.

There were a total of four fatal cases (mortality rate-0.53%). The first case was a 25-year-old male admitted with persistent fever for 11 days developed severe prostration, decreased urine

### Table 4: Laboratory profile of Dengue cases (n=751)

<table>
<thead>
<tr>
<th>Lab Parameters</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>13.47</td>
<td>1.96</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>42.09</td>
<td>7.83</td>
</tr>
<tr>
<td>Total Leucocyte count</td>
<td>4703.2</td>
<td>2295.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelet</th>
<th>Lowest Platelet count (c/mm)</th>
<th>No (Total 751)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20000</td>
<td></td>
<td>66</td>
<td>8.8</td>
</tr>
<tr>
<td>20001-40000</td>
<td></td>
<td>128</td>
<td>17</td>
</tr>
<tr>
<td>40001-60000</td>
<td></td>
<td>113</td>
<td>15</td>
</tr>
<tr>
<td>60,001-100000</td>
<td></td>
<td>248</td>
<td>33</td>
</tr>
<tr>
<td>100001-150000</td>
<td></td>
<td>144</td>
<td>19.2</td>
</tr>
<tr>
<td>&gt;150000</td>
<td></td>
<td>52</td>
<td>7</td>
</tr>
</tbody>
</table>

| Bil (mg/dl) | No (Total 751) | Percentage (%) |
|            |                |                |
| <1.0       | 668            | 88.9           |
| 1.0-2      | 63             | 8.4            |
| 2-5        | 11             | 1.5            |
| >5         | 9              | 1.2            |

| AST (IU/L) | No (Total 751) | Percentage (%) |
|           |                |                |
| <40        | 270            | 35.95          |
| 41-100     | 303            | 40.35          |
| 100-200    | 117            | 15.58          |
| 200-400    | 38             | 5.06           |
| 400-1000   | 13             | 1.73           |
| >1000      | 10             | 1.33           |

| ALT (IU/L) | No (Total 751) | Percentage (%) |
|           |                |                |
| <40        | 328            | 43.68          |
| 41-100     | 300            | 39.95          |
| 100-200    | 91             | 12.11          |
| 200-400    | 19             | 2.53           |
| 400-1000   | 5              | 0.67           |
| <1000      | 8              | 1.06           |
output, and dyspnea with refractory shock. The post-mortem revealed severe lymphocytomyelocarditis. The second patient was a 26-year-old male presented with capillary leak syndrome with refractory shock, AKI, and ARDS. Post mortem was suggestive of diffuse alveolar damage, bilateral patchy bronchopneumonia, and acute tubular necrosis. The third case was a 45-year-old male with a capillary leak with shock and subarachnoid hemorrhage. The fourth case was a 45-year-old lady who had a sudden onset headache and had intraventricular hemorrhage at a platelet count of 35,000/cmm (Figure 1).

**Discussion**

Dengue cases we encountered were mostly in Jul to Sep with 66.5 % of cases followed by Oct-Dec with 15.3% of cases. This pattern is similar to a western Indian study.13 The mean duration of admission after the onset of fever was 3.4 days (SD± 2.76). One Indian study at a tertiary care center showed a mean duration of 4.6 days and the late presentation could explain high mortality in that study and better outcome in our study.14 The mean hospitalization was 5.73 days (SD±2.75) (ranging 1-22 days). The productive age group from 18- 45 years was affected most with 82.5 % of all cases. This is similar to a study conducted by Kumar A et al which showed that the majority of dengue patients were from 15-44 years age group.15 The median age was 28 years in our study. The male to female ratio in our study was 2.83. This is in contrast to 1.85 shown in the North Indian study by Kumar A et al.16 The Taiwanese study showed more females than males (52.8% vs 47.2 %) indicating similar exposure of both sexes.17

In this study, fever is the most common presenting symptom in 746 out of 751 patients (99.33%). Other Indian studies in and around India and the world have also shown fever as the most common presenting symptom.18,19,12,20,21 Myalgia is the next common symptoms seen in 77.62% of cases(n=583). Lee et al studied myalgia to be less frequent 36.2%. The next common symptom was headache which was seen in 67.24 % case (n- 505). Lee et al showed a headache to be present in 41%.17 The shock was seen in 80 (10.65%) patients. A study by Siddharth Jain et al had similar observation with 12% of patients who had dengue shock syndrome.18 One often administers extra fluids that do not improve the shock and further worsen tissue hypoxemia due to respiratory fluid overload. The study showed bleeding manifestations in 97 patients (12.91%). A study in south India showed 4.3% of patients had bleeding episodes.21 The most common bleeding manifestation was petechiae 48 (6.39%). Bleeding manifestations were not very rare and could be fatal especially intracranial bleed. Platelet count was not always related to bleeding diathesis. A fatal cerebral intraventricular bleeding occurred in a patient with a 35000/cmm platelet count. One nonfatal intracerebral bleed occurred in a patient with a 65000/cmm platelet count (Figure 1).

Giddiness was seen in 46 (6.13%) patients. Giddiness, syncope, presyncope with the inability to stand, difficulty to stand, difficulty in walking to the bathroom, and severe prostration are features of severe dengue and need immediate attention. Persistent fever beyond seven days indicates grave prognosis with multifold complications like secondary Hemophagocytic Lymphohistiocytosis. We saw unusual thrombotic cases of pulmonary thromboembolism and cerebral venous thrombosis which are very rare in dengue.22 One case of Intravascular hemolysis was encountered.

The overall outcome of patient care in our study was excellent with 99.47 % of patients recovering completely. The mortality rate was 0.53%. Taiwanese study showed a mortality rate of 3.6 % in a tertiary care hospital. Mortality in Indian studies in tertiary care centers is around 2 % and 5.96 %.16-18. The low mortality in our study was mainly due to early recognition of warning symptoms, timely management to prevent complications, and intense monitoring and optimal supportive care.

**Conclusion**

The present study highlights the importance of dengue in India which affects the productive age groups, the need to be cautious while managing dengue, awareness of the atypical and unpredictable complications, and the potentially fatal outcomes. It is a multisystem disease requiring close monitoring of all systems and with close monitoring and supportive care, the outcome can be excellent.

**References**

Comparative Assessment of Revascularization Versus Drug Management in Coronary Artery Disease (CAD) Associated with Left Ventricular Dysfunction (EF <40% – A 12 Month Study with FDG PET & SPECT MPI Analyses

V Kumar¹, H Bashir², M Yadav², V Kumar³, M Bhargav³, S Jatin³, A Goel³, S Dhir³*, CP Roy³

Abstract

Aim of the study: Left Ventricular (LV) function and myocardial viability is the key predictor of prognosis after myocardial infarction. Management of ischemic cardiomyopathy (revascularization and or drugs alone) is the objective of this study.

Methodology: 72 patients were assigned to revascularization and medical management group based on the inclusion criteria. Follow up was done up to 12 months with advanced imaging techniques (FDG PET & SPECT MPI analyses).

Results: Subjects with significant viable myocardium, revascularization resulted in significant improvement in heart failure symptoms. The mean NYHA functional class improved from 2.9 ± 0.3 to 2.3 ± 0.5 (mean ± SD) after 6 months of revascularization (p < 0.01). This improvement in functional class was maintained after 12 months of revascularization (2.0 ± 0.4 (mean ± SD)). Subjects on medical management with a baseline NYHA functional class 2.7 ± 0.5, at 6 months of follow, there was no significant change in functional class (2.8 ± 0.3) (p < 0.24). However at 12 months follow up functional class had dropped to 3.0 ± 0.3, which was significant as compared to baseline (p < 0.03).

Conclusion: coronary revascularization has a protective effect on patients with ischemic coronary who have viable myocardium and reversible myocardial ischemia as assessed by 18F-FDG PET and SPECT MPI Imaging.

Introduction

The number of coronary artery disease (CAD) patients with ischemic cardiomyopathy has increased extensively over recent years. Left Ventricular (LV) function is a well-established and powerful predictor of prognosis after myocardial infarction. The occurrence of severe left ventricular systolic dysfunction after myocardial infarction, especially if associated with heart failure, is associated with very poor survival. Currently, several therapeutic options are available for patients with ischemic cardiomyopathy. Progress in pharmacologic therapy has contributed considerably to the survival of patients with heart failure. Revascularization is an alternative therapy, although the associated risk is increased in patients with a severely depressed Left Ventricular ejection fraction (LVEF). Moreover, not all patients with ischemic cardiomyopathy show improvement in contractile function after revascularization.¹

Decisions regarding high-risk revascularization are more difficult in the elderly with several comorbidities. In view of the high morbidity and mortality associated with revascularization procedures, careful selection of patients who may benefit from revascularization procedures appears to be warranted. Despite the higher clinical risk, the presence of ischemia or viability in these patients has been associated with improved outcomes after revascularization.² Identification of patients with ischemic but viable myocardium is important, as revascularization³ in these patients may be associated with substantial survival benefit, symptomatic improvement, and improved LV function.

The aim of our 12 month follow up study was to analyze the prognosis after coronary revascularization (Percutaneous coronary intervention/coronary artery bypass graft) or medical therapy in patients of coronary artery disease (CAD) with LV dysfunction (EF <40%) with viable myocardium as assessed by fluorodeoxyglucose (FDG) positron emission tomography (PET) and single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). The primary end points of the study was to assess change in ejection fraction, change in left ventricular end systolic volume index, end diastolic volume index and LV sphericity index, change in functional class. The secondary end points were to record any major adverse cardiac events (MACE).

Material and Methods

This prospective single center intervention study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethics approval was obtained from the Institutional Ethical Committee of the institute. Patients with stable CAD & associated LV dysfunction (ejection fraction ≤40%) were enrolled in the study. Diagnosis of CAD...
was made on the basis of history, electrocardiography (ECG) and one or more of the following investigations: coronary angiography (CAG), previous revascularization, history of previous myocardial infarction (MI ≥4 weeks) or positive stress perfusion imaging for presence of scar and or ischemia. Inclusion criteria for the subjects were: patient’s ≥18 years of age suffering stable coronary artery disease with LV dysfunctions (EF ≤40 %). Subjects with co morbidities e.g. chronic kidney disease (CKD), carcinoma, chronic liver disease (CLD), cerebrovascular accident (CVA) that would possibly affect their survival during the study duration, history of MI ≤4 weeks, patients unsuitable for revascularization and or requiring emergency revascularization or severe valvular disease indicating surgery, lack of consent would be excluded from the study. Informed written consent was obtained from all the enrolled subjects for the study.

Comprehensive demographic details, medical history (e.g. comorbid conditions, drug etc.) was recorded for the initial 92 enrolled patients. New York Heart Association (NYHA) functional class was assessed for the subjects for their symptoms and the functional status. All the subjects underwent FDG-PET and SPECT-MPI for viability and reversible myocardial ischemia. 20 patients had non-viable myocardium and were thus excluded from study. 72 met the inclusion criteria and were enrolled. 46 patients underwent revascularization and 26 patients refused revascularization and were put on medical therapy. Subjects were classified into 2 groups: revascularization group and medical management group. Decision on the modality of revascularization was made by the attending cardiologist who was not integral part of the study investigators. This was done to avoid any bias in the study results. 29 subjects underwent PTCA while 17 subjects underwent CABG. For both the groups few parameters were standardized: mean age, comorbid conditions, severity of the vessel disease and medications. 1) Mean age: revascularization group (63.3 ±11 years) and (61.9 ± 9 years) in the medical management group. 2) Hypertension & diabetes: revascularization group: 63.4 %, (n=27) diabetes mellitus 56 % (n=23); medical management group: Hypertension 70 % (n=14) diabetes mellitus 55 % (n=11). Majority of the subjects in both groups had double or triple vessel disease and were on aspirin, ACE inhibitors, beta blockers, statins, diuretics and nitrates.

Protocol for gated SPECT MPI and FDG PET computed tomography

SPECT and FDG PET help to evaluate cell membrane integrity and myocyte metabolism and thus cell viability. With SPECT, both stress-induced perfusion abnormalities and resting isotope uptake ≥50% to 60% predict functional recovery.6, 8 Patients were injected with 20 mCi of 99mTc-Tetrofosmin at rest and 180 degree Quantitative Gated SPECT imaging was performed after 60 minutes using data from RAO 45 TO LPO 135 (90 Degree mode). Following this patients were injected with 370 MBq of 18F-FDG (after insulin priming and glucose loading according to a standardized protocol. 20). Cardiac 18F-FDG PET scan was acquired on a whole body PET-CT scanner (GE DISCOVERY 600) after one hour. High resolution, 16 slice, CT scan was also obtained of the same area for attenuation correction. With FDG PET, the presence of reduced perfusion but normal or high FDG uptake (perfusion-metabolism mismatch) is indicator of myocardial viability. Reduced blood flow with reduced F-18 FDG uptake (matched defect) was used as the criterion for scar. Patients were classified according to extent and severity of mismatch. Patients with significant viable myocardium (>25%) were advised for revascularization treatment. Patients who underwent revascularization as well as those who preferred medical treatment were followed up at regular intervals.

Baseline 2D-echocardiography

Two-dimensional echocardiography was performed with a PHILIPS IE 75 machine equipped with a 2.5-MHz transducer. Patients were studied in left lateral decubitus, in parasternal short- and long-axis and apical four- and two-chamber views. The endocardial border at end-diastole and end-systole was planimetered including papillary muscles in the blood volume. End-diastole was defined as the frame with the largest cavity immediately before the onset of QRS complex and end-systole as the frame with the smallest cavity area. The LV volumes and ejection fraction were calculated according to the modified Simpson’s rule. The end-diastolic and end-systolic volumes were indexed (LVEDVI and LVESVI, respectively) by the body surface area. LVEDVI < 55.5 ± 8.7 mL/m² and LVESVI ≤ 22.1 ± 4.9 mL/m² were considered normal values. The LSVI was derived by the ratio of LV short- to long-axis dimensions in the end-systolic apical 4-chamber view. The higher the LSVI, the more spherical the shape.

Follow Up intervals

Patients enrolled in the study were followed at 3, 6 and 12 months. Patients underwent detailed clinical evaluation regarding symptoms and functional status, using NYHA functional class. 2D echocardiography was done at 6 and 12 months to assess LV systolic functions, LV end systolic volume and LV end diastolic volume. A ≥ 5% increase in EF was considered as significant improvement of global systolic function. An increase > 15% in the LVEDVI or LVESVI at follow up was defined ongoing LV remodeling. Significant LV reverse remodeling was defined by a >20% decrease in ESVI. Any adverse cardiac event in the form of myocardial ischemia, repeat hospitalization with heart failure and cardiovascular death occurring during this period were noted.

Statistical Analysis

The data obtained was subject to various statistical tests for significance. All continuous data were presented as mean ± SD. Survival probability of the entire patient population was estimated by use of the Kaplan-Meier method. Paired comparisons, between pre-revascularisation and follow-up data, was performed with Student’s t test or Fisher’s exact test as appropriate. Multiple groups were compared with a single-factor ANOVA and the F test. Differences between 2 proportions were compared with the chi 2 test or Fisher’s exact test, and results were given as percentages. The effect of covariates on symptom improvement was assessed by use of multiple logistic regression analysis.

Results

Baseline echocardiography

At baseline, all patients showed enlarged LV and depressed global function. LVEF of patients was 24 ± 7% (mean ± SD) and 25 ± 6 %
Table 1: Baseline clinical and demographic features

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Revascularisation group (n=41)</th>
<th>Medical management group (n=20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (YRS), mean (SD)</td>
<td>63.3(11)</td>
<td>61.9(9)</td>
<td>0.81</td>
</tr>
<tr>
<td>Males n(%)</td>
<td>26(63.4)</td>
<td>13(65)</td>
<td>0.79</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>27(65.8)</td>
<td>14(70)</td>
<td>0.56</td>
</tr>
<tr>
<td>Diabetes Mellitus n (%)</td>
<td>23(56)</td>
<td>11(55)</td>
<td>0.90</td>
</tr>
<tr>
<td>Dyspnea (NYHA)</td>
<td>2.9 ± 0.3</td>
<td>2.7 ± 0.5</td>
<td>0.12</td>
</tr>
<tr>
<td>Previous MI n (%)</td>
<td>17(41.4)</td>
<td>8(33.3)</td>
<td></td>
</tr>
<tr>
<td>Coronary anatomy n(%)</td>
<td></td>
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<tr>
<td>1-vessel disease</td>
<td>none</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>24(58.5)</td>
<td>13(65)</td>
<td>0.43</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>17(41.5)</td>
<td>7(35)</td>
<td>0.53</td>
</tr>
<tr>
<td>Baseline Echocardiographic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF % (mean ± SD)</td>
<td>24 ± 7</td>
<td>26 ± 6</td>
<td>0.81</td>
</tr>
<tr>
<td>End-systolic volume index (mL/m2) (mean ± SD)</td>
<td>82 ± 26</td>
<td>79 ± 20</td>
<td>0.30</td>
</tr>
<tr>
<td>Sphericity index (mean ± SD)</td>
<td>0.69 ± 0.14</td>
<td>0.65 ± 0.12</td>
<td>0.39</td>
</tr>
<tr>
<td>Baseline Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors %</td>
<td>73</td>
<td>75</td>
<td>0.88</td>
</tr>
<tr>
<td>Beta Blockers %</td>
<td>63.4</td>
<td>60</td>
<td>0.74</td>
</tr>
<tr>
<td>Nitrates %</td>
<td>58.5</td>
<td>65</td>
<td>0.21</td>
</tr>
<tr>
<td>Diuretics %</td>
<td>56</td>
<td>60</td>
<td>0.43</td>
</tr>
<tr>
<td>Calcium-channel blockers %</td>
<td>9.7</td>
<td>10</td>
<td>0.91</td>
</tr>
<tr>
<td>Aspirin %</td>
<td>95.1</td>
<td>99</td>
<td>0.92</td>
</tr>
</tbody>
</table>

in revascularization and medical management groups respectively (P = 0.23). In the revascularization group, LVEDVI was 119 ± 32 mL/m² (mean ± SD), LVESVI was 82 ± 26 mL/m² and LVSI was 0.69 ± 0.14. In the medical management group, LVEDVI was 113 ± 29 mL/m², LVESVI was 79 ± 20 mL/m² and LVSI was 0.65 ± 0.12 (Table 1). Thus, baseline LVEF and cardiac volumes were comparable in both the groups (P value not significant).

**Baseline functional status**

NYHA functional class of patients was 2.9 ± 0.3 (mean ± SD) and 2.7 ± 0.5 (mean ± SD) in revascularization group and medical management group respectively (Table 1). Thus baseline NYHA functional class was comparable in both the groups.

**Revascularization**

41 patients underwent successful coronary revascularization. (PTCA = 26, CABG =15). Patients were followed up for one year after enrollment. 2D echocardiography was done at 6 and 12 months to assess left ventricular ejection fraction (LVEF), left ventricular end systolic volume Index (LVESVI) and LV end diastolic volume index (LVEDVI) and left ventricular Sphericity Index (LVSI).

**Effect on LV function and volumes**

In revascularization group, LVEF improved from 24 ± 7 % at baseline to 27 ± 5 % (mean ± SD) after 6 months. After 12 months of revascularization, LVEF improved from 24 ± 7 % at baseline to 29 ± 8(mean ± SD) (P < 0.001). There was also significant reduction in LVEDVI, LVESVI and LVSI after revascularization. LVEDVI decreased from 119 ± 23 (mean ± SD) at baseline to 109 ± 24 at 6 months ((P < 0.001)) and 101 ± 29 at 12 months (P < 0.001). Similarly LVESVI decreased from 82 ± 19 (mean ± SD) at baseline to 75 ± 17 at 6 months (P < 0.001)) and 69 ± 16 at 12 months ((P < 0.001)) (Tables 2, 3). LVSI decreased from 0.69 ± 0.14 (mean ± SD) at baseline to 0.58 ± 0.11 at 6 months (p and 0.53 ± 0.12 at 12 months (P < 0.001) (Table 2, 3).Thus there was statistically significant improvement in LVEF and decrease in LVEDVI, LVESVI and LVSI after revascularization.

In medical management group, there was no statistically significant change in mean LVEF, LVESVI, LVEDVI and LVSI at 6 month follow up. LVEF was 25 ± 6 (mean ± SD) at baseline and 25 ± 7 % at 6 months follow up (p = 0.43). LVEDVI was 113 ± 29 mL/m² (mean ± SD) and 115 ± 27 at baseline and at 6 months respectively. LVESVI was 79 ± 20 mL/m² (mean ± SD) and 81 ± 19 at baseline and at 6 months respectively. LVSI was 0.65 ± 0.12 (mean ± SD) 0.66 ± 0.15 at baseline and at 6 months respectively. However at 12 months follow up, there was significant fall in LVEF and increase in LVESVI, LVEDVI and LVSI as compared to baseline. At 12 months LVEF was 23 ± 5 % (p < 0.01), LVESVI was 86 ± 17(p < 0.01), LVEDVI 121 ± 29 (p <0.01) and LVSI 0.65 ± 0.16 (p < 0.01).

When compared to medical management group, patients in revascularization group had statistically significant improvement in mean LVEF, LVEDVI, LVESVI and LVSI at 6 and 12 months of follow up (Tables 2, 3).

**Effect on functional status**

After revascularization all patients had a significant improvement in heart failure symptoms. The NYHA functional class improved from 2.9 ± 0.3 to 2.3 ± 0.5(mean ± SD)) after 6 months of revascularization (p<0.01). This improvement in functional class was maintained after 12 months of revascularization (2.0 ± 0.4 (mean ± SD)).

In patients who were on medical management, baseline NYHA functional class was 2.7 ± 0.5. At 6 months of follow, there was no change significant change in functional class (2.8 ± 0.3) (p0.24). However at 12 months follow up functional class had dropped to 3.0 ± 0.3, which was significant as compared to baseline (p 0.03). When compared to medical management group, patients in revascularization group had significant

Table 2: Change in LVEF, end-systolic volume index, end-diastolic volume index and sphericity index-6 Months after revascularization

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months after revascularisation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (mean ± SD)</td>
<td>24 ± 7</td>
<td>27 ± 5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End-systolic volume index (mL/m2)</td>
<td>82 ± 19</td>
<td>75 ± 17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End-diastolic volume index (mL/m2)</td>
<td>119 ± 23</td>
<td>109 ± 24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sphericity index</td>
<td>0.69±0.14</td>
<td>0.58 ± 0.11</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 3: Change in LVEF, end-systolic volume index, End-diastolic volume index & Sphericity index - 12 Months after revascularization

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 months after revascularisation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (mean ± SD)</td>
<td>24 ± 7</td>
<td>29 ± 8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End-systolic volume index (mL/m2)</td>
<td>82 ± 19</td>
<td>69 ± 16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End-diastolic volume index (mL/m2)</td>
<td>119 ± 23</td>
<td>101 ± 29</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sphericity index</td>
<td>0.69±0.14</td>
<td>0.53 ± 0.12</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
improvement in functional class at 6 and 12 months of follow up (Table 4).

**Effect of type of revascularization on functional status, LV function and volumes**

Out of 61 patient enrolled in this study, 26 patients underwent PTCA while as 15 patients underwent CABG. At follow-up there was no statistically significant difference in change functional status, LV function and volumes between the two groups when compared to baseline

**Major adverse cardiac events**

There were a total of 15 events, 7 in revascularization group and 8 in medical management group. Event rate was more in medical management group (30 %) than in revascularization group (14.6 %, p < 0.01). There were 2 deaths in medical management group; both were due to myocardial infarction. There was one death in revascularization group, which was due to sepsis syndrome. Hospitalization due to heart failure was more in medical management group (38 %) than in revascularization group (17 %, p < 0.05) (Table 5).

