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**Indian College of Physicians**

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Tuberculosis-A Tough Bug

Agam Vora

Introduction

Over hundred years after Robert Koch’s discovery of tubercle bacillus, Mycobacterium is still affecting mankind and may continue to do so in the near future. Tuberculosis is an age-old scourge to humankind which has afflicted throughout known history and human prehistory. Presently, the appearance of extensively drug-resistant tuberculosis (XDR-TB) in addition to multidrug-resistant TB (MDR-TB) has further complicated TB control at the global level. Equally alarming is the emergence of another form of virtually incurable drug-resistant isolates, known as extremely drug resistant TB (XXDR-TB). XXDR-TB isolates showed in-vitro resistance to all first- and second-line drugs tested. Such strains brought us back to the pre-antibiotic era and underlined the need to develop urgently new drugs and apply correctly the existing policies and strategies of TB control programs.  

Drug resistant (DR), Multidrug-resistant (MDR), extensively resistant (XDR) TB-Definitions

Development of resistance to Antitubercular drugs is a key health issue that threatens the progress made in the management of tuberculosis globally. The primary reason for development of drug resistance is inappropriate use of anti-tubercular drug regimen in drug susceptible TB patients. Depending upon the degree of drug resistance the patients are classified into various categories like mono-drug resistance, Poly-drug resistance, Multidrug-resistant TB (MDR), extensively resistant TB (XDR TB) etc.

The term drug resistance or DR-TB was used for mono-drug resistance (resistance to one first-line anti-tubercular drug only) and poly-drug resistance (resistance to more than one first-line anti-TB drug other than both isoniazid and rifampicin). Multidrug-resistant TB (MDR-TB) is TB that does not respond to at least isoniazid and rifampicin, the 2 most powerful anti-TB drugs. Pre-XDR was referred to as multidrug resistance along with resistance to a fluoroquinolone or second-line injectable agent but not both. XDR TB is MDR TB with concomitant resistance to any fluoroquinolone and to at least 1 of 3 injectable second-line anti-TB drugs: amikacin, kanamycin, or capreomycin.

Within a year of the first reports of extensively resistant TB (XDR-TB) in 2006, isolated cases were reported in Italy that had resistance to all first-line anti-TB drugs (FLD) and second-line anti-TB drugs (SLD) that were tested. In 2009, a cohort of 15 patients in Iran was reported which were resistant to all anti-TB drugs tested. The terms ‘extremely drug resistant’ (‘XXDR-TB’) and ‘totally drug-resistant TB’ (‘TDR-TB’) were given by the respective authors reporting this group of patients. 4 patients from India with ‘totally drug resistant tuberculosis’ (‘TDR-TB’) were described, along with subsequent reports of a further 8 cases. So the term TDR was coined for strains that are resistant to all the first line drugs as well as all the second line TB drugs that can be tested for. Different countries and indeed regions vary in which second line drugs they can test for. However, this term is not officially recognized by WHO yet.

Although the initial development of drug resistance in patients receiving anti-TB therapy is often due to multiple factors — primarily suboptimal drug concentrations and varying degrees of nonadherence to therapy — transmission of drug-resistant M. tuberculosis has been observed, particularly in countries with high numbers of patients coinfected with HIV. Due to their compromised immune systems, these patients are at higher risk for developing active TB infection and therefore may contribute significantly to the spread of MDR/XDR TB.

Prevalence of TB

Despite a concerted global effort to reduce the tuberculosis burden, TB is the ninth leading cause of death worldwide and the leading cause of death from a single infectious agent, ranking above HIV/AIDS. In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people (down from 1.7 million in 2000) and an additional 374 000 deaths among HIV-positive people. An estimated 10.4 million people were affected with TB in 2016 and 56% of these patients were found in these five countries: India, Indonesia, China, the Philippines and Pakistan. Drug-resistant TB is another continuing threat. In the year of 2016, there were 60 0000 new cases with resistance to rifampicin (RRTB), the most effective first-line drug, of which 490 000 had multidrug-resistant TB (MDR-TB). Out of these around 47% of cases were in India, China and the Russian Federation.

India accounts for one fourth of the global TB burden. According to WHO TB report 2017, for the year 2016 estimated incidence of TB in India is 2.79 million cases (including HIV+TB) & mortality rate of 425,000 (excludes HIV+TB). Global TB Report 2016 has estimated that India has highest burden of both TB and MDR TB. An estimated 1.3 lakhs incident multi-drug resistant TB patient emerge annually in India which includes 79000 MDR-TB Patients estimates among notified pulmonary cases. India has second highest number of estimated HIV associated TB. An estimated 1.1 lakh HIV associated TB occurred in 2015 and 37,000 estimated number of patients died among them.

Prevalence of TB in urban and rural population

Epidemiological variations in urban and rural population holds significance in highly populated and resource poor country like India. Considerable differences in incidence and prevalence of drug resistant TB cases have been reported in urban and rural settings in various clinical trials across the country.

Several studies on epidemiology of TB in urban/rural population from West of India included metropolitan cities such as Mumbai, Pune and major cities from Gujarat, underlining the rapid
management of drug resistant TB in Indian set up. The country has many problems of proper management by program personnel, continuous supply of quality assured drugs, implementation of DOTS in its true spirit, political commitment in form of monetary support, maintenance of quality assurance diagnostics, and proper reporting and recording of cases. While the availability of inexpensive drugs facilitates drug-resistant TB, it’s only one factor.

Inaccurate diagnostic testing of drug resistance is another important issue contributing to poor control of drug resistance to TB. The United Nations–based, Stop TB Partnership reports that India’s public health sector relies almost entirely on smear microscopy to diagnose TB. The drug-resistance testing is offered only to a small subset of all TB patients. Inadequate and inaccurate testing, and other issues, often means substandard treatment. About 60%–80% of Indian population with TB choose private over public care. But many private practitioners defy government rules and don’t report the disease, much less follow up with patients to ensure they are following standard treatment. Another factor contributing to the increase in DR-TB, is nonadherence to the AntiTB therapy, although concrete figures are elusive. Few patients quit when they begin to feel better after a few weeks, while others do so as the drugs are too expensive for them. Side effects, particularly with DR-TB treatment, can also lead to noncompliance.

Study by Dr Swapnil Jain & his group from Ujjain looks at the clinico radiological & socio economical profile of 474 patients of MDR TB in rural set up. They studied MDR TB patients over 3 years from 2013 to 2016 at DR TB center at Medical College & observed their socio economic, clinical & radiological pattern. It is seen that delay in diagnosis, improper treatment, lack of awareness, poor compliance, poor nutrition are few of the important features that needs urgent attention. Treatment of Associated co morbidity is of equal importance in overall management of patients. Their study observes significant prevalence of MDR TB in productive age group. This trend will have huge long term consequences on our country economy.

Way forward
Overall, the emergence of XDR-TB reminds that global TB control necessitates a sustained dedication by scientific, political and financial authorities. One of the important priorities is to effectively diagnose XDR-TB in clinical practice by strengthening the laboratories worldwide. All the reference laboratories in the country should be well equipped with high quality conventional Drug sensitivity testing (DST) for all the Second line drugs (SLDs) to diagnose XDR-TB effectively. Based on the current scenario, the effective management of XDR-TB depends on well thought out prescription of SLDs to reduce morbidity and mortality and transmission. The TB control programs should emphasize on policies focusing on the effective use of first-line drugs in every new patient so as to prevent the emergence of MDR-TB, XDR-TB and XDR-TB or TDR-TB.

Considering the mammoth impact of TB on Indian healthcare Prime Minister Narendra Modi has launched the TB Free India Campaign at ‘Delhi End TB Summit’ and has set a target for complete elimination of Tuberculosis (TB) by 2025, five years ahead of the global target of 2030. The government is implementing a national strategic plan (NSP) to end TB by 2025 for the next three years to ensure every TB patient has access to quality diagnosis, treatment and support. The new NSP adopts a multi-pronged approach which aims to detect all TB patients with an emphasis on reaching TB patients seeking care from private providers and undiagnosed TB in high-risk populations, treat all patients irrespective of where they seek care adopting a patient-centric approach, prevent emergence of TB in susceptible population groups and build empowered institutions and human resources to streamline implementation.

Considering the alarming rise in the incidence of drug resistance to anti TB drugs, this may be our last chance to combat this deadly disease. As my teacher Prof Dir Dr. K. C. Mohanty used to say, “Life takes one full circle!” We must choose wisely or having exploited all options, we will again be left banking on potions or prayers to control TB.

References
2. Faust AS. Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis
Immune Checkpoint Inhibitors Discovery Bag the Nobel

Vikram Londheyy

The Nobel Prize in Physiology and Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation. Cancer still continues to be the greatest health challenge as it kills millions globally. By stimulating the inherent ability of our immune system to attack tumor cells, this year’s Nobel Laureates have established an entirely new principle for cancer therapy. James P. Allison studied cytotoxic T lymphocyte antigen 4 (CTLA-4) that functions as a brake on the immune system. The potential of releasing this brake can unleash our immune cells to attack tumors. This concept has been utilised to create an anti-cancer drugs which have revolutionised the treatment of metastatic cancers. Simultaneously, Tasuku Honjo discovered a protein on immune cells responsible for programmed cell death (PD-1) which also operates as a brake. The seminal discoveries by these two Laureates constitute a landmark in the fight against cancer. Cancer therapeutics have earlier also received Nobel prizes. For e.g. Hormone treatment for prostate cancer (Huggins, 1966), chemotherapy (Elion and Hitchins, 1988), and bone marrow transplantation for leukemia (Thomas 1990).

The fundamental property of our immune system is the ability to discriminate “self” from “non-self” antigens. T cells that bind to non-self antigens trigger the immune system to engage in self-defense. T cell accelerators or T cell brakes can augment or ameliorate the T cell immune responses respectively. This intricate balance between accelerators and brakes is essential for tight control of the functioning of the T cell mediated immune response. Way back in 1990 James P. Allison at University of California, Berkeley studied the T-cell protein CTLA-4 and developed an antibody that could bind to CTLA-4 and block its function. He investigated if CTLA-4 blockade could disengage the T-cell brake and unleash the immune system to attack cancer cells. He was successful in treating the cancer in the experimental mice in 1994. Finally in 2010 his experiment got translated into an important clinical study which cured patients suffering from advanced melanoma and thus; the anti CTLA 4 drug Ipilimumab was born which received approval from FDA for the treatment of Refractory Melanoma.

In 1992, a few years before Allison’s discovery, Tasuku Honjo discovered PD-1, another protein expressed on the surface of T-cells. In animal experiments, PD-1 blockade was also shown to be a promising strategy in the fight against cancer, as demonstrated by Honjo. In 2012, a key clinical trial demonstrated the efficacy of anti PD-1 drugs in the treatment of patients with different types of cancer. Results were dramatic, leading to long-term remission and possible cure in several patients with metastatic cancer, a condition that had previously been considered essentially untreatable.

Immune checkpoint therapy for cancer today and in the future

After the initial studies showing the effects of CTLA-4 and PD-1 blockade, the clinical development has been dramatic. We now know that the treatment, often referred to as “immune checkpoint therapy”, has fundamentally changed the outcome for patients with advanced cancer. But similar to other cancer therapies, adverse side effects are seen, which can be serious and sometimes even life-threatening. They are caused by an overactive immune response leading to autoimmune reactions, but are usually manageable. Intense continuing research is focused on elucidating mechanisms of action, with an aim of improving therapies and reducing side effects. Of the two treatment strategies, checkpoint therapy against PD-1 has proven more effective and positive results are being observed in several types of cancer, including lung cancer, renal cancer, hepatocellular carcinoma, and melanoma. New clinical studies indicate that combination therapy, targeting both CTLA-4 and PD-1, can be even more effective, as demonstrated in patients with melanoma by combination of Ipilimumab (anti CTLA 4 antibody) and Nivolumab (anti PD1) or Pembrolizumab (anti PD-1 inhibitors). Thus, Allison and Honjo have inspired efforts to combine different strategies to release the brakes on the immune system with the aim of eliminating tumor cells even more efficiently. A large number of immune checkpoint therapy trials are currently underway against different types of cancer, and new immune checkpoint proteins are being tested as targets.

For more than 100 years scientists attempted to engage the immune system in the fight against cancer. “Immune Checkpoint” therapy has now revolutionized cancer treatment and has fundamentally changed the way we view how metastatic cancer can be managed.

References
Socio-economical and Clinico-Radiological Profile of 474 MDR TB Cases of a Rural Medical College


Abstract

Objective: To study the socio economical and clinico radiological profile of 474 diagnosed MDR TB cases who came for the initiation of MDR TB regimen in DRTB center of R.D. Gardi Medical college, Ujjain

Methodology: This is a retrospective and prospective observational study for a total period of three years from October 2013 to September 2016. The patients were evaluated clinically, radiologically and were investigated thoroughly according to PMDT guidelines and then were started on MDR TB treatment. The study was conducted at drug resistance tuberculosis center (DR-TB) managed by Department of Pulmonary Medicine.

Results: 474 cases were included in the study and we found that patients were in the age range of 10-84 years, maximum patients were in age group of 30 to 39 years, and mean age was 38 yrs. Male to female ratio was 2.73 to 1, most of the patients in the study were from rural area i.e. 61.6%. Illiteracy was found in 339 (71.5%) cases and out of these 339, 165 patients (48.6%) were defaulter, 101 (29.8%) are cases of relapse, 39 (11.5%) were failure, 34 (10.02%) of new cases. Maximum numbers of patients were in lower class accounting 63.7% and upper lower class 31.6%, lower middle class only 4.5%. Study also showed mean BMI was 14.9 kg/m² (range 5.7-25.4 kg/m²), 88.6% of patients were undernourished with BMI less then 18.5 kg/m². The most common symptoms was cough seen in 96%, followed by fever 67.5%, Dyspnea 52.7%, Anorexia 26.2%, chest pain in 19.8% and least common was haemoptysis seen in 7.6% of patient. Common co-morbidities with MDR-TB found was anemia in 176 out of 474 (i.e.37.1%), 123 (25.9%) COPD. Radiological severity showed 219 (46.2%) moderate lesion, 139 (29.3%) mild, 107 (22.6%) extensive lesion and 9 (1.9%) normal, 312 (65.8%) of patient are non-cavitary and 162 (34.2%) are cavitary in which 99 (20.9%) were unilateral and 63 (13.3%) are bilateral cavitary lesion. Defaulter are most common accounting of 218 (46.0%), relapse 139 (29.3%) and failure 68 (14.3%), new 48 (10.2%), most of them had taken more than one episode of ATT (72.8%). Most common source of ATT taken by patient is RNTCP it accounts 424 (89.5%) and 46 (9.7%) from private. 181 out of 474 (38.2%) cases delayed the treatment for 1-7 days, 82 out of 474 (17.3%) cases delayed treatment for 8-10 days, 96 out of 474 (20.3%) cases delayed treatment for 11-19 days and 115 out of 474 delayed the treatment for more than 19 days. 95 out of 474 cases i.e. 20.1% cases come from more than 150 km away from their residing area for the initiation of treatment.

Conclusion: The epidemiological picture of TB showed that males were predominant in our study however female were more affected in younger age group compared to male. More than 51% of the cases were in productive age group which affects the socioeconomic condition of family and society. More than 2/3 of patients were from lower socioeconomic group with low BMI. Therefore improving nutrition and immunity can play an important role. 2.3% of the cases were HIV reactive and were on ART. Co-morbidities like COPD and Diabetes were seen in our study which were statistically significant and had impact on the treatment outcome of results. Significant delay in initiation of MDR-TB regimen from date of DST was seen in 24.3% cases which is matter of concern. Most of the patients had taken ATT from RNTCP in which Defaulter and relapse was major contributor of MDR-TB suspect in our study and patient taking ATT privately were less. Large number of cases which resides more than 150 kilometers from DRTB center initiated the drug after a gap of more than 19 days from the date of DST.

Introduction

Tuberculosis now ranks alongside Human Immunodeficiency Virus (HIV) as a leading cause of death worldwide. Tuberculosis (TB) kills more adults in India than any other infectious disease. In India every day

- More than 6000 develop tubercular disease.
- More than 600 people die of tuberculosis (i.e. 2 death every 5 min).
associated tuberculosis occurred in 2014 and 31000 estimated number of patients died among them.\textsuperscript{1} A major obstacle to tuberculosis control is the emergence of \textit{mycobacterium} resistance to antitubercular chemotherapy.\textsuperscript{2} Multi drug resistant tuberculosis is caused by strains of \textit{Mycobacterium tuberculosis} that are resistant \textit{in-vitro} to isoniazid and rifampicin with or without other anti-tubercular drugs based on drug sensitivity test results from a Revised National Tuberculosis Control Program certified culture and drugs sensitivity tests laboratory. The outcome results of multi drug resistant tuberculosis patients remain suboptimal.

### Material and Methods

This is a retrospective and prospective observational study for a total period of three years from October 2013 to September 2016. The study was conducted at drug resistance tuberculosis center (DR-TB) managed by Department of Pulmonary Medicine. Our study was conducted in six districts (Neemuch, Mandsaur, Dewas, Ratlam, Shajapur, Ujjain) of western Madhya Pradesh linked to DR-TB center of Ujjain with population of 86,84,807 people (census 2011).

**Inclusion criteria:** All patient of multi drug resistance tuberculosis (MDR-TB) registered in DOTs plus site.

**Exclusion criteria:** Those cases were not included who were started on MDR TB regimen at the periphery and did not reported to DRTB center.

**Procedure planned:** All the multi-drug resistance tuberculosis (MDR-TB) cases which were diagnosed at drug resistance tuberculosis (DR-TB) center of R.D. Gardi Medical College or referred from other places for initiation of second line drugs underwent an initial evaluation of the patient was done which includes:

**Step 1**
- Demographic variables of patient which includes age, sex, education level.
- Detailed history of patient which include history of presenting illness, past history, personal history and family history
- General examination of the patient including vitals, height and weight
- Oxygen saturation of patient (SpO2) by pulse oximetry.

**Step 2**
- Basic investigations like:
  - Pathology- Complete Blood Count, blood grouping.
  - Biochemistry- random blood sugar, liver function test, renal function test, serum electrolytes, serum calcium.
  - Radiological test- chest x-ray
  - Cardiac evaluation-Electrocardiogram, echocardiography if required.
  - Special tests - HIV testing, HBsAg and thyroid profile.

**Step 3**
- Collection of data and analysis
- Descriptive data was collected and studied accordingly.
- Significant statistical test were applied.

### Observations and Results

A total of 474 MDR-TB patients were included in the study. The mean, mode, and median age are 38, 40, 36 year respectively and range is 10-84 year. Standard Deviation (SD) is 13.4 year. The total of more than 51% cases was in the age group between 20-49 years i.e. in the productive age group with Male: Female ratio equals to 2.73: 1 showing male were predominant. Female were more in younger age group compared to male with chi-square value 44.38 and p value is 0.00. study shows that most of patient belongs to rural area i.e. 61.6% with illiteracy in 71.5% of cases followed by primary school education in 19.4% cases, higher secondary education in 7% cases and graduate 2.10% cases. Maximum numbers of patient were in lower class accounting 63.7% and upper lower class 31.6%, lower middle class only 4.5%.

Mean body mass index (BMI) was 14.9 kg/m2,(range 5.7 – 25.4 kg/m2), maximum cases were undernourished with BMI less than 18.5 kg/m2 in which 72.2% were severely undernourished had BMI less than 16 kg/m2 followed by (8.6%) with moderate thinness and (7.8%) were mild thinness, a total of (11.2%) of patients had normal BMI and only one patient was overweight.

Smoking history was found to be in 168 (35.4%) of total patients with 91 patients (19.2%) with alcohol history while 81 patient consumed both alcohol and smoking. Most common symptoms was cough seen in 96%, followed by fever 67.5%, Shortness of breath 52.7%, anorexia 26.2%, chest pain in 19.8% and least common was haemoptysis seen in only 7.6% of patients.

The occupational profile of patients revealed that a majority of them were from labour class (36.3%) and farmer (31.2%) followed by housewife (15.2%), students (9.1%) and rest (8.2%) are driver, salesman, watchman, constable, electrician, LIC agent, shopkeeper etc. In our study we found that 11(2.3%) cases out of 474 were HIV positive and were on ART.

Table 1 shows most common co-morbidities and associated condition with MDR-TB is anemia in 176 out of 474 (i.e.37.1%), 123 (25.9%) COPD, 78 (16.5) Bronchiectasis, 50 (10.5%) heart disease, 39 (8.2) DM, 28 (5.9%) hepatic disease, 27 (5.7%) respiratory failure, 27 (5.7%) hypothyroid, 26 (5.5%) renal impairment, 21(4.4%) Effusion, 6(1.35) hyper thyroid, 5(1.1%) pyothorax, 2(0.4%) DVT, 2(0.4%) pregnancies, 1 (0.2%) pneumothorax. Study also show out of 27 patients having hypothyroidism 15 are male and 12 of them are female. Proportion of hypothyroidism is significantly higher in both and females as compared to hyperthyroidism, chi-square value 6.37 and p-value 0.04, statistically significant.

Most common site is lung parenchyma seen in 464 (97.9%) cases, and only 10 (2.1%) extra-pulmonary.
cases were found. A total of 6.8% (32 out of 474) cases had history of contact with patients of tuberculosis.

Radiological severity showed 219 (46.2%) cases with moderate, 139 (29.3%) with mild, 107 (22.6%) extensive lesion and 9 (1.9%) normal with 312 (65.8%) cases with non-cavitary lesion and 162 (34.2%) cases with cavitary lesion in which 99 (20.9%) were unilateral and 63 (13.3%) are bilateral cavitory lesion. Most of the cases 345 i.e. 72.8% took ATT for more than one episode and only 86 i.e. 16.9% took single episode of ATT while 49 i.e. 10.3% cases had no history of ATT prior to initiation of MDR-TB drugs. Regarding ATT taken by the patient prior to MDR-TB they were categorized as defaulter are most common accounting of 218 (46.0%), relapse 139 (29.3%) and failure 125 patients (26.1%) were defaulter, most of the patient are illiterate that is 339 (71.5%) and out of these 339, 165 patients (48.6%) were defaulter, 101 (29.8%) are cases of relapse, 39 (11.5%) were failure, 34 (10.02%) of new cases. Cases belonging to lower socioeconomic defaulter on treatment more often (Chi-square= 16.06 and p value 0.01). In our study, most common source of ATT taken by patient is from RNTCP and it accounts 424 (89.5%) cases and 46 (9.7%) cases took treatment from private sources.

181 out of 474 (38.2%) cases delayed the treatment for 1-7 days, 82 out of 474 (17.3%) cases delayed treatment for 8-10 days, 96 out of 474 (20.3%) cases delayed treatment for 11-19 days and 115 out of 474 delayed the treatment for more than 19 days. 94 out of 474 cases i.e. 20.1% cases come from more than 150 km away from their residing area for the initiation of treatment.

Cross tabulation was done between delay in treatment start and distance of patient from DRTB center (Chi-square= 11.557 and p value = 0.009) Concluding that person residing far from DRTB center initiated the drug after a gap of more than 19 days (26.3%). Logistic regression were applied and we found that chances of mortality in MDR-TB patients having COPD is 0.486 times higher as compare to non-COPD patients and chances of mortality in MDR-TB patients having diabetes is 0.325 times higher as compare to non diabetic patients.

### Discussion

Our study at Drug Resistance (DR-TB) centre mostly covered a rural population. Most of the patient in our study were from a low socioeconomic, background with low education level and were nutritionally challenged.

The study gave special attention to spatiotemporal pattern of the MDR-TB patients so that the spread of the cases can be analyzed along with the co morbidities associated with cases so that any factor could be found out that may prevent spread of the disease, resolving of these factor may also help in better compliance of treatment.

In the present study majority of the MDR-TB, cases (more than 51%) were in the productive age group (20-49 years); mean age was 38 years. In a retrospective study done in a TB unit in Mumbai, by Dholakia and Shah noted, that majority of the cases (67.6%) were in the age group 15-35 years with a mean age of 31years. Udwadia and Moharil, Sharma reported that prevalence of younger age group among MDR-TB patients with the mean age of their study groups being 29.7 years and 33.25 years respectively. As most of our patients are from economically productive age group and some are the sole source of income for the family, the illness will impose an economic burden at all level in society and for the nation. Financial and nutritional support of these patients now being planned by government and NGO is a useful step in the direction.

Males constitute 73.2% (347 cases) of patients included in this study while females were 26.8% (127 cases) with male to female ratio is 2.73 to 1. However, studies by Udwadia and Ibrahim reported female were predominant Our study almost coincide with Singh et al., Ibrahim et al., Songhua et al. but did not coincide with Udwadia et al. which is based on urban area and well educated class of society. Majority of our cases were male (73.2%) male predominance among MDR-TB cases has been also reported by other authors. Mean age of females (31.66±12.63) was less than that of males (40.33±13.03), which is statistically significant (t=6.46, p=0.000). Poulomi et al. also reported that mean age of female (28.59±12.50) was less than male (34.97±12.84).

Ibrahim et al. Males were significantly older than females [38.99 ± 12.01 versus 34.52± 14.36 years, (P <0.05)]. The T-test is 6.46. The p-value is 0.000. The result is significant at p <0.05. Conclude that young age group female more affected than male.

Most of patient belongs to rural area i.e. 61% of total and rest 31% resides in the urban area. Results were statistically significant (Z-score is 6.755 and p value is <0.05). Study, coincide with Ibrahim et al. which showed that 81.5% patients were lived in rural area and 18.5% of patients were in urban.

K.Aid et al. also reported that most of the patients were from rural area.

Most of the patients were illiterate 71.5% followed by primary school 19.4%, higher secondary 7% and graduate 2.1%. Khurram et al. reported 18 (60%) patients were illiterate in his study, Dholakia et al. only 14.17% of patients are illiterate did not coincide with our study, because this is urban based study. Songhua, et al. the education levels of the cases were as follows: 57 (58.2%) had finished elementary school or graduated from middle school and 17 (17.3%) had never been to school or did not finish elementary school.

Based on Kuppuswami scale, most of the patients in our study 302(63.7%), belongs to lower class followed by upper lower class 150 (31.6%) and lower middle 22 (4.5%) class respectively. Study coincide with Atre et al. study shows most of patient come under unemployed and unskilled worker. The long duration of debilitation further pushes the family to economic hardship.

420 patients (88.6%) were undernourished with BMI less than 18.5 kg/m2 in which 72.2% were severely undernourished had BMI less than 16 kg/m2 followed by 8.6% with moderate thinness and 7.8% were mild thinness. A total of 11.2% of patients had normal BMI and only one patient was overweight with Mean Body Mass Index (BMI) of 14.9kg/m2, (range 5.7-25.4).

The mean BMI of present study was less than other studies because
this is rural based study and majority of our patients belonged to lower socioeconomic class with poor nutritional status (Chi-square =86.96 and p value =0.000).

Regarding the associated addiction, it was seen that 35.4% of the included patients were smokers. Ibrahim et al\textsuperscript{14} shows 42.5% of the studied patients were tobacco smokers with significantly higher prevalence among males [56.8% of males verses 1.9% of females were tobacco smokers (p< 0.001)]. Khurram et al\textsuperscript{12} reported Eighteen (60%) patients were smokers, K.Aid et al\textsuperscript{11} who reported 74% were smokers which might be because of small sample size i.e.29 in which males were predominant. In present study cough was most common symptoms seen in 455 (i.e. 96%) of patient. Other studies in India to be shows that most common symptoms was cough by Udwadia et al,\textsuperscript{4} Mukherjee et al\textsuperscript{10} etc.

The occupational profile of our patients revealed that a majority of them were labour 36.3% followed by farmer 31.2% and housewife 15.2%. Yu et al\textsuperscript{8} also coincides with studies done by Singh et al\textsuperscript{6} and K. Aid et al\textsuperscript{11}. Patients were managed with insulin and in some cases oral hypoglycemic agent for the control of blood sugar. Suitable advices on diet and disease control were given. Kapadia et al\textsuperscript{17} did not reported any patient with thyroid abnormality, in our study out of 27 cases of hypothyroidism 15 were male and 12 were female (chi-square 6.37 and p value 0.04 i.e. <0.05).

In our study 123 of 474 (25.9%) are suffering from COPD, Kapadia et al\textsuperscript{17} study shows COPD is common comorbidities, Poulomi et al\textsuperscript{10} reported most common co-morbidities amongst study group (17.4%).

Assessment based on radiological severity was done and we found that 219(46.2%) had moderate lesion, 139 (29.3%) mild, 107(22.6%) extensive lesion and 9(1.9%) normal which were cases of extra pulmonary tuberculosis, endobronchial TB, laryngeal TB. Our study showed that 312 (65.8%) of patient had non-cavitary lesion and 162 (34.2%) cases had cavitary lesion out of which 99 (20.9%) were unilateral and 63 (13.3%) are bilateral cavitary lesion. K.Aid et al\textsuperscript{11} study do not coincide with our study shows 62 patients (52.1%) as minimal lesions, 53 patients (44.5%) as moderately advanced and 4 patients as far advanced lesions (3.4%). Ebru et al\textsuperscript{19} shows 51 (79.7%) patients had cavity and 34 (53.1%) patients had extensive disease whereas, 30 (46.9%) patients had limited disease. This study did not coincide with our study. Udwadia et al\textsuperscript{4} shows, 33 (42.3%) patients had unilateral disease while 42 (53.8%) had bilateral and advanced disease. Findings of our study do not coincide with Fawzy et al\textsuperscript{20} where minimal lesions were the most common presentation among his patients whereas in our study moderate presentation was dominant andAbdelazim et al who revealed that 58% of patients had far advanced lesion in chest X-ray followed by minimal lesion in chest X-ray 26%. Dhokalia et al\textsuperscript{1} shows a total of 20 of the 25 PTB cases had cavitory lesions, 13 single and 7 more than one cavity; 14 cavities were unilateral and 6 bilateral. A total of 20 of the 25 PTB cases had moderate to extensive lesions on x-rays.

Majority of cases belongs to defaulter that is 218(46.6%), 139(29.3%) were relapse followed by failure 68(14.3%) of previous anti-tuberculosis treatment. A study by ICMR shows most of patient belongs to failure followed by defaulter then relapse.

Study by Santha et al\textsuperscript{21} and Johnson et al\textsuperscript{22} coincide with our study reporting defaulter as most common group affected on basis of previous ATT taken by patient. We already know that our study is rural based so that lack of education, low income and lack of knowledge about the disease are contributing factors to default. However, studies by Poulomi et al,\textsuperscript{10} Ebru et al,\textsuperscript{19} which shows a high relapse rate as predominant group.

### Conclusion

MDR-TB is an important public health problem in India. The epidemiological picture of TB showed that males were predominant in our study however female were more affected in younger age group compared to male. More than 51% of the cases were in productive age group which affects the socioeconomic condition of family and society. More than 2/3 of patients were from lower socioeconomic group with low BMI. Therefore improving nutrition and immunity can play an important role. Majority of our patients were from rural area i.e. 61%. 19.2% cases were addicted to alcohol and 35.4% cases were addicted to smoking. Co-morbidities like COPD and Diabetes were seen in our study which were statistically significant and had impact on the treatment outcome of results. 6.8% of the cases had history of contact to cases of tuberculosis so all the contact must be screened up. Significant delay in initiation of MDR-TB regimen from date of DST was seen in 24.3% cases which is matter of concern Most of the patients had taken ATT from RNTCP in which Defaulter and relapse was major contributor of MDR-TB suspect in our study and patient taking ATT privately were less. Large number of cases which resides more than 150 kilometers from DRTB center initiated the drug after a gap of more than 19 days from the date of DST.

### Recommendations

Maximum cases of MDR-TB were in productive age group and the disease affects the socio economic status of family, so financial support can play an important support in the management of these cases i.e. some provision for providing them house hold jobs. Maximum number of cases had Anemia and lower BMI so nutrition may be added as integral part of the programme. Provision of long term oxygen therapy (LTOT) be considered in cases with poor lung reserve and respiratory failure. Cases with unilateral cavity can be considered for thoracic surgeries. Delay in initiation of DRTB regimen was seen in large no
of cases (24.3%) which leads to spread of disease and affect the outcome of disease so active surveillance of cases is essential. All the close contact of the patient should be screened for TB as significant cases (6.8%) had contact history of TB in family. De-addiction programme should be introduced in national programme as large no of cases in study were addicted to smoking and alcohol. Identification, effective management of co-morbidities and regular monitoring is very important in the cases which may help in better outcome of the result.

References


12. Muhammad Khurram, Haramma Tul Bushra Khair, Muhammad Fahim Department of Medicine, Rawalpindi Medical College, Rawalpindi, and the Nuclear Medicine, Oncology, and Radiotherapy Institute, Islamabad, Pakistan. J Infect Dev Ctries 2012; 6:29-32.


Urbanization, Human Development and Literacy and Syndemics of Obesity, Hypertension and Hyperglycemia in Rajasthan: National Family Health Survey-4

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Abstract

Objective: Non-communicable diseases (NCDs) are the new epidemic in India. District-specific prevalence of various NCD risk factors and their macrolevel determinants is unknown. We used National Family Health Survey-4 (NFHS-4) data to map the syndemics of obesity, hypertension and hyperglycemia in Rajasthan, the largest state of the country, and correlated their prevalence with selected social determinants of health - urbanization, human development index (HDI) and literacy.

Methods: Data on location-adjusted prevalence of various NCD risk factors among women (15-49y) and men (15-54y) were obtained from NFHS-4 data sheets. Heat maps were created to determine geographic distribution of obesity (body mass index, BMI ≥25 kg/m²), hypertension (known and/or BP ≥140/≥90 mmHg) and hyperglycemia (random glucose >140 mg/dl) in all the districts (n=33). We determined correlation of various social determinants with NCD risk factors.

Results: Significant geographic variation was observed in prevalence of obesity, hypertension and hyperglycemia in women and men. High prevalence of obesity and hypertension was observed in central and northwestern districts of the state. In women and men respectively, there was a significant positive correlation of obesity with urbanization (r=0.68, 0.51), HDI (r=0.70, 0.66) and female literacy (r=0.46, 0.34). Prevalence of hypertension also showed significant correlation with urbanization (r=0.18, 0.33), HDI (r=0.38, 0.52) and literacy (r=0.32, 0.21) while no correlation was observed with hyperglycemia.

Conclusion: There is significant geographic variation in prevalence of obesity, hypertension and hyperglycemia in Rajasthan. Significant correlation of obesity and hypertension with urbanization, human development and female literacy is observed.

Introduction

Urbanization is one of the most important social changes of the twentieth century. In western countries massive urbanization of rural population occurred in the last five hundred years but the most rapid change occurred in the 19th century.¹ On the other hand, this change began in low and lower-middle countries in the 20th century and is more rapid.¹ This has led to multiple changes in political, social and family structures. The outcomes of these changes are complex but lead to significant social changes.² These changes also impact health and are collectively known as social determinants of health. World Health Organization (WHO) defines social determinants of health as “the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms, social policies and political systems”.² Wilkinson and Marmot proposed the following social determinants as important for health: social gradient, stress, early life factors, social exclusion, work, unemployment, social support, addiction, food, and transport.³ In low and lower middle income countries other important factors are urbanization, human development and education.⁴ All these social determinants of health are associated with the epidemic of cardiovascular disease (CVD) and associated risk factors of smoking, obesity, hypertension and diabetes and are “causes of causes” of syndemics of CVD.⁵

Syndemics are defined as clustering of two or more diseases within a population that contributes to and results from persistent social and economic inequalities.⁶ It was initially reported as clustering of substance abuse, violence and AIDS.⁷ Presently focus has shifted from disease-specific and multimorbidity-based models to evaluate how social and economic conditions foster and exacerbate the diseases.⁸ In India there is dual burden of communicable and non-communicable diseases (NCDs).⁹ Sociocultural factors responsible for these associations have not been well examined. Macrolevel epidemiological studies could provide an impetus to study these associations. We examined data from the Fourth National Family Health Survey (NFHS-4)¹¹ using state-level and district-level data from published fact-sheets.¹² Hypertension and diabetes share common pathogenetic factors and overweight and obesity are important in pathogenesis of both the conditions especially in India.¹³ Socioeconomic factors are important in all of these.⁷ To evaluate presence of NCD risk factors in Rajasthan we mapped district level

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prevalence of overweight/obesity (body mass index \( \geq 25 \) kg/m\(^2\)), hypertension, and hyperglycemia (random glucose \( >140 \) mg/dl) from NFHS-4 fact-sheets.\(^{11}\) We also performed correlation of these conditions with district level data on urbanization, human development index (HDI) and female-literacy levels to determine the importance of these social determinants on obesity, hypertension and hyperglycemia to determine syndemicity in the largest Indian state.

**Methods**

We used the district level data for Rajasthan obtained during the district level health survey and published by NFHS-4.\(^{11}\) This is secondary analysis of the existing data and hence ethics clearance was not obtained. National Family Health Surveys are a series of nationally representative surveys that are periodically commissioned by government of India and performed under the guidance of International Institute of Population Sciences (IIPS), Mumbai, India; ORC Macro, Calverton, MD, USA and East-West Center, Honolulu, Hawai, USA. The studies are approved by the ministry of health of government of India and the research review board at IIPS, Mumbai. So far three surveys have been performed-NFHS-1 from 1992-1993, NFHS-2 from 1998-1999 and NFHS-3 from 2004-2005 [14]. NFHS-1 collected extensive information on population, health, and nutrition, with an emphasis on women and young children. Eighteen Population Research Centres located in universities and institutes of national repute assisted IIPS in all stages of conducting NFHS-1.\(^{15}\) The NFHS-2 was conducted in all the 26 states of India with additional data on quality of health and family planning services, domestic violence, reproductive health, anemia, nutrition of women and status of women. NFHS-3 used 18 research organizations including 5 population research centers who carried out surveys in 29 states of India. NFHS-4 was performed in 2015-16 and is focus of present article.\(^{15}\)

Detailed manuals for the conduct of NFHS-4 are available.\(^{16,18}\) Specific goals of NFHS-4 were: (a) to provide essential data on health and family welfare needed by the Ministry of Health and Family Welfare and other agencies for policy and program purposes, and (b) to provide information on important emerging health and family welfare issues. Specific objectives were to provide estimates of the levels of fertility, infant and child mortality, and other family welfare and health indicators by background characteristics at the national and state levels; and measure trends in family welfare and health indicators over time at the national and state levels. Besides the usual details of perinatal mortality, adolescent reproductive health, high-risk sexual behavior, safe injections, tuberculosis, and malaria and family welfare and health conditions among slum dwellers, this study for the first time was designed to obtain data on common non-communicable diseases such as hypertension and hyperglycemia (diabetes).\(^{19}\)

**Sampling**

The survey was implemented in both urban and rural areas.\(^{19}\) A uniform sample design was adopted in all the districts. IIPS, Mumbai selected primary sampling units for rural (villages) and urban (Census Enumeration Blocks, CEBs) areas following the NFHS sampling design. The field agencies were given a list of selected sampling units for each state or union territories that were selected for the fieldwork. When any regional linked primary sampling unit was selected, then mapping and household listing was undertaken for all the linked villages and urban blocks as a single unit. Prior to interviewing, all households located in the selected unit were listed as per the procedure by mapping and household listing teams. The list of households in each unit was used in selecting the final sample of households to be included in the NFHS-4 survey.

NFHS-4 was designed to provide information on various demographic parameters and other family welfare and health indicators by background characteristics at the national and state level and, for the first time, at the district level also. Because of need to report health indicators at the district level, the NFHS-4 sample size was increased to approximately 571,660 households, as compared with 109,041 households in NFHS-3.\(^{19}\) The survey used 4 schedules (Household, Woman’s, Man’s and Biomarker), and information was collected from all women aged 15-49 years and, in a sub-sample of households, men aged 15-54 years. This was expected to yield a total sample of 628,826 women and 94,324 men eligible for the interview. In these selected households, information on approximately 267,272 children below age 5 years was also obtained. In addition to the 29 states, NFHS-4 also included all six union territories and has provided estimates of most indicators at the district level for all 640 districts in the country as per the 2011 Census.\(^{19}\) The data were collected using Computer Assisted Personal Interviewing on mini-laptops. The domain of clinical, anthropometric and biochemical testing was expanded in NFHS-4 to include random blood glucose and blood pressure (BP) measurements with estimates to be reported at the district level for women age 15-49 and men age 15-54. All these components in the field were evaluated using portable equipment. A recently developed, improved model of the HemoCue instrument was used for anemia testing. A battery-operated portable glucometer was used for blood glucose testing. An automatic and battery operated BP instrument was used. Lancets and all blood contaminated materials were disposed in a biohazard bag according to an established protocol. Only medical or other personnel with specific training on the procedures and on universal precautions regarding blood-borne pathogens were involved in conducting the anemia and blood glucose testing. NFHS-4 was conducted in two phases, and each phase covered almost an equal number of states/groups of states and union territories.\(^{19}\) The two phases helped in managing the whole operation of implementation more efficiently. Identical strategy was used for Rajasthan state which was part of the second phase.