**Discussion**

Left ventricular (LV) function is among the most important determinants of prognosis in patients with coronary artery disease (CAD). It is well established that patients with impaired LV systolic function represent a high risk group with significantly greater annual mortality than those with preserved LV function, and that survival rates decline in proportion to the severity of LV dysfunction. The growing number of patients with ischemic LV dysfunction contributes importantly to the increasing morbidity and mortality of heart failure.

Along with the advances in surgical and percutaneous myocardial revascularization that have occurred during the past two decades, numerous studies have demonstrated that LV dysfunction in many patients is a potentially reversible phenomenon, related to myocardial stunning, myocardial hibernation or a combination of these two pathophysiology processes, and in these patients LV function may improve substantially, and even normalize, after revascularization.

As many as 40% of patients undergoing coronary artery bypass surgery with preoperative LV dysfunction manifest a significant increase in LV ejection fraction when evaluated several months after operation. The likelihood that segmental and global ventricular function will improve after revascularization can be ascertained using imaging methods that provide evidence of myocardial viability in dysfunctional regions. The methods with the greatest evidence base for predicting recovery of ventricular function are those that provide confirmation of preserved metabolic activity, cell membrane integrity or contractile reserve in dysfunctional regions, and hence positron emission tomography (PET), single photon emission tomography (SPECT) with thallium-201 or technetium-99m perfusion tracers and low dose dobutamine stress echocardiography (DSE) have emerged as accurate and accepted methods for viability assessment.

Recent data indicate that contrast-enhanced magnetic resonance imaging also holds great promise in this arena. The predictive accuracies vary considerably among the various studies, related in part to methodological differences, patient selection factors and timing of the repeat evaluations revascularization, but in general PET and SPECT have higher sensitivity (with greater negative predictive value) and DSE has higher specificity (with greater positive predictive value) regarding improved wall motion and increased ejection fraction after revascularization.

Positron emission tomography (PET) imaging with F-18-fluorodeoxyglucose (FDG) is considered the most sensitive viability imaging method for predicting LV function recovery. Several observational studies have shown that FDG PET can identify patients with viable myocardium who are at high risk for cardiac events if they do not undergo timely revascularization. Dahl et al found that combined nuclear imaging using sestamibi SPECT and FDG PET with quantitative tracer uptake analysis allows detection myocardial viability in regions with reduced perfusion and function with prognostic implication.

There have been a number of retrospective analyses, each involving relatively small numbers of patients that have addressed the prognostic implications of viability testing in patients with CAD and LV dysfunction. Studies have demonstrated that revascularization in patients with ischemic cardiomyopathy and viable myocardium improves regional and global LV function. A substantial amount (> 25% of the LV) of viable myocardium is necessary to result in improvement in LVEF. The meta-analysis by Allman et al demonstrates significant differences in survival depending on the presence or absence of myocardial viability and, in patients with dysfunctional but viable myocardium, striking differences in outcome between patients treated medically and those treated with revascularization. Marcelo et al found that in patients with ischemic cardiomyopathy, the magnitude of improvement in heart failure symptoms after CABG is related to the preoperative extent and magnitude of myocardial viability as assessed by use of PET imaging. Patients with large perfusion-metabolism mismatches exhibit the greatest clinical benefit after CABG.

In our study we found that in subjects with significant viable myocardium, revascularization resulted in significant improvement in heart failure symptoms. The mean NYHA functional class improved from 2.9 ± 0.3 to 2.3 ± 0.5 (mean ± SD) after 6 months of revascularization (p < 0.01). This improvement in functional class was maintained after 12 months of revascularization (2.0 ± 0.4 (mean ± SD). When compared to medical management group, patients in

### Table 4: Impact of revascularization on NYHA (New York Heart Association) functional class

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Mean NYHA class</th>
<th>6 months after revascularisation</th>
<th>12 months after revascularisation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.9 ± 0.3</td>
<td>2.3 ± 0.5 P &lt; 0.01</td>
<td>2.0 ± 0.4 P &lt; 0.01</td>
</tr>
</tbody>
</table>

### Table 5: Frequency of secondary events

<table>
<thead>
<tr>
<th>Events</th>
<th>Revascularisation (n=41)</th>
<th>Medical management (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>7 (17.00)</td>
<td>8 (38) †</td>
</tr>
<tr>
<td>Rate</td>
<td>Cardiovascular death</td>
<td>nil</td>
</tr>
<tr>
<td></td>
<td>Non-cardiac death</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hospitalization with HF</td>
<td>6 (14.6%)</td>
</tr>
</tbody>
</table>

† HF = heart failure; p < 0.01
Revascularization group had significant improvement in functional class at 6 and 12 months of follow up.

Improvement of LVEF after coronary revascularisation has been described in variable proportions of patients with ischemic cardiomyopathy and substantial myocardial viability. Bax and colleagues showed that LVEF improved in 82% of patients with substantial viable myocardium. In current study revascularization was associated with statistically significant increase in mean LVEF at 6 and 12 months follow up. The improvement in LVEF translated into clinical benefit in terms of improved NYHA functional class and less hospitalizations with heart failure.

Increased LV volumes and cavity size predict poor outcome in patients with ischemic cardiomyopathy. Studies have shown that coronary revascularization resulted in a significant reduction of LV volume in patients with ischemic cardiomyopathy and viable myocardium. Revascularization of jeopardized myocardium may have a beneficial effect by attenuating LV dilatation and remodeling, reducing ventricular arrhythmias and the risk of fatal ischemic events. Dalle Mule et al showed a decrease in LV volumes 3 months after revascularization only in patients with substantial viability during 201 Tl imaging. Senior and coworkers demonstrated that coronary revascularization resulted in a significant reduction of LV volume in 32 patients with ischemic cardiomyopathy and viable myocardium. Rizzello et al studied 100 patients with ischemic cardiomyopathy and found that a substantial amount of viable myocardium prevents ongoing LV remodeling after revascularization and is associated with persistent improvement of symptoms and better outcome. In our study we found that revascularization was associated with significant reduction in mean LV volumes (i.e. LVEDVI, LVESVI and LVSII). We also noticed that patients who underwent revascularization had less rate of hospitalization with HF as compared to medical management group.

Revascularisation in patients with viable myocardium may have survival benefit. A meta-analysis conducted by Allman et al and a more recent one by Bourque et al included studies with SPECT, PET and echocardiography with more than 1000 patients and found a close relationship between myocardial viability and significantly improved survival rates after revascularisation. Based on our results, we conclude that coronary revascularization has a protective effect on patients with ischemic cardiomyopathy who have viable myocardium and reversible myocardial ischemia as assessed by 18F-FDG PET and SPECT MPI Imaging.

Conclusion

Left ventricular (LV) function is among the most important determinants of prognosis in patients with coronary artery disease (CAD). It is well established that patients with impaired LV systolic function represent a high risk group with significantly greater annual mortality than those with preserved LV function, and that survival rates decline in proportion to the severity of LV dysfunction. Differentiation between LV dysfunction caused by infarction, necrosis, and scar tissue formation versus LV dysfunction due to ischemic but viable myocardium has important implications. Identification of patients with ischemic but viable myocardium is important, as revascularization (4-6) in these patients may be associated with substantial survival benefit, symptomatic improvement, and improved LV function

Assessment of myocardial viability is important in the management of patients with ischemic cardiomyopathy. 18F-FDG PET is considered the most sensitive means of assessing viable myocardium and hence predicting LV functional recovery post–coronary revascularization.

In patients with ischemic cardiomyopathy and a substantial amount of viable myocardium, revascularization may be associated with significant improvement in left ventricular ejection fraction. Revascularization in such patients may result in positive remodeling with improvement in left ventricular volumes. This improvement in left ventricular ejection fraction and left ventricular volumes is likely to translate into improvement in symptoms of dyspnea. On the other hand optimal medical management alone in such patients may result in gradual decline in left ventricular ejection fraction with increase in left ventricular volumes.

References

Identification of Missing Probes in rpoB gene in Rifampicin Resistant PTB and EPTB Cases Using Xpert MTB/RIF Assay in Sirmaur, Himachal Pradesh

Vipin Kumar1, Manju Bala2, Anil Kanga3, Neha Gautam4*

Abstract

Introduction: India has the highest number of TB (27%) and MDR/RR-TB (24%) cases among the notified TB patients. Xpert MTB/RIF assay is a fully automated cartridge-based real-time PCR to detect MTB and resistance to rifampicin within two hours using three specific primers and five unique molecular probes to target the rpoB gene. This study was done to detect RR-TB cases and frequency of missing probes, which target mutations in rpoB gene, in the different groups of study population in Sirmaur district of Himachal Pradesh.

Methods: All, pulmonary and extrapulmonary specimens, were processed for AFB microscopy and Xpert MTB/RIF assay to diagnose TB and RR-TB

Results: Xpert detected MTBC in 721 patients. Using AFB microscopy, only 284 samples were positive. Of these MTB positive patients, 671 had pulmonary TB and 50 were EPTB cases. Resistance to RIF was detected in 31 (4.29%) cases of which resistance in presumptive tuberculosis group and presumptive drug resistant tuberculosis was 1.51% and 9.30% respectively. Twenty-eight (4.17%) PTB cases and three (6%) EP-TB cases were resistant to RIF. The frequency of probe E was highest (77.41%) and mutation combination of probes C and D and E and D was 3.22%.

Conclusion: Drug resistance in the MTBC is mainly conferred through point mutations in specific gene targets in the bacterial genome. Molecular assays like Genexpert gives rapid diagnosis and Rifampicin resistance. This study helps to provide baseline data of mutations with in the 81 bp of rpoB gene and stresses the need to further evaluate the mutation patterns in this part of the country.

1Senior Resident, 2Associate Professor, 3Professor, 4Assistant Professor, Microbiology, Dr. YS Parmar Govt Medical College, Nahan, Himachal Pradesh; Corresponding Author
Received: 19.10.2019, Accepted: 25.07.2020
Introduction

Tuberculosis (TB) is a global health problem and remains one of the world’s deadliest communicable diseases. India alone has the highest number of TB (27%) and multidrug resistance/rifampicin resistance tuberculosis (MDR/RR-TB) (24%) cases among the notified TB patients followed by Indonesia, China, Philippines, Pakistan, Nigeria and South Africa. Extrapolarynog tuberculosis (EPTB), which accounts for around 15-20% of all notified TB cases, is a persistent global health issue. Although drug resistant extrapolarynog tuberculosis (DR-EPTB) is uncommon, but increasing rates of drug resistance in pulmonary TB has intensified our fear for DR-EPTB too. A rapid, sensitive and specific diagnosis and sensitivity testing method ensures sensitive and specific diagnosis and its presence, is needed for accurate diagnosis of RR-TB. The aim of this study was detection of RR-TB cases and frequency of missing probes which target mutations in 81 bp of rpoB gene in the different groups of study population in Sirmaur district of Himachal Pradesh.

Material and Method

A total of 2957 samples from patients with suspected pulmonary and extrapolarynog tuberculosis received between September 2016 to April 2018 at designated microscopy center, Dr YS Parmar Government Medical College, Nahan, Himachal Pradesh were included in the study. These specimens included sputum, cerebral spinal fluid (CSF), pleural fluid, gastric aspirate, pus and tissue biopsy.

All specimens were processed for AFB microscopy and Xpert® MTB/ RIF (Cepheid) assay to diagnose TB and RR-TB. For Xpert assay; one ml of clinical specimen and two ml of Xpert reagent was added in a 50 ml falcon tube, shaken vigorously and incubated for 15 minutes at room temperature. Two ml of the mixture was transferred to Xpert cartridge and the cartridge was loaded into the device as per manufacturer’s instructions. Finally, the results were interpreted by the Xpert system and displayed automatically after 90 minutes.

Detection of MTR

The sample was labelled as MTB positive when at least two of the five probes give positive signals with a cycle threshold (CT) of ≤38 cycles. The concentration of bacilli depend on the CT range (high, <16; medium, 16–22; low, 22–28; very low, >28). Detection of rifampicin resistance

RIF resistance is identified by either rpoB mutations that completely inhibit probe hybridization leading to absence of probes (missing probes) or by rpoB mutations that permit partial probe hybridization and cause difference between the first (early CT) and the last (late CT) MTB-specific beacon (ΔCT) of more than 3.5 cycles. On the basis of CT values, frequencies of mutant probes were investigated in all RR- TB cases.

Results

There was a male preponderance amongst the total 2957 patients that were tested during the study period. The age of the patients ranged from 1 year to 98 years. There were 2644 pulmonary samples and 313 extrapolarynog samples. Genexpert detected MTBC in 721 patients. The age of these TB positive patients ranged from 9 to 80 years with the highest percentage in adult age group. (80.58%) Around 64% of cases were males with a male to female ratio of 1.8:1. Using AFB microscopy, only 284 samples were

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Table 1: Rifampicin resistant tuberculosis in different groups of study population

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>MTB Not detected n=2236</th>
<th>MTB detected n=721</th>
<th>Rifampicin resistant tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatrics</td>
<td>209</td>
<td>21</td>
<td>0.19 (0.00)</td>
</tr>
<tr>
<td>(n=230)</td>
<td></td>
<td></td>
<td>0.02 (0.00)</td>
</tr>
<tr>
<td>Adult (16-60 yrs) (n=2042)</td>
<td>1461</td>
<td>581</td>
<td>5/362 (1.38%)</td>
</tr>
<tr>
<td>Geriatric (&gt;60 yrs) (n=685)</td>
<td>566</td>
<td>119</td>
<td>2/82 (2.4%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=1668)</td>
<td>1206</td>
<td>462</td>
<td>7/278 (2.51%)</td>
</tr>
<tr>
<td>Female (n=1289)</td>
<td>1030</td>
<td>259</td>
<td>0/185 (0.00%)</td>
</tr>
<tr>
<td>TB type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1973</td>
<td>671</td>
<td>6/424 (1.4%)</td>
</tr>
<tr>
<td>(n=2644)</td>
<td></td>
<td></td>
<td>22/247 (8.9%)</td>
</tr>
<tr>
<td>Extrapulmonary (n=313)</td>
<td>263</td>
<td>50</td>
<td>1/39 (2.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>2236</td>
<td>721</td>
<td>7/463 (1.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24/258 (9.30%)</td>
</tr>
</tbody>
</table>

Table 2: Correlation of different missing probes of rpoB gene in rifampicin resistance cases in different groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Probe types</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>C and D</th>
<th>E and D</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>New (Presumptive TB)</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Presumptive drug resistant TB</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Sample type</td>
<td>PTB</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>EPTB</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
</tbody>
</table>
positive. Of these 721 MTB positive patients, 671 had pulmonary TB and 50 were EPTB cases (Table 1).

Resistance to RIF was detected in 31 (4.29%) cases of which resistance in presumptive tuberculosis group and presumptive drug resistant tuberculosis was 1.51% and 9.30% respectively. Twenty-eight (4.17%) PTB cases and three (6%) EP-TB cases were resistant to RIF. RIF resistance was more in male patients as compared to females. RR was detected 24 adults, seven geriatric patients and none of the paediatric case was resistant to RIF.

Interestingly, of the total of 2957 specimens, 2673 were smear negative out of which 17.40% were detected as MTB positive by genexpert and RR was detected in 3.99% cases.

The frequency of the probes missing in RR cases was as follows: A (1/31), B (2/31), C (1/31), D (1/31), E (24/31), C and D (1/31) and E and D (1/31). The frequency of probe E was highest (77.41 %) and mutation combination of probes C and D and E and D was 3.22 %. The details of missing probes in various subpopulations are given in Table 2. In this study, three specimens were detected MTB positive and indeterminate resistant to RIF in Xpert assay. Fresh sputum specimens of those patients were sent to Intermediate Reference Laboratory, Dharmpur for culture and Line Probe Assay (LPA) and were confirmed as RIF sensitive.

Discussion

Tuberculosis remains a major public health problem in the developing world and stands in the way of development. India has been ranked as the highest burden country, therefore rapid and accurate detection of tuberculosis and rifampicin-resistance, not only guides individual patient treatment but also helps to control the increasing rate of tuberculosis. RIF resistance is of epidemiological significance and a useful indicator for MDR-TB strains as more than 90 % RIF resistant strains are also resistant to isoniazid. Gene-Xpert has revolutionized diagnosis of PTB and EPTB due to its speed, simplicity and less biohazard problems and its ability to detect the resistance to RIF in less than two hours.

In our study 24.38 % cases were MTB positive and more men than women were diagnosed with tuberculosis. Our results are similar to other studies from the surrounding region and developed world. Our results revealed that majority of the patients were in adult age group (15-60 years). This is in line with other studies wherein studies from India, Nepal and Ethiopia have showed that 77.5%, 71.6% and 86.16% of the patients belonged to the age group of 15-45 years. According to Global TB report 2018, around 10.0 million people (range, 9.0–11.1 million) developed TB disease in 2017 out of which 58% were men and overall 90% were belongs to the adults (aged 215 years) age group. The reason for high incidence of TB in these sub populations may be more out-door activities related to their occupation. Male preponderance in tuberculosis could be attributed to underreporting and under diagnosis of tuberculosis in women or gender based differences in access to health care.

In our study, resistance to RIF was seen in 4.29% cases. We found RIF resistance in presumptive tuberculosis was 1.51% which is lower than the rates reported by Indian authors and our annual status report (2018) by Central TB Division. Internationally, the RIF resistance rates in this category of patients range from as low as 2.7% as seen in American and African regions to as high as 27% in South East Asian region. Two of our neighbouring countries, Bangladesh and Nepal, have reported very high RIF resistance rate of 50% and 86.5% respectively which is an area of concern. The samples included in the Nepal study were from a reference centre where culture positive cases from various geographical regions are referred, while the Bangladesh study was carried out in a hospital where suspected MDR-TB cases from all over the country were referred to. This could be the possible reason for such high resistance rates.

RR in presumptive drug resistance tuberculosis was found to be 9.30% in our study. High RR of more than 50 % has been reported from various parts of our country wherein, Raizada et al., Tripathi et al. and Singhal et al. reported the rifampicin resistance rates of 51%, 56.32% and 55.2% respectively. This is higher than national observation of 11.61%. The reason could be selection bias of the patients in these studies. However, other studies by Kumar et al., Sharma et al. and Desikan et al. reported 25.8%, 22% and 10.6% of MDR-TB respectively by using LPA as a modality for detecting resistance. Previous study from Himachal Pradesh also reported high RR of 25.9% in MDR suspected cases. According to Global TB Report 2018 among TB cases; 3.5% of new TB cases and 18% of previously treated cases had MDR/RR-TB globally. The countries with the largest numbers of MDR/RR-TB cases (47% of the global total) were China, India and the Russian Federation. The highest proportions (>50% in previously treated cases) are in countries of the former Soviet Union.

Disparity in drug resistance rates could be attributed to differences in awareness of studied populations about drug resistance, access to healthcare, incoherent patient diagnosis, treatment, and follow-up and poor adherence to long treatment regime. The high level of RR might be because RIF is currently used for the treatment of many other infectious diseases. Since RIF is main sterilising drug for TB management, resistance to this drug has enormous implications for TB-control programs.

EPTB accounts for 10-15% of all TB cases in India and 14% in world. TB can affect any body organ, lymphadenitis and pleural effusion, being the most common forms of EPTB. Diagnosis of EPTB is lacking in rural health facilities that are used by about 70% of the population in developing countries. EPTB is often hard to diagnose because of difficulty of sampling and paucibacillary nature of samples. Therefore, there are very few reports of drug resistant EPTB as these patients are usually not included in drug resistance surveys. In our study, among the 50 EPTB cases, 6% were RIF resistant. Studies from India reveal RIF resistance in 9.94% to 19% in EPTB cases. Studies from Nepal and Bangladesh found resistance to rifampicin in Extra-pulmonary tuberculosis in 60% and 40.57% cases respectively.

Xpert assay indicates RR by absence or mutation in at least any one of the five probes targeting 81 bp-RRDR region of rpoB gene. The probe E was the most common missing probe in our study (77.41%) followed by probe B which is in line with other studies from India. Our neighboring countries; Pakistan and Bangladesh have also reported high mutation in the probe E; 76.96% and 64.83% respectively. Similar
findings have been reported from other African countries. The most common mutations in the 81 bp were found to be at codon 531 (proline E on the Xpert® MTB/RIF assay) by Tripathi and Anupurba, by Thakur et al. and Maurya et al. from India using LPA as a modality to detect RR. Similar results have been reported by Yue et al. who found the frequency of mutation to be highest at codon 531 (41%) detected by DNA sequencing.

Xpert assay does not provide information of specific mutations in the rpoB gene therefore we cannot use gene-Xpert as an epidemiological tool to study RR-TB. However, data of studies could be used to assess trends over time, identify pockets of transmission or investigate outbreaks, in resource poor settings where genotypic methods like MIRU-VNTR, RFLP, spoligotyping and sequencing are more difficult to implement.

Limitations of our study

As we did not perform culture or drug susceptibility testing (DST) by any other method, we were not able to calculate the proportion of false positive and negative results of the Xpert assay. Sequencing for rpoB gene, which is the gold standard, was not done for the detection of mutation; therefore, the specificity and sensitivity of the assay to detect mutations in the rpoB gene could not be estimated.

Conclusion

Widespread access to accurate DST is essential for effective diagnosis and treatment of drug-resistant TB. Drug resistance in the MTBC primarily occurs due to point mutations in specific gene targets in the bacterial genome. Molecular tests such as Xpert MTB/RIF and LPA are increasingly being used for rapid testing and thus prompt introduction of appropriate treatment for drug-resistant TB. Our study shows the RIF resistance rates among different group of suspected TB patients in Northern region of India. This study helps to provide baseline data of mutations with in the 81 bp of rpoB gene and stresses the need to further evaluate the mutation patterns in this part of the country.

References

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Cardiac Involvement in Vasculotoxic and Neurotoxic Snakebite – A not so Uncommon Complication

Sunil Kumar K¹, Joseph K Joseph¹, Stigi Joseph², Abraham M Varghese¹*, Manoj P Jose¹

Abstract

Background: Cardiac toxicity following snakebite envenomation has been previously observed, but not studied in detail, especially the involvement in neurotoxic bites. This prospective observational case study evaluates the incidence of cardiac toxicity along with the difference between vasculotoxic and neurotoxic bites and analysing the predictors for development of cardiotoxicity.

Method: 96 patients who had snake bite envenomation were evaluated for features of cardiotoxicity with clinical features, ECG, echocardiogram and troponin-I levels.

Results: Cardiac toxicity was observed in 42.7% of patients, the majority were either ECG changes, noted in 34.3% and rise in troponin-I, noted in 21.9% of patients. Other changes included echocardiographic changes in 4.2%, and Takotsubo cardiomyopathy in 1%. There was no significant difference in the incidence of cardiotoxicity between the neurotoxic (41.7%) and vasculotoxic (42.9%) (p value =1) snake bites, even though the predominant changes seen in neurotoxic snake bites were ECG changes. There were no deaths in the current study. None of the demographic or clinical parameters studied could predict the development of cardiac events.

Conclusion: Cardiac toxicity is a well defined complication of poisonous snake bite and incidence is more frequent than previously thought. Both vasculotoxic and neurotoxic snake bites are associated with cardiac toxicity and is not associated with increase in mortality.