**Interview and assessments**

The detailed interviewer manual is available at NFHS-4 website.\(^{17}\) In the first step a Household Questionnaire permits the interviewer to identify women and men who are eligible for interview with the relevant Individual Questionnaire. Women age 15-49 years and men age 15-54 years who are members of the household were interviewed. The Household Questionnaire also permits the interviewer to identify women, men, and children who are eligible for anthropometric measurement, anemia...
Table 1: Prevalence (%) of various social determinants and non-communicable disease risk factors in different districts of Rajasthan in women (15-49 y) and men (15-54 y)

<table>
<thead>
<tr>
<th>District (alphabetic)</th>
<th>Sample size</th>
<th>Urbanization</th>
<th>Human Development Index</th>
<th>Literacy Rate</th>
<th>Overweight (BMI &gt;25 Kg/m²)</th>
<th>Hypertension (known or BP ≥140/90 mmHg)</th>
<th>Hyperglycemia (glucose &gt;140 mg/dl)</th>
<th>Hyperglycemia (glucose &gt;160 mg/dl)</th>
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<td>10.4</td>
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</table>

Additional notes:
- **Hypertension** is defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg.
- **Hyperglycemia** is defined as fasting glucose levels ≥140 mg/dl.
- **BMI** is calculated as weight in kilograms divided by squared height in meters (BMI = weight (kg) / height (m)^2).
- **BP** was measured using an Omron BP Monitor to determine the prevalence of hypertension. BP of each respondent was taken on three separate occasions and the readings recorded in the biomarker questionnaire with interval of 5 minutes between readings.
- **Glucose** was measured using the glucose oxidase method for laboratory estimations. The readings were considered equivalent to blood glucose levels in the range of 10-600 mg/dl.

**Statistical analyses**

NFHS-4 data were manually obtained from the website. Descriptive statistics are reported. Body mass index (BMI) was calculated by dividing weight in kilograms by squared height.
in meters [BMI= weight in kg/ (height in m)$. Underweight was diagnosed when BMI was <$18$ kg/m$^2$ and overweight and obesity was considered when BMI was $\geq 25$ kg/m$^2$. Hypertension was diagnosed when either the participant was a known hypertensive on medical treatment or systolic BP was $\geq 140$ mm Hg and/or diastolic BP $\geq 90$ mmHg according to standard definitions. Non-fasting blood glucose estimation was performed in the NFHS-4 survey. Two criteria for diagnosis of hyperglycemia were adopted, high and very high glucose with random values $>140$ mg/dl and $>160$ mg/dl respectively. The urban-rural prevalence of risk factors and other conditions has been adjusted to the population proportions at each district to provide district-level estimates. Data of women and men are reported separately.

We developed heat-maps of each of the risk factors in each district of Rajasthan state using Microsoft Excel program in MS Office Version 14.0. Prevalence of various risk factors is reported from green (low prevalence) to red (high prevalence) according to percent prevalence of risk factors separately in men and women in each district of Rajasthan. Urbanization index was derived as proportion of urban to total population of each district available from the NFHS data sheets. Human Development Index of various districts was obtained from Government of Rajasthan report. Female and male literacy levels were obtained from NFHS-4 fact sheets. Pearson’s correlation coefficient (r) as well as Spearman’s correlation coefficient (rho) were calculated to determine significance of associations of these risk factors. Logarithmic correlation of district level prevalence of obesity BMI $\geq 25$ kg/m$^2$, hypertension and hyperglycemia (random blood glucose $>140$ mg/dl) was performed using graphics program in MS Excel. P values less than 0.05 were considered significant.

**Results**

NFHS-4 adopted a two-stage sampling design in rural and urban areas of each district of India. Survey interviewed 601,509 households, 699,686 women and 103,525 men from 28,583 primary sampling units composed of villages in rural areas and census enumeration blocks in urban areas in 640 districts of the country. In Rajasthan data are available from all the 33 districts (Table 1). In Rajasthan 34915 households were evaluated with sample size of 41965 women aged 15-49 years and 5892 men aged 15-54 years.

Data regarding various risk factors- overweight or obesity (BMI $\geq 25$ kg/m$^2$), hypertension and hyperglycemia (random capillary glucose $>140$ mg/dl) in women and men are shown in Table 1. There is a wide variation in prevalence of these risk factors in women as well as men. Prevalence of obesity in women and men is significantly greater in central and northwestern districts (Figure 1). In women and men, respectively, low prevalence of obesity ($<5\%$) is in 6 and 14 districts, moderate prevalence 5-15% in 18 and 13 districts and high prevalence ($>15\%$) in 9 and 6 districts (Table 1).

Prevalence of hypertension also shows significant regional differences. Among women its prevalence is significantly greater in eastern districts while in men is more in central and northwestern districts of the state (Figure 1). Prevalence of hypertension is more in men than in women. Hypertension prevalence among women is low in most of the districts of the state while in men almost a third of districts have high prevalence (Table 1). Regional variation is also observed in prevalence of hyperglycemia (Figure 1). Among women prevalence of hyperglycemia is significantly greater in eastern regions of the state while in men is more in southeastern and central districts. There is a low prevalence of hyperglycemia among women in most of the state while in men more than half of the districts have moderate or high prevalence.

We performed correlation analysis of prevalence of obesity with hypertension and hyperglycemia in women and men. Obesity prevalence shows a significant positive correlation with hypertension in both women ($r=0.45$, rho$=0.48$) and men ($r=0.43$, rho$=0.57$) ($p<0.001$). Prevalence of obesity shows a significant positive correlation with hyperglycemia in women ($r=0.20$, rho$=0.11$) but not in men. Analysis of association with hypertension and hyperglycemia prevalence showed a weak positive correlation in men ($r=0.11$, rho$=0.07$) and an insignificant negative correlation in women ($r=-0.07$, rho$=-0.10$). Correlation of hypertension prevalence with severe hyperglycemia (blood glucose $>160$ mg/dl) also shows insignificant results ($r$ value, women $0.07$; men $0.11$; rho value, women $0.10$, men $0.07$).

Correlation (parametric and non-parametric) of obesity hypertension and hyperglycemia with macrolevel social risk factors- urbanization, HDI and female literacy is reported in Table 2. Urbanization significantly correlated with obesity and hypertension in both women and men (Figure 2). District-level HDI also positively correlated with obesity and hypertension (Figures 3) and so did female literacy (Figure 4). There is insignificant correlation of hyperglycemia with all the social determinants studied.

**Discussion**

This study shows that there are significant regional differences in prevalence of major non-communicable
Table 2: Correlation of urbanization, human development and educational status with obesity, hypertension and hyperglycemia

<table>
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<tr>
<th></th>
<th>Obesity</th>
<th>Hypertension</th>
<th>Hyperglycemia</th>
</tr>
</thead>
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<td>Spearman rho</td>
<td>Pearson r</td>
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<tr>
<td><strong>Urbanization index</strong></td>
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<td>Women</td>
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<td>0.591***</td>
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<td>Men</td>
<td>0.509**</td>
<td>0.484**</td>
<td>0.328*</td>
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<td><strong>Human development index</strong></td>
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<td>Men</td>
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<td><strong>Educational status</strong></td>
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<td>Women</td>
<td>0.458**</td>
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<tr>
<td>Men</td>
<td>0.336*</td>
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</table>

*p<0.05, **p<0.01, ***p<0.001

Fig. 2: Logarithmic correlation of district-level urbanization with prevalence of overweight/obesity, underweight, hypertension and hyperglycemia in women and men

Diseases risk factors—obesity, hypertension and hyperglycemia—in Rajasthan, the largest state of the country. There is a significant positive correlation of obesity and hypertension with macrolevel social determinants of health—urbanization, human development index and female educational status.

Previous studies from India have reported regional differences in prevalence of cardiovascular diseases and their risk factors. Registrars General of India reported greater age-adjusted cardiovascular mortality in southern and eastern states of the country. Coronary heart disease (CHD) mortality was greater in south India while stroke was more common in the eastern Indian states. Epidemiological studies have reported that CHD prevalence is greater in South Indian states as compared to others. Geographic variation in cardiovascular risk factors has been reported in previous reviews. To determine regional variation in cardiovascular risk factors, India Heart Watch study was performed in 11 cities in the country and reported that compared with national average, prevalence of most risk factors was significantly lower in cities of eastern region with lower prevalence of overweight, hypertension, hypercholesterolemia, diabetes and metabolic syndrome. It was also observed that cities with low social and human development index had lowest prevalence of these risk factors similar to the present study. The first phase of ICMR-INDIAB study was performed in 4 states (Tamilnadu, Maharashtra, Jharkhand and Chandigarh) and reported interstate variations in cardiovascular risk factors. However, there are no epidemiological studies that compared within-state differences in prevalence of risk factors and our results cannot be compared to previous data from India. Multiple studies from UK, USA and other developed countries have reported large regional differences in prevalence of various cardiometabolic risk factors. Our data shows that similar differences exist in Rajasthan.

Previous NFHS reports have highlighted regional differences in multiple social determinants of health including literacy, access to health care, family violence and smoking. The present study, derived from the NFHS-4 data, for the first time has reported that there are significant within state differences in various non-communicable disease risk factors. Important omissions in NFHS-4 are lack of data on important lifestyle determinants of various cardiovascular risk factors. We have no district specific data on smoking, alcohol intake, healthy diet (high fruits and vegetables,
low saturated and trans fats) and physical activity. This is a major study limitation. It is hoped that the next rounds of NFHS shall focus on these important determinants or “causes of causes” of cardiovascular and other non-communicable diseases.

Our study shows that there is a significant positive correlation of important CVD risk factors (obesity and hypertension) with macrolevel social determinants- urbanization, HDI and educational status (Table 2). This is in contrast to developed countries where CVD risk factors are greater in more deprived populations and low socioeconomic locations. Our data suggest that in India (and other lower-middle income countries) the cardiovascular disease epidemic is still not fully mature. It has been reported that in earlier phase of epidemiological transition the prevalence of CVD and its risk factors is greater in more literate people living in affluent regions. Once the transition matures, there is inversion of the disease pattern with greater CVD and risk factors among the deprived. Eckert and Kohler performed a systematic review of urbanization and health in developing countries. Accordingly, the urbanization was associated with
a lower risk of undernutrition and a higher prevalence of overweight and risk factors for chronic diseases, similar to the present study.

This study has a few strengths and multiple limitations. Strengths include population wide sampling and vast geographic representation. The foremost limitation is inclusion of only young adults (women 15-49y, men 15-54y) for assessment of various NCD risk factors- obesity, hypertension and hyperglycemia. This has resulted in a significantly lower prevalence in the NFHS as compared to earlier population based studies in different regions of India. Secondly, although the criteria for measurement and diagnosis of hypertension are according to international guidelines, the diagnosis of hyperglycemia is based on ill-defined criteria. WHO has recommended measurement of either a fasting glucose alone or fasting and 2-hour post-glucose estimation for diagnosis of diabetes. In the present study the random capillary blood glucose of >140 mg/dl has been taken as hyperglycemia and >160 mg/dl as severe hyperglycemia. Both these criteria are not according to any national or international guidelines. This may have resulted in a falsely skewed distribution of hyperglycemia. This is apparent when we correlate prevalence of obesity and hypertension with hyperglycemia. No significant correlation emerges. Thirdly, we have performed only a macrolevel analysis using the NFHS-5 fact-sheets available at the website. It is likely that when individual level data are similarly analyzed different results may emerge. Fourthly, we have not reported on other major lifestyle CVD risk factors including smoking, tobacco use, alcohol abuse, unhealthy diet and sedentary lifestyle as these data are not available. We have also not evaluated associations of the prevalence of hypertension and hyperglycemia with available health systems and availability of appropriate health care. And finally, we have not identified regional differences in causes of deaths in the present study, nor gleaned data from Registrar General of India database on district level mortality. Other limitations are sampling bias, small urban representation in smaller districts and failure to adjust for regression-dilution bias especially in hypertension.

In conclusion, the present study shows that there are significant regional differences in prevalence of various non-communicable disease risk factors (obesity, hypertension and hyperglycemia) in Rajasthan. Positive association of multilevel social determinants (urbanization, human development index and literacy) with obesity and hypertension shows that these factors are important. The WHO Commission on Social Determinants of Health suggests focus on multiple factors to ameliorate socioeconomic disparities in risk factors. These include focus on better daily living, creating mechanisms to avoid and manage inequitable distribution of power, money and resources and implementation of policies to improve health. The present study shows that the syndemics of obesity and hypertension are associated with urbanization and greater human development in India. This shows that urbanization and human development has not led to better health outcomes in contrast to high-income countries.

Focus on improved quality of urban living which has been suggested by Lancet Commission on Urban Health is important. This commission has reported that cities are complex systems and urban health outcomes are dependent on many interactions. Inequalities in health outcomes should be recognized at the urban scale and creating good health needs dialogue between stakeholders to improve decision making and practices. Improving human development to decrease non-communicable disease outcomes is difficult but can be achieved through implementation of policies for risk factor control and individual empowerment.

References
Knowledge and Awareness of the Health Care Workers about the Hepatitis B Infection and their Vaccination Status in a Newly Started Medical College

Kansara Dev¹, Kuyare Sunil S², Gupta Abhay³, Khote Gajanan⁴, Shukla Akash⁵, Kishore Bisure⁶*

Abstract

Introduction: Healthcare workers (HCWs) are at high risk of hepatitis B virus infection (HBI) and so the present study was carried out to assess the knowledge of HCWs in a tertiary care medical college about HBI and hepatitis B vaccine (HBV).

Methods: After obtaining approval from Institutional Ethics Committee and informed consent from the study participants, HCWs that included teaching faculty, resident doctors, medical students, nurses, laboratory technicians, administrative staff and support staff (ward boys, attendants and sweepers) were administered a validated questionnaire. Descriptive statistics was applied for the categorical variables and the Chi-square test of association was used to assess the statistical significance of variables.

Results: A total of 300 HCWs were recruited for the study. Although, the overall knowledge amongst all the HCWs was found to be 68%, only 35.3% HCWs knew the transmission risk by needle stick injury (NSI). Similarly, only 40% correctly knew the precautions to be taken for preventing an NSI and 17% for the steps to be taken to disinfect a blood splash. Almost 92.7% (278/300) HCWs were aware about the availability of a vaccine, of which only 41% (1123/300) knew that vaccine will not work in case the patient is already infected. When asked about the steps to be taken in case of an NSI in non-vaccinated HCWs, only 54.7% (164/300) replied about treatment with both immunoglobulin and vaccination. A total of 160 (53.3%) HCWs were found to be vaccinated. The most common reason for not taking vaccination included an improper understanding of HBV and the infection it causes.

Conclusion: To conclude, the study highlights good knowledge about hepatitis B infection with requirement of more emphasis on the practical aspects of management in a case of NSI/blood splash and can guide to improve the vaccination status and knowledge of HBI amongst HCWs.

Introduction

Hepatitis B infection (HBI) is a blood-borne viral disease affecting the general population with India being in its intermediate prevalence zone. The prevalence of HBI in the general population varies between 3.1 and 11%¹⁴ and nearly a million deaths have been reported annually due to chronic liver disease complicating HBI.¹

Health care workers (HCWs) have been identified amongst the ‘high risk’ population for contracting the disease.¹ HCWs are exposed to patients with HBI as well as asymptomatic carriers of the Hepatitis B virus (HBV) and thus are at higher risk of acquiring the disease. A report has estimated that HCWs are at a four times greater risk for HBI as compared to the general public.⁵, ⁶ Interestingly, surgeons, laboratory staff and staff dealing with hemodialysis are at a greater risk as compared to physicians and dentists.⁶

The most common mode of transmission is via a needle stick injury (NSI) and through an increased exposure to blood and body fluids.², ⁷, ⁸ Prevalence of HBI amongst HCWs due to NSI has been reported being between 1 and 31%, the variability being attributed to differences in the respective diagnostic methods.⁹ The WHO has estimated that 3 million NSIs occur every year amongst HCWs, 66,000 (2.2%) of which result in the victim developing serological positivity for HBI.³, ⁴ The HCWs infected with Hepatitis B while on duty have been reported to be 1% from an Indian study.³

HBI can be prevented by an effective vaccination schedule which has an efficacy of upto 95%. In India introduced the Hepatitis B vaccine for vaccinating HCWs in 2002, and since then a drastic reduction in the prevalence of HBI was observed.¹⁰ However, there were no standard monitoring procedures for vaccination of HCWs, leading to a poor coverage in this population. Further, the efficacy of Hepatitis B vaccine was adequate only if three doses were administered.¹¹ Lack of awareness of HBI along with a poor coverage of vaccination program are major hurdles in prevention of the disease amongst HCWs.², ⁵, ¹¹

The term HCWs in our study includes not only clinicians, surgeons and medical students but also laboratory personnel, administrative staff, support staff (ward boys, attendants, sweepers). However, the same is not true for a large majority of other similar studies who have focused either on medical students or nurses only.¹²-¹⁴ Hence, we initiated the present study to assess...
the knowledge of HBI and HBV in a recently functioning medical college from India.

Methodology

Study design and ethics
A cross-sectional, questionnaire-based qualitative study was carried out amongst the health care workers (HCWs) of a newly started medical college in Mumbai between May and September 2016. The study was initiated after the approval from the Institutional Ethics Committee and after obtaining informed consent from the study participants.

Study participants and study procedure
The following categories of HCWs were included: teaching faculty, resident doctors, medical students, nurses, laboratory technicians, administrative staff and support staff (ward boys, attendants and sweepers).

A structured questionnaire was prepared by the study team - which included two medical students, a microbiologist and a gastroenterologist - and was subsequently administered to the study participants. The questionnaire (Appendix) was validated for content validity and field validity. Test-retest reliability was assessed using Cohen’s kappa coefficient (0.8). The questionnaire had the following themes: demographic and general information of the participants, gender, employment status, year of appointment in the present institute, years of experience at present institution, overall years of experience in the hospital set up/medical field; The second theme was related to the knowledge and awareness of the participant in regards to HBI and the last one was about knowledge about HBV.

Statistics
Descriptive statistics using proportions was carried out for all the variables. Chi-square test was carried out for association of categorical variables. With a type 1 error of 5%, power of 80% and population size of 1000 and an expected prevalence of 50%, sample size has been calculated to be 280, rounded to 300.

Results

Demographics
The validated questionnaire with reliability coefficient of 0.8 (Cohen’s kappa co-efficient), was administered to the HCWs. A total of 454 HCWs gave consent for participation and the questionnaire was subsequently provided to them. 66.1% of them (300/454) returned completely filled questionnaires.

Of these 300, 16.0% (48/300) questionnaires were received from faculty teachers, 13.7% (41/300) were resident medical doctors (hereby will be called as residents), 17.3% (52/300) were first year medical students, 13.0% (39/300) were nursing staff, 16.7% (50/300) were laboratory technicians, 12.0% (36/300) were administrative staff and 11.3% (34/300) were support staff.

Of the 300 HCWs, 42.0% (126/300) were men, and the rest 58.0% (174/300) were women with mean (SD) age of 32 (11) years. Amongst the HCWs who were working, 45.0% (135/300) had experience of less than one year, 30.3% (91/300) had experience between one to five years, and 24.7% (74/300) had experience of more than five years in the medical field.

Knowledge about Hepatitis B infection
The overall knowledge amongst all the HCWs was found to be 68.0%.

90.0% of HCWs knew that Hepatitis B is a virus (Table 1). However, correct knowledge about its transmission, risk to HCWs, signs and symptoms, asymptomatic phase, treatment modality, infective agents and preventive measures were found to be slightly above 60%. Surprisingly, only 35.3% (106/300) HCWs knew the chances of HBI transmission by needle stick injury (NSI) to be 30%. Similarly, only 39.8% (78/196) correctly knew the steps to be taken for preventing needle stick injury and 17.3% (29/168) for disinfecting a blood splash.

Knowledge about modes of transmission and clinical features of HBV

The responses regarding the correct knowledge about the transmission of HBV were given correctly by more than 70% HCWs for all the modes of transmission, except for blood donation (44.0%), contaminated food (62.0%) and contaminated water (62.0%). HCWs were well acquainted with infective agents for transmission of HBI (>60% answered correctly). However, knowledge about saliva being a mode of transmission (36.0%, 108/300); urine not being one (49.7%, 149/300) and for amniotic fluid being one (59.7%, 179/300) (which may not be known to some) was low. Knowledge was found to be better in residents (90.4%) followed by faculty (89.4%) and lowest amongst administrative staff (45.6%) and support staff (37.9%).

Regarding the clinical features of HBI, most of the questions were answered correctly (>70.0%). However, symptoms like diarrhoea (40.0%), breathlessness (53.3%) and the asymptomatic phase (41.7%) were poorly known. Nearly 4/5 of the study participants correctly identified the precautions related to blood transfusion and using a condom during sexual intercourse.

Knowledge about Hepatitis B vaccine
Of the total, 92.7% (278/300) HCWs were aware of the availability of vaccine, of which only 41% (123/300) knew that vaccine will not work in case patient is already infected prior to vaccination.

Although 64.7% (194/300) HCWs had knowledge regarding the number of doses required to constitute a complete course of vaccination, only 32.3% (97/300) HCWs knew about the importance of carrying out the
subsequent anti-HBs titer test for checking the efficacy of vaccination. The HCWs agreed that there is a need for anti-HBs testing post vaccination (78.7%, 236/300) but almost the same number (83.7%) wanted the test to be done even for the general public, which is not required.

When asked about the precautions and actions to be taken following a needle stick injury (NSI) in non-vaccinated HCW, only 54.7% (164/300) replied regarding treatment with both immunoglobulin and vaccination. However, when asked if the same incidence occurred with a prior vaccinated HCW, only 18.7% (56/300) replied that there is no need for treatment in regards to hepatitis B.

When asked about the appropriate time for taking vaccination, 67.2% (195/300) responded that the vaccination can be taken anytime whereas 26.9% (78/300) and 5.9% (175/300) said during childhood and during adulthood respectively.

Sub-group analyses of knowledge of the study participants

Table 2 lists the differences observed in the proportion of study participants with correct knowledge on various aspects of HBI and HBV. As expected, a statistically significant increase in proportion of overall knowledge of HBI was observed with faculty and resident doctors followed by other streams of participants. However, the knowledge of faculty and residents who are actually been approached for treatment/guidance in case of an NSI/ blood splash was found to be poor (almost less than 30%), the same was nil for support staff and only 2.8% for administrative staff.

Vaccination status of HCWs

Of the total, 53.3% (160/300) HCWs were found to be vaccinated, which includes 83.33% (40/48) faculty; 87.8% (36/41) residents; 32.7% (17/52) medical students; 66.7% (26/39) nurses; 64% (32/18) laboratory staff; 25% (9/36) admin staff and none (0/34) of the support staff.

Of the total, only 17.3% HCWs had got themselves tested for HBI. Only 45.0% (72/160) took the booster dose and only 21.9% (35/160) had tested for anti-HBs titer post vaccination. 40.0% (64/160) were vaccinated ‘on the job’ whereas 33.1% (53/160) during college. 20% said that they were vaccinated during their childhood while 6.3% (10/160) were unaware when they were vaccinated. 43.7% (131/160) took the complete course of vaccination while 7.7% (23/160) took less than three doses.

Motivation factors for vaccination

Of the total, 36.3% (109/300) HCWs responded to the question related to the motivation factor for vaccination of which 33.9% (37/109) replied that they took vaccination as they were aware of HBI while 12.8% (14/109) took due to job related needs and 11.9% (13/109) opined that this was a pre-requisite for their jobs. 10.0% (11/109) said that they had fear of getting infected or they saw a hepatitis B infected patient. Guidance of family members [8.3% (9/109)] and that of a family doctor [5.5% (6/109)], hospital policy and teacher’s motivation [3.7% (4/109)] were also motivational factors. 2.8% (3/109) HCWs took vaccination at their vaccination program while another 3 took the vaccination on their own. 0.9% (1/109) each was inspired to take vaccination from reading books, watching television, under influence of peers and informed during an orientation program for MD students. 0.9% (1/109) HCW did not know his/ her motivation factor for vaccination.

Reasons for not taking vaccination

Of the total, 46.7% (140/300) HCWs provided 174 reasons for not taking vaccination. The most common reason was lack of knowledge of the existence of the vaccine [32.1% (45/140)]. Lack of knowledge of HBI [20% (28/140)] and lack of knowledge of necessity of vaccination [28.6% (40/140)] were also common. The other reasons were a lack of time for vaccination [11.4% (16/140)]; or the conception that the vaccine is only for children [7.1% (10/140)] or that the vaccine is too expensive [7.1% (10/140)].

Training program for creating awareness about HBI and HBV

Of the total, 6.3% (18/288) HCWs underwent training related to HBI. 98.3% (283/288) voiced their desire to participate in such training programs.

Discussion

This study was carried out in response to the recent decision by the Ministry of Forest, Environment and Climate Change (MoFECC), Government of India of mandatorily monitoring and administering the complete course of hepatitis B vaccination to all HCWs.

The medical college in which the present study was carried out, started in 2015. However, the hospital attached to it was established in 1970. The hospital started out with only 30 beds, but presently boasts a bed strength of 636.

It was observed that 33.9% (154/454) HCWs did not return the questionnaire and thereby declined to participate in the study indicating a lack of knowledge, possibly due to apathy and/or low level of awareness about hepatitis B infection in a proportion of HCWs.

Nearly 2/3rd of the participants had fair knowledge regarding HBI and 93% were aware of the availability of HBV but only half of them were vaccinated.

Greater proportion of patients with adequate knowledge of HBI was observed in our study compared to previous other studies. However, we observed a poor understanding of the study participants (particularly support staff) regarding the precautions to be taken in case of a NSI and blood splash. This reiterates the need for undertaking training sessions at frequent intervals to sensitize all
HCWs for incorporating a safe practice. It was also found that nearly 1/4th of the study participants were lacking knowledge of the modes of transmission of HBI which was much lower than the estimates of other studies. This could possibly be due to a misunderstanding between Hepatitis B virus and other hepatitis viruses. Additionally, similar to other studies, saliva was not identified as an infectious sample in our study.

This study highlights that the knowledge of women is significantly higher (p=0.002) than men which is similar to the findings of Ghomraoui et al., 2016 and Thakur Singh et al., 2015. However, Tatsilong et al., 2016 has shown men to be 3.2 times more knowledgeable than women, while Abiola et al., 2016 has shown no statistically significant difference between genders. This observation could also be attributed to more number of female nurses participation in this study, who deal with patients with HBI on a daily basis. It was also found in the present study that a significant difference in knowledge existed between faculty, residents, support staff and administrative staff, as was also observed in other similar studies.

When compared with the years of experience in medical field, surprisingly, the HCWs with less than or equal to one year of experience had more knowledge as compared to other groups. This is contradictory to the findings of other similar studies, which show no significant difference of knowledge between groups with different years of experience in the medical field. This could be attributed to recently acquired knowledge of the newly joined HCWs or to better health education in school/colleges or to a wider media related awareness.

It was found in this study that fair knowledge regarding HBV was prevalent amongst HCWs, unlike a recent study from Korea among Family Medicine residents where the authors have reported an appropriate knowledge among just 10% of the study participants. Although fair knowledge of HBV was observed amongst all the study participants, only 50% of treating doctors (faculty and residents) knew about the correct management of NSI in vaccinated, as well as non-vaccinated HCWs. This is notable, especially because most of the other cadres have reported to be relying on doctors to provide appropriate management of an NSI.

We also observed a low vaccination status of HCWs in the present study, which is similar to the findings of other similar studies. The outlined reasons for not vaccinating were also similar to other similar studies.

**Strengths and limitations of this study**

The present study gives an in-depth view of the existing knowledge and awareness about hepatitis B infection and the present vaccination status of the HCWs thereby giving direction for further planning about training sessions and vaccination program at the institute.

The present study used an extensive validated questionnaire with Cohen’s kappa co-efficient of 0.8. This study was carried out in a newly started medical college. All the employees themselves filled the questionnaire, thus reducing the possibility of investigator bias. The participants were from diverse occupational classes thus providing the complete representation of a health institution.

**Limitations**

We could not highlight the reasons for not knowing the steps of management for NSI/blood splash as we did not expect such poor knowledge for the same. The education level of the participants was not noted for the present study.

The sample size was not large enough for sub-stratification and post-hoc sub-group analysis.

**Conclusion**

To conclude, the study highlights good knowledge about HBI and a need to emphasize on the practical aspects of management in case of NSI/blood splash. This may improve the vaccination status and knowledge of HBI amongst HCWs.

**Acknowledgements**

We are grateful to all the Health care workers who have willingly participated in this research.

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**Availability of data and materials**

Data will be available from the corresponding author upon request.

**References**


Catheter Related Right Atrial Thrombus in Patients on Maintenance Hemodialysis: Results of a Single Centre Retrospective Study from a Tertiary Care Hospital

Shrirang Bichu1, Parag Tilve2, Tushar Dhakate3, Pranit Kakde3, Nikhil Bhasin3, Pankaj Jawandhiya3, Abhishek Dixit3, Pranesh Jain4, Viswanath Billa5, Ashok Kirpalani6, Pravin Amin7

Abstract

Objective: To study the magnitude of the complication of catheter associated right atrial thrombus (CRAT) in patients with tunnelled central venous hemodialysis catheters (THC) for maintenance hemodialysis (MHD).

Material and methods: A retrospective study was conducted among patients with end stage kidney disease (ESKD) with THC for MHD who had undergone screening for CRAT with a 2D-echo (2DE) just before removal of the THC. The occurrence of CRAT and other clinical parameters were documented in these patients.

Results: A total of 28 patients (mean [SD] age 51 [15.2] years; females 17 [60.7%]) were included in the study. CRAT was observed in 5 (17.9%) patients. There was no difference in mean age in patients with or without thrombus (48±13.02 vs 51.61 ± 15.78 years; p = 0.61). History of diabetes and hypertension was present in 2 and 2 patients respectively. There was no significant difference in the period the THC was in place in patients with or without CRAT (13±7.8 months vs 10.57±5.66 months; p = 0.54). There was no association between catheter related blood stream infection (CRBSI) and CRAT (p = 0.29)

Conclusion: The incidence of CRAT in patients with THC for MHD was 17.9%. Patients with THC for MHD should be examined for presence of CRAT before removal of THC to prevent fatal pulmonary thromboembolism.

Introduction

Patients suffering from end stage kidney disease (ESKD) need renal replacement therapy for life sustenance. Renal replacement therapy includes three modalities namely, hemodialysis, peritoneal dialysis and kidney transplantation. Hemodialysis is the most frequently used renal replacement modality in India and elsewhere. An appropriate vascular access is necessary to carry out hemodialysis. Of the three types of vascular accesses used frequently, central venous dialysis catheters, arteriovenous grafts and arteriovenous fistula (AVF), the latter is the most appropriate option.1 It is recommended to create an AVF when the estimated glomerular filtration rate (eGFR) falls below 25 ml/min, well before MHD is needed.2 However, most patients are not compliant and need a central venous hemodialysis catheter to commence hemodialysis. Many other patients present late needing immediate dialysis, in which situation a central venous hemodialysis catheter is the only available option. Hence majority of patients initiate dialysis with a central venous hemodialysis catheter.3

Hemodialysis catheters are either non – tunnelled or tunnelled, the latter being preferred both by clinicians and patients. THCs are superior to non – tunnelled catheters as the incidence of venous thrombosis and stenosis is less and the tunnelling and cuff reduce the chances of CRBSI. These properties ensure that they can be retained in situ for a prolonged period.4 However, they are more expensive and trained personnel are needed to insert them under fluoroscopy.

The frequency of insertion of THC has increased considerably in India. When compared to an AVF, THC have higher risk of infection, thrombosis and catheter related dysfunctions resulting in higher morbidity and mortality.5 In view of these observations THC should only be used as a bridge till AVF matures and can be accessed for hemodialysis.6

THC may lead to asymptomatic catheter-associated right atrial thrombus (CRAT) which may contribute to increased morbidity and mortality.8 The incidence of CRAT has been reported to be 18 % in patients with THC.9 Removal of THC in patients with a CRAT may lead to pulmonary embolism and death.10 In our centre we documented a case of CRAT diagnosed as an incidental finding on 2D echocardiography (2DE). Following this observation all patients in our unit are screened for CRAT before removal of THC. There has been only one study reported, looking at the incidence of CRAT in patients with THC. Currently there are no published data from India on the incidence of CRAT in patients with THC.

Objectives

To study the magnitude of the complication of CRAT in patients with THC for MHD in ESKD patients and to understand the factors associated with
The procedure was done in the hospital’s ethics committee. CRAT formation.

Materials and Methods

This is a retrospective, observational study conducted at Bombay Hospital Institute of Medical Sciences, a tertiary care hospital in Mumbai. ESKD patients on MHD having a THC in situ between August 2017 to July 2018 who underwent 2DE before removal of the THC as a part of the unit protocol, were included in the study. Patients who died or were lost to follow-up were excluded from the study. Patients with acute kidney injury were excluded from the study.

The THCs were inserted by the same experienced critical care consultant under ultrasound guidance. The procedure was done in the interventional radiology laboratory. All THCs were Palindrome® manufactured by Covidien (now Medtronics). The tip was placed in the mid right atrium in 26 patients and at the junction of superior venacava and right atrium in 2 patients.

The 2DE studies were carried out by the same experienced cardiologist using Philips EPIQ 7C machine. Assessments were performed in apical, parasternal and subcostal views in accordance with the current recommendations. When CRAT was identified, its size, mobility, echogenicity and attachment to the

### Table 1: Baseline demographic characteristics of study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>51 (15.2)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>11 (39.3%)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>17 (60.7%)</td>
</tr>
<tr>
<td>Mean (SD) BMI (kg/m²)</td>
<td>24 (5.5)</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>22 (78.6%)</td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>10 (35.7%)</td>
</tr>
<tr>
<td>Diabetes and hypertension both</td>
<td>9 (32.1%)</td>
</tr>
<tr>
<td>Mean (SD) duration of hemodialysis during screening (months)</td>
<td>32.4 (24.9)</td>
</tr>
<tr>
<td>Mean (SD) amount of heparin used (IU)</td>
<td>6196.4 (1796.8)</td>
</tr>
<tr>
<td>Mean (SD) duration of THC in place before removal (months)</td>
<td>11 (6)</td>
</tr>
</tbody>
</table>

### Table 2: Laboratory parameters in study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin g/dl (n=28)</td>
<td>9.90 (1.24)</td>
</tr>
<tr>
<td>Albumin g/dl (n=28)</td>
<td>3.34 (0.73)</td>
</tr>
<tr>
<td>Calcium mg/dl (n=27)</td>
<td>6.31 (3.41)</td>
</tr>
<tr>
<td>Phosphorous mg/dl (n=27)</td>
<td>4.95 (1.69)</td>
</tr>
<tr>
<td>Uric acid mg/dl (n=26)</td>
<td>5.67 (2.69)</td>
</tr>
</tbody>
</table>

THC were assessed.

The frequency of occurrence of CRAT was documented along with the duration of THC in situ, use of antplatelets or anticoagulants, use of erythropoietin, history of thrombosis of previous non-tunnelled dialysis catheter or AVF, heparin usage, any variation in heparin locks, demographic characteristics, comorbid conditions, cause of ESKD, type and frequency of dialysis, blood pump speeds and blood tests (haemoglobin, complete blood count and complete biochemistry) were recorded. Any complications related to THC insertion were recorded.

This study protocol was approved by the hospital’s ethics committee.

### Statistical Methods

A t-test was performed for comparing the means of 2 set of continuous data. Fisher’s exact test and Pearson Chi-Square tests for comparing two categorical datasets were used. Variables were expressed as “mean ± standard deviation”, while categorical variables were expressed as number and percentage. R programming language was used for doing these statistical tests. To check if CRAT was linked to some parameters and if there were any nonlinear relationship between the various variables and CRAT, classification and regression trees method was used. A p level less than 0.05 was considered significant in the statistical analysis.

### Results

A total of 28 patients were included in the study. The baseline demographic characteristics and the laboratory parameters of overall study population are shown in Tables 1 and 2 respectively.

The mean (SD) age of overall patient population was 51 (15.2) years. The study population was dominated by females (17[60.7%]). History of hypertension was more common than history of diabetes in study population (78.6% vs 35.7%). Three patients (10.71%) had ischemic heart disease.

Viral serology was negative in all patients except one who had presence of HCV antibodies. Another patient showed presence of antinuclear antibodies.

CRAT was observed in 5 (17.9%) of the 28 studied patients. The demographic characteristics, cause of CKD, history of diabetes and hypertension and duration of THC are shown in Table 3. The characteristics of CRAT on 2DE study are shown in Table 4.

Out of the 5 patients, 3 were males and 2 were females. The mean age in patients with or without thrombus was 48±13.02 and 51.61 ± 15.78 years, respectively, with no significant difference (p = 0.61).

The range of duration of hemodialysis during screening ranged from 10 months to 72 months. The duration of THC in these patients ranged from 8 months to 24 months. The mean duration of THC in patients with or without CRAT was 13±7.8 months and 10.57±5.66 months. There was no significant difference in duration of THC between the two groups (p = 0.54).

Two patients had history of diabetes whereas history of hypertension was present in all 5 patients. Of the 10 diabetic patients, 2 (20%) had CRAT, while 3 of the 18 non-diabetic individuals (16.7%) had CRAT, with no significant difference between the groups (p = 1.0). CRAT formation was detected in 22.7% (5/22) of the hypertensive patients and in none of the

### Table 3: Characteristics of patients with CRAT

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>BMI (kg/m²)</th>
<th>Cause of CRAT</th>
<th>History of DM</th>
<th>History of HTN</th>
<th>Duration of HD during screening (mths)</th>
<th>Duration of THC (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>F</td>
<td>26.15</td>
<td>LN</td>
<td>No</td>
<td>Yes</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>47</td>
<td>F</td>
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</table>

*CGN: Chronic glomerulonephritis; LN: Lupus nephritis; DN: Diabetic nephropathy; DM: Diabetes mellitus; HTN: Hypertension; HD: Hemodialysis

### Table 4: Characteristics of CRAT

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>CRAT size (cms)</th>
<th>Fixed to CVC</th>
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<td>RWMA, LVH</td>
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<td>60</td>
<td>4 × 2</td>
<td>Yes</td>
<td>immobile</td>
<td>LVH</td>
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</tbody>
</table>

LVH: Left ventricular hypertrophy; RWMA: Regional wall motion abnormality
non-hypertensive patients (p = 0.55).

A total of 10 (35.7%) patients in the study were on antplatelets. All patients were receiving erythropoietin. None of the patients were on any form of anticoagulation therapy. All patients received fractionated heparin during hemodialysis. All patients received thrice a week hemodialysis. Both ports of the THC were locked with unfractionated heparin solution in all patients.

**Discussion**

A large proportion of patients with ESKD needs THC for initiating MHD as they present late with ESKD needing immediate dialysis or they may have refused an AVF earlier. Some patients need THC because of secondary AVF failure. In this study 12(42.8%) patients had THC as their first vascular access, 8(28.5%) had it after an initial non-tunnelled dialysis catheter and 8 (28.5%) had THC placed because of secondary AVF failure.

THC placement procedure may be complicated by arterial punctures, pseudoaneurysm, hematoma, air embolism, pneumothorax and malposition. None of these complications were encountered in the current study, as the procedure was performed by an experienced operator, under ultrasound and fluoroscopic guidance in the interventional radiology laboratory.