Introduction

According to World Health Organization (WHO) there are around 5 million snake bites every year worldwide which causes nearly 100,000 deaths and 400,000 develop permanent disability. It remains as a major public health problem in many countries and WHO had added snakebite to the list of Neglected Tropical Diseases in 2017. Various studies suggest that bites with envenomning constitute 12%-50% of the total number of bites in Asia and 18%-30% in India and Pakistan. Snakebite related deaths occurred mostly in rural areas (97%), were more common in males (59%), than females (41%), and peaked at ages 15-29 years (25%) and during the monsoon months of June to September. Eighty percent of individuals bitten by snakes first consult traditional practitioners before visiting a medical centre in the developing countries. Poor health services, difficult and untimely transportation facilities, wrong traditional beliefs, erroneous identification of snake, delay in anti-snake venom administration and unavailability of anti-snake venom all contribute to the poor outcome in snake bite victims. Highest incidence and mortality due to snake bites is reported from South and Southeast Asian countries having extensive agricultural practices and diversity in snake species, the cobra (Naja naja), common krait (Bungarus caeruleus), and Russell’s viper (Daboia russelii), accounts for 97% of all snakebite related deaths.

The clinical picture of snake bite is usually dominated by local reaction, renal, neurological and haemorrhagic manifestations based on the toxins in snake venom. Cardiac manifestations have been reported previously in some studies. A study on 1051 patients from central Kerala in India showed cardiac complications in 4.3% patients, and another study from Sri Lanka showed cardiac complication in 3-12% of 336 snake bite patients studied. Cardiac toxicity can occur in the form of hypotension, arrhythmias, changes in electrocardiogram especially ST segment and T wave changes and myocardial infarction. There are very few case reports of pulmonary edema, myocarditis, stress cardiomyopathy in the literature due to snake bite envenomation. Though these are rarely seen, cardiac complications can significantly alter the outcome of that particular bite victim and as they are commonly from resource poor settings where advanced cardiac investigations are not readily available and possible for everyone. Mechanism by which cardiac complication occurs is also not very clear, but could be a direct toxic effect on myocardium, vasospasm induced by various toxins in the venom or due to coagulopathy causing secondary cardiac damage. There are only very limited data available regarding cardiac effect of snake venom both from clinical and toxicological aspects. This study is an attempt to identify the clinical and laboratory features of cardiac involvement of snake bite, whether any of the presenting features can predict the onset of cardiac toxicity and the difference between neurotoxic and vasculotoxic bites with respect to cardiac involvement.

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The observational study was conducted from August 2015 to March 2017 at a tertiary referral hospital in Southern India which treats around 18 to 20 snake bites and to analyse whether any difference of cardiac involvement exists between neurotoxic and vasculotoxic bites. The secondary aims were to study the incidence of cardiac involvement in snake bite. Eighty-one (87.5%) were vasculotoxic and 12 (12.5%) were neurotoxic. The median age of the group was 45 ranging from 18 to 96 years.

Materials and Methods

Study design: This prospective observational study was conducted from August 2015 to March 2017 at a tertiary referral hospital in Southern India which treats around 18 to 20 snakebite patients per month, of which 80-90% are due to vasculotoxic snakes. The procedures followed in the study were in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. The study was approved by institutional (Little Flower Hospital and Research Centre, Angamaly, Kerala, India) Ethics Committee and informed written consent was obtained from all the study participants. The primary objective of the study was to assess the extent of cardiac involvement in snake bite. The secondary aims were to study the difference of cardiac involvement between neurotoxic and vasculotoxic snake bites and to analyse whether any of the clinical manifestation can predict cardiac involvement.

Sample size calculation: The extent of cardiac involvement in one previous study was 4.3%. If an absolute error of 5% and a type I error of 5% were assumed the study size will be a minimum of 63 patients. To increase the accuracy, all cases arrived during study period were included which made it to 96 patients.

Vasculotoxic envenomation was diagnosed when following a snakebite the patient had a typical clinical presentation including limb oedema with fang marks and/or bleeding manifestation along with a positive 20-minute whole blood clotting test (WBCT) and the snake was identified by the victim or witnesses after comparing with a displayed specimen in hospital or the snake was brought to the hospital dead or alive1,2.

Neurotoxic snake bite was diagnosed with history of snake bite and any neurological signs including drowsiness, paraesthesia, abnormalities of taste and smell, “heavy” eyelids, ptosis, external ophthalmoplegia, paralysis of facial muscles and other muscles innervated by the cranial nerves, nasal voice or aphonia, nasal regurgitation, difficulty in swallowing secretions, respiratory and generalised flaccid paralysis and with or without signs of local envenomation1,2. For the study purpose hypotension is defined as <90 /60 mmHg and hypertension is defined as >140/90 mmHg.

Cardiac involvement was defined as the presence of 1) Electrocardiographic (ECG) changes 2) Echocardiographic (ECHO) changes 3) elevation of myocardial enzymes 4) presence of any new unexplained cardiac events.

Patients with previous renal dysfunction, previous cardiac problems, chronic liver disease, chronic obstructive pulmonary disease, pre-existing neurological disorders except for completely recovered stroke were excluded from the study. After admission, data for the study was collected from the patients by direct interview with patient or patient’s relatives/ bystanders and obtaining history, clinical examination and relevant diagnostic investigations performed.

Study procedure: Detailed history was taken regarding the site of bite, application of tourniquet, vomiting, abdominal pain, and pain over the bite site, bleeding from bite site, bleeding from gums, urine output, and any neurological abnormality during admission. Vital signs including pulse rate, blood pressure, respiratory rate, temperature and oxygen saturation in the pulse oximeter (SpO2) were recorded. Detailed local examination and systemic examination were performed. Investigations including complete haemogram, liver function tests, serum creatinine, ECG, ECHO and Troponin I were done in all patients with envenomation. Additional investigations including coronary angiogram and cardiac MR imaging were performed in indicated cases. Patients received polyvalent ASV (Bharat Serum and Vaccines, Ltd) which was administered as per the WHO guidelines for management of snakebites11. Other supportive measures were given based on clinical features, type of envenomation and organs affected.

Statistical methods: Data were evaluated using SPSS version 24. Categorical variables were expressed as proportions and compared using chi-square test or Fisher exact test. The Student t test was used to compare mean values of normally distributed quantitative variables. Logistic regression was used to determine factors that predicted cardiac toxicity using variables that had p-value <0.05.

Results

Ninety six patients with poisonous snake bite were included in the study of which 84 (87.5%) were vasculotoxic and 12 (12.5%) were neurotoxic. The characteristics of patients divided into vasculotoxic and neurotoxic bites are summarised in Table 1. Sixty two (65%) patients were males and the median age of the group was 45 ranging from 3 to 75 years. All bites were in upper or lower limbs. Whole blood clotting test time (WBCT) was prolonged in 81 (96.4%) of vasculotoxic bites and 3

Table 1: Demographics and clinical features

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=96)</th>
<th>Vasculotoxic n=84 (87.5%)</th>
<th>Neurotoxic n=12 (12.5%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45(27.75-55)</td>
<td>45 (28-55)</td>
<td>49.5 (21.5-55)</td>
<td>0.53</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 62 (65%)</td>
<td>53(63%)</td>
<td>9 (75%)</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>Female 34 (35%)</td>
<td>31(37%)</td>
<td>3 (25%)</td>
<td></td>
</tr>
<tr>
<td>Bite site</td>
<td>R upper limb 12 (12.5%)</td>
<td>11 (13.1%)</td>
<td>1 (8.3%)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>L Upper limb 8 (8.3%)</td>
<td>7 (8.3%)</td>
<td>1 (8.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R Lower Limb 38 (39.6%)</td>
<td>34 (40.5%)</td>
<td>4 (33.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L Lower Limb 38 (39.6%)</td>
<td>32 (38.1%)</td>
<td>6 (50%)</td>
<td></td>
</tr>
<tr>
<td>Bite to whole blood clotting test time prolongation in hours</td>
<td>4.26±3.1</td>
<td>4.27±3.16</td>
<td>4.16±0.76</td>
<td>0.87</td>
</tr>
<tr>
<td>Swelling at the site</td>
<td>89 (93%)</td>
<td>79 (94%)</td>
<td>10 (83%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16 (16.6%)</td>
<td>16 (19%)</td>
<td>0 (0%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (10.4%)</td>
<td>9 (10.7%)</td>
<td>1 (8.3%)</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>15 (15.6%)</td>
<td>15 (17.9%)</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Regional Lymphadenopathy</td>
<td>40 (41.7%)</td>
<td>39 (46.4%)</td>
<td>1 (8.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypotension</td>
<td>13 (13.5%)</td>
<td>11 (13.1%)</td>
<td>2 (16.7%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (15.6%)</td>
<td>13 (15.5%)</td>
<td>2 (16.7%)</td>
<td>1</td>
</tr>
<tr>
<td>Acute renal injury</td>
<td>35 (36.5%)</td>
<td>33 (39.3%)</td>
<td>2 (16.7%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Capillary Leak syndrome</td>
<td>10 (10.4%)</td>
<td>10 (11.9%)</td>
<td>0 (0%)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*Median (inter quartile range); †Mean (standard deviation)
Table 2: Cardiac changes

<table>
<thead>
<tr>
<th>Change</th>
<th>Total (n=96)</th>
<th>Vasculotoxic (n=84)</th>
<th>Neurotoxic (n=12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG changes*</td>
<td>33 (34.3%)</td>
<td>28 (33.3%)</td>
<td>5 (41.7%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Troponin</td>
<td>21 (21.9%)</td>
<td>20 (23.8%)</td>
<td>1 (8.3%)</td>
<td>0.05</td>
</tr>
<tr>
<td>ECHO changes</td>
<td>4 (4.2%)</td>
<td>4 (4.8%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1 (1%)</td>
<td>1 (1.2%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Total Cardiac involvement</td>
<td>41 (42.7%)</td>
<td>36 (42.9%)</td>
<td>5 (41.7%)</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: *Details of ECG change in Table 3.

Table 3: ECG changes

<table>
<thead>
<tr>
<th>ECG change</th>
<th>Total (n=96)</th>
<th>Vasculotoxic (n=84)</th>
<th>Neurotoxic (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>16 (16.7%)</td>
<td>14 (16.7%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Early repolarisation</td>
<td>1 (1%)</td>
<td>1 (1.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>ST elevation</td>
<td>5 (5.2%)</td>
<td>4 (4.8%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>T inversion</td>
<td>10 (10.4%)</td>
<td>8 (9.5%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Tachycardia (unexplained)</td>
<td>11 (11.5%)</td>
<td>9 (10.7%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Brugada pattern</td>
<td>1 (1%)</td>
<td>1 (1.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Poor R wave progression</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>PACS</td>
<td>1 (1%)</td>
<td>1 (1.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>ST depression</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (8.3%)</td>
</tr>
</tbody>
</table>

(25%) of neurotoxic bites. Mean time from bite to prolongation of WBCT was 4.26 hours ranging from 1 hour to 17 hours. Swelling at the local site was described in 89 (93%) of patients, other symptoms include abdominal pain in 16 (16.6%), vomiting in 10 (10.4%), bleeding manifestation from various sites in 15 (15.5%), regional lymph node in 40 (40.7%), hypotension in 13 (13.5%), hypertension in 15 (15.6%), acute renal injury in 35 (36.5%) and capillary leak syndrome in 10 (10.4%) patients.

Cardiac involvement which was defined as any or a combination of changes described below was observed in 41 (42.7%) of patients and are summarized in Table 2. The majority was either ECG changes, noted in 33 (34.3%) and rise in troponin, noted in 21 (21.9%) patients. Other changes included Echocardiographic changes (regional wall motion abnormalities) in 4 (4.2%) and Takotsubo cardiomyopathy in 1 (1%).

ECG changes which are summarized in Table 3 included bradycardia in 16 (16.7%), early repolarisation in 1 (1%), ST elevation in 5 (5.2%), T wave inversion in 10 (10.4%), unexplained tachycardia in 11 (11.5%), Brugada pattern in 1 (1%), poor R wave progression in 1 (1%), premature atrial complexes (PACS) in 1 (1%) and ST depression in 1 (1%) patient.

42.9% of vasculotoxic snake bites and 41.7% of neurotoxic snake bites developed cardiac toxicity, difference of which was not statistically significant (p=1). All patients with neurotoxic bites who developed cardiac toxicity had ECG changes, but one patient developed elevation in troponin. There was no death in the current study.

Binomial logistic regression was used to find any factors which could predict cardiac involvement (Table 4). Factors analysed include age, gender, type of snake, site of bite, duration of bite to whole blood clotting test time, swelling at the site of bite, abdominal pain, vomiting, bleeding from any sites, regional lymph node enlargement, hypotension, hypertension, acute renal injury and development of capillary leak syndrome. But none of these factors reached level of significance to predict cardiac involvement either in univariate or multivariate analysis.

**Discussion**

In this study cardiac involvement was described in 42.7% of patients with toxic snake bite. In a study from north-eastern Nigeria involving 108 patients with Viperidae snakebite, electrocardiographic abnormalities were seen in more than 60% of patients, and troponin T was elevated in 2% of patients. A study from Papua New Guinea, using ECG and cardiac troponin T levels, concluded that myocardial injury is uncommon following elapid snakebites. In another study from South Korea the incidence of acute cardiovascular events was shown to be about 13.8%. Previous studies from India have shown varying cardiac involvement.

A study by Anitha MS et al showed ECG changes as high as in 94% of patients and enzyme changes in 48%. Another study by Ramakrishna CD et al all showed ECG changes in 31.5% and echocardiogram changes in 1.5%. A third study by Nayak et al showed a 25% cardiotoxicity in Viperidae bite.

There is a wide variation in the incidence of cardiotoxicity between various studies, major contributor might be variation in definition of various cardiotoxic features, for example some studies included all tachycardia but some did not consider sinus tachycardia as significant abnormality. There could be other explanation like the composition of venom accounting for this variation. Our study showed sinus bradycardia as the major rhythm abnormality in contrast to other studies by Dissanyake et al, Ramakrishna et al and Anitha MS et al where sinus tachycardia was the major abnormality. Menon JC et al, reported ECG features suggestive of myocardial infarction in three patients, paroxysmal supraventricular tachycardia, left bundle branch block and transient atrial fibrillation in one patient each. Our study did not show any major ECG abnormalities similar to that.

Cardiac enzyme elevation was noticed in 21.9% of patients in our study whereas study done by Anitha et al documented a higher percentage (48%), however the cardiac enzymes considered in that study was CKMB and SGOT whereas present study was done using troponin I (the cardiac specific enzyme) elevation in association with envenomation. Similarly studies from Mishra et al, Lalloo et al and Mohapatra et al studied only SGOT or CKMB. Elevated troponin level was found in 24.6% patients in the south Korean study which is comparable to our study.

Our study also demonstrated rare complications like Takotsubo cardiomyopathy in a patient with vasculotoxic snake bite (Russell’s viper). It is interesting to note that neurotoxic snake bite was also associated with cardiotoxicity but majority of them were ECG changes. Several other factors age, gender, type of snake, site of bite, duration of bite to whole blood clotting test time, swelling at the site of bite, abdominal pain, vomiting, bleeding from any sites, regional lymph node enlargement,
hypotension, hypertension, acute renal injury and development of capillary leak syndrome were also analysed for predicting cardiac involvement but none of them were found to be statistically significant as predictors. There were no deaths observed in this study suggesting that cardiac involvement in poisonous snake bite is not a bad prognostic marker like some other complication like capillary leak syndrome. This is similar to other studies like the South Korean study which also did not see any increase in mortality with cardiotoxicity.

Mechanism by which cardiotoxicity develops remains unclear, but the possible mechanisms include direct cardiotoxicity to the myocardium, hypovolemic shock due to increased vascular permeability, hypercoagulable state leading to vascular thrombosis and direct vasospasm triggered by the venom, but there needs to be more research to elucidate the mechanism of cardiotoxicity in snake bite envenomation.

A major limitation of our study was its observational approach. We were unable to investigate for significant biological markers, cardiac MRI, serial ECGs, serial echocardiograms and follow up Troponin which would have confirmed the reversibility of cardiac toxicity. None of the factors we considered in our study were predictors for cardiac toxicity, prompting the need for evaluation of toxins and biological markers as possible predictors.

In conclusion we have demonstrated that cardiac toxicity is a clearly defined toxicity following snake bite envenomation and is more common than previously thought. Neurotoxic snake bites are also associated with cardiac toxicity especially ECG abnormalities. None of the demographic factors or clinical features studied could predict the development of cardiac toxicity. Cardiac toxicity is not associated with increase in mortality, but it is important to recognize the event as it will alter the supportive management in these patients.

Authors’ contributions

SKK, JKJ, SJ, and MPJ conceived the study, designed the study protocol and carried out the clinical assessment; AMV analyzed data; SKK and AMV drafted the manuscript; MPJ, SJ and JKJ critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Ethical approval: The study was approved by institutional (Little Flower Hospital and Research Centre, Angamaly, Kerala, India) Ethics Committee and informed written consent was obtained from all the study participants.

Table 4: Predictors of development of cardiac toxicity in snake venem envenomation

<table>
<thead>
<tr>
<th>Cardiac involvement</th>
<th>No Cardiac involvement</th>
<th>Univariate p value</th>
<th>Multivariate p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=55(%)</td>
<td>n=50(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12 (29.2%)</td>
<td>22 (40%)</td>
<td>0.291</td>
</tr>
<tr>
<td>Vasculotoxic</td>
<td>36 (87.8%)</td>
<td>48 (87.2%)</td>
<td>1</td>
</tr>
<tr>
<td>Site of bite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right upper limb</td>
<td>4 (9.75%)</td>
<td>8 (14.5%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Left upper limb</td>
<td>5 (12.2%)</td>
<td>3 (5.5%)</td>
<td>0.291</td>
</tr>
<tr>
<td>Right lower limb</td>
<td>17 (41.3%)</td>
<td>21 (38.2%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Left lower limb</td>
<td>15 (36.6%)</td>
<td>23 (41.8%)</td>
<td>1</td>
</tr>
<tr>
<td>Swelling</td>
<td>38 (89.2%)</td>
<td>51 (92.7%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8 (18.9%)</td>
<td>8 (14.5%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (9.7%)</td>
<td>6 (10.9%)</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>5 (11.1%)</td>
<td>10 (18.1%)</td>
<td>1</td>
</tr>
<tr>
<td>Regional lymphadenopathy</td>
<td>20 (48.7%)</td>
<td>20 (36.4%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (7.3%)</td>
<td>10 (18.2%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (19.5%)</td>
<td>7 (12.7%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Acute renal injury</td>
<td>17 (41.5%)</td>
<td>18 (32.7%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Capillary leak syndrome</td>
<td>5 (12.1%)</td>
<td>5 (9.1%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Age</td>
<td>44.5 (18.3)</td>
<td>41 (16.8)</td>
<td>0.57</td>
</tr>
<tr>
<td>Duration of bite to prolongation of whole blood clotting test time</td>
<td>4.32 (2.99)</td>
<td>4.2 (3.2)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

References

Echocardiographic Pattern of Congenital Heart Diseases in Adolescent and Adult population of Western Rajasthan

Rohit Mathur1*, Sanjeev Sanghvi2, Anil Baroopal3, Aditya Kumar2, JP Soni4

Abstract

**Background:** Nearly one third of all major congenital anomalies are due to congenital heart disease (CHD). Globally the prevalence of CHD in adults varies from 0.66 to 40.0 per 1000 study population. In India the prevalence of CHD is 1.09 to 543 per 1000 study population. CHD is a major global health burden because of increased mortality and morbidity associated with it. Early diagnosis and management can be helpful in improving survival rates, quality of life and prognosis in patients suffering from CHD.

**Aims and Objectives:** The aim of this study was to assess the echocardiographic profile of CHD in Western Rajasthan, India in population above 12 years of age.

**Methods:** This retrospective study was carried out at department of Cardiology and Pediatrics of Dr. S. N. Medical College and attached group of hospitals in Jodhpur, Rajasthan, India. The presence of CHD among all patients above 12 years of age who underwent transthoracic echocardiography over a period of around 4 years from July 2014 to April 2018 was analyzed.

**Results:** A total of 256 patients above 12 years of age were identified as having CHD out of the 33,228 patients who underwent echocardiography during the study period, thus giving a prevalence of 7.7 per 1000 study population. Amongst the total diagnosed CHD cases, 137 (53.52%) patients were male with male to female ratio of 1.15:1. CHDs were diagnosed more commonly between 13 to 24 years of age (54.69%). The commonest type of CHD in the present study was atrial septal defect (27.34%) whereas the most common cyanotic CHD was tetralogy of Fallot (10.94%).

**Conclusion:** Prevalence of CHD in study cohort of age more than 12 years in Western Rajasthan, India was 7.7 per 1000 study population. Profile of CHDs in the present study was similar to that in published literature. We propose to do larger and targeted studies in this age group because many CHDs will become inoperable or even if operated will leave some or other cardiac dysfunction beyond adolescence.

Introduction

Congenital heart disease (CHD) is the most common form of major birth defects. Nearly one third of all major congenital anomalies consist of heart defects.1 To provide effective and optimal target strategies for prevention and management of CHDs, it is very important to understand the distribution of these anomalies in the population. The most commonly used parameter for assessment of CHD occurrence is birth prevalence per 1000 live births.2 The birth prevalence of CHD increased progressively over a period from 1970 to 2017 with maximum increase during 2010 to 2017 reaching a peak of 9.4 per 1000 live births in 2017.3

The prevalence of CHD in the adults is determined by survival rates, which in turn, depend primarily on the availability of high quality cardiac surgery. In 2000, the prevalence of CHD was 11.89 per 1000 children, 4.09 per 1000 adults, and 5.78 per 1000 in the general population. The prevalence of severe CHD was 1.45 per 1000 children and 0.38 per 1000 adults.4 A Quebec population-based study estimated that, in the year 2010, the prevalence of CHD in adults (18 years of age and older) was 6.1 per 1000 study population.5 Worldwide prevalence of CHD ranges from 0.66 to 40.0 per 1000 study population.6-7 The prevalence of CHD in India has been reported to be from 1.09 to 543 per 1000 study population.6-8 If not corrected early in life, most of the CHDs will become uncorrectable or will leave some permanent damage by adolescence. That’s why it is important to know the disease burden in this age group so that aggressive measures can be taken to improve outcomes. To the best of our knowledge, so far no study has been done for echocardiographic pattern of CHDs above 12 years of age in India.

Methods

This was a retrospective study conducted in the departments of Cardiology and Pediatrics of Dr. S. N. Medical College and attached group of hospitals, Jodhpur, India. Dr. S. N. Medical College is a tertiary care and teaching institute which caters to patients belonging to all strata of society from Western Rajasthan. Medical and echocardiographic records of all patients above 12 years of age, who visited the outdoor and indoor patient departments of Cardiology and Pediatrics from July 2014 to April 2018, were thoroughly analyzed in detail for age, sex and echocardiographic findings.

Congenital heart disease in the present study was defined as “a gross structural abnormality of heart or..."
intrathoracic great vessels that is actually or potentially of functional significance excluding the systemic great arteries and veins regardless of the age of detection as defined by Mitchell et al.10 Echocardiographic examination was conducted using M-mode, two-dimensional, color Doppler, pulse and continuous wave Doppler echocardiogram. Left parasternal, short axis, suprasternal, apical and subcostal views were all scrutinized. Definitive diagnosis of CHD was made by 2-D and color Doppler transthoracic echocardiography.

**Inclusion criteria**

- Patients diagnosed as having CHD by clinical and transthoracic echocardiographic examination above 12 years of age were included in the study.