Other complications seen with THC include CRBSI, catheter malfunctioning, venous thrombosis and stenosis. In the current study, 3 THCs were removed because of malfunctioning, 4 because of CRBSI, 1 following successful live related kidney transplantation and 19 following AVF maturation and 1 patient died with THC in situ. None of the patients in the study had venous thrombosis. Six patients (21.4%) out of the 28 studied had CRBSI. Four of these had their THCs removed, 2 of whom had CRAT. Two patients were treated appropriately with antibiotics and did not require removal of THC for CRBSI. These two were removed later after AVF maturation. 33.3% (2/6) patients with CRBSI had CRAT. This association was not statistically significant (p = 0.2855). Dilek et al too in their study did not find any correlation between CRBSI and CRAT.

CRAT is a less frequently observed complication but has serious life-threatening implications. In the current study, CRAT was observed in 17.8% (5/28). There is limited data regarding the frequency of occurrence of CRAT. In the only study looking at the incidence of CRAT, the incidence found was to be 18% (9/50). Since CRAT is largely asymptomatic, it generally goes undetected in clinical practice and hence the incidence of this serious complication is underestimated or may go undetected. CRAT was detected by 2DE in most published data. Magnetic resonance imaging and computerised tomography scan have been used to detect intracardiac thrombi. But 2DE is freely available, is non-invasive with no risk of radiation and is a cheaper screening tool prior to THC removal. The sensitivity and specificity of 82.2% and 95.3% respectively of 2DE in detecting intracardiac thrombi ensures its efficacy.

What predisposes patients to develop CRAT is unclear. The duration of the THC in situ does not seem to be a risk factor for CRAT. In the current study the duration of THC in patients with or without CRAT was 13.0 ± 7.81 and 10.56 ± 5.66 months respectively, and this was not significant (p = 0.5384). This is comparable to outcomes in previously published data. The age, BMI, cause of kidney disease, use of antiplatelets, haemoglobin values, history of secondary AVF failure due to thrombosis, low ejection fraction or diastolic dysfunction had no relation to CRAT formation. All patients were on similar protocol of unfractionated heparin during dialysis. All patients received erythropoietin for the treatment of CRAT and venous thrombosis, as this increases the risk of bleeding.

The treatment options include anticoagulation, endovascular techniques and surgery. Anticoagulants have been proposed as the first-line treatment of CRAT provided there are no contraindications. If anticoagulation is used, 2DE at regular intervals should monitor progress. Endovascular techniques may be considered if facilities are available in the institute. Surgical thrombectomy can be considered in cases where the thrombus is more than 6 cms. Both endovascular and surgical techniques carry a certain element of risk leading to serious complications.

In this study, of the five patients with CRAT three were treated with anticoagulation. These three patients had large CRAT measuring 4 × 2 cms, 3 × 3 cms and 3.5 × 2.5 cms. One of the patients died of an unrelated cause. Complete resolution of the CRAT in the other two patients occurred after 4 months. This ensured that the risk of pulmonary thromboembolism was mitigated while removing the THC. The remaining two of the five patients with CRAT needed removal of the THC because of infections. One had fungal...
The frequency of occurrence of this fatal pulmonary thromboembolism is probably more adherent to the THC, which needs to be proved.

In a retrospective analysis of reported cases the overall mortality was 18.3% (13/71), significant predictors being advanced age, presence of complications and non-removal of the THC. In another retrospective study looking at the incidence of CRAT, a mortality of 44.4% (4/9) over a 2 years follow-up was reported. The current study data did not show any significant relationship between the presence of CRAT and mortality. Out of the five patients with CRAT, one died due to an unrelated cause.

Although all efforts are made to counsel patients with chronic kidney disease to have an early AVF placed when the eGFR is 25 ml/min, most patients do not comply resulting in the need for THC to initiate hemodialysis. CRAT was found in 17.8% (5/28) of patients in the current study. With the more widespread usage of THC in recent years, an increased number of CRAT may be encountered. Since the risk of fatal pulmonary thromboembolism is high during the removal of the THC, mandatory screening with a 2DE before removal may reduce fatal outcomes. The frequency of occurrence of this complication and being primarily asymptomatic but potentially life threatening, screening for CRAT once in two months could be beneficial in early diagnosis and possible therapy with anticoagulation with finally removal of THC. A larger prospective observational study is needed to validate this.

Conclusion

The frequency of CRAT in patients with THC was 17.9% in the current study. There is limited data about incidence of CRAT in Indian patients on MHD. The present study provides insights into the possibility of asymptomatic CRAT in patients with THC used for MHD. The results may provide guidance in ensuring screening for asymptomatic CRAT with a 2DE before removal of THC thus reducing the risk of serious pulmonary thromboembolism.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Association of Plasma Procalcitonin with Various Components of Metabolic Syndrome and Insulin Resistance in Urban Indian Population: A Novel Biomarker

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Abstract

Rationale: Chronic low-grade inflammation is proposed as the keystone in pathogenesis of metabolic syndrome. The inflammatory biomarker Procalcitonin which is produced by adipose tissue, can serve as a biomarker for insulin resistant state present in metabolic syndrome.

Objectives: To evaluate the association of plasma Procalcitonin (PCT) with components of metabolic syndrome (abdominal obesity, dyslipidemia, hypertension, and hyperglycemia) and with insulin resistance as compared to healthy controls.

Design: In this case-control study Plasma Procalcitonin was measured in patients with metabolic syndrome and compared to healthy controls. Its association was investigated with insulin resistance, individual components of metabolic syndrome, cardiovascular complications and microalbuminuria.

Result: Plasma Procalcitonin was significantly higher (mean 0.55 ± 0.60 ng/ml, Median 0.156 ng/ml) in 53 patients with metabolic syndrome (n = 53) as compared to 26 healthy controls (p <0.001). PCT significantly correlated with level of Insulin Resistance (p<0.01), Waist Circumference, S. Triglycerides, S. VLDL (p <0.05), fasting blood glucose (p <0.01) and inversely with S. HDL (p<0.05). PCT was significantly higher in patients with cardiovascular complication (n=16/53, z = -7.137) and in those with microalbuminuria (n=18/53, z = -7.265) as compared to cases without complications.

Conclusion: Raised plasma procalcitonin levels in the normal range are associated with insulin resistance and components of the metabolic syndrome (abdominal obesity, hypertriglyceridemia, high VLDL, low HDL and hyperglycemia), suggesting its role as a promising biomarker.

Introduction

Metabolic syndrome is a growing epidemic in India affecting more than one-third population in large cities. Metabolic syndrome (MS) which is a clustering of metabolic risk factors (at least three out of five components) namely abdominal obesity, hypertension, hyperglycemia, high serum triglyceride levels and low serum HDL. MS harbingers the co-occurrence of risk factors for both type 2 diabetes and cardiovascular diseases (CVD) which have been attributed to the underlying insulin resistance (IR). MS being a constellation of conditions, there is lack of any one specific and sensitive laboratory parameter which can facilitate its prompt detection. Also, estimation of insulin resistance is a tedious process. Hence, a reliable biomarker for the diagnosis of MS and insulin-resistant state is the need of the hour.

Chronic low-grade inflammation is the key pathophysiological factor related to insulin resistance and thus to all the components of MS, for which secretory role of adipose tissue has been implicated. Procalcitonin is a polypeptide precursor of hormone calcitonin that is released in response to systemic inflammation not only by neuroendocrine cells of the lungs, intestine, and thyroid (C cells), but also by adipose tissue. Thus plasma procalcitonin can serve as a potential biomarker for detection of obesity-related low-grade inflammation even in the very early stages. Available data in this regard is scarce and there is no data from India. Abbasi et al have described plasma procalcitonin to be associated with obesity, insulin resistance and all components of MS in a study from Netherland. Indians with MS are phenotypically different from Caucasians, they tend to develop hypertension, hyperglycemia, and hypertriglyceridemia at lower levels of BMI and Waist Circumference. Furthermore, Indians have an excess of truncal subcutaneous fat which positively correlates with insulin resistance. This makes the generalization of existing data to Indian population difficult.

The objective of this case-control study was to assess plasma procalcitonin levels in patients with metabolic syndrome as compared to healthy controls and to study its association with Insulin Resistance and components of the Metabolic syndrome; namely dyslipidemia, hypertension, hyperglycemia and abdominal obesity. We also aimed

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to gauge the association of plasma procalcitonin with complications of metabolic syndrome at presentation and during short-term follow-up.

Participants and Methods

This prospective case control study was performed on patients presenting to a tertiary referral center in Mumbai from Sept 2011 to June 2015 after obtaining permission from the institutional ethics committee. Patients aged more than 18 years with Metabolic Syndrome were enrolled as cases (n=53) after voluntary informed consent. MS was defined as per International Diabetes Federation (IDF) consensus 2006 definition as participants having increased waist circumference (South Asian cutoff ≥ 90cm for men and ≥80cms for women) plus any two of the following: Triglycerides ≥ 150 mg/dl or treatment for triglycerides; HDL cholesterol < 40 mg/dl in men and < 50 mg/dl in women or treatment for HDL; Systolic BP > 130 or diastolic BP > 85 mm Hg or treatment for hypertension; Fasting plasma glucose ≥ 100 mg/dl, or treatment for type 2 diabetes.

Patients on lipid lowering drugs, with S. Creatinine > 1.2 mg/dl and those who had any evidence of infections were excluded. Age and sex matched healthy volunteers were recruited as controls (n=26).

For all the participants, complete medical history and physical examination including BMI and anthropometric measurements were recorded. Complete lipid profile, fasting plasma insulin, fasting blood glucose, microalbuminuria, electrocardiogram and echocardiography were performed for all the participants. Insulin resistance was calculated by the homeostasis model assessment for insulin resistance (HOMA-IR) using the formula: Fasting Glucose (mg/dl) X Fasting Insulin (mIU/ml) / 405.10,11

Plasma Procalcitonin (PCT) was analyzed using fully automated PCT sensitive KRYPTOR Random Access Analyzer.12,13 (BRAHMS PCT sensitive LIA; Hennigsdorf, Germany). Blood sample volume needed was 50 µl, collected in EDTA aliquots with an incubation time of 19 minutes. Its measuring range is between 0.02 and 5000 ng/ml. The functional assay sensitivity (defined as the lowest analyte concentration that can be determined with an inter-assay CV < 20%) was 0.06 ng/ml with a probability of 95%. Its Analytical sensitivity (the detection limit calculated using the imprecision profile) is 0.019 ng/ml with a probability of 95 %. The intra-assay Coefficient of Variation (CV) and the inter-assay CV is 2-3% on the whole PCT concentration range. The antibodies used in this assay show no cross-reaction with human calcitonin (up to 2.5 ng/ml), human ketalocalcin (up to 10 ng/ml), human α-CGRP and β-CGRP (up to 4 µg/ml). This assay technique has been described previously.12

All participants were screened for cardiovascular complications and microalbuminuria at the time of presentation and for next 3 months of follow-up.

Descriptive statistics were reported as frequency and percentage for categorical variables and mean and SD for continuous variables. Multivariate adjusted linear regression analysis was used to assess the independent predictor of IR. Correlation between plasma PCT, IR and various components of MS. IR was calculated using Pearson correlation coefficient (2 tailed tests). Mann-Whitney test was used to compare plasma PCT levels in cases versus controls; and also, amongst cases which had complications of metabolic syndrome. "p value" ≤ 0.05 from two-sided tests was considered statistically significant.

Results

There were 30 (56.6%) males in the cases group (those with MS). Of 26 controls, 14 (53.8%) were males. Cases and controls were matched with respect to age and gender. Demographic, anthropometric, clinical and biochemical parameters of cases and controls are described (Tables 1, 2). Plasma Procalcitonin (PCT) levels were higher in cases (Mean 0.55 ± 0.60 ng/ml; Median 0.156ng/ml; Range 0.002 – 1.990) as controls (Mean 0.001 ± 0.0 ng/ml; Median 0.00ng/ml; Range 0 – 0.01). This difference was statistically significant (Mann - Whitney “z” : -7.02). PCT significantly correlated with level of Insulin Resistance as measured by HOMA-IR (Pearson correlation coefficient 0.771; p<0.01) (Figure 1). Amongst the various components of MS, PCT significantly correlated with Waist Circumference, S. Triglycerides, S. VLDL (P< 0.05) and with fasting blood glucose. (P< 0.01) and inverse significant correlation with S. HDL (Figure 2 and Table 3). However, there was no significant correlation between PCT and Systolic/ diastolic BP, S.
Cholesterol and S. LDL. Amongst all the components of MS, only fasting blood glucose was found to be independent predictor of IR on multivariate regression analysis (p<0.001).

PCT was significantly higher in patients with cardiovascular complication (n=16/53, z = -7.137) as compared to cases without complications. This partially conforms with findings of Abassi et al. where both procalcitonin and insulin resistance were associated with all the components of metabolic syndrome in Dutch population. This can be attributed to the ethnic differences and hence future studies are warranted to explore the role of procalcitonin and insulin resistance in Indian Population.

The fact that Procalcitonin is implicated in the pathophysiology of metabolic syndrome is further amplified by the finding that cases with metabolic syndrome with complications (cardiovascular and renal) had higher levels of Procalcitonin as compared to those without. This points towards the higher level of inflammation in this subset of population, which is at a higher risk for complications and thus will be maximally benefitted by aggressive therapeutic measures.

With the help of advanced PCT sensitive KRYPTOR Random Access Analyzer, it is now possible to measure plasma Procalcitonin within the normal range, with lowest detectable value of 0.06ng/ml. As there was no data addressing value of in plasma Procalcitonin in the general population, healthy age and sex matched controls were recruited only for the comparison of procalcitonin levels. We found that the level of plasma Procalcitonin was significantly lower in controls as compared to cases.

The importance of plasma procalcitonin as a biomarker for metabolic syndrome is highlighted by the fact that it is an easily available, one-time test which doesn’t require fasting samples and the results are available within 25 minutes of centrifugation of the sample. Thus, it saves time and resources and is ideal for a developing country like ours. The scope of plasma procalcitonin can be extended to screening of relatively younger obese population who have not yet developed all the components of MS, but are at significantly higher risk as result of obesity related inflammation. This, if proved in larger prospective studies, may help detection of this younger population which will benefit maximally from rigorous life style modifications and timely pharmacological intervention. This may lead to prevention of further complications.

Smaller sample size and shorter duration of follow-up were notable limitations of our study. Also, as our participants belonged to urban India, our results may be not be generalizable to whole population. This paves way for larger population-based study with longer follow-up for assessment of the role of procalcitonin as a biomarker for insulin resistance and metabolic syndrome.

In conclusion, our findings based on urban tertiary referral center data, suggest that higher plasma procalcitonin levels in the normal range are associated with insulin resistance and increased measures of abdominal obesity (waist circumference), other components of the metabolic syndrome (hypertriglyceridemia, low HDL, high VLDL and hyperglycemia) and higher rates of complications. Thus, plasma procalcitonin is a promising novel biomarker for chronic low-grade inflammation secondary to adipocyte...
S. Procalcitonin and waist circumference

We acknowledge the cooperation of all our patients.

References

Fig. 2: Correlation of S. Procalcitonin with components of metabolic syndrome
Adherence of Observational Studies Published in Indian Journals to STROBE Statement

Vetrivel Babu Nagarajan¹, Shruti Bhide², Hemant R Kanase¹, Anirudha Vyankatesh Potey³, Firoz Tadavi⁴

Abstract

Purpose/Aim: Quality of reporting is very important in medical research. To ensure a uniform and detailed reporting of observational studies experts came out with a checklist of items, named ‘Strengthening the Reporting of Observational Studies in Epidemiology’ (STROBE). The present study examines the adherence of observational studies published in selected Indian journals from 2011-2015 to STROBE Statement.

Methods: 7 open access Indian journals, belonging to different specialities were selected. All the observational studies were assessed by 5 independent reviewers for the adherence to STROBE checklist as ‘yes, partly and no’. The completeness of reporting was also assessed.

Results: A total of 271 articles were examined. Only 10 items (Abstract, Background/rationale, Objectives, Study Setting, Data sources/measurement, Quantitative variables, number of Participants at each stage, Characteristics of study participants, Key results) out of the 22 items and their subdivisions of STROBE were adhered to, in more than 70% of articles. Other 10 items (bias, subgroup analysis, addressing missing data, sensitivity analysis, reason for non-participation, flow diagram, missing data) had adherence in less than 30% of the articles. The completeness of reporting was 50.5%, 49.12% and 43.06% in cross-sectional, cohort and case control study, respectively.

Conclusion: The overall reporting was suboptimal. The completeness of reporting did not differ in the three types of observational study designs.

Introduction

Over the years the number of scientific articles published across various fields have increased. These articles aim to promote the scientific understanding and health care. Quality of reporting is very important in medical research. Poor reporting of the studies may lead to poor assessment of the scientific research and misinterpretation of the results of the study.¹ To ensure this, various guidelines were developed by experts like the CONSORT for Randomized Control Trials, PRISMA for systematic reviews and meta-analysis, STARD for Diagnostic Studies, and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) for observational studies.²³ Studies have shown that 9 out of 10 articles published in clinical speciality journals are observational studies.³ To ensure a uniform and detailed reporting of observational studies, STROBE statement was introduced in 2007.⁴ The STROBE statement has 22 items which detail and guide the authors reporting of various parts of the article like title and abstract, introduction, methods, results and discussion.⁵ Many journals recommend adherence to the STROBE statement to improve the quality and completeness of reporting observational studies. There is a lack of assessment of quality of reporting of observational studies in Indian journals. Hence, we decided to assess the reporting of the observational studies published in some Indian journals dealing with different specialities in accordance with the strobe statement.

Methodology

We selected 7 Indian journals that are available in public domain belonging to the following specialities: dermatology, anaesthesia, pharmacology, rheumatology and chest medicine. Study was initiated after obtaining exemption (EC/OA-166/2016) from the Institutional Ethics committee.

All original research articles published in the selected journals between 2011-2015 were screened and observational studies were included for analysis. Review articles, RCTs, lectures, special contributions, case reports, seminars, training and education, summaries of domestic and foreign theses, research topic announcements, posters and animal studies were excluded. Genetic linkage studies, infectious disease modelling or case reports and case series as STROBE recommendations do not specifically address topics and they were excluded.

The selected observational studies were classified into case control, cohort and cross-sectional studies. Adherence of the articles to the items in STROBE checklist were reviewed by two reviewers. The checklist was marked ‘yes’ if the item was described well, ‘partly’ if described partially, and ‘no’ if not addressed at all. In case of any discrepancies between the two reviewers, all the authors reviewed and reached a decision. The percentage of articles complying with the STROBE checklist were calculated. The completeness of reporting was assessed using the formula (Yes/
The completeness of reporting was compared between different observational study designs using Kruskal Wallis test.

The adherence of all articles to the individual items of STROBE is given in Table 1.

The adherence of the articles according to the type of study designs is given in Table 2.

The overall mean Completeness of Reporting (COR) was 49.86 ± 13.46%. According to type of study design, the COR for cross sectional studies was 50.5 ± 12.15% for cohort studies was 49.11 ± 17.54% and for case control studies was 44.39 ± 16.34%. The COR score of between the different study designs did not differ significantly (p = 0.1460).

Results

After screening 1092 articles from the 7 journals published between the years 2010 to 2015, 271 articles were selected and categorized into cross sectional, cohort and case control studies (Figure 1).

The adherence of all articles to the individual items of STROBE is given in Table 1.

The adherence of the articles according to the type of study designs is given in Table 2.

The overall mean Completeness of Reporting (COR) was 49.86 ± 13.46%. According to type of study design, the COR for cross sectional studies was 50.5 ± 12.15% for cohort studies was 49.11 ± 17.54% and for case control studies was 44.39 ± 16.34%. The COR score of between the different study designs did not differ significantly (p = 0.1460).

Discussion

In the present study, most commonly reported items (>70%) were background and objectives, settings, outcome, key results and interpretation. Items with low reporting (<30%) were bias, sample size calculation, flow diagrams and addressing the missing data. Study design, study size, statistical methods used, limitations of the study, generalisability of the study and funding were adhered in 30-70% of the article. These findings were similar across all three categories of observational studies.

Few studies have assessed the compliance of articles with STROBE in different specialties. Langan et al observed that dermatology journals had low reporting regarding sample size calculations (7%), missing data (6%), losses to follow-up (12%), and statistical methods (14%) and the source of funding (9%). Kim et al observed poor reporting in case control and cohort studies published in Korean Journal of Family Medicine regarding study designs (10%), bias (13%) and study size (0%). Similar findings were noted in the present study.

Titles have a major impact on the article citations. Several factors like length of the title and presence and absence of certain words decide the impact and citation of the article. As per STROBE statement, the type of the study should be mentioned in the title. Although this might not help much in the overall narrative of the article, it helps in the ease of identification by the readers and indexing in digital libraries. In the current study, only 19% of the studies mentioned about the type of study in the title. Only 15% of the articles mentioned the type of the study in the title in case control and cohort studies published in Korean Journal of Family Medicine while that in dermatology journals, it was 87%.

Skipping the type of study in title may not impact the interpretation of the study much but not explaining the type of study and key elements in the body of the article will affect the reporting quality of the study. This puts readers at a disadvantage in identifying the type of study and affects the overall comprehensibility. STROBE recommends the authors to mention the type of study clearly as case control, cohort or cross sectional. In the current study, only 50% of articles mentioned type of study, while in dermatology journals, reporting was high about 70%.

The trend of not reporting the bias is uniform across the journals. In majority of articles the issue of bias and ways to address bias was not handled adequately. Not reporting bias can alter the conclusions and hence the interpretations of the results of the study. Bero quotes that “lack of reporting bias can make the findings more reasonable than they actually are”. In current study, only 12% articles mentioned bias and the ways to address the bias. Comparable results were reported by Sorenson et al (3%) in observational studies describing hand surgery and Kim et al (13%) in articles of Korean Journal of Family Medicine, while Langan et al reported a little higher percentage of reporting bias (31%). Researchers should report the identified potential sources of bias to make the reporting comprehensive for the readers.

STROBE mandates the authors to detail method of determining the sample size. Reporting sample size helps the readers to make their own decisions on whether the associations were really significant or by chance. Mentioning only the number of patients recruited for the study may leave the reader perplexed about the adequacy of the sample size. 34% of articles in this study reported how the study size was obtained. Comparing this with other studies, 4.5% in dermatology journals, 17% in plastic surgery journals shows that reporting sample size is an area of
Another area where there was poor reporting was in the statistics section, whereby most articles (52%) mention the type of statistical test to be used, they fail to mention how the missing data (1%) and loss to follow up (1%) was addressed in cohort and case control studies. In the present study, 95% of the articles deliberate the key results and 87% interpret them in the discussion section. 64% of the articles discussed the generalizability of the findings of the study. Only about 40% of the articles mentioned the limitations of their study. Although, there is a fear of rejection in authors if limitations are discussed, explaining limitations helps in a great way to prevent misunderstanding and helps in future to plan a better study.13

It is found that across the studies done checking the compliance to STROBE checklist, some of the items had low reporting percentages consistently like bias, sample size calculation, flow diagrams, addressing the missing data and limitations, while some had consistently high reportage. In the present study items which had more than 70% compliance across the studies were abstract, background and rationale, the study objectives, the inclusion criteria, participants. Plausible explanation for this may be due a fact only a very few journals have endorsed STROBE as a requirement of article submission for the authors. Journals like PLOS One has published a strong endorsement for STROBE checklist in their editorials.6 However, a study found that this kind of endorsement led to a little change in reporting observational studies.4 Items

### Table 1: STROBE statement adherence of all the articles (n=271)

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like finance and declaring the conflict of interest remains in the purview of the editorial decisions of the respective journals. In the present study 57% mentioned about the funding sources. No articles declared the funding source in the 35 articles studied describing hand surgery.¹²

A study by Garin et al¹³ in the dermatology journals published between 2004 and 2010, found an overall improvement in reporting the observational studies which was not attributed to STROBE checklist. A systematic review by Rao et al¹⁶ in journals publishing articles related to CKD, concluded that only four items (objectives reporting, choice of quantitative groups and description of and carrying out sensitivity analysis) out of the 22 items of the STROBE had some improvement after STROBE statement. A systematic review by Stevens et al¹⁷, on relation to the journals endorsement of reporting guidelines to completeness of reporting led to the finding that the completeness did not change despite the journals’ endorsement of guidelines. A Randomized Control Trial by Cobo et al¹⁸ on the quality of manuscripts reviewed using reporting guidelines including STROBE found that adhering to the reporting guidelines improved the final quality of the manuscript, however they failed to demonstrate it conclusively. They also concluded that the authors follow conventional reviews than adhering to the guidelines, which probably indicates difficulties faced by the authors in following the reporting guidelines.

The study had few limitations. The journals selected for evaluation were not specific to any specialty, and many specialty journals were not included. The timeline for selection of the articles was arbitrarily fixed from 2011 to 2015.

Conclusion

The overall reporting of articles according to STROBE was suboptimal. Items such as bias, flow diagram, missing data, subgroup analysis, mentioning of the type of article in the title, had less than 30% adherence, some of the items such as abstract, background, rationale, key results, interpretation of results, objectives and study settings had a good 70% of articles adhering to them. The completeness of reporting did not differ in the three types of observational study designs.

References

Thrombophilia Profile of Portal Vein Thrombosis in Young

Chilaka Rajesh1, Manish Manrai2*, AP Dubey3, Rajat Shukla4, Atul Jha5, Rajan Kapoor6

Abstract
The abdominal vein thrombosis is an unusual and rare, but potentially a life threatening form of thrombosis. Much is known, studied and published about the venous thrombosis in the lower limbs and to some extent in upper limbs, where as the abdominal vein thrombosis still remains an unexplored area. The diagnosis of abdominal venous thrombosis has increased with awareness of the entity and the availability of better imaging modalities. Despite advances made in the management of venous thrombosis, the knowledge of events predisposing to abdominal thrombosis is largely unknown. This gap in knowledge needs to be studied and analyzed for better patient management. The study aims at analysing various risk factors in patients of abdominal venous thrombosis.

Portal vein thrombosis is common among abdominal vein thrombosis. It can occur in patients without co-existent liver disease and its prevalence has been reported to lie between 0.6% and 44%. Both hereditary and acquired risk factors have been implicated in the etiopathogenesis. Many of these risk factors are also known risk factors for more common venous thrombosis such as deep vein thrombosis of lower limbs and pulmonary thromboembolism, whereas some are specific for abdominal vein thrombosis. Most studies on etiological factors for abdominal vein thrombosis included selected patient groups and only have a limited sample size. This study enrolled 70 patients of abdominal vein thrombosis, out of 70, 38 patients were diagnosed as PVT. Mean age of patients was 37.6±10.3 years.

Among hereditary causes, hyperhomocysteinemia was the most common cause. Acquired risk factors like Myeloproliferative Neoplasms present in 06 patients (15.8%) and Anti Phospholipid Antibody syndrome was diagnosed in 04 (10.5%). Exposure to high altitude present in 09 (23.7%) patients of Portal vein Thrombosis. Hence abdominal venous thrombosis requires extensive thrombophilia evaluation, as management differs in various acquired factors like Myeloproliferative neoplasms and Anti Phospholipid Antibody syndrome.

Introduction
The abdominal vein thrombosis is an unusual and rare, but potentially a life-threatening form of thrombosis. Most commonly it includes hepatic vein thrombosis (Budd- Chiari syndrome), portal vein thrombosis (PVT), rare forms such as splenic vein thrombosis, and mesenteric vein thrombosis. The splanchnic venous system consists of the portal vein (formed by the union of the superior mesenteric vein and the splenic vein) and its branches that direct blood flow from the gastrointestinal organs to the liver. The terminal portal venules drain into the sinusoids, after which the blood flows from the small to large hepatic veins, ultimately reaching the inferior vena cava.

PVT, a rare disorder, occurs commonly in patients with chronic liver disease, characterized by thrombosis in extra-hepatic portal veins with or without involvement of intra hepatic branches. Patients may present with variceal bleed, splenomegaly or in rare cases with bowel infarction, if it extends to involve mesenteric veins. Though PVT can occur in patients without co-existent liver disease, its prevalence has been reported to lie between 0.6% and 44% with an increasing frequency in decompensated disease and/or concomitant hepatocellular cancer,1,2

Both hereditary and acquired risk factors have been implicated in the etiopathogenesis of abdominal vein thrombosis. Several of these risk factors are also known risk factors for more common venous thrombosis such as DVT and PTE, whereas, some are specific for abdominal vein thrombosis. Most studies on etiological factors for abdominal vein thrombosis included selected patient groups and only have a limited sample size. The exact prevalence of inherited deficiencies of the natural anticoagulants anti thrombin,3 protein C and protein S is difficult to determine in patients of abdominal vein thrombosis, because low levels of these factors may also be caused by reduced liver synthesis function, which frequently occurs in these patients. Timing of testing for these factors, as well as long term treatment with Vitamin K antagonists in these patients also hampers the accurate diagnosis.

Myeloproliferative neoplasms (MPN) defined as clonal haematopoietic stem cell disorders characterised by an excessive production of mature and functional granulocytes, red blood cells and/or platelets are implicated in 30-40% of patients with abdominal vein thrombosis as well as rarely in other types of VTE. JAK2V617F mutation, a common gain of function mutation leading to development of MPN, is present in nearly all patients with polycythemia vera and in about 50% of patients with essential thrombocythemia and primary myelofibrosis. The same mutation has been described in large number of patients with abdominal vein thrombosis. Though the exact pathogenetic mechanism of thrombosis in MPNs is not known, but besides characteristic erythrocytosis and

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Received: 12.06.2018; Accepted: 16.08.2018
thrombocytosis, platelet and leucocyte functional abnormalities seem to have a pathogenetic role.\(^3\)-\(^10\)

There is limited Indian data regarding thrombophilia profile in patients with portal vein thrombosis. In this study we analyzed the clinical and risk factor profile in patients of PV. Also, we tried to determine the prevalence of MPNs and JAK2V617F mutation as well as their diagnostic role in these uncommon disorders.

### Materials and Methods

Our study was a cross sectional observational study, including 38 patients of PVT, who presented to Gastroenterology and Hematology departments of Army Hospital Research and Referral, New Delhi from October 2015 to April 2017. The diagnosis of PVT was confirmed by appropriate radiographic imaging such as Doppler ultrasonography, computed tomography and magnetic resonance imaging. A recently formed thrombus is virtually anechoic. Doppler imaging will show absence of flow in part or all of the lumen. A CT scan without contrast can show hyper attenuating material in the PV. After injection of contrast agent, lack of luminal enhancement is seen. Interview technique was used to collect the information regarding acquired risk factors such as oral contraceptive use, pregnancy, cirrhosis, infection, neoplasm, abdominal surgery, regarding prior episode of thrombosis and family history of thrombosis. All cases of cirrhosis were excluded in this study.

Blood samples were collected in 3.2% trisodium citrate (1:9), EDTA vials and plain vials. A complete hemogram, liver function tests and renal function tests were done in all cases. Extensive thrombophilia workup was done in all patients, but focusing cases. Extensive thrombophilia workup was done in all patients, but focusing cases. Extensive thrombophilia workup was done in all patients, but focusing cases. Extensive thrombophilia workup was done in all patients, but focusing cases. Extensive thrombophilia workup was done in all patients, but focusing cases. Extensive thrombophilia workup was done in all patients, but focusing cases. Extensive thrombophilia workup was done in all patients, but focusing cases.

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PVT: Portal vein thrombosis; MVT: Mesenteric vein thrombosis; SVT: Splenic vein thrombosis; HVT: Hepatic vein thrombosis

Table 1: Types of abdominal vein thrombosis

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<td>Factor V Leiden mutation</td>
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<td>SCT</td>
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<td>AT III deficiency</td>
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<table>
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<th>Acquired causes</th>
<th>N (%)</th>
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<td>JAK 2 positive MPN</td>
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<td>APLA syndrome</td>
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MPN: Myeloproliferative neoplasms; AT III: Antithrombin III; ET: Essential thrombocytosis; SCT: Sickle cell trait antibodies (Lupus anti coagulant, Anti B2 glycoprotein I antibodies and Anti cardiolipin antibodies) and Paroxysmal nocturnal hemoglobinuria (PNH), which are not affected either by the timing of testing or does not require stopping of anticoagulant therapy. JAK2 mutation study was done by PCR followed by polyacrylamide gel electrophoresis. PNH flow cytometry was done by FLAER (Fluorescein labeled proaerolysin method). The LAC (lupus anticoagulant) and ACA (anticardiolipin antibody) were tested twice twelve weeks apart in positive cases.

<table>
<thead>
<tr>
<th>Percentage</th>
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| Pain abdomen was most common presenting symptom in 26 (68.4%) patients, whereas 12 patients had an incidental diagnosis. Among hereditary causes of thrombophilia, hyperhomocysteinemia was the most common entity found in 10 (26.3%) patients, followed by Protein C and S deficiency in 06 and 04 patients respectively. Acquired thrombophilic risk factors for thrombosis were present in 10 (26.3%). JAK2 mutation positive with MPN was detected in 05 (13.2%) patients, whereas JAK2 negative MPN (Essential thrombocytoisis) was present in one patient of PVT (Table 2). Antiphospholipid antibody (APLA) positivity was diagnosed in 04 (10.5%) of 38 patients. PNH flowcytometry was positive for none of the patients. Exposure to high altitude present in 09 (23.7%) patients of PVT.

### Discussion

Both hereditary and acquired risk factors have been implicated in the etiopathogenesis of abdominal vessel thrombosis, however some factors are specific for it. Our present study conducted at tertiary care hospital of armed forces primarily focuses on acquired and inherited thrombophilic factors with special emphasis on exposure to high altitude. JAK2 mutation and myeloproliferative neoplasms (MPN). There is an ease with evaluation of acquired thrombophilic factors in comparison to most of the inherited factors as testing for acquired factors is independent of timing of tests, and does not require cessation of oral anticoagulants. There is very limited data on incidence of these acquired thrombophilic factors including exposure to high altitude, JAK2, PNH and APLA syndrome in patients with abdominal vein thrombosis.

We found Portal vein thrombosis (PVT) as the most common site of thrombosis, detected in 38 (54%) of 70 patients diagnosed as abdominal vein thrombosis, which is commensurate with previous Indian and Western studies. An Indian Study by Prabha Sawant et al has reported 90% PVT among patients with abdominal vein thrombosis, in a study consisting of 30 patients.\(^11\)

There is very limited data regarding association of abdominal vein thrombosis and exposure to high altitude area (HAA). It was
suggested that at such extreme altitudes, pronounced dehydration due to increased respiration might predispose to thrombosis. Reduced activity, decreased thirst and appetite, compounded by hyperviscosity, associated endothelial damage and alterations in coagulation factors are implicated in pathogenesis of thrombosis. Anand et al reported 17.4% cases of abdominal vein thrombosis in patients exposed to HAA with mean duration of 10.2 months. Since our centre is a service hospital mainly catering to serving soldiers posted at different locations in the country, association with HAA exposure was extensively evaluated in our study. We found 09 (23.7%) patients had exposure to HAA, with stay above 3000 meters for mean duration of 12 months.

JAK2 mutation was detected in 13.2% (5/38) of PVT. Hemoglobin and leucocyte counts were significantly higher in JAK2 positive patients as compared to JAK2 negative patients (p<0.01) with the mean hemoglobin (16.05 ± 2.02 gm/dl) and the mean total leucocyte count (9246 ± 4251.21/mm³) was found. 05 patients of PVT with JAK2 mutation had MPN on bone marrow evaluation. Most of the studies have not included JAK2 and MPN evaluation in patients with abdominal vein thrombosis. Our study has demonstrated significantly higher prevalence of JAK2 in these patients as compared to study published by Shetty et al which has found JAK2 in 8.8% and 5% in patients of BCS and PVT respectively. We should suspect and consider testing for JAK2 mutation whenever there is normal to high hemoglobin, leucocyte or platelet counts in a patient with large spleen or portal hypertension.

Anti phospholipid antibodies as a risk factor for abdominal vein thrombosis is not extensively studied, and also there is lack of definite Indian or western data about its prevalence in such patients. Our data concludes higher prevalence of APLA syndrome in patients with PVT as compared to the study by Rajani et al (10.8 vs 7%). Though prevalence of APLA has been estimated to be around 5-15%, but most of these studies have taken single measurement, whereas for the correct diagnosis of the antiphospholipid syndrome, these should be measured at two different occasions 12 weeks apart. Hence abdominal venous thrombosis requires extensive thrombophilia evaluation especially for acquired factors like JAK 2 mutation analysis for MPN in patients with high counts and APLA antibodies for diagnosis of APLA syndrome. It will be helpful for appropriate management as treatment differs in each one of them.

Hence abdominal venous thrombosis requires extensive thrombophilia evaluation especially for acquired factors like JAK2 mutation analysis for MPN in patients with high counts and APLA antibodies for diagnosis of APLA syndrome. It will be helpful for appropriate management as treatment differs in each one of them.

References
Efficacy of SGLT2 Inhibitors as the Fifth Drug in the Management of Type 2 Diabetes Mellitus in Asian Indians not Controlled with at least 4 Oral Antidiabetic Drugs

Vijay Panikar1, Shashank R Joshi1, Narayan Deogaonkar2, Jimit Vadgama3*, Nikhil Nasikkar3, Tejas Kamat3, Saalim Sheikh3, Chandni C Jain3, Tejal Wagle3

Abstract

Aim: To evaluate the efficacy of SGLT2 inhibitors as an add-on therapy along with stricter lifestyle modification in Asian Indian type 2 diabetes mellitus (T2DM) patients with inadequate glycemic control despite receiving an optimum dose of at least 4 oral antidiabetic drugs (OADs).

Methods: A retrospective analysis of data of 808 T2DM patients being treated with an SGLT2 inhibitor (Dapagliflozin, Empagliflozin or Canagliflozin) as an add-on drug in patients with inadequate glycemic control despite receiving optimum doses of at least any four OADs (metformin, sulphonylureas, pioglitazone, DPP4 Inhibitors, alpha-Glucosidase Inhibitors) and who preferred not to initiate insulin.

Results: The average age of the patients included was 51.63 years (SD ± 9.88). 57.7% were males. Average weight was 81.95±16.08 kg. Mean duration of diabetes was 34.08±39.04 months. The mean baseline fasting plasma glucose was 198.21 ± 38.21 mg/dl and mean post prandial plasma glucose was 264.22 ± 45.22 mg/dl. The baseline HbA1c was 8.92 ± 1.47 %. Total 87.4 % of the cases responded to addition of SGLT2 inhibitors during a mean follow-up period of 6 months.

The fasting plasma glucose (FBS) was reduced by -63.65 ± 19.93 mg/dl to a mean FBS of 134.57 ± 33.65 mg/dl (P=0.001). The post prandial plasma glucose (PPBS) was reduced by -79.28 ± 23.57 mg/dl to a mean PPBS of 184.94 ± 38.34 mg/dl (P=0.001). The mean HbA1c reduced significantly by -1.63 ± 0.99 % (P=0.001). The mean weight reduction at 6 months of therapy was -3.8 % decrease from baseline (P=0.001). The mean HbA1c reduced significantly by -1.79 ± 2.03 % (P=0.001).

Conclusion: SGLT2 inhibitors are effective in achieving desired glycemic goals even when used as a fifth add-on drug along with strict lifestyle modification in patients with inadequate glycemic control despite receiving an optimum dose of at least 4 oral antidiabetic drugs (OADs). SGLT2 inhibitors can be effectively used at any stage of diabetes.
There are very few studies available which have looked at the benefits of using multiple oral anti diabetic agents (triple or quadruple therapy) with complementary mechanisms of action. In addition, patients who refuse to initiate insulin are now more receptive and committed to follow diet, exercise and other lifestyle interventions strictly in their desire to avoid insulin initiation.

According to our knowledge, the current study is the first of its kind to evaluate the efficacy of the currently available SGLT2 inhibitors as an add-on therapy along with stricter lifestyle modification in Asian Indian T2DM patients who were treated with at least 4 OADs and failed to attain glycaemic control.

Methods

A retrospective observational study was carried out in patients with T2DM who were being treated and regularly visiting the Diabetes Specialty Clinic, Mumbai. Patients with poor glycaemic control despite receiving optimum doses of at least any four OADs (metformin, sulphonylureas, pioglitazone, DPP4 Inhibitors or alpha-Glucosidase Inhibitors) were treated with any one of the SGLT2 inhibitor (Dapagliflozin, Empagliflozin or Canagliflozin) as an add-on drug. The treatment regimen was decided during consultation.