**Exclusion criteria**

- Patients who had been enrolled previously and present on follow up visits
- Acquired heart diseases (rheumatic fever, rheumatic heart disease, myocarditis, pericardial disease)
- Mitral valve prolapse
- Cardiomyopathy (dilated, hypertrophic or restrictive)
- Congenital arrhythmias (such as Long QT syndrome, Wolf-Parkinson-White syndrome)

**Data analysis:** The collected data was entered into a Microsoft office excel spread sheet and analyzed. Ratios and percentages were used for evaluation.

**Results**

During the study period of 4 years, a total of 33,228 patients were examined and underwent detailed transthoracic echocardiographic examination. Out of these, 256 patients above 12 years of age were diagnosed to have CHD, thus giving a prevalence of 7.7 per 1000 study population. A male to female ratio of 1:1.15:1 was observed with 137 (53.52%) males and 119 (46.48%) females amongst the total diagnosed CHD cases.

Age distribution of the 256 cases of CHDs is shown in table 1. Out of the total diagnosed CHD cases, 54.69% were between 13 years to 24 years, 22.66% were between 25 years to 36 years, 14.06% were between 37 years to 48 years, 12.50% were between 49 years to 60 years, and only 8.59% were above 48 years of age in the present study. The oldest patient reported was 67-year-old and the youngest was 1-year-old.

Age and sex distribution of acyanotic CHDs is shown in Table 2. Tetralogy of Fallot (TOF) and Ebstein anomaly were the commonly observed cyanotic CHDs in the present study. Cyanotic CHDs were also most commonly diagnosed between 13 to 24 years of age (13.28%).

**Discussion**

The adult CHD population is one of the fastest growing group of patients in cardiology. Contributing factors includes the improvement in CHD prenatal detection and treatment, novel surgical and interventional procedures, and the improvement in the organization of care. Echocardiography in clinical practice improves the ability to diagnose asymptomatic patients and patients with only mild lesions. Marelli et al. found that the prevalence of CHD in children from 1 to 12 years remained constant over the study period of 1985 to 2000 but the prevalence in adolescents (13 to 17 years) and adults (18 to 40 years) increased, along with a

**Table 1: Age distribution of 256 cases of CHDs**

<table>
<thead>
<tr>
<th>Age of CHD</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 year-24 year</td>
<td>140</td>
<td>54.69</td>
</tr>
<tr>
<td>25 year-36 year</td>
<td>58</td>
<td>22.66</td>
</tr>
<tr>
<td>37 year-48 year</td>
<td>36</td>
<td>14.06</td>
</tr>
<tr>
<td>49 year-60 year</td>
<td>17</td>
<td>6.64</td>
</tr>
<tr>
<td>61 year-above</td>
<td>5</td>
<td>1.95</td>
</tr>
<tr>
<td>Total</td>
<td>256</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 2: Age and sex distribution of acyanotic CHDs**

<table>
<thead>
<tr>
<th>CHD</th>
<th>13 year-24 year</th>
<th>25 year-36 year</th>
<th>37 year-48 year</th>
<th>49 year-60 year</th>
<th>61 year-above</th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
<th>Percentage of all CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>26</td>
<td>17</td>
<td>12</td>
<td>11</td>
<td>4</td>
<td>43</td>
<td>23</td>
<td>19</td>
<td>27.34</td>
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<tr>
<td>VSD</td>
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<td>4</td>
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<td>0</td>
<td>31</td>
<td>20</td>
<td>11</td>
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<td>BAV</td>
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<td>5</td>
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<td>PAPVC</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.39</td>
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<tr>
<td>Total</td>
<td>106</td>
<td>48</td>
<td>32</td>
<td>17</td>
<td>4</td>
<td>106</td>
<td>101</td>
<td>207</td>
<td>80.86</td>
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</table>

**Table 3: Age and sex distribution of cyanotic CHDs**

<table>
<thead>
<tr>
<th>CHD</th>
<th>13 year-24 year</th>
<th>25 year-36 year</th>
<th>37 year-48 year</th>
<th>49 year-60 year</th>
<th>61 year-above</th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
<th>Percentage of all CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOF</td>
<td>21</td>
<td>4</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>17</td>
<td>28</td>
<td>10.94</td>
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<tr>
<td>Ebstein anomaly</td>
<td>4</td>
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<td>1</td>
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<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>3.13</td>
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<td>1</td>
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<td>Single ventricle</td>
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<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>10</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>31</td>
<td>18</td>
<td>9.14</td>
</tr>
</tbody>
</table>

Abbreviations: ASD atrial septal defect; AVCD atrioventricular canal defect; BAV bicuspid aortic valve; CoA coarctation of aorta; PAPVC partial anomalous pulmonary venous connection; PDA patent ductus arteriosus; PFO patent foramen ovale; PS pulmonary stenosis; VSD ventricular septal defect.
Table 4: Prevalence of CHD in world studies

<table>
<thead>
<tr>
<th>Author, Ref No.</th>
<th>Country</th>
<th>Study population</th>
<th>Method</th>
<th>Number studied</th>
<th>Prevalence / 1000 study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billett et al. 2008</td>
<td>UK</td>
<td>Community (0 and above years)</td>
<td>Clinical + Echo Prospective</td>
<td>3200000</td>
<td>3.05</td>
</tr>
<tr>
<td>Giannoglou et al. 2009</td>
<td>Greece</td>
<td>Hospital (18-66 years)</td>
<td>Clinical + Cath Retrospective</td>
<td>18473</td>
<td>12.67</td>
</tr>
<tr>
<td>Videbaek et al. 2009</td>
<td>Denmark</td>
<td>Community (16 and above years)</td>
<td>Cross-sectional</td>
<td>-</td>
<td>3.4</td>
</tr>
<tr>
<td>Shina et al. 2011</td>
<td>Japan</td>
<td>Community (15 and above years)</td>
<td>-</td>
<td>10,44,79,000</td>
<td>3.92</td>
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<tr>
<td>Ejim et al. 2014</td>
<td>Nigeria</td>
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<tr>
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<td>9476</td>
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<td>Clinical + Echo Retrospective</td>
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<td></td>
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<tr>
<td>Aleman-Ortiz et al. 2018</td>
<td>Mexico</td>
<td>Hospital (18 and above years)</td>
<td>Clinical + Echo Retrospective</td>
<td>45068</td>
<td>7.8</td>
</tr>
<tr>
<td>Jang et al. 2018</td>
<td>Korea</td>
<td>Community (20 and above years)</td>
<td>Clinical + Echo Retrospective</td>
<td>-</td>
<td>0.66</td>
</tr>
<tr>
<td>Wu et al. 2018</td>
<td>Taiwan</td>
<td>Community (18-59 years)</td>
<td>Clinical + Echo Retrospective</td>
<td>-</td>
<td>2.17</td>
</tr>
</tbody>
</table>

Abbreviations: Cath — catheterization; Echo — echocardiography.

Table 5: Prevalence of CHD in Indian studies

<table>
<thead>
<tr>
<th>Author, Ref No.</th>
<th>City</th>
<th>Study population</th>
<th>Method</th>
<th>Number studied</th>
<th>Prevalence / 1000 study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vijayalakshmi et al. 1995</td>
<td>Bangalore</td>
<td>Hospital (3 months-69 years)</td>
<td>Clinical + Echo + Cath Retrospective</td>
<td>6985</td>
<td>543</td>
</tr>
<tr>
<td>Ramegowda et al. 2006</td>
<td>Mysore</td>
<td>Hospital (0-23 years)</td>
<td>Clinical + Echo Prospective</td>
<td>30800</td>
<td>4.67</td>
</tr>
<tr>
<td>Jatav et al. 2014</td>
<td>Karimnagar</td>
<td>Hospital (0-25 years)</td>
<td>Clinical + Echo Retrospective</td>
<td>13554</td>
<td>8.55</td>
</tr>
<tr>
<td>Dixit et al. 2015</td>
<td>Varanasi</td>
<td>Hospital (0-68 years)</td>
<td>Clinical + Echo Retrospective</td>
<td>34,517</td>
<td>19.14</td>
</tr>
<tr>
<td>Bhardwaj et al. 2016</td>
<td>Himachal Pradesh</td>
<td>Community (0 and above years)</td>
<td>Clinical + Echo Retrospective</td>
<td>1882</td>
<td>6.37</td>
</tr>
<tr>
<td>Dhar et al. 2018</td>
<td>Uttrakhand</td>
<td>Hospital (16 and above years)</td>
<td>Clinical + Echo Retrospective</td>
<td>2,19,400</td>
<td>1.09</td>
</tr>
<tr>
<td>Present study, 2018</td>
<td>Jodhpur</td>
<td>Hospital (13-67 years)</td>
<td>Clinical + Echo Retrospective</td>
<td>33,228</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Abbreviations: Cath — catheterization; Echo — echocardiography.

clear increase in complexity of disease. CHDs can be classified into 3 groups; mild, moderate and severe lesions considering severity, late complications and effects of surgery. Survival to adulthood varies with severity of CHD, with 98% of patients with mild CHD, 90% of those with moderate CHD, and only 56% of those with severe forms surviving to adult ages. Survival of the population as a whole to adulthood was 81% during the period 1970 to 1974, increasing to 88.6% in 1990 to 1992. Globally high prevalence of CHD was found in hospital based studies such as in Thailand (40.0/1000) and Nigeria (25.0/1000) as shown in Table 4.

A few prevalence studies have been conducted in adults in India and majority of them were hospital based as shown in Table 5. Vijayalakshmi et al. observed a very high prevalence of 543 per 1000 study population as compared to other Indian studies as they also included the patients who underwent cardiac catheterization and angiographic studies. A high CHD prevalence of 19.14 per 1000 individuals in general population and a lower 2.4 per 1000 individuals in adults of age 18 years and above was observed by Dixit et al. Higher CHD prevalence of 7.7 per 1000 study population was observed in the present study compared to previously done studies in India.

A female preponderance in the gender distribution of CHD was observed by most of the studies conducted across the world. However a male preponderance with male to female ratio of 1.15:1 was observed in the present study, correlating well with other Indian studies. The reason for male preponderance in present study may be due to higher child mortality in females, underreporting of female patients due to low literacy, social and cultural factors, neglect and lack of awareness for women in Western Rajasthan. Female preponderence in CHDs was observed by Bhardwaj et al. and Dhar et al.

More than half the number of cases (54.69%) were diagnosed between 13 to 24 years of age in the present study which was consistent with study by Dhar et al. in which 58.75% cases were detected between 15 to 30 years of age. Majority of studies across the world showed ASD as the most common acentonic CHD. Whereas VSD was most common acentonic CHD observed in few studies. Most common CHD observed in the present study was ASD accounting for 27.34% of cases. This finding may be attributed to the fact that ASD produces less and slowly progressing hemodynamic complications so that more individuals with this condition survive to adulthood. This was consistent with other studies done in India as shown in Table 6 except the study done by Ramegowda et al. and Jatav et al. in which VSD was the commonest CHD observed. Dixit et al. observed VSD as most common CHD in general population and ASD as most common CHD in adult patients. TOF was the most common cyanotic CHD observed in 10.94% cases in the present study, correlating well with other Indian studies as shown in Table 6 except the study done by Dhar et al. in which Ebstein anomaly was the most common cyanotic CHD. Similarly, TOF was also the most common cyanotic CHD observed in studies across the world as shown in table 4 except the study done by Aleman-Ortiz et al. in which Ebstein anomaly was most common.

Limitations: Limitation of the present study is that it does not reflect true community prevalence because data have been collected from patient record files of hospitals.

Conclusion

Prevalence of CHD in study cohort of age more than 12 years in Western Rajasthan, India was 7.7 per 1000 study population. Profile of various CHDs in the present study was largely similar to the preexisting studies. ASD was the commonest lesion and CHDs were more common in males. In the present day scenario of precise
diagnostic modalities, any clinical suspicion of CHD should be confirmed by echocardiography to clinch the diagnosis, timely manage and prevent complications of CHDs.

What this Study Adds

This study reveals alarming high prevalence of CHD in adolescents and adults in this geographic area. It should initiate a population/community based epidemiological study to look for exact prevalence of CHD in Western Rajasthan. As Western Rajasthan is a relatively large geographic area and the study centre is the only tertiary centre catering to such a large area, conducting a community based study will also identify the pockets of area where CHDs are more prevalent. This information can then be used for preventive or therapeutic strategy making programs.

References

Current Clinical Evidence of Trimetazidine in the Management of Heart Disease in Patients with Diabetes

Sharvari Mahajan1, AU Mahajan2

Abstract
Diabetes Mellitus (DM) is a global health burden and the leading cause for cardiovascular (CV) disease. The differential presentation of CV disease in DM is related to the metabolic derangements leading to deterioration of myocardial cell function and its serious consequences. Therefore, there is a need for early and effective treatment intervention for this myocardial cell metabolic dysfunction. DM and myocardial ischemia (MI) share a common metabolic dysregulation mediated via increased fatty acid oxidation that makes the diabetic heart susceptible to myocardial ischemia and reduced myocardial performance during ischemia compared to non-diabetic heart. Modulation of myocardial free fatty acid metabolism should be the key target for metabolic interventions in patients with Diabetic CV complications. Trimetazidine, a fatty acid metabolic modulator, has shown to improve CV outcomes in diabetes. The present review summarizes the clinical evidence and relevance of trimetazidine as an anti-anginal and anti-ischemic agent in patients with DM. Evidence suggested that trimetazidine could significantly improve clinical outcomes in patients with angina or heart failure and diabetes. Administering trimetazidine in patients with diabetes undergoing revascularization could also provide significant clinical benefits. Current clinical practice guidelines also recommend trimetazidine as a first-line agent for selected patients or as a second-line treatment option for angina patients.

Introduction
Diabetes Mellitus (DM) is a global health issue and a leading cause of cardiovascular (CV) diseases. According to International Diabetes Federation estimates, about 463 million people were living with DM in 2019 and the numbers are expected to rise to 700 million by 2045. Patients with DM have a two- to four-fold increased risk for CV events compared to their peers without diabetes.

The clinical presentation, pathophysiology of myocardial ischemia, and the progression of both atherosclerosis and heart failure (HF) in patients with DM is different from those without DM. Coronary artery disease (CAD) in patients with DM is characterized by a higher incidence of multi-vessel disease and more diffuse distribution of atherosclerosis compared to those without DM. Similarly, patients with DM exhibit lower high-density lipoprotein levels, raised triglycerides, and atherogenic low-density lipoproteins compared to those without DM. Moreover, enhanced lipoprotein oxidation results in endothelial vasculature and smooth muscle cell cytotoxicity contributing to atherogenesis. Coronary atheroma from patients with DM exhibit more lipid-concentration, macrophage infiltration, and subsequent thrombosis than in tissues from those without diabetes suggesting an increased vulnerability for coronary thrombosis in such patients. Cardiac autonomic neuropathy, a frequent complication of DM is also associated with high mortality and sudden death possibly related to “silent” myocardial infarction and reduced heart rate variability. Silent ischemia in patients with DM has important implications for reduced appreciation of ischemic pain impairs the timely recognition of myocardial ischemia or infarction, thereby delaying appropriate therapy.

The Framingham heart study shows that the risk of HF in presence of diabetes compared to without diabetes is 2.4-fold and 5-fold higher in men and women, respectively. In addition, CV disease occurs approximately 10 years later in women than in men; however, in DM, this “female protection” might not defend against CV injury suggesting a key role of sexual hormones in development of diabetic cardiomyopathy (DCM). DCM is observed in 12% of patients with DM, independent of CAD, valve disease, or hypertension leading to overt HF and death. Based on these data, according to the current Framingham Risk Score Adult Treatment Program III guidelines, DM is considered a CAD risk-equivalent, and secondary prevention of CAD is recommended for all adult patients with DM.

The differential presentation of CV disease in DM is related to the metabolic derangements characterized by accumulation of glucose fatty acid (FA) metabolic intermediates in the cells leading to deterioration of myocardial cell function (Figure 1). The metabolic consequences of both short- and long-term myocardial ischemia are serious; therefore, early and effective treatment is required for this metabolic problem. In this context, trimetazidine, a FA metabolic modulator, has shown to improve CV outcomes in diabetes. Trimetazidine optimizes energy utilization and maintains a proper energy supply during ischemia. The present review summarizes the clinical evidence and relevance of trimetazidine as an anti-anginal and anti-ischemic agent in patients with DM.

Alteration in cardiac energy metabolism in DM
In a normal heart, FA oxidation normally produces up to 70% ATP from...
aerobic metabolism that requires 10% more oxygen than glucose breakdown. However, the normal heart can switch to other substrates enabling it to adapt under varied tissue perfusion, hormonal regulation, and the amount of cardiac work.

During and after a period of ischemia, myocardial energy metabolism alters due to an acute change in oxygen availability, change in myocardial exposure to energy substrates, and deregulation in myocardial energy generation processes. Ischemia-induced decreased synthesis of malonyl-coenzyme A (malonyl-CoA), an inhibitor of FA β-oxidation, increases FA oxidation inhibiting pyruvate dehydrogenase (PDH) suppressing glucose oxidation. However, glycolysis is not suppressed equally leading to accumulation of lactate and protons in the myocardium. The resultant anaerobic metabolism decreases ATP production leading to contractile dysfunction.

During reperfusion, FA oxidation becomes the predominant energy source and significantly outmatches glucose oxidation leading to decreased myocardial glucose uptake, lipolysis and overall reduction in insulin sensitivity and secretion.

The diabetic heart is overly dependent on FA oxidation contributed by elevated circulating FA, protein upregulations, and decreased glucose uptake resulting from insulin deficiency (Figure 2). The amount of ATP produced per mole of oxygen is less when FA rather than glucose is used as a substrate for energy production and this increases the overall oxygen demand. In addition, overactive FA oxidation results in uncoupling of mitochondria and increased production of protons from uncoupling of glycolysis. Collectively, these factors contribute to accumulation of metabolic intermediates of glucose and FA, leading to deterioration in myocardial cell function and a reduction in the efficiency of the heart per mole of oxygen utilized. Reduced cardiac efficiency further exacerbates the imbalance between the oxygen supply and demand that occurs during ischemia.

Similar to the ischemic heart, the altered processes of FA β-oxidation resulting from reduced cardiac malonyl-CoA levels and protein upregulation contribute to increased FA β-oxidation in the diabetic heart. Further, peroxisome proliferator-activated receptors (PPAR-α) also enhance expression of PDH kinase 4 resulting in deactivation of PDH. Enhanced uptake, FA oxidation, and PPAR-α expression indirectly correlate to cardiac glucose transporter, resulting in glucose uptake inhibition, oxidation, and consumption by the heart as a typical characteristics of diabetes.

In summary, DM and MI share a common metabolic dysregulation mediated via increased FA oxidation that makes the diabetic heart susceptible to MI and reduced myocardial performance during ischemia compared to nondiabetic hearts. Overall, myocardial free FA metabolism modulation should be the key target for metabolic interventions in patients with CV complications with and without DM.

Clinical evidence

Patients with stable CAD and DM

Angina pectoris is a clinical condition comprising of precordial discomfort, pressure, or pain caused by transient myocardial ischemia. Symptoms usually occur due to atheromatous narrowing of one or more coronary arteries. Patients with stable angina uncontrolled on monotherapy of nitrates, β-blockers, or calcium-channel blockers are often treated with combinations of these drugs. The most often evaluated parameters were: number of weekly angina attacks and mean nitroglycerin consumption per week, and time to 1-mm ST-segment depression. Over recent decades, trimetazidine has been studied thoroughly for its efficacy and safety in patients with CAD and several meta-analyses have confirmed the antianginal efficacy of trimetazidine in patients with stable CAD. Compared with placebo, trimetazidine alone or as add-on to conventional anti-anginal agents is effective in treating stable angina with fewer adverse events. Several studies have demonstrated the...
results of randomized studies have also been corroborated by two real-world observational studies. The DIETRIC study reported significant reduction in angina episodes and number of nitroglycerin tablets used per week (all \( P < 0.001 \)); and improvement in all exercise parameters. 

**Patients with left ventricular dysfunction**

Patients with DM and chronic heart failure (CHF) show endothelial dysfunction due to high oxidative stress. The metabolic action of trimetazidine may prevent the consequences of oxidative stress and improve myocardial functions when LV (Left Ventricle) function is impaired; it can also reduce the reverse remodeling of chronically dysfunctional myocardium. In HF, trimetazidine improves contractility, ventricular function and functional capacity.

In the study by Belardinelli et al, trimetazidine improved endothelium-dependent relaxation (determined by intra-arterial infusion of acetylcholine) and decreased systemic oxidative marker levels in patients with CHF secondary to ischemic cardiomyopathy. Further, a meta-analysis of 17 clinical trials showed that trimetazidine therapy significantly improved left ventricular ejection fraction (LVEF) in patients with both ischemic and non-ischemic HF. It is also documented that trimetazidine decreased hospitalization for cardiac causes (RR 0.43; \( P = 0.03 \)), improved clinical symptoms and cardiac function with LV remodeling. Gunes et al also demonstrated that patients with both DM and ischemic HF tend to have greater improvement in LVEF without DM (\( P = 0.063 \)).

**Patients with DM undergoing revascularization**

Reperfusion of the ischemic heart leads to the generation of oxygen free radicals that can damage cardiac cells. This may happen in general coronary syndromes such as unstable angina, vasospastic angina, myocardial infarction with or without ST-segment elevation, whether or not followed by thrombolysis or angioplasty procedures, as well as in CV surgery and in elective angioplasty.

Efficacy of trimetazidine in patients with DM when used as an adjunct to other agents.

The TRIMetazidine in POLand-1 (TRIMPOL-1) study significantly improved exercise-induced ischemia and time to onset of angina, and decreased severity and the intensity of angina pain. Trimetazidine also reduced weekly anginal attacks and nitrate consumption, and was well tolerated in this population. The
proved to be beneficial for myocardial protection during procedures involving reperfusion injury.43-46 Earlier reports also showed good clinical responses of trimetazidine in patients with angina coexistent with DM.37,47 These may compensate for the deterioration in glucose uptake by myocardial cells resulting from the altered insulin levels, and may even have a cardio-protective effect in patients at risk of diabetic cardiomyopathy.48

In the prospective study, Xu et al49 reported significant improvement in incidence and severity of angina pectoris, silent Myocardial infarction and angina-free survival in the trimetazidine group compared to those in placebo groups at 2-year follow-up of elderly patients with CHD and DM after drug eluting stent (DES) implantation. In trimetazidine-treated patients, LV function and structure were found to be stable with slightly better E/A ratio (The E/A is a marker of the LV function). It represents the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave) at 2-year follow-up. It was suggested that adjunctive therapy with trimetazidine after DES implantation could have a beneficial effect on recurrent angina pectoris as well as LV function and structure in elderly patients with multi-vessel CHD and DM.49 Recently published, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of trimetazidine after Percutaneous Coronary Intervention (PCI) (ATPCI) in 3007 patients at 365 centers in 27 countries across Europe, South America, Asia and North Africa.50 After a median follow-up of 47.5 months (IQR 42.3–53.3), incidence of primary endpoint events was not significantly different between trimetazidine and placebo. However, some benefits were observed in subgroup of patients with diabetes. Additionally, this study showed that there were no concerns for safety issues with long term use of trimetazidine.

**Adverse events with trimetazidine**

Trimetazidine was well tolerated with lower incidences of adverse events in most patients.51 In studies with an active comparator, the dropout rates were less as compared to other antianginal drugs.52 In ATPC1 study treatment-emergent adverse events in patients with long-term use of trimetazidine were comparable to those with placebo.50 Moreover, patients with trimetazidine reported similar neurological symptoms to that of placebo (7.7%, trimetazidine [drug-induced Parkinsonism <0.1%] vs. 7.0%, placebo).50 For patients with moderately reduced kidney function and for elderly patients, the dose of trimetazidine should be reduced to 35 mg per day from 70 mg per day to allow prolonged renal elimination of the drug.51

**Clinical practice guidelines: trimetazidine recommendations for treatment of heart disease in patients with DM**

The 2019 European Society of Cardiology (ESC) guidelines51 recommend trimetazidine as a second-line treatment to reduce angina frequency and improve exercise tolerance, in patients who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, Calcium channel blockers, and long-acting nitrates (Class 2a, Evidence level B). In patients with low heart rate (HR) and low BP, trimetazidine is indicated as first-line drug to reduce angina frequency and improve exercise tolerance (Class 2b, Evidence level C). However, in selected patients, trimetazidine as an adjunct is also indicated to use as first-line treatment according to HR, BP and tolerance (Class 2b, Evidence level B).51 Management standards for stable CAD in India52 recommend trimetazidine as an alternative therapy especially when 

**Summary**

The differential presentation of CVD in DM is associated with metabolic derangements leading to deterioration of myocardial cell function. By inhibiting 3-KAT, trimetazidine shifts the energy-substrate metabolism from FA oxidation to anaerobic glucose metabolism. In several studies trimetazidine has shown to reduce the number of weekly angina attacks, mean nitroglycerin consumption per week, and time to 1-mm ST-segment depression; and improved ventricular function in patients with DM and stable CAD when used early as an adjunct to other agents. Trimetazidine was also suggested as a safe and effective anti-anginal treatment option in persistent angina in presence of HF. Peri-procedural and post-DES implantation use of trimetazidine has demonstrated improvement in the incidence and severity of angina pectoris, silent MI, angina-free survival, and PCI-induced myocardial injury. Current clinical practice guidelines recommend trimetazidine as a first-line agent for selected patients or as a second-line treatment option for angina patients. Overall, early initiation of trimetazidine as an adjunct treatment to relieve angina could be beneficial in patients with non-insulin dependent DM.

**Acknowledgement**

Authors acknowledge CBCG Global Research for providing medical writing assistance for development of this manuscript.

**References**

6. Moreno PR, Murcia AM, Palacios IF, et al. Coronary composition and macrophage infiltration in atherectomy...
Abridged Prescribing Information: COMPOSITION:

Glycomet GP 0.5: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 500 mg and glimepiride USP 1 mg.

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Glycomet GP 4 FORTE: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 4 mg.

Glycomet GP 1 FORTE: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 0.5 mg.

INDICATIONS:

Glycomet GP is indicated for the management of patients with type 2 diabetes mellitus (T2DM) when diet, exercise and single agent (metformin hydrochloride or glimepiride alone) do not result in adequate glycemic control.

DOSAGE AND ADMINISTRATION:

Dosage of Glycomet GP should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin 2000 mg and glimepiride 12 mg. Initially, 1 tablet of Glycomet GP should be administered once daily, with or without a meal. Patients should not be advised to report to their physician for transit through the gastrointestinal (GI) tract may result in the tablet remaining intact. Patients who tolerate the tablet intact should be advised to use the tablet as directed. The usual dose: 1 tablet of Glycomet GP should be administered once daily, with or without a meal. Patients should be advised to report to their physician for transit through the gastrointestinal (GI) tract may result in the tablet remaining intact. Patients who tolerate the tablet intact should be advised to use the tablet as directed.

CONTRAINDICATIONS:

In patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, metformin or any of the excipients of Glycomet GP; pregnancy and lactation; severe renal impairment (serum creatinine >5 mg/dl or 133 mmol/l, or a glomerular filtration rate ≤30 ml/min/1.73 m²); acute or severe illness which may cause tissue hypoxia (myocardial infarction, shock, cardiac/respiratory failure) hepatic insufficiency, acute alcohol intoxication, alcoholism.

WARNINGS:

Keep out of reach of children. Patients should be advised to report promptly exceptional stress situations (e.g. trauma, surgery, febrile infections) blood glucose regulation may deteriorate and a temporary change to insulin may be necessary to maintain good metabolic control. In case of lactic acidosis, patient should be hospitalized immediately.

PRECAUTIONS:

In the initial weeks of treatment, the risk of hypoglycemia may be increased and necessitates especially careful monitoring. Serum creatinine levels should be determined before initiating treatment and regularly thereafter: at least once every 6 months, whenever a change in treatment is planned, and whenever the patient is at risk of developing renal dysfunction. In patients in whom such study is planned, Glycomet GP should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and then re-evaluated and found to be normal. Use of Glycomet GP should be discontinued 48 hours before any surgical procedure.

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INDICATIONS: Metformin hydrochloride may be administered in monotherapy or as an add-on to oral antidiabetic agents for the management of hyperglycemia in type 2 diabetes mellitus (T2DM) in adults. It is also effective in combination with insulin therapy for the control of hyperglycemia in patients with T2DM who require insulin doses exceeding the total daily insulin requirements.

ADMINISTRATION: Oral tablets should be taken once or twice daily with or without meals. Tablets may be taken without regard to meals, but if it is taken with meals, it will help control your blood sugar levels. Tablets may be swallowed whole, or they may be crushed and taken with liquid. The dosage is based on your medical condition and response to therapy. The starting dose is usually 500 mg twice daily (total daily dose of 1000 mg) with each meal, with a maximum total daily dose not to exceed 2000 mg. Doses may be increased every week as needed up to a maximum of 2000 mg daily (1000 mg twice daily). If you are also taking other anti-diabetic agents, your doctor may start you on a lower dose (500 mg once daily) and increase it gradually. Careful monitoring of your blood sugar levels is essential. After meals, the tablets must be swallowed whole, without chewing, crushing, or breaking them. Swallowing the contents of the capsule whole will allow the tablets to work properly. Do not chew, crush, or divide the tablet. If you miss a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and continue your regular dosing schedule. Do not take a double dose to make up for a missed one.

WARNING: Metformin is contraindicated in patients with type 1 diabetes mellitus, insulin dependent diabetes mellitus, severe renal impairment, severe heart failure, or hepatic failure. It should also be used with caution in patients with coronary artery disease, peripheral vascular disease, or history of cerebrovascular accident.

SIDE EFFECTS: The most common side effects of metformin are nausea, vomiting, diarrhea, and flatulence. Other possible side effects include headache, dizziness, weakness, and dizziness. Severe side effects include lactic acidosis, which is a rare but potentially fatal complication of metformin use. This condition can cause symptoms such as fatigue, shortness of breath, abdominal pain, and low blood sugar levels.

ADVERSE REACTIONS: Metformin is generally well tolerated. Common side effects include nausea, vomiting, diarrhea, and flatulence. Rare but serious side effects include lactic acidosis and pancreatitis. Metformin should be discontinued immediately if any of these symptoms occur.

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¹ Ref: https://www.escardio.org/TheESC/PressOffice/PressReleases/Fear-of-COVID-19-keeping-many-those-at-risk
² Ref: https://www.escardio.org/TheESC/PressOffice/PressReleases/Fe

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Erectile Dysfunction: A Review on Prevalence, Perceptions, Diagnosis and Management in India

Basu Debasis¹, Sam Priya Ann², Fulmali Sourabh Bhimrao³, Menezes Sonia⁴

Abstract

Erectile dysfunction (ED) is defined as the inability to achieve or maintain penile erection sufficient to permit satisfactory sexual activity. The prevalence increases with age. Basic and clinical research is identifying the neurovascular and humoral control of the mechanisms. The initial evaluation should differentiate erectile dysfunction from premature ejaculation and loss of libido. Myocardial insufficiency, hypogonadism and peripheral neuropathy should be looked for. Initial laboratory investigations should be restricted to identifying previously undetected medical illness that may directly contribute to erectile dysfunction. Discussing the available options with the couple is an important aspect. If erectile dysfunction is secondary to other treatable disorders these should be treated simultaneously. When other diseases that require intervention are ruled out and if there are no contraindications, therapy may be initiated with a phosphodiesterase inhibitor. In selected cases, psychosexual therapy may be beneficial. If phosphodiesterase inhibitors are contraindicated, vacuum constriction devices may be tried. Further options include intracavernosal injection, intraurethral instillation, penile revascularization and prosthesis. The availability of effective and well-tolerated oral medications has dramatically changed the clinical approach to erectile dysfunction. Pharmacotherapy is the preferred cost-effective first-line therapy in the vast majority of patients. A stepped-care approach is followed in the primary care and family practice settings. Appropriate urological, endocrine and psychiatric referrals, and shared decision-making with the couple will enable effective treatment of men with erectile dysfunction.

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain penile erection sufficient to permit satisfactory sexual intercourse.¹ It is a highly prevalent clinical condition that affects the physical well-being and quality of life of Indian men and their partners. The term ‘impotence’ was used in the past to describe this condition; however its lack of precision and negative connotations led to it being replaced by the more specific term ‘erectile dysfunction’.

In this paper, we review the prevalence of ED in India and discuss perceptions associated with male sexual dysfunction, and provide an overview of the diagnostic approach and treatment options available for the management of ED. An improved understanding of the causes of ED, and what measures can be taken to reduce its impact will serve to improve the quality of life of patients and their partners.

Causes

The causes of ED can be broadly classified into two categories - organic or psychogenic. The International Society of Sex and Impotence Research defines psychogenic ED as the persistent inability to achieve or maintain an erection satisfactory for sexual performance, owing predominantly or exclusively to psychologic or interpersonal factors.² The importance of the psychogenic component is often understated; however self-confidence, anxiety, partner communication and conflict are important contributing factors. Organic causes of ED are physical health conditions that result in poor erectile function. The importance of organic causes of ED links to their being an early predictor of cardiovascular disease and other health complications in the future.³

It was earlier presumed that men over the age of 40 experiencing ED typically have organic causes, and younger men with sexual dysfunction have psychogenic causes, however current literature shows that organic causes such as vascular, hormonal, neurogenic and drug-related factors play a significant role in the development of ED even among younger men.⁴,⁵

Erectile Dysfunction and Comorbidities

ED can have a much higher prevalence in individuals with other comorbidities. The risk factors for conditions like coronary artery disease are similar to that of ED. The association of coronary heart disease and ED was studied using the results of the MMAS study, when it was found that endothelial dysfunction, coronary heart disease and ED are closely associated in epidemiological analyses.⁶ They found that ED and coronary heart disease have certain modifiable risk factors such as cigarette smoking and obesity. Smoking and obesity nearly doubled the likelihood of ED at follow-up (24% vs. 14%, adjusted for age and covariates, p=0.01). Similarly diabetes mellitus is also comorbidity for ED, with prevalence being two to three times more common in diabetic patients than in those without diabetes.⁷ Organic ED is caused by endothelial dysfunction; one of the mechanisms for this being oxidative stress, which is also

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Patient with self-reported ED

Medical and psychosocial history
- Identify sexual problems other than ED
- Identify common causes of ED
- Identify reversible risk factors for ED
- Assess psychosocial status

Focused physical examination
- Penile deformities
- Prostatic disease
- Signs of hypogonadism
- Cardiovascular and neurological status

Laboratory tests
- Glucose lipid profile if not assessed in the last 12 months
- Total testosterone (morning sample)

Fig. 1: Diagnostic work-up for ED

brought about by modifiable lifestyle factors. Diabetes can contribute to ED via neuropathy that may alter neural pathways leading to an erection. The risk of diabetes associated ED increases with age, duration of diabetes and the development of diabetic neuropathy.

Prevalence and Perceptions in India

The oldest reference to impotence was made in the Samhita of Sushruta, around the eighth century BC in India. An attempt was made to describe the causes of the condition, suggesting at least four, i.e. voluntary, congenital, praecox and diseases of the genital organs. In fact, the ancient Hindus believed that impotence could also be of mental origin, from intercourse with an unpleasant woman.

The prevalence of erectile dysfunction is associated with age. The Massachusetts Male Ageing Study (MMAS) was the first population-based study on ED, and is the largest study to provide information on prevalence and incidence of ED. It showed a clear correlation between ED and an increase in age. About 8% of men in their forties had complaints of symptoms of ED; about 40% of men in their sixties had similar complaints. With an increasing ageing population, estimates show that the prevalence of ED will double between 1995 and 2025 and will affect roughly 322 million men by this time period. An epidemiological study of sexual disorders conducted in a south Indian rural population through a door-to-door survey of about 1529 people (742-males; 787-females) showed that 1 in 5 males were found to have sexual dysfunction, with ED being the most prevalent (15.77%). Male sexual disorders were most prevalent from 41-60 years of age.

Despite its high prevalence and a growing repository of scientific information on ED, the perceptions and attitudes regarding sexual dysfunction are obscure. Due to the sensitivity of the topic, healthcare professionals sometimes avoid candid discussions about sexual matters, which further leads to patients not availing of the benefits of treatment for sexual dysfunction. There is a significant psychosocial impact on men with ED, and studies have showed that sexual function is closely related to one’s self-esteem. Predictors of treatment seeking behaviour, and barriers to getting treatment were studied across six countries, and the results showed that most men with ED did not seek treatment. Common barriers to seeking treatment included the perception that ED was a normal part of ageing (43.6%), waiting for it to go away on its own, (31.4%) and embarrassment in talking about the condition (26.9%). In a study examining men’s sexual attitudes towards ED, about two-thirds did not perceive ED as predominantly a medical condition. 28% regarded it as a natural consequence of ageing, 26% saw it as a phenomenon that can be settled easily, and 12% considered it a transient phenomenon that did not require medical attention.

Diagnosis of Erectile Dysfunction

A multidisciplinary approach is recommended, including a detailed medical and sexual history, psychosocial evaluation, physical examination and basic laboratory studies. In addition, obtaining information on the patient and their partners’ sexual expectations and motivations through an interview with a specialist would be a useful tool to set treatment goals. It is important to obtain the sexual history to assess the difference between ED, age related changes in sexual desire, and ejaculatory disturbances. Specific risk factors such as cardiovascular disease, diabetes, smoking, endocrine disorders (as indicated by decreased sexual desire or a hypogonadal history), pelvic trauma and blood lipid abnormalities can be identified in the general medical history (Figure 1). The medical history can sometimes reveal psychological problems that may require referral to a specialist. For example, certain indications such as deep-rooted psychiatric problems, complex endocrine disorders, lifelong ED, or CNS disorders may indicate the need for a psychiatric referral.

As per the European Association of Urology Guidelines on Male Sexual Dysfunction (2010), this is the basic work-up which must be performed in every patient with ED.

Erectile Dysfunction in Young Patients

In young patients, there is a more significant psychological impact associated with ED, and it is crucial for the treating urologist to handle the visits delicately and ensure that a rapport is built. Patients often present with unrealistic expectations of cure, and psychiatric diagnoses such as depression, anxiety or PTSD. In many cases, the patient history can reveal that the ED is situational. These patients respond well to low-dose PDE5-Is. If the history indicates a psychogenic component, it is beneficial to refer these patients to a therapist or counselor who can address their concerns and help build an alliance with the patient and their family if present.

Treatment Options

The treatment of erectile dysfunction should factor in the needs of the patient and their partner. Efficacy of therapy is best achieved by including both partners in selection of treatment plans in order to individualize treatment options based on their expectations. The initial treatment selection depends on the medical, sexual and psychological factors associated with the disease in each individual patient which can be assessed during the diagnostic work-up. It is important to consider psychotherapy or behavioural therapy in patients and their partners where erectile dysfunction occurs without organic causes. First-line therapy consists of lifestyle changes that may minimize the risk factors associated with ED. Subsequent treatment options include phosphodiesterase type 5 inhibitors (PDE5-Is), vacuum constriction devices, intra-urethral prostaglandin suppositories and surgical implant of a penile prosthesis. Refer to figure 2 for an algorithm on treatment of ED.

Non-pharmacological Management of ED

Lifestyle Modifications

First-line therapy focuses on
Table 1: Properties of Sildenafil and Tadalafil\textsuperscript{5,25-28}

<table>
<thead>
<tr>
<th>Properties</th>
<th>Sildenafil</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{max}$ (hrs)</td>
<td>30-120 mins.</td>
<td>30-360 mins.</td>
</tr>
<tr>
<td>Serum half-life (hrs)</td>
<td>3-5</td>
<td>17.5</td>
</tr>
<tr>
<td>Onset of action</td>
<td>14-60 mins.</td>
<td>16-45 mins.</td>
</tr>
<tr>
<td>Therapeutic window</td>
<td>4 hrs.</td>
<td>36 hrs.</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>PDE5 inhibitor; increased cGMP levels</td>
<td>PDE5 inhibitor; increased cGMP levels</td>
</tr>
<tr>
<td>Administration</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>41%</td>
<td>80%</td>
</tr>
<tr>
<td>Interactions</td>
<td>Interacts with food</td>
<td>Unaffected by food and alcohol</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Nitrates-containing compounds, serious cardiovascular events, α blockers</td>
<td>Same as sildenafil</td>
</tr>
<tr>
<td>Efficacy</td>
<td>&gt;65%</td>
<td>&gt;65%</td>
</tr>
<tr>
<td>Most common adverse effects (when compared to placebo)</td>
<td>Headache, flushing, dyspepsia, nasal congestion, alteration in color general myalgia, nasal congestion vision</td>
<td>Headache, dyspepsia, back ache, nasal congestion, alteration in color general myalgia, nasal congestion vision</td>
</tr>
<tr>
<td>Protein binding</td>
<td>96%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Table 2: Potential interactions of sildenafil and tadalafil via CYP450 and dose adjustments\textsuperscript{5,25-28}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism pathway</th>
<th>Drug interactions</th>
<th>Specific administrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>Major: 3A4 Minor: CYP2C9</td>
<td>• 3A4 inhibitors</td>
<td>• Barbiturates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nitrates</td>
<td>• Carbamazepine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• α-blockers</td>
<td>• Phenytoin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HIV protease inhibitors</td>
<td>• Rifampicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CYP inhibitors</td>
<td>• For patients older than 65 years, recommended 25 mg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Antidepressants (tricyclics, venlafaxine, mirtazapine)</td>
<td>• For hepatic impairment, 25 mg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Antipsychotics</td>
<td>• For severe renal impairment, 25 mg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anticonvulsants</td>
<td>• Same as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tamoxifen</td>
<td>• For mild moderate renal impairment, 2.5 mg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cyclosporine</td>
<td>• Not recommended for severe renal impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Alcohol</td>
<td>• For mild hepatic impairment, 10 mg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HIV protease inhibitors</td>
<td>• No dose adjustment required for geriatric patients</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>3A4</td>
<td>Same as above</td>
<td>• For patients older than 65 years, recommended 25 mg.</td>
</tr>
</tbody>
</table>

lifestyle changes and monitoring use of drugs that may contribute to ED. For decades, it has been assumed that reduced sexual functioning is a natural part of ageing. However more advanced epidemiological research and investigation into potential causes has shown that many causes of ED are modifiable, treatable, and can be prevented; such as sedentary lifestyle habits, obesity, and drug use.\textsuperscript{5,25-28} Diet plays a role in the improvement of sexual health, a diet rich in whole grain, fruits, vegetables, legumes, walnuts, and olive oil (commonly known as the Mediterranean diet) was associated with improvement in ED with metabolic syndrome.\textsuperscript{25} A randomized controlled study by Esposito et al. showed that lifestyle changes and healthy behaviours such as a reduced calorie diet and increased physical activity improve erectile function in obese men, and reduced sexual dysfunction by about a third.\textsuperscript{25} The Massachusetts Male Ageing Study (MMAS) showed that body mass index and television viewing were positively associated with erectile dysfunction and moderate alcohol consumption and being a nonsmoker were inversely associated with risk for erectile dysfunction.\textsuperscript{25} With the prevalence of obesity in urban India on the rise, and about 107 million people currently predicted to be obese; our health system needs to be equipped to tackle a potential increase in cases of ED.\textsuperscript{24} As per the guideline recommendations of the European Association of Urology, lifestyle changes and risk factor modification must precede or accompany treatment for ED.\textsuperscript{17}

Pharmacological Management of Erectile Dysfunction

First-line Therapy - Phosphodiesterase Type 5 Inhibitors (PDE5-Is)

PDE5-Is are most effective oral drugs in ED management and have been the backbone of pharmacological treatment since the late-1990. In India, the two commonly prescribed PDE5-Is are sildenafil and tadalafil. Sexual stimulation is necessary for the working of PDE5-Is; these agents improve sexual function, but not libido.\textsuperscript{25} Selection of PDE5-Is depends on the frequency of sexual activity and the patient’s experience taking the drug. The properties of sildenafil and tadalafil are summarized in Table 1.

Pharmacotherapy of ED in Elderly Patients

Due to a large number of drugs taken for other conditions in a geriatric population, it is crucial to assess drug-drug interactions, particularly between PDE5-Is and other drugs. As discussed above, PDE5-Is have an excellent safety profile, however there can be potentially dangerous pharmacodynamic interactions in patients taking nitrates. Concurrent PDE5-I treatment and α-blockers can cause postural hypotension. The pharmacokinetic interactions via cytochromes (CYP) should also be monitored in patients taking several drugs.Sildenafil undergoes metabolism through the hepatic isoenzyme cytochrome P450 through CYP3A4, and through the minor CYP2C9 pathway. Therefore, drugs
that alter the functioning of these enzymes can affect the concentration of sildenafil in the plasma. It is known that warfarin can lead to an increased risk of bleeding when taken with sildenafil. Likewise since tadalafil is metabolized largely by CYP3A4, all substances that inhibit this enzyme can change the pharmacokinetic profile of the drug. The table 2 summarizes some potential interactions of sildenafil and tadalafil via CYP450 along with dose adjustments in case of certain comorbidities:

**Second-line Therapy**

As per guideline recommendations, patients who have not responded to phosphodiesterase type 5 (PDE5) inhibitor therapies should be informed of the benefits and risks of other treatments. Second-line self-injection with vasoactive agents, vacuum erection devices, and surgical approaches with inflatable penile prostheses offer ED management with high potential for patient and partner satisfaction. Training must be provided to physicians on self-administration of the injection. Intracavernous injection therapy has shown treatment satisfaction rates of 87-93.5% in patients and 86-90.3% in their partners. However, the complications include penile pain, prolonged erections, priapism and fibrosis, leading to a high discontinuation rate. Newer delivery mechanisms for alprostadil have emerged, making it more user-friendly for patients. These can be in the form of a pen-device similar to insulin dispensers.

Vacuum constrictive devices consist of three components: a vacuum cylinder, a pump and constriction rings. They work by creating a negative pressure to draw blood into the penis, which is maintained using the constriction rings at the base of the penis. These devices are cost-effective. However, the erections created are unnatural, and users report a cold penis sensation when using these devices. Reasons for dissatisfaction were reported as penile numbness, penile pain, delayed ejaculation and inconvenience.

**Third-line Therapy: Surgical Interventions**

Third-line therapy for ED consists of surgical implantation of a penile prosthesis if patients are nonresponsive to pharmacotherapy or if they want a more permanent solution. Once the prosthesis is implanted, the tissue is permanently changed and no further smooth muscle relaxation can occur. There are two types of penile prostheses available, either semi-rigid or inflatable (two-piece or three-piece). The three-piece inflatable device produces more natural erections, whereas the two-piece device has fewer mechanical complications and has a simpler surgical implantation procedure. The semi-rigid prosthesis results in a constantly rigid penis, and is typically chosen in patients that are older with less frequent intercourse. Possible adverse events associated with surgical interventions for ED are infections, which occur in 1-2% of patients, auto-inflation, and erectile length loss (particularly in patients with Peyronie’s disease and after radical prostatectomy). Guidelines recommend that surgery should be reserved for men in whom less invasive, reversible treatment is unsuccessful or contraindicated. (26) Other surgical treatments for erectile dysfunction include arterial bypass procedures, however these are only recommended for patients who have had traumatic injuries of penile arteries (and can potentially lead to cure of the erectile dysfunction).