Inclusion Criteria

- Patients who had records of regular follow up for ≥ 6 months.
- Patients who had poor glycaemic control despite taking at least 4 oral hypoglycaemic drugs (metformin, sulphonylureas, pioglitazone, DPP4 Inhibitors or alpha-glucosidase Inhibitors). (Poor glycaemic control was defined as FPG≥130 mg/dl, PPG≥ 180 mg/dl, HbA1c >7.0)
- Patients who wanted to avoid insulin initiation.
- Patient who had no contraindication for SGLT2 inhibitors.

Exclusion Criteria:

- Patients who were on insulin or previously were on insulin.
- Patients in whom SGLT2 inhibitor therapy were stopped due to:
  - Urinary tract infection
  - Mycotic genital infection
  - Unable to bear cost
  - Symptomatic / troublesome polyuria due to SGLT2i.

Patient’s weight, fasting plasma glucose (FPG), post prandial glucose (PPG) and HbA1c, was regularly assessed during routine clinic visits. All clinical parameters were electronically recorded. At each visit to the clinic, patients were motivated to strictly adhere to the suggested diet, exercise and life style modifications by the treating physician, dietician and diabetic educator. At each visit compliance to both drugs and adherence to lifestyle were recorded.

A total of 808 patients who met the inclusion criteria were considered for the final analysis. Glycemic control was defined by FPG level of ≤ 130 mg/dl and PPG level of ≤ 180 mg/dl. Changes in patient’s weight, HbA1c, post prandial glucose (PPG) and fasting Plasma glucose (FPG) before and after 6 months of SGLT2 inhibitor treatment were recorded and analysed. Statistical calculations were performed with SPSS software. Statistical tests (Student’s t test and Chi square test) were considered significant if P-value was <0.05 at confidence interval of 95%.

Results

A total of 808 patients meeting the inclusion criteria were selected for this study. Out of 808, 57.7% (n=466) were male and 42.3 % (n=342) were females. Patient population had a mean age of 51.63 years (SD ± 9.88) and a mean weight of 81.95 kg (SD ± 16.08). The mean duration of diabetes was 34.08 months (SD ± 39.04) (Table 1).

The percentage of patients on pre-existing OADs such as Sulphonylureas, Metformin, DPP4 inhibitors, Pioglitazone and / or Alpha Glucosidase Inhibitors (AGIs) were as follows in Figure 1.

The baseline treatment regimen included any of the four OAD’s prior to starting on SGLT2 inhibitors. SGLT2 inhibitor therapy was commenced soon after quadruple OAD therapy failure to maintain target blood glucose levels (FPG level of ≤130 mg/dl and PPG level of ≤180 mg/dl). The mean time for follow up was of 6 months. Out of total 808 patients, 87.4% (n=706) responded to the addition of SGLT2 inhibitors as a fifth drug and were able to achieve glycemic control of FPG ≤130 mg/dl and PPGs ≤180 mg/dl. Only 12.6% (n=102) failed to achieve target glycemic levels (Table 2).

The FPG, PPG and weight were analysed initially at baseline and then at each visits after starting add on SGLT2 therapy. The Mean FPG and PPG before adding of SGLT2 inhibitor were 198.21 ± 38.21 mg/dl and 236.9 ± 29.5 mg/dl respectively, which were reduced to 134.57 ± 33.65 mg/dl and
Discussion

In this study we have found that addition of an SGLT2 inhibitor as a fifth drug to the treatment regimen of patients uncontrolled on 4 OAD’s can achieve good glycemic control and can delay the initiation of insulin therapy. It is important to note that the patients were motivated to adhere to a stricter lifestyle.

The 2015 ADA position statement and European Association for the Study of Diabetes about the management of hyperglycaemia in T2DM recommends SGLT2 inhibitor as one of the treatment options in metformin-failing T2DM patients. Various randomized controlled trials have established the efficacy of SGLT2 inhibitors as monotherapy, dual and triple oral therapy.

The American Diabetes Association/European Association for the Study of Diabetes Joint Task Force recommends triple OAD therapy in some patients where agents with complementary mechanisms of action should be used. However there are no studies which have reported the efficacy of SGLT2 inhibitors as an add-on to triple or quadruple oral combinations. There is only one case study in which SGLT2 inhibitor has been added as an add-on to triple combination therapy of metformin, glimepiride, and sitagliptin. After three months of therapy, the patient HbA1c was 6.9% with fasting and postprandial glucose levels to target levels. The mean HbA1c showed a significant fall of -1.63%, which can be a synergistic effect of multiple OADs working on different pathophysiologic mechanisms of type 2 diabetes along with stricter adherence to lifestyle modification. The synergistic effects of two OADs, which work on different pathophysiologic mechanisms of type 2 diabetes, have already been studied and have shown synergistic HbA1c reduction beyond simple addition.

The current study also did emphasize on strict adherence to lifestyle modification in study population, who were highly motivated due to their desire to avoid insulin initiation. In current study, addition of an SGLT2 inhibitor was able to reduce mean weight by 3.03 kg from baseline, which may have further helped in reducing insulin resistance and ultimately superior HbA1c reduction. In addition, almost 80% patients were able to control their diabetes within 4 months of treatment, out of which around 40% had achieved goal in initial 2 months. Our study reflects real life experience and demonstrates that addition of SGLT2 inhibitors as a fifth drug along with strict lifestyle modification will help patients control their diabetes for a prolonged period, delaying insulin initiation.

This study has some limitations because of its retrospective nature. Other important features, such as

Table 2: Outcome of patient achieving target glycemic levels

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No of cases (N=808)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>706</td>
<td>87.4</td>
</tr>
<tr>
<td>Failure</td>
<td>102</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Table 3: Changes in mean FPG, PPG, HbA1c and weight among study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline (X ± SD)</th>
<th>End (X ± SD)</th>
<th>Difference (Baseline - End) (X ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>198.21 ± 38.21</td>
<td>134.57 ± 33.68</td>
<td>-63.65 ± 19.93</td>
<td>0.001</td>
</tr>
<tr>
<td>Post-prandial blood glucose (mg/dL)</td>
<td>264.22 ± 45.22</td>
<td>184.94 ± 23.37</td>
<td>-79.28 ± 23.37</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean HbA1c (%)</td>
<td>8.92 ± 1.47</td>
<td>7.29 ± 1.15</td>
<td>-1.63 ± 0.99</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>81.03 ± 16.73</td>
<td>77.98 ± 16.42</td>
<td>-0.30 ± 1.46</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 4: Duration required for attaining target glycemic control in 706 (87.37%) responders in the study

<table>
<thead>
<tr>
<th>Outcome (Months)</th>
<th>No of cases (N=706)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 m</td>
<td>283</td>
<td>40.1</td>
</tr>
<tr>
<td>2 – 4 m</td>
<td>288</td>
<td>40.8</td>
</tr>
<tr>
<td>4 – 6 m</td>
<td>066</td>
<td>90.3</td>
</tr>
<tr>
<td>&gt; 6 m</td>
<td>069</td>
<td>90.9</td>
</tr>
</tbody>
</table>

Table 5: Association between age group, sex, duration of diabetes and response among study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No of cases (N=808)</th>
<th>Response No. (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 55 years</td>
<td>483</td>
<td>439 (90.9)</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Age ≥ 55 years</td>
<td>325</td>
<td>267 (82.2)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>466</td>
<td>424 (91)</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Female</td>
<td>342</td>
<td>282 (82.5)</td>
<td></td>
</tr>
<tr>
<td>Duration &lt; 5 years</td>
<td>245</td>
<td>225 (91.8)</td>
<td>P = 0.011</td>
</tr>
<tr>
<td>Duration ≥ 5 years</td>
<td>563</td>
<td>481 (85.4)</td>
<td></td>
</tr>
</tbody>
</table>
Introduction

Hyponatremia has been shown to be an independent predictor of mortality. Patients with type 2 diabetes who require further improvement in glycaemic control despite the being on 4 OADs, SGLT2 inhibitor as a fifth drug can be considered. They are highly efficacious when added as fifth drug can be effectively used at any stage of diabetes and can delay insulin initiation in Type 2 diabetes patients not controlled on multiple OADs.

References

3. ADA, Standards of Medical Care in Diabetes. Diabetes Care 2017; 40S1-5019.

Efficacy and Safety of Oral Tolvaptan Therapy in Hospitalized Cirrhotic Patients with Hyponatremia

Ravinder Garg¹, Kamalpreet Kaur²*, Simmi Aggarwal³, Navtej Singh⁴

Abstract

Background: Tolvaptan is an orally administered, nonpeptide, selective arginine vasopressin V(2) receptor antagonist that increases free water clearance, thereby correcting and increasing the low serum sodium levels in patients of cirrhosis, where hyponatremia is an major encountered problem.

Aims: Evaluate the efficacy and tolerability of tolvaptan in cirrhotics with symptomatic hyponatremia that resist correction with fluid restriction. Intellectual improvement assessed using Short Portable Mental Status Questionnaire (SPMSQ) pre and post therapy(on conclusion). Adverse drug reactions monitored to assess safety.

Methodology: Study design: Prospective, pre and post drug efficacy and safety evaluating study with permission from ethical committe. Study Population: one hundred cirrhotic patients, irrespective of etiology, with hyponatremia, who fulfill the inclusion criteria. Protocol: All enrolled patients, treated with oral Tolvaptan at doses of 15 mg once daily in addition to the concurrent treatment regimen. Tolvaptan therapy was concluded as soon as the patient reached the normal sodium levels, which were monitored daily.

Results: Our study population had a majority of Hepatitis C patients (49%). Mean sodium levels at baseline were 125.79 + 3.49 which had a significant (130.25+3.28), and highly significant (133+ 3.19) change post 48 and 72 hours. In clinical parameters, urine output was altered significantly (pre drug mean 1530.76+619.02 to post drug mean of 1783+563.01. Body weight and Abdominal girth changes were not significant.

Conclusion

Patients with type 2 diabetes who require further improvement in glycaemic control despite the being on 4 OADs, SGLT2 inhibitor as a fifth drug can be considered. They are highly efficacious when added as fifth drug can be effectively used at any stage of diabetes and can delay insulin initiation in Type 2 diabetes patients not controlled on multiple OADs.
The symptoms are primarily neurological and relate to the rapidity of fall of serum sodium.

Usually from no symptoms at mild hyponatraemia to seizures, coma, permanent brain Hyponatraemia in clinical practice damage, respiratory arrest, brain-stem herniation and death may occur if severe low levels of sodium occurs. The options for treatment of euvolemic hyponatremia and hypervolemic hyponatremia are fluid restriction, 3% saline administration and use of loop diuretics. The major problems encountered in this conventional therapy are:

- Water restriction is slow to work and difficult to sustain due to inherent increased thirst sensation in these patients resulting in poor compliance.

- Saline administration can also be problematic in patients with hypervolemic hyponatremia as it can further cause volume expansion.

One major class of upcoming drugs approved for hyponatremia are the VAPTANS. Vaptans are vasopressin receptor antagonists, they acts by increasing electrolyte free-water excretion and thereby increasing serum sodium concentration and can be a better treatment option citing two reasons:

- Greater ease in terms of titrating the correction rate of hyponatremia with vaptan than with hypertonic saline.

- No risk of pulmonary edema in response to vaptan as opposed to hypertonic saline

Considering the scarcity of data from Indian context, the present study was envisaged to assess efficacy and safety of tolvaptan in cirrhotic patients.

Material and Methods

Study Population: The study population included a total of 100 clinically and radiologically confirmed cirrhotic patients with hyponatremia, irrespective of etiology, who fulfilled the inclusion criteria and gave a written consent to participate in the study. Cases were enrolled from the Department of Medicine, G.G.S. Medical College & Hospital, Faridkot. Sample size: Using a two sided paired t test, achieving at least 80% power and a significance level of 0.05, the sample sizes calculated (Mean=1 meq/l, SD=1 meq/l) t73 patients. (Mean=1 meq/l, SD=3 meq/l). Recruitment of 100 patients were planned keeping in view the drop outs. The Inclusion criteria were as follows: (a) Age more than 18 years; (b) Hospitalised patients with clinically and radiologically confirmed cirrhosis; (c) Serum sodium level less than 135mmol/L; The Exclusion criteria included those with (a) Hypovolemic hyponatremia (b) Anuria (c) Patients who are unable to respond appropriately to thirst (d) Serum creatinine more than 3.5 mg/dl (e) Pregnant females (f) Concurrent drug therapy of CYP3A4 inhibitors like (ketoconazole, itraconazole, ritonavir, clarithromycin (g) Any co-morbid cognitive disorder (like Alzheimer’s) (h) Those not responding post 7 days of therapy (i) Hepatic encephalopathy.

After ethics committee approval (vide letter no BFUHS/2015/156), all enrolled patients, according to our study protocol, were treated with oral Tolvaptan at doses of 15 mg once daily in addition to the concurrent treatment regimen. As per the study protocol Tolvaptan administration was restricted to 7 days. Tolvaptan therapy was concluded as soon as the patient reached the normal sodium levels, which were monitored daily. Those with unaltered levels were labelled as non responders to 15 mg Tolvaptan and were excluded from the study. Comparison of clinical and investigational parameters (reduction of ascites, body weight, abdominal circumference) between day of enrolment (i.e before the therapy) and at conclusion of therapy were done. All patients underwent the following investigation performed after hospital admission.

- Complete hemogram, blood sugar, liver function test, Renal function test, PTI, INR, Total Serum Proteins, Serum Albumin.
- Serum electrolytes (daily until 7th day or discharge).
- Ultrasound, Chest X-ray and electrocardiogram.

Efficacy assessment

Primary Outcome Measure: The proportion of subjects with normal serum sodium level (135-145 mmol/l) evaluates the efficacy of tolvaptan in cirrhotic patients with hyponatremia.

Secondary Outcome Measures

- Change in sodium level from baseline and other electrolytes.
- Change in body weight.
- Reduction in Ascites (measuring urine volume over 24 hrs, abdominal circumference and edema).
- Intellectual improvement.

Intellectual improvement was assessed using Short Portable Mental Status (SPMSQ) pre and post therapy (on conclusion). This Questionnaire consists of ten questions which are to be answered without any memory aid. Total numbers of errors based upon the answers to the 10 questions were compared and analysed accordingly.

Addressing safety:

- By monitoring the adverse drug reactions after inclusion of the tolvaptan in treatment schedule.
- Renal function monitoring.

Statistical Analysis

Paired t test, pre and post drug therapy, was applied with presentation of data in appropriate mean and Standard deviations wherever required.

Results

Out of 100 patients recruited, 5 were labelled as non-responders, amid the unaltered levels of electrolytes (specifically sodium) to 15 mg of Tolvaptan. Excluding the non responder group from the results, 95 patients showing a positive response post 15 mg of therapy constituted our study group of responders. 3 other patients were excluded because of progressive hepatic encephalopathy in the disease course. So a total of 92 patients were included. The baseline demographic and clinical profile of patients is shown in Table 1. Based on sodium level the patients were categorised in three groups A, B, C and D as shown in Table 2. Maximum number of patients presented with sodium levels between 125 and 130 (i.e Group B 44.5%), followed by sodium levels of 120-124 meq/L (i.e Group C) as evident.

The results of comparison of clinical and investigational parameters before and after the drug administration drug are tabulated in Table 3. A significant increase in serum sodium concentration post 24 and 48 hours and highly
Table 1: Demographic profile

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>92</td>
</tr>
<tr>
<td>Age (year)</td>
<td>56.25±9.45 (Mean±SD)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>67 72%</td>
</tr>
<tr>
<td>Female</td>
<td>25 27%</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Educated</td>
<td>36 40%</td>
</tr>
<tr>
<td>Uneducated</td>
<td>56 60%</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Farmer</td>
<td>48 52%</td>
</tr>
<tr>
<td>Self employed</td>
<td>21 23%</td>
</tr>
<tr>
<td>House wife</td>
<td>23 25%</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>90 98%</td>
</tr>
<tr>
<td>Unmarried</td>
<td>2 2%</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>08 8.7%</td>
</tr>
<tr>
<td>Wilsons disease</td>
<td>01 1%</td>
</tr>
<tr>
<td>Oesophageal varices</td>
<td>22 24%</td>
</tr>
<tr>
<td>Cirrhosis etiology</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>49 53%</td>
</tr>
<tr>
<td>HCV</td>
<td>45 49%</td>
</tr>
<tr>
<td>HBV</td>
<td>22 24</td>
</tr>
<tr>
<td>HCV</td>
<td>45 49%</td>
</tr>
<tr>
<td>HBV</td>
<td>22 24</td>
</tr>
</tbody>
</table>

Table 2: Baseline sodium levels of the patients

<table>
<thead>
<tr>
<th>Serum Sodium (meq/L)</th>
<th>Total no. of patients (n=92)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (&gt;131)</td>
<td>17</td>
<td>18.5%</td>
</tr>
<tr>
<td>Group B (125-130)</td>
<td>41</td>
<td>44.5%</td>
</tr>
<tr>
<td>Group C (120-124)</td>
<td>29</td>
<td>31.5%</td>
</tr>
<tr>
<td>Group D (&lt;120)</td>
<td>05</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

Table 3: Clinical and Investigational parameters before and after the drug

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre drug value Mean (SD)</th>
<th>Post drug value Mean (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium baseline (meq/L)</td>
<td>125.79±3.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post 24 hours</td>
<td>125.79±3.49</td>
<td>127.28±3.23</td>
<td>0.029*</td>
</tr>
<tr>
<td>Post 48 hours</td>
<td>125.79±3.49</td>
<td>130.25±3.28</td>
<td>0.001*</td>
</tr>
<tr>
<td>Post 72 hours</td>
<td>125.79±3.49</td>
<td>133±3.19 (sample size decreased)</td>
<td>0.001*</td>
</tr>
<tr>
<td>&gt;72 hrs</td>
<td>125.79±3.49</td>
<td>134.17±3.17</td>
<td>0.001*</td>
</tr>
<tr>
<td>Potassium (meq/L)</td>
<td>4.05±0.611</td>
<td>4.03±0.57</td>
<td>0.81</td>
</tr>
<tr>
<td>Chloride (meq/L)</td>
<td>91.9±4.25</td>
<td>92.11±4.54</td>
<td>0.74</td>
</tr>
<tr>
<td>Blood urea (mg/dl)</td>
<td>44.16±3.96</td>
<td>45.53±4.22</td>
<td>0.068</td>
</tr>
<tr>
<td>Serum Creatinine (meq/L)</td>
<td>1.26±0.49</td>
<td>1.35±0.48</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Clinical parameters

Abdominal girth 59.83±16.26 58.91±16.144 0.7
Body weight 65.21±12.62 64.86±12.786 0.84
Urine output 1530.76±619.02 1783±563.01 0.043

Table 4: Comparison of SPMSQ score

<table>
<thead>
<tr>
<th>SPMSQ Score</th>
<th>No. of patients(n)</th>
<th>Pre drug score (Mean +SD)</th>
<th>Post drug score (Mean +SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>17</td>
<td>9.85±0.36</td>
<td>9.93±0.27</td>
<td>0.16 (NS)</td>
</tr>
<tr>
<td>Group B</td>
<td>41</td>
<td>9.53±1.45</td>
<td>9.62±1.57</td>
<td>NS</td>
</tr>
<tr>
<td>Group C</td>
<td>29</td>
<td>9.2±0.68</td>
<td>9.7±0.57</td>
<td>&lt;0.5(S)</td>
</tr>
<tr>
<td>Group D</td>
<td>05</td>
<td>8.60±0.55</td>
<td>9.40±0.55</td>
<td>0.09(NS)</td>
</tr>
</tbody>
</table>

Discussion

Male predominance was clearly seen with Male to female ratio being 2.6:1. Alcoholism predominantly in males can be attributed as one of the major contributors of CLD and hence this ratio. Earlier reports too cite alcohol as a major contributor of cirrhosis. Decrease in initiating age to consume alcohol in on rise in India. Decrease in initiating age to consume alcohol in on rise in India. Decrease in initiating age to consume alcohol in on rise in India. Decrease in initiating age to consume alcohol in on rise in India. Decrease in initiating age to consume alcohol in on rise in India. Decrease in initiating age to consume alcohol in on rise in India. Decrease in initiating age to consume alcohol in on rise in India. Decrease in initiating age to consume alcohol in on rise in India. Decrease in initiating age to consume alcohol in on rise in India. Decrease in initiating age to consume alcohol in on rise in India.