**Conclusion**

ED is highly prevalent among men, particularly with an ageing population. The management of ED in India must include establishing respectful, healthy communication regarding sexuality, given the sensitive nature of the topic of erectile dysfunction. There is a definite need for greater awareness about sexual disorders to increase knowledge and influence treatment-seeking behavior. We must also consider the increase in risk factors for ED such as obesity, sedentary lifestyle and diabetes mellitus, due to which we can expect to see an increase in the prevalence and impact of ED. A multidisciplinary approach to diagnosis and treatment is required, taking into account the desires of the patient and their partner so that quality of life serves as the endpoint for treatment.

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References


Palliative and End of Life Care in India – Current Scenario and the Way Forward

Smriti Bag1, Sumita Mohanty2, Nerbadyswari Deep3, Naveen Salins4, Sonamali Bag5

Abstract

India, being home to one –sixth of the world’s population has a huge burden of suffering from life limiting diseases. It is estimated that in India the total no. of people who need palliative care (PC) is likely to be 5.4 million people a year. Though PC was introduced nearly 30 years ago, it is still in its infancy with less than 1% of patients having access to PC. India ranks at the bottom of the Quality Of Death Index in overall score. Obstacles are too many and not only include factors like population density, poverty, geographical density, restrictive policies regarding opioid prescription, workforce development at base level but also limited national PC policy and lack of institutional interest in palliative care. However there has been a steady progress in the past few years through community owned PC services. South Indian state of Kerala which has 3% of Indian population, stands out in terms of achieving coverage of palliative care. On the national level recent years saw several palpable changes including the creation of a National Programme for Palliative care and also the Parliament amended India’s cumbersome Narcotic Drugs and Psychotropic Substances Act (NDPS) thus overcoming many of the legal barriers to opioid access.

Initially WHO and now the IAPC has taken over the responsibility of spreading the message of palliative care in India. But we still have a long way to go. Education of the professionals and sensitization of the public through awareness campaigns are vials for improving access to PC in India. Process of implementing PC plan into action requires strong Advocacy, political support and integration across all levels of care.

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Introduction

India with a 1.2 billion population has a huge burden of suffering from life limiting diseases. Less than 1% of its population has access to pain relief and palliative care. The ‘Quality of death ‘index measures the current end-of-life care environments across 40 countries. The report identifies poor access to pain relief, a lack of palliative care at national level and cultural taboos as the main barriers to countries providing a good ‘Quality of death ‘and thus a good quality of life at the end of life. India ranks at the bottom of the Quality of Death Index in overall score and scores badly on many other indications. Furthermore, India ranks poorly regarding the knowledge of existence of hospice care, reflecting a general lack of awareness.

What is Palliative Care

The World Health Organisation defines palliative care (PC) as an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through prevention and relief of suffering by means of early identification, assessment and treatment of pain and other distressing problems – physical, psychosocial and spiritual. Palliative Care starts as supportive care from the time of diagnosis of life-threatening illness and continues as terminal care if illness progress until death of the patient. In fact the need for emotional support may be most when the diagnosis is broken to the patient. It even extends beyond the death of the patient which is known as Bereavement Care. In PC the primary aim is not to prolong life but to make life which remains as comfortable as possible. Hence the goal is to improve quality of life (QOL) of both patients and families by responding to pain and other distressing symptoms as well as to provide a good nursing care and psychosocial and spiritual support.

Hospice care is comfort care without curative intent whereas PC is comfort care with or without curative intent. Objective of both hospice and palliative care is pain and symptom relief but the goal tends to be different. In hospice care goal is to provide comfort and QOL as well as to avoid aggressive futile care. PC involves an interdisciplinary multi-dimensional team including the patient, family, palliative medicine physician, primary care physician, nurses, social worker, pharmacists, spiritual leader, counsellor, speech, physical and occupational therapists, dieticians and volunteers. It can be given in patient’s home, at hospital, nursing home or private hospice facility.

PC improves health care quality in three domains: the relief of physical and emotional suffering, improvement and strengthening of the process of patient-physician communication and decision making and assurance of co-ordinated continuity of care across multiple health care settings: hospital, home, hospice and long-term care.

Need of Palliative Care in India

It is estimated that in India the total number of people who need PC is likely to be 5.4 million people a year, stressing on the need to expand the coverage of PC services and integrate services.

1. Late diagnosis and inadequate pain relief : It is estimated that in India around 1 million people are diagnosed with cancer every year with over 80% of cancer presenting at stage 3and4 when treatment is less effective and palliative care becomes absolutely essential. There is also a sizable number of patients with HIV/AIDS. It has been estimated that 60% of the people dying annually will suffer from prolong illness. That means there will be a sizable number of aged who will be needing palliative care. In fact that according to WHO, there were 60 million people above 65 years of age in 2010 in our country and that this figure will increase to 227 million by 2050 constituting 20% of the total population. Non-communicable diseases (NCD) including injuries account for 62% of disease burden as on 2004 and contribute to half (50%) of all mortality in India. Longterm care for such patients is emerging as a major health care issues in India. So all of them are in dire need of palliative care. Less than 3% of India cancer patients have access to adequate pain relief.

2. Lack of palliative care facilities: In India the coverage of PC services is extremely patchy, services being concentrated in large cities and regional cancer centres with exception of Kerala, where the services are more widespread. The problem of inadequate pain relief is owing to the poor availability of morphine, lack of skills among professionals to prescribe morphine, fear of side effects and a fear of addiction of morphine among professionals, patients and their family.

3. Poor quality of death index: The economist intelligence unit has given India the lowest ranking in end-of-life care across the world among 40 countries. In India there is very little awareness about palliative and end-of-life care which is complicated by the perception that Hospice care is often

![Fig. 1: Palliative care development in India and world](image-url)
associated with giving up.

4. Lack of medical infrastructure: The majority of the urban poor to rely on government run hospitals, which are overcrowded and is the least of their priorities. It is natural that they would devote their limited resources to patients who can be cured. Again in the rural areas, the doctor and hospitals are few and far apart. The vast distance and poor transportation facility prevent these patients from getting medical relief.

History of Palliative Care

Hospices were originally the places of rest for the travellers/pilgrims in 11th century. In 17th century a religious order established hospices for the dying poor, where they offered food, clothing, shelter as well as minimal medical care. Modern hospice is relatively a new concept but originated and gained momentum in UK after the foundation of St. Christopher’s hospice in London in 1967.12

Dame Cicely Mary Saunders is the founder of modern Hospice movement, who revolutionised PC in India and helped people to die with dignity free from fear and pain.12 She was originally a medical social worker, then she became a registered nurse, finally advanced her carrier to become a palliative care physician. She got inspired by a polish patient David Thasma who was dying from cancer to open St. Christopher’s hospice. She had three aims for foundation of hospice: to provide care in both hospice and patient’s home, to encourage teaching and training of doctors/nurses to promote research and in to the care and treatment of the dying. In 1986, Prof. D’Souza opened the first hospice in India ‘Shanti Avedna Ashram’.

Timeline of Palliative Care Development in India (Figure 1)

Concept of Palliative care is a relatively new in India, having been introduced over past 30 years. Since then hospice and palliative care services have been developed through the efforts of committed individuals including Indian health professionals as well as volunteers in collaboration with international organisations and individuals from other countries.13 The Government of India initiated a National Cancer Control Programme in 1975 which was modified in 1984 to make pain relief one of the basic services to be provided at the primary health care level.14 Palliative care was born in India as the Shanti Avedna Sadan in Mumbai, a hospice in 1986.15 Over the next five years it established two more branches, one in Delhi and one in Goa but patients outside these institutions had no access to PC. Two major developments occurred in 1990s. One was the formation of Pain Palliative Care Society (PPCS) in Calicut, Kerala in 1993. The other was the formation of Indian Association of Palliative Care (IAPC) in 1994. PPCS was formed as a registered charitable trust based on purely volunteerism which grew up as an outpatient service latter adding on a home visit programme with the help of WHO in 2010, (Neighbourhood Network in Palliative Care).16

PC was initiated in Gujarat under the department of Anaesthesiology at Gujarat Cancer and Research Institute (GCRI), a regional cancer centre in western India. One of the important steps in the history of palliative care development in India also began from here, formation of Indian Association of Palliative care (IAPC) with the help of WHO.17 Over the next few years, in the later part of 1990s, several new palliative care centres were started such as the Guwahati Pain and Palliative Care Society in Assam, Jivodaya Hospice in Chennai, Can support in Delhi, Lakshmi palliative Care in Chennai and Karunasraya hospice in Bangalore. Some regional centres like Trivendrum, Bangalore and Delhi which already had pain management programmes also included PC in their service. Though every year few centres were added, the growth was limited considering the enormity of Indian population. In 2003, a Non-Government Organisation called Pallium India under the chairmanship of Prof. M.R. Rajagopal was initiated with the help of WHO to improve access to PC outside Kerala. In 2008, Kerala became the first state to declare a palliative care policy integrating it into health care. At this time, access to opioids was not easy. In 1985 Narcotic substances and psychotropic substance (NDPS) Act of India was formed which had a negative impact.18 In the 13 years which followed the enactment of the NDPS Act, morphine consumption in the country fell by an alarming 92% from around 600 kg to mere 48 kg. In 1997, India’s per capita consumption of morphine ranked among the lowest in the world (113th of 131 countries). During the same period, global consumption of morphine had increased by 437%.19 The Government of India in 1998 gave instruction to all government to amend their narcotics regulation, simplifying them. But the response from state government was so poor such that workshops were done in many states to improve the situation.

If we take morphine consumption in the country as the index for access to palliative care, there has been little progress in last few years as can be seen in the Figure 2.20 In 2000, the peak was caused by large scale purchase of morphine by the Government of India using funds from WHO for free distribution to Regional cancer centres. The bulk of it was never used and was eventually destroyed after expiry date. The drop in consumption from 2002 to 2006 was caused by a breakdown in the Government opium and alkaloid factory following which production of

![Fig. 2: Consumption of morphine in India, 1998-2014 (Courtesy: Dr. MR Rajagopal, Pallium India)](image)
morphine was reduced.

Current Facilities and Provisions

In a study published in 2008\textsuperscript{13} MC Dermott E et al. identified 139 palliative care services in India serving 1.2 billion people out of which 83 centres in Kerala which contains 3\% of India’s population. These services are usually concentrated in large cities and regional cancer centres with the exception of Kerala where it is more widespread. As of 2014 in Kerala, more than 170 institutions stock and dispense morphine. NNPC in Kerala is often cited as only “beacon of hope” contributing to two third of India’s palliative care services and one of the largest network in the world. India has a huge burden of suffering from life limiting diseases. It is estimated that 5.4 million people in a year are in need of palliative care in India.

Challenges to Progress of Palliative Care in India

1. Challenges before us is to reach people living with chronic incurable diseases in the background of poverty and apparent lack of resources. When chronic life-threatening illness strikes, it becomes a crippling blow for them. In low resource settings where the number of people requiring care is high and the number of doctors and nurses available to provide care is low, PC can be effective by involving community caregivers and volunteers supervised by nurses trained in palliative care. Therefore there is crucial need of community or home-based palliative care with care being taken to the door step of the patient.\textsuperscript{21} A study conducted at Cipla palliative care in Pune showed that 83\% of people in India would prefer to die at home surrounded by their loved ones.\textsuperscript{22}

Home based PC is care provided to people with chronic debilitating and progressive diseases that are potentially life limiting (cancer, end stage cardiac, renal and respiratory diseases, HIV/AIDS and chronic neurological and psychiatric disorders) in the home or live-in environment of the patient.

Advantages of home-based PC are provision of comfort of patients in familiar surroundings, increased effective care and spreading awareness in the community. It can also be cost-effective as it doesn’t entail doctor and nurses fees and travelling to the hospital repeatedly for follow up visits and unnecessary investigations and treatments. However, due to lack of PC at end of life, patients receive inappropriate aggressive medical interventions at the end of life which drains the resources of patients and family and has forced up to 78\% of patients in advanced stages of illness to leave hospital and ICUs against medical advice (LAMA). 80-85\% of the population in India spend out of pocket for their health related expenses. Around 40-60 million families are becoming poorer every year to increasing health related costs and most of these costs related to aggressive medical interventions at last few days of life.\textsuperscript{23} This ultimately results in “holistic suffering” instead of “holistic care” for the dying person and the family.

2. Recent trends in health care decreases the chances of cancer patients having access to PC. These range from the limited availability of PC services to the philosophy of patient care that dominates our health care system that is mostly disease oriented.

3. Another aspect of care that is currently lacking in current health care system is communication about patient goals and preferences for care. When patients are asked what kind of care they want when serious life-threatening diseases occurs, their preferences include pain and symptom control, avoidance of prolongation of the dying process, sense of control, concern for family burden and an opportunity to strengthen relationships with loved ones. However research does not demonstrate that patient’s preferences are adequately met. An early and effective communication help both patient and family digest and accept the diagnosis and gives them a direction to move in.\textsuperscript{24}

4. Consent for PC must be obtained from competent patients and should not be assumed. Full disclosure is required so that the patient realises that he or she will be cared by a multidisciplinary team.

5. Limited evidence for palliative care needs more of studies that will provide strong evidence to guide better decisions regarding symptom management, different health care models, decision-making approaches about treatment options, communication on sensitive topics such as death and support for family/caregivers. In fact evidence based palliative care is need of the hour.

6. Medical insurance does not play a significant role in hospice and palliative care provision in India

Milestones Achieved

1. Designation of the Institute of Palliative Medicine(IPM) at Calicut, Kerala as a WHO collaborating centre for community participation in palliative care and long term care in 2010 and pallium India’s Trivendrum Institute of Palliative Sciences(TIPS) as a WHO collaborating centre for training and policy on access to pain relief in 2012 were two significant events contributing to further progress.\textsuperscript{26}

2. Recognising the education of professionals was the key to improvement of PC in the country. PC activists after several trials the six week course in ‘Essentials of palliative care’ for doctors and nurses started by PPCS became widely popular and has been replicated in 33 institutes in the country at present. One year fellowship programme was also started by several institutes. Continued advocacy by PC community in 2010Medical Council of India accepted palliative medicine as a medicine speciality and announced a postgraduate course in the subject. Subsequently in 2012,\textsuperscript{25} the first MD course was started at the Tata Memorial Hospital, Mumbai with two places per year. Subsequently IRCH, New Delhi and recently GCRI, Ahmadabad has started the course.

3. NDPS Act has been amended by the Parliament in February 2014\textsuperscript{26} which enables Registered Medical Institutes (RMI) to procure morphine by obtaining a single license for the state drug controller rather than five. This is a huge step forward.

4. National Programme in Palliative Care (NNPC), twelfth 5 year plan in 2012 makes a special provision for PC is an important and essential part of cancer care therapy. At least 10\% of the budget needs to be earmarked for their services at all level of cancer care. For palliative care, there will be dedicated 4 beds, at the district hospital. Doctors, nurses and health workers will be trained in basics of palliative care.

5. Indian society of critical care medicine as instrumental in initiating decision on EOLC (end-of-life care) in advanced critically ill patients. Initial work published in 2005, highlighted on
limiting life-prolonging interventions and providing PC to end of life, in intensive care units. The consensus ethical position statement on guidelines for end of life and palliative care in Indian intensive care was published in 2012. Recently in March 2019, KMC, Manipal published a document on “guidelines on limitation of life sustaining treatment” named as BLUE MAPLE by Salins N et al. It is an attempt to improve quality of care of the dying with an ethical framework and through a professional and family/patient concuss process. Before life ends, understand and evaluate the choice of medical treatment offered, methodised action plan for limitation of life sustaining treatment and end of life care.

6. If we take per capita consumption of opioids as a criterion for access to PC, this has been on plateau for many years now. There has been a lot of progress in PC in India but the fact remains that despite the passing of almost 30 years of palliative care activity in the country, even today it reaches only about 1% of the people in India.

The Way Forward...

1. Each state need to develop its own policy that suits its needs and its social and cultural background. Community models for the provision of home-based PC need to be implemented all over the country. Empowerment of family members and volunteers to be effective palliative caregivers might prove to be the most realistic approach for meaningful coverage, especially in rural areas

2. A change in health care to include PC early in the course of cancer care can begin to familiarise the family with PC services, start communication about death earlier in the course of cancer treatment and provide an opportunity for discussion of goals of care among the physician, patient and family.

3. Though some major barriers to access to PC in India have been overcome but implementation of created policies and laws still requires massive efforts by both the government system and Non-Government Organisations. Five years after the amendment of NDPS Act in 2014 opioids like oral morphine remain inaccessible for 98% of the population of India.

4. There is an acute shortage of trained PC physicians, so clinicians should attend local and national presentations on PC to increase their knowledge base.

5. Introduction of palliative medicine into the curriculum of undergraduate education of doctors and nurses is recommended as an efficient way to broaden the base of PC coverage at the national level.

6. Research in PC is very much essential to deliver a high quality palliative care. In fact many of the developments like megestrol for cancer cachexia, bisphosphonates for pain in bone metastasis, opioids for palliation of breathlessness in terminal illness have come from research in palliative care.

Future scope for PC in the country lies in the provision of facilities and medicines, sustainability of services, support from the community, government, media and team building for palliative care. Recent declaration by the WHA (World Health Assembly) asking all member states to integrate PC with routine health care comes as a major tool in advocacy and hopefully will boost the current efforts.

References


Coronavirus Disease-19 (COVID-19) and Heart Failure: Current Perspective

Avinash Mani¹, Vineeta Ojha², Manoj Kumar Dubey³

Abstract

COVID-19 has been the biggest pandemic which the world has seen in recent times. The SARS-Cov-2 infection has the potential to cause multi-organ dysfunction. Though the virus predominantly affects the lungs, it can affect the heart in myriad ways. Heart failure (HF) is one such complication caused by the virus, both in patients with and without cardiovascular diseases. Different mechanisms have been proposed for the pathogenesis of HF in COVID-19 ranging from direct viral injury to indirect immune mediated damage. Patients can have different clinical presentations with either acute heart failure or chronic heart failure. Early recognition and prompt management is the need of the hour to prevent any mortality and morbidity.

Summary: COVID-19 can affect the heart in many ways. This article describes the mechanisms, clinical presentations and management of heart failure caused by COVID-19 infection.

Introduction

The ongoing Coronavirus disease-2019 (Covid-19) pandemic has affected around 200 countries worldwide. Till date, the total confirmed cases worldwide have crossed the 2 million mark with around 150,000 deaths. Covid-19 predominantly affects the respiratory system causing severe pneumonia/acute respiratory distress (ARDS). Varied effects on cardiovascular system are seen in form of acute coronary syndrome, myocarditis and heart failure. Majority of these patients have comorbidities with hypertension being the most common.¹ Heart failure is a global health problem with significant mortality and morbidity. The ongoing pandemic has the potential to exacerbate this problem, thus causing significant burden on health resources which are already saturated due to high load of covid patients.

Pathogenesis

SARS-CoV-2 is a novel coronavirus which bears 80% similarity to the genetic structure of the SARS-CoV which caused the SARS outbreak in 2013.² The SARS-CoV-2 virus contains multiple glycoprotein spikes (S protein) on their surface giving it a halo like appearance. The viral structure of the novel coronavirus has evolved from the SARS-CoV of 2013, thus having increased stability and increased affinity for receptor binding.³ Human angiotensin converting enzyme 2 (ACE 2) receptor has been identified as the target SARS-CoV-2.⁴ The host protease TMPRSS2 is responsible for priming the spike S protein which facilitates viral entry into cells.⁵ ACE 2 is present on a variety of tissues including heart, lung alveolar epithelial cells, kidney and gastrointestinal system. ACE 2 receptors are localized on the cell membrane and their turnover is increased in stress states/pro-inflammatory conditions like heart failure. Circulating ACE2 levels are increased due to cleavage of protein from membrane by ADAM17 protease.⁶ This increased turnover and expression of ACE2 on cardiac cells makes it susceptible to viral infection. SARS-CoV-2 can lead to myocardial injury via both direct and indirect mechanisms.

1. Direct mechanisms: SARS-CoV-2 can directly enter cardiomyocytes via ACE2 receptors. Under normal circumstances, ACE2 protein acts on angiotensin II and converts it to angiotensin 1-7. Angiotensin 1-7 has vasodilatory and anti-inflammatory action, thus balancing the pro-inflammatory effects of angiotensin II. During Covid-19 infection, the virus binds to ACE2 protein and enters the target cell. Simultaneously, it also causes downregulation of overall ACE2 activity of the cell.⁷ This downregulation of activity prevents ACE2 from acting on angiotensin II which causes unopposed activation of RAAS axis. This predisposes to a pro-inflammatory state associated with adverse cardiac remodeling, fibrosis and cardiomyocyte damage. Post viral entry, viral replication occurs inside cardiomyocytes and assembled virions are released, thus disabling or destroying the host cell in the process.

2. Indirect mechanisms

1. Pro-inflammatory cytokine mediated damage: SARS-CoV-2 infection triggers a dysregulated immune response by causing depletion of lymphocytes with marked reduction in number of CD4+/CD8+ T lymphocytes.⁸ There is increased activation of mononuclear cells (macrophages) which produce pro-inflammatory cytokines like Interferon-beta, TNF and IL-6. These cytokines recruit more inflammatory cells and induce apoptosis of T-lymphocytes.⁹ There is increased activation of mononuclear cells (macrophages) which produce pro-inflammatory cytokines like Interferon-beta, TNF and IL-6. These cytokines recruit more inflammatory cells and induce apoptosis of T-lymphocytes.⁹ There is increased activation of mononuclear cells (macrophages) which produce pro-inflammatory cytokines like Interferon-beta, TNF and IL-6. These cytokines recruit more inflammatory cells and induce apoptosis of T-lymphocytes.

Dysfunctional antibodies, not effective in neutralizing the virus, perpetuate the immune response. This dysregulated activation of macrophages produces abundance of pro-inflammatory cytokines –
producing a cytokine storm.11

Inflammatory cytokines like TNF, IL-6, IL-18 cause damage to cardiac myocytes. They induce cardiac myocyte hypertrophy and re-expression of fetal gene program leading to adverse cardiac remodeling. Increased levels of proinflammatory cytokines can lead to transient and sustained contractile dysfunction via nitric oxide mediated mechanisms.12 Cardiomyocyte apoptosis is also induced by activation of extrinsic and intrinsic apoptotic pathways.13 Extracellular matrix remodeling via induction of cardiac fibroblasts and matrix metalloproteinases is also noted.14 In patients with heart failure, inflammatory cytokine levels are already elevated. Superimposed viral infection will exacerbate the overall cardiac damage and can worsen heart failure symptoms.

ii. Microvascular dysfunction: Increased cytokine production due to SARS-Cov-2 infection can lead to vascular endothelial damage causing microcirculatory dysfunction. ACE2 receptors localized on the pericytes of cardiac cells promote viral infection which can lead to endothelial dysfunction causing micro-infarcts. This exacerbates any pre-existing tissue damage and reduce overall cardiomyocyte function.

iii. Hypoxia mediated damage: SARS-Cov-2 primarily affects the respiratory system and the resultant hypoxemia causes tissue damage in various organs leading to multi-organ dysfunction. Hypoxia induces production of hypoxia inducible factor (HIF) which modulates the transcription of various genes. HIF regulates nitric oxide production and macrophage activation which can affect cardiac remodeling.15

The pathogenesis of heart failure in Covid-19 has been summarized in Figure 1.

**Epidemiology and clinical presentation**

There is scarce data at present regarding the incidence of heart failure in patients suffering from Covid-19. Majority of data available comes from the outcomes of patients hospitalized with Covid-19 related pneumonia. In a study cohort of 191 patients who were admitted with SARS-Cov-2 in China, heart failure was noted in 23%(n=44) patients during the hospitalization period. The incidence of heart failure was significantly higher in non-survivors as compared to survivors (52% vs 12%, p<0.0001).16 Patients who had cardiovascular disease at baseline were at higher risk of having complications and in-hospital mortality.17 In a cohort of 274 cases which included both deceased and recovered patients, heart failure was noted in 34% with prior history of cardiovascular disease whereas 19% without any history of cardiac disease developed de-novo heart failure.17

Patients with Covid-19 can present as:

i. Acute heart failure: Patients without underlying cardiac disease can present with acute decompensated heart failure resulting from myocarditis. De-novo presentation with cardiogenic shock has also been reported in patients infected with SARS-Cov-2.18

Heightened sympathetic stimulation as a result of the infection can precipitate stress cardiomyopathy.

ii. Exacerbation of chronic heart failure – Patients with underlying cardiovascular disease (CVD) are at high risk of contracting Covid-19. They may have exacerbation of pre-existing heart failure symptoms. Heart failure patients may also have ventricular arrhythmias either due to virus induced myocardial injury or underlying structural heart disease.

Significant majority of patients admitted with Covid-19 have baseline cardiovascular risk factors and have higher mortality rates.19 Covid-19 affected patients who have baseline cardiovascular disease and elevated troponins have highest mortality as compared to those without history of cardiovascular disease(69% vs 37%,p<).20 Progressively increasing troponin and BNP levels is a bad prognostic marker as it portends to higher chance of mortality. Heart failure patients also have elevated levels of inflammatory markers (ESR, CRP, LDH) which have been shown to correlate with disease severity.20

**Diagnosis**

History and clinical examination point to the diagnosis. Echocardiographic features of reduced LV function (LVEF 40%) and global hypokinesia point to diagnosis of myocarditis whereas apical ballooning with basal hypercontractility point towards stress cardiomyopathy. Biomarkers like troponins and natriuretic peptides are frequently elevated and may indicate severity of disease. Cardiac magnetic resonance (CMR) imaging can be used to detect presence of myocardial edema (T2 hyperintense) as well as presence of necrosis and scar (Late gadolinium enhancement). CMR can also be helpful in differentiating viral myocarditis from stress cardiomyopathy.

**Management**

Treatment strategies are tailored according to the clinical presentation of the patient.

i. Management of Covid related heart failure: Acute heart failure patients will require inotropes for stabilization of hemodynamic status. Diuretics will form the mainstay of therapy. Patients refractory to diuretics may also need vasodilator therapy. In patients with suspected myocarditis, pulse steroid
(intravenous methylprednisolone 1 gm x 3 days) therapy is needed to control disease activity. Patients having malignant arrhythmias associated with heart failure will need anti-arrhythmic drugs and DC cardioversion if necessary. Fluid balance needs to be maintained in a proper manner.

ii. Management in pre-existing CVD: Chronic heart failure patients need to be continued on guideline directed medical therapy (GDMT) including beta blockers, ACEI/ARB and mineralocorticoid receptor antagonists. Intravenous diuretics may be needed in patients with volume overload. Use of drugs which can precipitate HF like NSAIDs should be strictly avoided.

iii. Covid-19 specific therapy: A number of drugs are being tried for specific therapy. Hydroxychloroquine,21 lopinavir/ritonavir and remdesivir22 have been tried for their anti-viral properties with modest efficacy. In patients suspected to be having cytokine storm, IL-6 inhibitors (tocilizumab) have been tried for their anti-viral activity. Patients can have de-novo heart failure or exacerbation of pre-existing heart failure. Prompt diagnosis and management is necessary to prevent morbidity and mortality.

Compliance with Ethical Standards

Conflict of interest: None of the authors have any conflict of interests to declare.

Ethical approval: This article does not contain any studies performed on human participants by any author.

References


Experience Cough Free Zone

In Dry and Allergic Cough
Grilinctus®
(Dextromethorphan HBr 5 mg, Chlorpheniramine Maleate 2.5 mg, Guanfacine 50 mg and Niacinamide 50 mg/5 ml)

Grilinctus-L®
(Levodropramine Fumarate Eq. to Levodropramine HCl 20 mg/5ml)

In Productive Cough
Grilinctus-BM®
(Terbutaline Sulphate 2.5 mg and Bromhexine HCl 4 mg/5ml)

Grilinctus-LS®
(Levodropramine 1 mg, Ambroxol hydrochloride 50 mg, Dextromethorphan 50 mg/5ml)

SUGAR FREE
To Side the Patients or their Family Members: A Doctor’s Eternal Dilemma

B Sadananda Naik

Abstract
The family members of the patient play a significant role in the medical management. However, physician’s primary responsibility is towards his patient and not to heed to the requests of the family members. All the medical professionals should be well equipped to face multiple dilemmas in their carrier.

“Doctor, please advise my mother to defer her travel plan to join the marriage party at Mumbai this week end”, pleaded one of my patient’s son. He had arrived few minutes before the stipulated appointment time and managed to sneak into my consultation room. His, seventy year old mother had got discharged from the hospital a week back following the treatment for ischaemic heart disease with heart failure. Their family was supposed to attend a wedding ceremony at Mumbai in the week end. The patient was adamant and insisting that, she be included in the family team travelling to Mumbai. But, all her family members were very apprehensive to permit her to accompany them, in view of her cardiac ailment.

I said, “let me check her and will decide what best can be done” as I did not want to lie to my patient and betray her trust. On examination, I found her alright but when I asked about her overall improvement, she said, “I am better by 75%” but she did agree that there was still some limitations in her daily physical activities. I advised her to adhere to the medications prescribed, avoid strenuous physical activities and instructed her to visit me after a fortnight. I consciously, avoided talking about her travel plan to Mumbai. As the mother and son duo about to leave the consultation room, I just over heard them talking, “when he has forbidden me to carry out any physical activities, how can I ask him about my Mumbai travel?” muttered the old lady, on being questioned about the doctor’s permission to travel.

Hence, the day was saved for me. However, it was quite difficult for me to forget the incident. Several doubts started creeping up my mind like, what if the patient was totally fit to travel. Am I not guilty of betraying the trust of my patient for the sake of full filling her family member’s undue request? And what if, I had allowed the lady to travel and her ailments worsened at Mumbai, as feared by the family?

This kind of strange requests coming from the family members of the patients are not new to the doctors practising in India. The family members do approach the doctors with all sorts of strange requests with the pretext of “in the best interest of the patient’s health”. Name a few, “not to divulge the medical diagnosis to the patient”, hide the fact that “the fellow passengers are no more” to the lone survivor of road traffic accident, recouping in the hospital etc. etc. These are very tricky situations for the doctors and there is always a dilemma, whether to tell the truth to the patient or act as per the request of the family members. In the back drop of glorious uncertainty of the medical science, the doctors are always at the receiving end, irrespective of side favoured and the final outcome of our action.

The family members of the patient are very valuable members of the health care team. They are useful source of patient’s health information and play a key role in planning of suitable treatment. A good rapport between the physician and the family members of the patient is crucial, in handling complex social, medical, emotional issues involved in health care. However, physicians should remember that their primary responsibility is towards their patient and not to address the issues raised by the family members. It is the primary duty of the physician to provide the opportunity to the patient to express himself in the absence of family member, if the situation arises.¹

Medical professionals should be equipped to handle ethical, moral, legal dilemmas in their carrier. Most of the times these dilemmas are very complex and contradictory to each other as well and there are no readymade formulae available. Moreover, there are no win win situations and everyone involved, end up losing something. But, all the decisions of the medical professionals should be patient centric and in the best interest of the patient even though they are not fair to everyone involved. Only then, the medical professionals would be in a position to defend and justify themselves and their actions, if at all there is a feeling of mistrust regarding the medical management amongst the people involved including the patient and his family members.²

References

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A Rare Neurotoxic Red-tailed-skink Bite

Meena Kumari¹, Raj Kumar¹, Rathna Kumar², Abinaya³

Case Report

35 years old female, hailing from Senkottai, along the Western ghats, Tirunelveli, came to the hospital with history of skink bite. Patient was sleeping on the floor and a skink somehow entered the bedding, bit the patient behind her left knee. Aroused by pain she found the skink still biting and removed it. Patient developed dyspnea after 1 hour and she was brought to the hospital. The relatives brought the skink along (Figure 1). The skink which bit the patient was brought by the patient’s attender and was identified as Lygosoma punctatum. The patient was not a known diabetic or hypertensive. On admission, patient was conscious, oriented, pulse-98/min, BP- 120/80 mmHg, SP02 95%. Examination of the cardiovascular system was normal. Lungs were clear but respiration was shallow. There were no bleeding manifestations. Patient had bilateral complete ptosis (Figure 2) and in view of impending respiratory failure, she was intubated and connected to ventilator. She moved all 4 limbs, plantar was bilaterally flexor. She was treated with neostigmine and atropine as for a neurotoxic snake bite. She showed modest improvement over 3 days. Unfortunately she succumbed to pneumonia, sepsis and multiorgan failure on day 7.

Investigations: TC-22300 Cells/cumm, DC: Polymorphs 92%, lymphocytes 3%, eosinophils 5%Hb 13%, platelet count 3.04 laes/cumm. Renal and liver function tests were normal initially. ECG was normal. Chest X-ray showed right lower lobe consolidation probably ventilator associated.

Discussion

Skinks are lizards belonging to family Scincidae. They are insectivorous and usually do not harm humans. There are 14 genera of skinks of which Mabuya beddomi, M.multifasciata (Travancore ground skink), Eutropis multifasciatus (common Indian skink), E. macularia, E. bibroneii are the common ones found in Tamilnadu. Bites are rare, though it may result in bleeding from the wound of the bitten animal.

The composition of the oral secretion is not known. It is also unclear whether the bite is venomous or not. There are two species of venomous lizards in the world. Both belong to the genus Heloderma and found in Americas. Only animal studies are available related to the lizard venoms. Helodermatid venom is similar to elapid venom. The Heloderma venom is a mixture of protein and nonprotein substances, including serotonin, phospholipase A 2, bradykinin releasing substances and hyaluronidase. Two substances -gilatoxin and helothermine are neurotoxic. Gilatoxin appears to be a presynaptic neurotoxin and produce hypothermia, lethargy, convulsions, paralysis of limbs and death in mice. Helothermine is a kallikrein like substances which produces hypothermia, blocks calcium channels and target the ryanodine receptors.

Conclusion

This case has been presented to increase the awareness of neurotoxic red tailed skink bites and to provoke discussion regarding treatment with neostigmine. It was a well-known fact in the villages that a skink bite is rare but lethal, especially that of a red tailed skink. There is not much literature about the clinical features and treatment aspects of skink bite.

References

Acquired Haemophilia

Krishnarathanam Kannan1, Thayumanavan Girija2, Shiva Kumaran Gurusamy3, Chaithanya Dwarkanathan4

Case summary

A 44 year old male presented with a short history of extensive ecchymosis over the upper and lower limbs and anterior abdominal wall as shown in the figures 1-3. At presentation his haemoglobin was 3 g/dl. He had no past history of any bleeding diathesis in his childhood. He has had various surgical interventions for different ailments with no excessive bleeding episodes in the post operative period thereby excluding any pre-existing congenital coagulation factor deficiency. Apart from the low haemoglobin, other parameters such as the platelet count, the total white blood cell count and the differential count were within normal limits. His coagulation profile showed an abnormal activated partial thromboplastin time (APTT) of 67.5 seconds with a normal prothrombin time and a normal serum fibrinogen. The mixing APTT test with normal plasma (50:50 mix) showed no correction (immediate mixing as well as post 2 hour incubation at 37 C). This indicated the presence of an inhibitor. Initial screening of inhibitors such as lupus anticoagulant, cardiolipin antibodies and beta-2 glycoproteins were all negative. Inhibitor assay to factor VIII showed a high titre of inhibitor by Bethesda assay with a value of 750 Bethesda units. Inhibitor assay to factor IX could not be performed. Further testing for factor assay revealed a severe deficiency of both factor VIII (FVIII) and factor IX (FIX) with 1% and 5% activity respectively.

This is a case of acquired haemophilia due to presence of inhibitor to factor VIII although we could not prove inhibitors to factor IX. This case highlights the need to look for acquired coagulation abnormalities with an isolated prolonged APTT which do not get corrected by mixing with normal plasma.

The patient was treated with factor VIII bypass activity (FEIBA) and immunosuppressive therapy with anti CD 20 monoclonal antibody rituximab and prednisolone. Patient did not respond to treatment and passed away due to a cardiac event.

Discussion

Acquired haemophilia A is a rare condition due to auto antibodies directed against FVIII with considerable morbidity and mortality. The incidence of acquired haemophilia increases with age with an incidence of 14.7 per million/year in people above 85 years of age.1 The condition is uncommon in children. The bleeding patterns in congenital and acquired haemophilia are very different. Patients with acquired inhibitors tend to bleed more in skin and mucous membranes (like our patient) whereas patients with congenital haemophilia tend to bleed in joints with haemarthrosis.2,3 Treatment is directed towards managing the haemorrhagic complications with either FEIBA or recombinant activated factor VII (rVIIa).4 The other aspect of management is inhibitor eradication therapy through immunosuppressive agents like prednisolone, cyclophosphamide, azathioprine and rituximab.5

References

Isolated Oculomotor Nerve Palsy – A Rare Initial Manifestation of Tuberculous Meningitis

Akhilesh Kumar Singh¹, Prabhat Agarwal², Rohit Baiswar³

Abstract
Tuberculous meningitis (TBM) is a sub-acute / chronic meningitis known for its diverse manifestations which may lead to delayed diagnosis. An isolated oculomotor nerve palsy as an initial presentation of TB meningitis is quite rare. One such case has presented here; A 18 year female presented to us with ptosis of the left eye. Complete neurological examination revealed it to be a case of isolated 3rd cranial nerve palsy. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) brain revealed no significant abnormality. Cerebrospinal fluid (CSF) analysis was done and diagnosis of Tuberculous Meningitis was confirmed. This case report focuses on the fact that tuberculous meningitis should be included in the differential diagnosis of isolated oculomotor nerve palsy.

Introduction
Tuberculous meningitis is common infection of the central nervous system particularly in developing countries like India where Tuberculosis is so rampant. Early diagnosis and treatment are very vital key factors as any delay in management can be potentially hazardous in the form of neurological sequelae and even death. This disease entity has very variable modes of presentation ranging from simple headache to frank altered sensorium. Isolated oculomotor nerve palsy is such a rare presentation of tuberculous meningitis. This uncommon presentation should be kept in mind whenever such case is encountered by clinicians.

Case Report
A 20 year old female came to our hospital with gradual onset progressive drooping of eyelid of the left eye for last 20 days (Figure 1). She also complained of binocular diplopia. She observed that diplopia increased on right gaze. She did not have headache, fever, nausea, vomiting, seizure, altered sensorium and orbital pain. She denied any prior illness like diabetes mellitus, hypertension and thyroid disease. Her vitals were normal. Neurological examination of the patient revealed presence of isolated left third nerve palsy (ptosis, pupillary dilatation, absence of light reflex, loss of extra ocular movements attributed to third cranial nerve). Rest of the examination was within normal limit.

Routine laboratory investigations including complete blood counts, liver and renal function tests were within normal limit. Thyroid function tests, C-reactive protein and Anti-nuclear antibodies were within normal range. Chest X-ray and ultrasonography abdomen were normal. MRI brain revealed slight ventriculomegaly. Lumbar puncture was performed because of presence of this slight ventriculomegaly. Examination of cerebrospinal fluid (CSF) showed cell count of 104/mm³ (lymphocytes 78%, neutrophils 18%, monocytes 4%), protein 115 mg/dl and sugar level of 30 mg/dl. Gram negative and Zehl Neelsen staining for Acid fast bacilli were negative. Polymerase chain reaction for tuberculosis came to be positive.

Based on the above mentioned CSF findings, patient was put on anti tubercular therapy (rifampicin, isoniazid, ethambutol and pyrazinamide) in appropriate doses. Adjunctive steroid was also given in standard dose. After two weeks of therapy ptosis improved. A second CSF study was performed on 21st day of therapy which revealed improvement in parameters (Table 1).

Table 1: CSF findings

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<thead>
<tr>
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<th>Total and differential cell count</th>
<th>Protein</th>
<th>Sugar</th>
<th>ADA</th>
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<tr>
<td>Day 1</td>
<td>TLC= 104/ mm³</td>
<td>115 mg/dl</td>
<td>80 mg/dl</td>
<td>9.61 IU/l</td>
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<td></td>
<td>N= 18%</td>
<td>L=78%</td>
<td>M= 4%</td>
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<td>Day 21</td>
<td>TLC=20/ mm³</td>
<td>70 mg/dl</td>
<td>55 mg/dl</td>
<td>8.30 IU/l</td>
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<td>N=10%</td>
<td>L=95%</td>
<td>M=5%</td>
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CSF profile of the patient on day 1 and day 21 (after ATT); TLC – total cell count, N- neutrophils, L- lymphocytes, M- monocytes, ADA- adenosine deaminase

Discussion
Whenever a case of an isolated oculomotor nerve palsy is encountered, a careful search for the common causes should be sought which include brain stem infarct, multiple sclerosis, tumours, aneurysms, cerebral herniation, cavernous sinus thrombosis, carotid cavernous fistula, diabetes mellitus, Tolosa hunt syndrome, myasthenia

Fig. 1: Complete left sided ptosis due to 3rd cranial nerve palsy

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<td></td>
<td>N=10%</td>
<td>L=95%</td>
<td>M=5%</td>
<td></td>
</tr>
</tbody>
</table>

CSF profile of the patient on day 1 and day 21 (after ATT); TLC – total cell count, N- neutrophils, L- lymphocytes, M- monocytes, ADA- adenosine deaminase
Right Atrial Extension of a Giant Retroperitoneal Leiomyosarcoma

Sonal Saran¹, Pushpinder S Khera², Poonam Elhence³

Abstract
Leiomyosarcoma of vascular origin is rarely seen occurring in the Inferior Vena Cava. We report a rare case of a young male with giant retroperitoneal leiomyosarcoma which extended into the right atrium.

Introduction
Of the many abdominal tumors which invade inferior vena cava (IVC) and extend into right atrium, renal cell carcinoma is the most frequent.¹ Leiomyosarcoma (LMS) of the IVC and adrenal gland are among the subtypes of retroperitoneal sarcomas which have a tendency to invade IVC and extend into right atrium.²⁻³

Case Report
A 32 years male was admitted with history of upper abdominal discomfort and pain which had progressed over a period of 2 months. A large firm mass was palpated in the right hypochondrium and lumbar region. Triple phase computed tomography of the abdomen was performed which showed a large heterogeneous infiltrating mass in the right upper retroperitoneum. The mass measured 23 cm (cranio-caudal) x 17 cm (transverse) x 17.5 cm (antero-posterior) in dimensions. The lesion extended from the undersurface of right lobe of liver (which is infiltrated by the mass) to the level of right renal hilum. Antero-posteriorly the mass extended from the right paravertebral region till the anterior abdominal wall. The hepatic flexure and ascending colon were displaced anteriorly by the mass. The right adrenal gland was not visualized separately. The upper pole of right kidney was infiltrated by the mass with posterior displacement of hilar vessels. The mass showed areas of hemorrhage, necrosis and solid enhancing nodular tissue within it (Figure 1).

The tumor thrombus in IVC extended into the hepatic part of IVC and right atrium. The azygous system was dilated as a result of the IVC obstruction. Moderate ascites was also seen (Figure 1).

The possibility of renal tumor was excluded by the fact that the epicenter of the mass was outside the kidney with secondary involvement of the renal parenchyma. The imaging differentials were primary retroperitoneal tumor, adrenal tumor and tumor arising from the IVC.

An ultrasound guided biopsy was performed and histopathological sections showed a tumor composed of spindle to oval pleomorphic cells with eosinophilic cytoplasm, indistinct cell borders and oval to elongated moderately pleomorphic nuclei. Few bizarre cells and an occasional mitosis were also noted. On immunohistochemistry, the tumor cells were positive for smooth muscle actin (SMA), epithelial membrane antigen (EMA), focally positive for Desmin and negative for cytokeratin, S-100 protein, CD117 and CD10 (Figure 2).

The histopathological impression was high grade leiomyosarcoma. Clinico-radiological correlation led to the diagnosis of LMS arising from IVC, adrenal or primary retroperitoneum. Due to the poor general health status, the patient expired without any further treatment.

References

¹Assistant Professor, Department of Radiology, Subharti Medical College, Meerut, Uttar Pradesh; ²Associate Professor, Department of Radiology; ³Additional Professor, Department of Pathology, AIIMS, Jodhpur, Rajasthan

Received: 04.10.2016; Accepted: 05.08.2019
Discussion

LMS is a malignant tumor of smooth muscle cells which originate most commonly in the uterus and retroperitoneum. In retroperitoneum, most common site of origin is IVC. LMS of vascular origin is rarely seen occurring most commonly in the IVC. Conversely, primary malignancies of the IVC are rare, with LMS representing the vast majority. LMS of IVC was first described by Dzsinich et al. in 1992. Contrary to our case, LMS of IVC is...
LMSs remain asymptomatic for long time. This leads to the delayed diagnosis with dismal prognosis. LMSs involving IVC is intra-luminal in only 5% cases. In rest 95%, extraluminal growth is seen which can be mistaken for masses of adjacent organs and so the differential diagnoses should include primary tumors of these organs. Pre-operative assessment for resectability requires modern imaging techniques such as ultrasonography, echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI). Combination of modern vascular surgery with chemotherapy and/or radiotherapy is required for proper management. Aggressive surgical removal with negative margins is essential followed by venous reconstruction by prosthetic replacement of the IVC whenever considered necessary. The material of choice for prosthetic replacement is reinforced polytetrafluoroethylene (PTFE).

Kieffer E et al evaluated 22 cases of LMSs and concluded that Creation of an arterio-venous fistula eliminates the need for long-term anticoagulation therapy and ensures patency.

**Conclusion**

In conclusion, our case reminds us of the possibility that retroperitoneal LMSs can invade IVC and right atrium as can other renal and hepatic malignancies. The IVC should be examined by CT or MRI, especially in a case of a right retroperitoneal tumor. Image guided biopsy provides definitive pre-operative diagnosis.

**References**

Fever with Rash: A Clinical Dilemma

Nirupam Prakash¹, Jeevan Prakash²

Abstract

Rash associated with a febrile illness often poses challenges in diagnosis. The clinical knowledge of pathogenesis, onset and characteristics of rash is therefore essential to make an early diagnosis and for successful management of the disease. We present herewith a case of a young man with acute febrile illness and rash which raised doubts with regards to the possible etiological diagnosis and necessitated detailed work up which revealed a diagnosis of COVID-19. The case being highlighted as often the history and clinical presentation may seem to be obvious but an atypical uncommon presentation which in this case was a maculopapular rash may not fit the picture of a single etiological diagnosis according to the known medical literature.

Fever with rash is a common presentation which poses a challenge in daily clinical practice. It is often said that the eyes do not see what the mind does not know. A detailed history and systematic clinical examination often provides clinical clues to the diagnosis in a clinically unsuspecting case. The temporal association of rash with fever, its characteristics, distribution, hemorrhages and associated arthralgias or organomegaly often clinches the diagnosis. We discuss herein an unusual case of acute febrile illness presenting with rash which posed diagnostic uncertainties.

Case Presentation

We present herewith a case of Mr AK, 25 years age, resident of Lucknow, who presented with low grade intermittent fever for the past three days with cough and coryza for two days and reddish, non-pruritic rash on the forearms since one day in last week of July 2020. The rash was maculopapular, perifollicular in appearance and some of these seemed to be fluid-filled (Figure 1). There were no patechiae or pustules. The subject complained of generalised malaise and distaste for food. There was no history of drug intake or cutaneous allergic reactions in the past. Further, there was no eschar or history of travel to scrub typhus endemic areas. The rash was non-petechial and unlike classical description of white islands in a sea of red in acute dengue fever which blanches on pressure.¹ His symptoms and history of contact with a suspected COVID case with recent travel history led us to suspect the possibility of COVID-19.

Skin is often said to be the reflection of the internal disease. While we have known COVID-19 as a disease with predominantly respiratory symptoms, skin afflictions are not unknown. Unlike infection with other β-coronaviridae, skin eruptions have been characteristically observed in COVID-19.² However, skin eruptions are variable and may present depending on the stage and severity of disease. The mechanism underlying the skin eruptions is not exactly known.

¹Consultant Physician, CGHS Lucknow, Uttar Pradesh; ²Head Department of Critical Care Medicine, Era’s Lucknow Medical College, Lucknow, Uttar Pradesh

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Fig. 1: Maculopapular rash on the ventral aspect of both the forearms
Speculations exist that the mechanism of cutaneous eruptions may be similar to viral exanthema resulting from immune response to viral nucleotides, systemic consequences of vasculitis or thrombotic vasculopathy from COVID-19 or drug-induced. Various drugs advocated in treatment of COVID-19 themselves are known to produce maculopapular eruptions like azithromycin, tocilizumab, convalescent plasma, chloroquine and lopinavir/ritonavir. Further, high level of expression of ACE2 receptors on the skin especially, the basal layers of epidermis and skin vessels have been documented, making skin the likely target for SARS-CoV2 infection.

Skin eruptions manifested in nearly 20% of subjects with COVID 19 and may be the only presenting symptom. A Spanish nationwide study reported skin eruptions in 120 subjects out of a total 375 individuals diagnosed with COVID 19. They observed five characteristic skin manifestations of COVID 19 viz. urticarial, vesicular, maculopapular rash, chilblains-like eruptions, livedo and necrosis. Of these 23-44% of skin eruptions have been observed to be morbilliform or maculopapular rash and gradually subside on their own. The vesicular rash and pemisosis-like eruption are seen in milder COVID infection while Livedo and necrosis are indicative of a severe COVID-19 disease resulting from vascular and clotting abnormalities consequent to thrombocytopenia, elevated D-dimer assays, increased prothrombin time, disseminated intravascular coagulation.

While COVID feet/toes with chilblains-like appearance (resulting from vasculitis) and livedo and necrosis (thrombotic manifestation of severe COVID-19) present late, other skin eruptions appear early along with other COVID symptoms. The vesicular rash of COVID-19 is monomorphic unlike the polymorphic eruptions of Varicella. The importance of more common maculopapular rash is highlighted especially in COVID-19 subjects who present without respiratory symptoms. The maculopapular rash occurs early in disease along with other symptoms of COVID-19 and reported to be itchy in nearly half of the subjects. The maculopapular eruptions may have a perifollicular distribution with varying degrees of desquamation. They might resemble pityriasis rosacea or infiltrated plaques with pseudovesicular appearance or develop punctiform or large purpura or likeness to erythema multiforme. The average duration of rash is around 8 days and is associated with greater severity of disease. Although our case had characteristics similar to the rash described in literature, he had a mild COVID illness. He presented with low grade fever, mild coryza and sought medical consultation for bilateral non-pruritic maculopapular eruptions, noticed on arms on the 3rd day of illness. The markers of inflammation and liver transaminases were within normal range throughout the course of illness. But he had a persistent RT-PCR for COVID in the mid range (29-39) even after 15 days of presentation which was concerning as some researchers consider a Ct value more than 34 to be the cut off criteria to consider the individual non-infectious and eligible for discharge from hospital. The persistent positive RT-PCR could also have been due to persistent RNA fragments in the respiratory epithelia but is debatable.

The maculopapular rash in COVID is early in onset and therefore may serve as a basis of diagnosis in pauci-symptomatic subjects in areas where diagnostic facilities are limited. The case is being discussed to highlight that COVID-19 is a great masquerader having varied systemic manifestations, and should be considered in the differential diagnosis of subjects with fever without exanthema to avoid misclassification. Skin eruptions in COVID-19 have been described variously as varicella like lesions, dengue-like, urticarial, acro-ischaeemia and plaque-like. The realization that fever with rash could be due to COVID-19 disease would help diagnose the disease early and help institute steps to contain its spread in the masses. Recently the American Academy of Dermatology has launched a COVID-19 registry to track cutaneous manifestation arising in COVID-19 subjects at the time of disease presentation.

References

COVID-19 Philately Part-2

Jayant Pai-Dhungat

Novel corona virus was discovered during the end of yr.2019 and labeled Covid19. However, the world has felt the staggering impact of this pandemic only during the year 2020. In the last 6 months we have witnessed devastating pandemic of such enormous proportion in which high virulence of covid 19 virus without any previous experience has lead to alarming death rate. The year 2020 will make a lasting impression on the history of humankind as it will be remembered as starting of post-covid era.

Iran was the first country in the world to issue a commemorative postal stamp honouring covid warriors in April 2020. China soon issued set of 2 stamps on two occasions during the year. Indonesia, Serbia, Spain and many others have followed. Idea of issuing these stamps is to honour the frontline workers and increasing public awareness.

We have learned many things in 6 months but still there is much to learn.

One of the most important lessons learnt is that Covid-19 is a disease of the entire body, and not just lungs.

ARDS associated with viral pneumonias in the precovid era differ in the fact like Patients appear relatively comfortable in spite of significant hypoxia; hence called ‘happy hypoxia’. Involvement of lungs is seen typically as bilateral, peripheral ground glass opacities.

There is greater need of oxygen therapy rather than ventilators, and when ventilators are used very high PEEP is necessary. Difficulty in weaning off oxygen is observed and some patients even have been discharged with domestic O2

An elderly person with co-morbidities is the single most important factor in increasing mortality. While many young people without comorbidities have succumbed to the infection.

Diffuse alveolar damage is evident on post mortem examinations. However, platelet fibrin thrombi in small pulmonary arteries indicate coagulopathies like DIC.

Severe Covid-19 cases have been known to result in a cytokine storm, which has emerged as one of the common causes of death in patients. This occurs when the body’s immune system goes into an overdrive causing lung injury and multi-organ failure. Several studies suggest that the drug tocilizumab has been effective in managing cytokine storm, when IL-6 levels are high.

The list of symptoms on the radar has widened as Covid-19 is also believed to be manifesting in skin rashes, diarrheas, anosmia and ageusia in some.

Role of several therapies is becoming clear with time. Dexamethasone plays a very critical role in saving lives. Timely use of Remdesvir, Tocilizumab, ecosprin, LMWH have saved lives. Oxygen therapy at times in prone position should be administered early as the symptoms crop up.

Convalescent plasma therapy is associated with some promise, but not everyone is convinced of its efficacy. Pediatric cases have risen since July 2020 and MIS-C or multi-system inflammatory syndrome may be encountered on occasions.

Time alone will tell us about long term consequences, reinfection, herd immunity, effective antiviral agents, and active or passive vaccines

Only silver lining for India is for reasons that are as yet unclear, COVID-19 mortality in India seems relatively low when compared with many other countries.

*Professor of Medicine (Retd.), TN Medical College, Hon. Physician, Bhatia Hospital, Mumbai, Maharashtra
Clinical and Lab Characteristics of End Stage Renal Disease Patients with COVID-19

Deependra Kumar Rai
Additional Professor and Head, AIIMS, Patna, Bihar

Sir

In December 2019, a series pneumonia cases with unknown cause were observed in Wuhan, Hubei Province, China.1,2 Later on it was identified that the disease was caused by “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2). On February 11, 2020, the World Health Organization officially changed the name of the disease caused by SARS-CoV-2 to coronavirus disease 2019 (COVID-19). Clinical characteristics of patients with COVID-19 have been well described in previous studies.3 However, there are limited data about the clinical characteristics of patients with end-stage renal disease (ESRD) and COVID-19.

This was a retrospective analysis of patients with ESRD admitted between 1st June to 31st July 2020 with COVID-19. All the patients with ESRD who were on Renal replacement therapy and admitted in Pulmonary and Urology ward of AIIMS Patna with COVID-19 were enrolled for study. Patients who developed AKI during hospitalisation were excluded from study.

Six patients were admitted in the study period. Fever was found in 3 patients while cough and breathlessness in 2 and 1 patients respectively. Only one patient was categorised under severe category, and required oxygen therapy. One patient was asymptomatic, diagnosed to have COVID-19 when investigated before haemodialysis. All the patients were hypertensive but Diabetes was found in only two patients. Leukopenia (<3500/µl and leucocytosis (>10,000/µl) were found in 2 patients each. Raised neutrophil lymphocyte ratio is one of the poor prognostic markers. It was found elevated in 5 patients and highest level was 15.98. All the 6 patients had elevated liver enzymes. Among inflammatory markers, serum ferritin, Lactate dehydrogenase (LDH) and C-reactive protein (CRP) were elevated in all patients. D-dimer was elevated in 5 patients while it was not available in one patient, (Table 1).

Considering CKD as immunocompromised condition, covid infection is not severe and most of the patients recovered with conservative treatment.

References

| Table 1: Clinical and Lab characteristics of end stage renal disease (CKD-5) patients with COVID-19 |
|---|---|---|---|---|---|---|---|
| Age (years) | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | All |
| M/F | 49 | 66 | 57 | 45 | 70 | 56 | 57.1± 9.57 |

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<tr>
<th>Symptoms</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
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<tr>
<td>Fever</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>3/6</td>
</tr>
<tr>
<td>Cough</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2/6</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>1/6</td>
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<tr>
<td>Severity</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
<td>Asymptomatic</td>
<td>Severe</td>
<td>Mild</td>
<td>1/6 (Severe)</td>
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<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
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<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
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<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<td>1/6</td>
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<th>Lab investigation</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
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<tbody>
<tr>
<td>Hb</td>
<td>9</td>
<td>9.1</td>
<td>3.5</td>
<td>9.5</td>
<td>7.7</td>
<td>12</td>
<td>8.46±2.81</td>
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<tr>
<td>TLC</td>
<td>2.23</td>
<td>3.68</td>
<td>2.62</td>
<td>8.92</td>
<td>10.21</td>
<td>16.66</td>
<td>7.38±5.64</td>
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<tr>
<td>Platelet count</td>
<td>367 N/A</td>
<td>114</td>
<td>159</td>
<td>131</td>
<td>114</td>
<td>177±107.79</td>
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<tr>
<td>N</td>
<td>80.3</td>
<td>75</td>
<td>62.2</td>
<td>79.4</td>
<td>88.5</td>
<td>91.1</td>
<td>79.41±10.35</td>
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<tr>
<td>L</td>
<td>18.4</td>
<td>6.8</td>
<td>27.5</td>
<td>13.7</td>
<td>9.6</td>
<td>5.7</td>
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<td>NLR</td>
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<td>11.02</td>
<td>2.26</td>
<td>5.79</td>
<td>9.21</td>
<td>15.98</td>
<td>8.1±5.0</td>
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<tr>
<td>SGOT</td>
<td>189</td>
<td>118</td>
<td>47</td>
<td>67</td>
<td>70</td>
<td>127</td>
<td>103±52.37</td>
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<tr>
<td>SGPT</td>
<td>273</td>
<td>100.2</td>
<td>54.6</td>
<td>185.1</td>
<td>28</td>
<td>719</td>
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<td>S-creatinine</td>
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<td>8.41</td>
<td>12.59</td>
<td>8.6</td>
<td>13.3</td>
<td>6.49</td>
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<td>Blood urea</td>
<td>144.3</td>
<td>193</td>
<td>342.4</td>
<td>145.7</td>
<td>334.3</td>
<td>207</td>
<td>227.78±69.25</td>
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<td>CRP</td>
<td>55.18</td>
<td>76.98</td>
<td>21.7</td>
<td>8.97</td>
<td>297.3</td>
<td>180.63</td>
<td>106.79±111.45</td>
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<td>Procalcitonin</td>
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<td>0.15</td>
<td>0.1</td>
<td>0.17</td>
<td>1.9</td>
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<td>0.5±0.78</td>
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<td>Ferritin</td>
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<td>1650</td>
<td>587</td>
<td>661.8</td>
<td>490.03</td>
<td>600.13</td>
<td>939.82±552.85</td>
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<td>D-dimer</td>
<td>1.19</td>
<td>1.28</td>
<td>N/A</td>
<td>0.85</td>
<td>1.42</td>
<td>2.5</td>
<td>1.44±0.62</td>
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<tr>
<td>LDH</td>
<td>1041</td>
<td>790</td>
<td>667.2</td>
<td>550.9</td>
<td>1079</td>
<td>645</td>
<td>795.51±218.91</td>
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</table>

Symptoms was described in categorical scale and Lab parameters in mean ±SD.
Indian College of Physicians

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

5.2.1.1 Minimum experience of 10 years after Post Graduation.
5.2.1.2 Continuous membership of the Association of Physicians of India for not less than 7 yrs.
5.2.1.3 Should have made a significant contribution to research / teaching / development in the field of medicine.
5.2.1.4 Should have contributed to API by way of scientific or Organizational works.

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

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

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

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

• The Proposer / Seconder should not propose / second more than 3 nominees for award of ICP in a particular year.
• It is responsibility of the Nominee / applicant to get the proposal completed by the proposer and seconder along with the citation.
• API Membership No. of the proposer / seconder should be entered by the proposer / seconder themselves.
• The proposer should satisfy the requirements for proposal as under:-
  ❖ The Nominee is a life member of API
  ❖ The Nominee has completed 10 years after post-graduation
• The Nominee should read the Form carefully before filling the columns, to project their achievements appropriately.
• The Nominee should list their achievements in appropriate columns.
• Proof of qualifications, publications, honours, awards, must be submitted as supporting data. The supporting data should be numbered parawise (eg 1., 2., 3., etc). For more than one supporting documents, the numbering should be in alphabets (eg 1 (a), (b), (c), etc).
• No hand written applications will be accepted.
• One original and seven Xerox copies to be submitted
• Last date for receiving application form is 30th November, 2020.

Dr. Mangesh Tiwaskar
Hon. General Secretary

Dr. A.M. Bhagwati
Jt. Secretary

Available on API and JAPI Websites : www.apiindia.org & www.japi.org

Format for Submission of Bio - Data of The Nominee for Consideration for
Award of Fellowship of Indian College of Physicians.

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

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

3. Date of Birth
   Address Residence  
   Address Office

4. Tel.:  
   Fax:  
   E-mail:  
   Mobile

5. Postgraduate degree in Medicine  
   Year of passing  
   Institute  
   University

   Other Professional Qualifications  
   Year  
   Speciality / Subjects  
   University / Institute
   a.  
   b.  
   c.  
   d.  

   Certificates Attached

6. Experience in Medical Profession after Postgraduation in Medicine
   Name of Hospital / Clinic / Organisation & Location  
   Number of Beds (if applicable)  
   Period Served year wise (From-To)

7. Publications: List below. (If number of publications in Journals exceeds 8, publications which can qualify as research papers may be listed under Research section 9.)
   a) Number of Publications in Indexed National / International Journals.  
   b) Number of Chapter in Books / monograms  
   c) Editorship of National level or State level: Book / Monogram / Update Series

8. Honours And Awards (list below with photocopy of proof)
   (a) Oration in National / State Association Meeting
   Title of Oration  
   Organisation  
   Year
## (b) Award National / International / or State level

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<tr>
<th>Title of Award</th>
<th>Organisation</th>
<th>Year</th>
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<th>9. Research work (list below)</th>
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<tr>
<td>(a) Research sanctioned &amp; funded by Research Agency</td>
</tr>
<tr>
<td>(b) Departmental Research. (To qualify, the findings should be published in National/International Journal) Do not include papers already listed under Publications</td>
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<th>10. Contribution to API (list below and attach proof)</th>
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<td>Post held in Organisation / Meeting</td>
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<tr>
<th>11. Participation in CME or Scientific Sessions of API or ICP as Faculty</th>
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<tbody>
<tr>
<td>Speaker / Chairperson / Other</td>
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<table>
<thead>
<tr>
<th>12. Social welfare / Community service. (Include under the headings given below, with documentary evidence)</th>
</tr>
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<tbody>
<tr>
<td>(a) Emergency services during National calamities (Quakes/ Floods/Cyclones, etc)</td>
</tr>
<tr>
<td>(b) Public education Programme (Radio), TV talk / writing in news papers .</td>
</tr>
<tr>
<td>(c) Service in Rural Areas</td>
</tr>
</tbody>
</table>

| Service | Evidence |

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

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

Last date for receiving the application form is 30th November, 2020.

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

Citation

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

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<tr>
<th>Name</th>
<th>Membership No.</th>
<th>Signature Proposer</th>
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<th>Name</th>
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Note: The Fellowship form should be proposed and seconded by Founder Fellow / Fellow of ICP only. In case there are more than 3 nominations by any proposer/seconder, the first three nominations in order of receipt in API Office and complete in all respects will be considered for award of Fellowship of ICP and the others rejected for consideration.
In GERD, POWER OF ORIGINAL RESEARCH AMPLIFIED

Ganaton Total

Enteric coated Itopride Hydrochloride SR 150 mg & Pantoprazole Sodium 40 mg Capsules

High on Safety, High on Efficacy

Improves TLESRs

Superior Safety Profile

Better Efficacy Profile

DOSE: 1 capsule/day for 4 weeks

References:
*Trademark of Abbott Group of Companies. Itopride is efficacious in reducing TLESRs which is considered as a root cause of GERD. Itopride does not cross the blood brain barrier, thus not shown CNS side effects like extra pyramidal symptoms in published literature. However, clinical trials have reported side effects like nausea, abdominal pain, diarrhoea and constipation. These frequency however, did not differ from the group treated with placebo. Pantoprazole is studied in more than 100 clinical trials showing good efficacy and superior safety profile. *Does not cross the blood brain barrier, hence no extra pyramidal side effects.

Abbreviated Prescribing Information

Enteric coated Itopride Hydrochloride SR 150 mg & Pantoprazole Sodium 40 mg Capsules

Ganaton Total

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains

Itopride Hydrochloride equivalent to Itopride 45 mg (an enteric coated pill: Itopride Hydrochloride SR 135 mg) & Pantoprazole 40 mg (an extended release pill: Pantoprazole q.d. Cotrimoxazole)

THERAPEUTIC INDICATIONS

Treatment of Gastroesophageal Reflux Disease not responding adequately to proton pump inhibitors.

POSSIBLE AND METHOD OF ADMINISTRATION

Administer Ganaton Total capsules to be swallowed intact on an empty stomach or at least 1 hour after a meal. Do not crush, chew or open. Do not exceed the stated dosage. This drug may be used concomitantly in combination with anti-secretory agents and non-steroidal anti-inflammatory drugs. The microsomal oxidation pathways are not involved in the metabolism of the drug. No reliable data are available regarding the safety of co-administration with warfarin. Caution is advised when using other drugs known to interact with antacids and histamine H2-receptor blockers. Do not give to children or adolescents under 16 years of age. Patients over 65 years of age may require a dose reduction. It should be administered with meals or within 1 hour of meals. Do not exceed the recommended dose. There is no experience with use of this combination in children under 16 years of age.

For full prescribing information, please consult Medical Science Website, Abbott India Limited, Plot 16, Godrej BKC, Plot no. G-68, BKC, Near MCA Club, Bandra (E), Mumbai - 400091

Abbott India Ltd.
Plot 16, Godrej BKC, Plot no. G-68, BKC, Near MCA Club, Bandra (E), Mumbai - 400091
In Stage I hypertension

Olmesar
Olmesartan Medoxomil 10 / 20 / 40 mg Tablets

Best in Class A Class Apart

Olmesartan has more effective action in BP lowering, compared to other ARBs

Also Available

Olmesar
Olmesartan Medoxomil 10 / 20 / 40 mg Tablets

Olmesar-A
Olmesartan Medoxomil 10/40 mg + Amlodipine 5 mg Tablets

Olmesar-CH
Olmesartan Medoxomil 20/40 mg + Chlorothiazide 12.5 mg Tablets

TriOlmesar
Olmesartan Medoxomil 20/40 mg + Amlodipine 5 mg + Hydrochlorothiazide 12.5 mg Tablets

TriOlmesar-CH
Olmesartan Medoxomil 20/40 mg + Amlodipine 5 mg + Chlorothiazide 12.5 mg Tablets

Olmesar-M
Olmesartan Medoxomil 20 mg + Moxypen 500 mg Tablets

COMING SOON

Olmesar Plus

ARBs - Angiotensin II Receptor Blockers
Stefano Omboni et al; Management of arterial hypertension with ARBs: Current evidence and the role of olmesartan, Cardiovascular Therapeutics. 2018:36:e12471

Abridged Prescribing Information:
Composition: Each Olmesar 10/20/40 tablet contains Olmesartan 10/20/40mg. Indication: Hypertension. Dosage: Adult: 20 mg once daily when used individually, increase to 40 mg after 2 weeks of therapy if required. Children (age 6 to 16 years): 10 mg once daily for patients who weigh 20 to <35 kg or 20 mg once daily for patients who weigh ≥35 kg. Increase to a maximum of 20 mg for patients who weigh <35 kg or 40 mg once daily for patients who weigh ≥35 kg after 2 weeks of therapy if required. Contraindications: Hypersensitivity to Olmesartan, co-administration with aliskiren in diabetic patients, 2nd and 3rd trimester of pregnancy, biliary obstruction. Special Precautions: Assess renal function, BP & volume status during initiation of therapy & dose escalation periodically thereafter. Use with caution in elderly. Children ≤1 year of age must not receive Olmesartan for hypertension. In patients whose renal function may depend on activity of the renin-angiotensin-aldosterone system (e.g., patients with severe CHF), treatment may be associated with oliguria &/or progressive azotemia, rarely resulting in acute renal failure &/or death. Symptomatic hypotension may be anticipated after initiation of treatment in patients with an activated renin-angiotensin system, such as volume &/or salt-depleted patients. In patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN may occur. Adverse Drug Reactions: most commonly observed adverse reaction is Hyperuricaemia, Diarrhea, Headache other ADRs may be Rhinitis, Pharyngitis, Cough, Pain, Angioedema, Pruritus, Rash, Urticaria, Hypokalaemia, Hypotension & Muscle spasm.

Full prescribing information is available upon request.
In CAD and Heart Failure,

RX

BISOLONG

(Bisoprolol 2.5 / 5 mg Tablets)

BISOPROLOL IMPROVES SURVIVAL...PROLONGS LIFE

Bisoprolol is included in 2019 WHO* Essential Medicine list¹

Presenting The Most Appropriate Antibiotic Power in RTI

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For outright Success

Preferred Option in Cephalosporins in 12 countries
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7 International Clinical Trials in 1910 RTI Patients
• 94.4% bacterial eradication in RTI
• 100% success rate as switch over therapy

Robust Indian Data in AECOPD
77.36% Clinical Success & Decreased exacerbations from > 1.5 /2 to avg. 1.3

USFDA approved