Severe complications such as encephalopathy. The initial research started with Studies of Ascending Levels of Tolvaptan (SALT1 and SALT2) Trials which first assessed the use of tolvaptan for hyponatremia were designed to focus specifically on changes in serum sodium in patients with hyponatremia from multiple disorders including cirrhosis, SIADH, heart failure. The superiority was apparent in all end points like change from baseline, time to serum sodium normalisation, percentage with serum normalisation, in cirrhotic subgroup as compared to placebo. These results first established that improvements in serum sodium concentration were well maintained over longer periods with an acceptable adverse event profile. Other Studies with shorter term administration of tolvaptan (up to 1–2 weeks) and have shown a significant improvement with p value <0.003.

As per our knowledge, none of the studies in Indian cirrhotic population has been reported so far, except from south Indian centre by Patra et al which established the efficacy in acute decompensated heart patients. In our study too, significant changes in serum sodium status of the patients were

practices especially in Malwa region of Punjab.
observed. We further compared the values post 24, 48 and 72 hours with the baseline as the results were evident in many patients post 24 hours itself.

Ascites reduction by tolvaptan therapy reported in previous studies is reported in patients of ascites in hepatic oedema16 as well as in refractory ascites79 However in our study, though urine output was increased significantly but the change in ascites measured by abdominal girth was not very appreciating. As per our study protocol we terminated the therapy as soon as sodium levels were normal, this could explain the non significant change in ascites and the body weight. However, further studies with longer duration of therapy and with dose escalation are warranted in this regards.

The improvement of hyponatremia and its co-relation with reduced occurrence of hepatic encephalopathy80,81 and improved quality of life82 is well documented. In our study too, the patients of group C with sodium levels of <124 were gaffe prone reflected with a mean score of 9.2±0.6 which however significantly improved at conclusion of therapy. Group A and B patients did show a pre drug value of 10 itself unlike most of patients in group C (with mean values as shown in Table 3) supporting the fact that progressive decreasing sodium affect the mental status.

**Limitation of the study**

Controlled studies during longer periods of time are needed to evaluate the safety, efficacy, and applicability of these agents in patients with cirrhosis with hyponatremia.

**Conclusion**

Hyponatremia has long been associated with worsened clinical outcomes in patients with cirrhosis and can be an important survival predictor. Our study concludes 15 mg of Tolvaptan therapy is safe and effective in reversing hyponatremia in cirrhotic patients and can help preventing the neurological complications occurring due to hyponatremia.

**References**

Allergic Cough
Smoker’s Cough
Drug Induced Cough
Cough with RTI
Cough with Bronchial Asthma and Bronchitis
Cough with LPRD/GERD

Free From Cough Discomfort

In Dry and Allergic Cough

Grilinctus®, Syrup
(Dextromethorphan HBr 5 mg, Chlorpheniramine Maleate 2.5 mg, Guaifenesin 50 mg and NHCl 60 mg/5 ml)

In Productive Cough

Grilinctus®-BM, Syrup
(Terbutaline Sulphate 2.5 mg and Bromhexine HCL 8 mg/5 ml)

Grilinctus®-LS, Syrup
(Levosulbutamol 1 mg + Ambroxol Hydrochloride 30 mg + Guaifenesin 50 mg/5 ml)
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Start with

Glycomet®-GP 1
Metformin Hydrochloride 850 mg SR + Glimperide 1 mg

Glycomet®-GP 2
Metformin Hydrochloride 850 mg SR + Glimperide 2 mg

Glycomet®-GP FORTE
Metformin Hydrochloride 1000 mg SR + Glimperide 1 mg

Glycomet®-GP2 FORTE
Metformin Hydrochloride 1000 mg SR + Glimperide 2 mg

Glycomet®-GP 3/850
Metformin Hydrochloride 850 mg SR + Glimperide 3 mg

Glycomet®-GP4 FORTE
Metformin Hydrochloride 1000 mg SR + Glimperide 4 mg

Start Early with

Glycomet®-GP 0.5
Metformin Hydrochloride 500 mg SR + Glimperide 0.5 mg

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↓

Uptitrate to

Glycomet® Trio 1mg/0.3mg Metformin HCl 500 mg SR + Glimepride 1 mg + Voglibose 0.3 mg

Glycomet® Trio 2mg/0.3mg Metformin HCl 500 mg SR + Glimepride 2 mg + Voglibose 0.3 mg

In Obese Type 2 Diabetes with HbA1c > 9%

Start Early

Glycomet® Trio Forte 1mg Metformin HCl 1000 mg SR + Glimepride 1 mg + Voglibose 0.2 mg

Glycomet® Trio Forte 2mg Metformin HCl 1000 mg SR + Glimepride 2 mg + Voglibose 0.2 mg

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**Ecosprin® AV 150/20**
(Enteric Coated Aspirin 150 mg + Atorvastatin 20 mg)
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Etiological Patterns, Liver Fibrosis Stages and Prescribing Patterns of Hepato-Protective Agents in Indian Patients with Chronic Liver Disease

Gourdas Choudhuri1*, Sujit Chaudhari2, Dattatray Pawar3, Dyotona Sen Roy3

Abstract

Objective: Considering the paucity of relevant data for chronic liver disease (CLD) from India, this PAN-India study was conducted to assess the current etiologic spectrum of CLD, stage of liver fibrosis at presentation and the prescribing patterns of hepato-protective agents by gastroenterologists in Indian real-world setting. This data would aid in early detection and formulation of effective management strategies for CLD in India.

Materials and Methods: In this cross-sectional, multicentric, epidemiological study, consecutive patients (18 ≥ 65 years) diagnosed with CLD, assessed for liver fibrosis by Vibration Controlled Transient Elastography (VCTE), were evaluated for etiology by standard clinical and laboratory criteria and grouped in to alcoholic liver disease (ALD)/non-alcoholic fatty liver disease (NAFLD)/viral liver disease/drug induced liver injury (DILI)/others. The doctors’ prescription was studied in each case to note the pattern of hepatotropic medications prescribed, in addition to other specific agents.

Results: Out of 504 enrolled patients with CLD (mean age: 47.9±11.81 years; men: 67.9%), 39.7% had NAFLD, 25.6% had ALD, 17.5% had hepatitis B (HBV), 7.9% had hepatitis C (HCV), 1.6% had autoimmune hepatitis, 0.4% had DILI and 7.3% had other causes of liver disease. Diabetes (15.9%), hypertension (12.9%), hypothyroidism (3.0%), dyslipidemia (1.2%) and obesity (0.4%) were the commonly reported comorbidities. Liver stiffness corresponding to the diagnosis of F4 liver fibrosis stage was reported in 77.5% HCV, 62.0% ALD, 54.0% NAFLD and 37.5% HBV patients. About 12.5% HCV, 8.0% NAFLD, 5.4% ALD, and 1.1% HBV patients reported F3 liver fibrosis stage. About 38.3% patients were on hepatoprotective drugs; commonly prescribed drugs were ademetionine (23.8%), ursodeoxycholic acid (17.9%) and drugs of herbal origin (11.3%).

Conclusion: NAFLD is emerging as a predominant etiology of CLD in India, followed by ALD, HBV, and HCV. However, significant regional differences regarding predominant etiology was noted within the country. It was further noted that significant number of patients had advanced fibrosis based on VCTE assessment. This study emphasizes the need for appropriate risk evaluation and early assessment of severity of liver disease, for adequate disease management.

Introduction

Liver disease continues to be a significant health problem in India. According to the recently available World Health Organization data, liver disease deaths in India has reached 259,749 i.e., 2.95% of total deaths.1,2 The age-adjusted death rate is 22.93 per 100,000 of population, ranking India 63rd in the world.1 Liver diseases can result from a spectrum of etiologies such as alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), viral infections (hepatitis B virus [HBV] or hepatitis C virus [HCV]), autoimmune liver disease and drug-induced liver injury (DILI).

Reports of etiologic assessment of CLD published in the past 25 years indicates that hepatitis B, hepatitis C and ALD are the leading causes of liver disease in India.3-7 However, a surge in the incidence and prevalence of NAFLD in India has been recently noted, with the global epidemic of obesity, hypertension and type-2 diabetes mellitus (T2DM).8 NAFLD has also been recognized as one of the most important causes of CLD in western countries as well.8,9 This recent paradigm shift in etiologic spectrum of CLD in India could be attributed to the improved access to vaccination, tests and treatment, coupled with accelerated urbanization and adaptations such as sedentary lifestyle, fatty food, uncontrollable blood sugar, obesity, smoking and high alcohol intake.

Another recent development is the decline in importance and use of liver biopsy as a primary diagnostic tool for CLD and the advent of clinically validated, quantitative, non-invasive technique such as Vibration Controlled Transient Elastography (VCTE), which provides a more realistic depiction of CLD, with much wider acceptability in staging liver fibrosis. The use of VCTE has been evaluated in CLDs and is strongly correlated to hepatic fibrosis in chronic HBV, HIV/HCV coinfection, NAFLD, ALD, cholestatic diseases and autoimmune hepatitis.10-13 In addition, VCTE has been predictive for hepatic decompensation; rendering it useful to both help stratify cirrhotic patients into different risk categories, as recommended by the 2015 BAVENO VI guidelines for management of patients with compensated advanced...
CLD, and to screen for cirrhosis or detect undiagnosed CLD in the general population. Moreover, VCTE has been recommended by the latest European Association for the Study of the Liver (EASL) clinical practice guidelines for the management of patients with viral hepatitis infection; and has been considered as a clinically useful tool for identifying advanced fibrosis in patients with NAFLD as per the American Association for the Study of Liver Diseases (AASLD) guidelines.

Vergniol et al. in a study in 1,457 patients with chronic HCV reported that liver stiffness measurement (LSM) by VCTE has superior diagnostic performance for predicting 5-year survival compared with biopsy. In another study in patients with various conditions, Kibansky reported excellent diagnostic performance of VCTE for predicting a composite outcome including death, decompensation, and hepatocellular carcinoma.

Hence considering the growing burden of CLD, recent shift in the etiologic spectrum, and the lack of relevance given to the condition, there is a need to understand the trend of CLD and its etiologies in India; to comprehend the fluctuation of its various aspects, which in turn would be helpful in strategizing the management facets of CLD in tertiary care settings. Hence this study was conducted to assess the current etiology spectrum of CLD, and stage of liver fibrosis at presentation in Indian real-world setting. The prescribing patterns of hepatoprotective agents by gastroenterologists in Indian real-world setting was also ascertained in this study.

Table 1: Liver Stiffness Cut-Offs in Chronic Liver Diseases

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>F0-F1</th>
<th>F1</th>
<th>F1-F2</th>
<th>F2-F3</th>
<th>F3</th>
<th>F3-F4</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis C</td>
<td>1.5–7.1</td>
<td>7.2–4.7</td>
<td>8.8–9.5</td>
<td>9.6–12.5</td>
<td>12.6–14.5</td>
<td>&gt;14.5</td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>1.5–7.2</td>
<td>7.3–8.1</td>
<td>8.2–10.5</td>
<td>10.6–11.0</td>
<td>11.1–18.2</td>
<td>&gt;18.2</td>
<td></td>
</tr>
<tr>
<td>NAFLD</td>
<td>1.5–7.1</td>
<td>7.1–8.7</td>
<td>8.7–10.3</td>
<td>&gt;10.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol liver disease</td>
<td>1.5–7.5</td>
<td>7.6–9.5</td>
<td>9.6–12.5</td>
<td>&gt;12.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic cholestatic disease</td>
<td>0.7–1.1</td>
<td>7.2–11.1</td>
<td>11.2–14.7</td>
<td>14.8–15.6</td>
<td>15.7–17.3</td>
<td>&gt;17.3</td>
<td></td>
</tr>
<tr>
<td>Biliary diseases</td>
<td>1.5–7.1</td>
<td>7.1–11.1</td>
<td>11.1–14.7</td>
<td>14.7–15.6</td>
<td>15.6–17.3</td>
<td>&gt;17.3</td>
<td></td>
</tr>
<tr>
<td>HIV/HCV coinfection</td>
<td>1.5–7.2</td>
<td>7.2–11.9</td>
<td>11.9–14.6</td>
<td>&gt;14.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis C recurrence</td>
<td>1.5–6.3</td>
<td>6.3–7.9</td>
<td>7.9–8.5</td>
<td>8.5–11.9</td>
<td>11.9–14.5</td>
<td>&gt;14.5</td>
<td></td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>&lt;0.45</td>
<td>6.45</td>
<td>8.75</td>
<td>12.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DILI</td>
<td>&lt;7</td>
<td>7.1</td>
<td>9.5</td>
<td>12.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data represented in kPa; These cut offs have been mentioned as an indication for the physicians to make a diagnosis, it shall in no case replace their judgment. This guide is based on a selection of clinical studies from the existing literature reporting use of the VCTE. This guide is not intended to be used as a conversion table from liver stiffness readings in kilopascals (kPa) to fibrosis stage. This guide can in no way replace the judgment of the physician who is ultimately responsible for the final diagnosis.

Methods

This cross sectional, multicentric, epidemiological, PAN-India study was conducted across 15 private clinics and polyclinics in India, between March to June 2017. The centres were selected across four geographically different regions: north (Delhi, Gaziabad, Lucknow Ludhiana), south (Chennai, Bangalore), west (Mumbai, Pune, Satara, Ahmedabad, Vadodara), and east (Agartala, Guwahati, Kolkata).

Consecutive patients (18 ≥ 65 years) diagnosed with CLD, assessed for liver fibrosis by VCTE, were evaluated for etiology by standard clinical and laboratory criteria, and grouped as ALD, NAFLD, viral liver disease, DILI, and others. Pregnant or lactating women, patients with prior diagnosis of hepatitis A, hepatitis D or hepatitis E, hepatitis C patients with minimal fibrosis (≥F1), significant fibrosis (≥F2), advanced fibrosis (≥F3) and cirrhosis (F4); demographics and clinical profile of CLD patients; and the pattern of hepatoprotective medications prescribed, in addition to other specific agents, in patients with CLD.

Definitions used in this study

Liver Stiffness Measurement

The VCTE (FibroScan) examination was performed as per the manufacturer’s recommendations. Based on the cut-offs provided in the below Table 1, the LSM was used to categorize liver fibrosis/cirrhosis stage as minimal fibrosis (≥F1), significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4).

Child-Pugh score

Severity and staging of liver disease was recorded, if available. The clinical findings were used in association with laboratory studies to calculate Child-Pugh Score. The Child-Pugh score was calculated by adding the score of five factors (ascites, bilirubin, albumin, prothrombin time and encephalopathy) and ranged from 5 to 15. Child Pugh score between 5 and 6 indicated class A; 7 to 9 indicated class B and score of 10 or above indicated class C.

Statistical analysis

Continuous variables were summarized using descriptive statistics (number of observations, mean, standard deviation [SD], median, minimum and maximum inter-quartile range [IQR]). Categorical and discrete variables are presented in percentage. Tests were done at 2-sided 5% level of significance. All the statistical analyses were performed using SAS® software 9.4 (SAS Institute Inc., Cary, N.C.).

Results

Demographics and patient characteristics

A total of 504 patients were enrolled in this study. The mean age of the population was 47.9 ± 11.81 years. Majority of patients were men (342 [67.9%]) and married (470 [93.3%]).
Nearly half (247 [49.0%]) of the patients were graduates or post graduates (Table 2). Socioeconomic status showed that nearly half (248 [49.2%]) of the enrolled patients belonged to upper middle class, followed by lower middle class (120 [23.8%]).

**Table 2: Baseline Demographic Characteristics**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Overall (N=504)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.), Mean (SD)</td>
<td>47.9 (11.81)</td>
</tr>
<tr>
<td>Gender n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>342 (67.9%)</td>
</tr>
<tr>
<td>Female</td>
<td>162 (32.1%)</td>
</tr>
<tr>
<td>BMI (Kg/m²), Mean (SD)</td>
<td>25.8 (4.31)</td>
</tr>
<tr>
<td>Waist circumference (cms.)</td>
<td>90.5 (10.22)</td>
</tr>
<tr>
<td>Socio-economic status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Profession</td>
<td>103 (20.4%)</td>
</tr>
<tr>
<td>Semi-Professional</td>
<td>108 (21.4%)</td>
</tr>
<tr>
<td>Clerical, shop-owner, farmer</td>
<td>134 (26.6%)</td>
</tr>
<tr>
<td>Skilled worker</td>
<td>48 (9.5%)</td>
</tr>
<tr>
<td>Semi-skilled worker</td>
<td>12 (2.4%)</td>
</tr>
<tr>
<td>Unskilled worker</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>95 (18.8%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Profession or honors</td>
<td>16 (3.2%)</td>
</tr>
<tr>
<td>Graduate or post graduate</td>
<td>258 (50.4%)</td>
</tr>
<tr>
<td>Intermediate or post high school diploma</td>
<td>102 (20.2%)</td>
</tr>
<tr>
<td>High school certificate</td>
<td>74 (14.7%)</td>
</tr>
<tr>
<td>Middle school certificate</td>
<td>43 (8.5%)</td>
</tr>
<tr>
<td>Primary school certificate</td>
<td>12 (2.4%)</td>
</tr>
<tr>
<td>ILLiterate</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>Score</td>
<td></td>
</tr>
<tr>
<td>Score &lt; 5 lower class</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>Score 5 – 10 upper lower class</td>
<td>50 (9.9%)</td>
</tr>
<tr>
<td>Score 11–15 lower middle class</td>
<td>120 (23.8%)</td>
</tr>
<tr>
<td>Score 16 – 25 upper middle class</td>
<td>248 (49.2%)</td>
</tr>
<tr>
<td>Score 26 to 29 upper class</td>
<td>83 (16.5%)</td>
</tr>
</tbody>
</table>

**Table 3: Co-morbidities reported in >1% patients**

<table>
<thead>
<tr>
<th>Condition</th>
<th>N=504 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any comorbidity</td>
<td>202 (40.1%)</td>
</tr>
<tr>
<td>No</td>
<td>302 (59.9%)</td>
</tr>
<tr>
<td>Details of comorbidity</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>80 (15.9%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65 (12.9%)</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>25 (5.0%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15 (3.0%)</td>
</tr>
<tr>
<td>Gastrointestinal bacterial infection</td>
<td>15 (3.0%)</td>
</tr>
<tr>
<td>Gastrointestinal fungal infection</td>
<td>15 (3.0%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (2.8%)</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>12 (2.4%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>10 (2.0%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>6 (1.2%)</td>
</tr>
<tr>
<td>Hyperchlorhydria</td>
<td>6 (1.2%)</td>
</tr>
</tbody>
</table>

A total of 202 (40.1%) patients reported associated comorbidities. T2DM (80 [15.9%]), hypertension (65 [12.9%]), hypothyroidism (15 [3.0%]), dyslipidemia (6 [1.2%]) and obesity (2 [0.4%]) were the commonly reported comorbidities (Table 3). The predominant signs and symptoms associated with CLD were abdominal pain (154 [30.6%]), fatigue (103 [20.4%]), nausea (89 [17.7%]), vomiting (72 [14.3%]), ascites (65 [12.9%]), and decreased appetite (56 [11.1%]).

**Etiological profile**

The mean SD age at the time of diagnosis of CLD was 46.5± 11.74 years. The mean SD duration of CLD was 1.5± 2.26 years. Of the enrolled patients with CLD, 200 (39.7%) had NAFLD, 129 (25.6%) had ALD, 88 (17.5%) had HBV, 40 (7.9%) had HCV, 8 (1.6%) patients had autoimmune hepatitis, 2 (0.4%) patients had DILI and 37 (7.3%) had other causes.

Out of 504 CLD patients, 65 (12.9%) were newly diagnosed cases versus 439 (87.1 %) patients who were previously diagnosed. Similar pattern of CLD etiology was observed in previously and newly diagnosed patients. Summary of patient disposition by zone is depicted in Table 4.

**Severity and Staging of Liver Disease**

The median liver stiffness was maximum in patients with autoimmune hepatitis, followed by ALD, idiopathic diseases, HCV, HBV, NAFLD, and DILI (Table 5). Liver stiffness corresponding towards the diagnosis of F4 liver fibrosis stage was reported in 77.5% HCV (n=31), 62.0% ALD (n=80), 46.0% NAFLD (n=92) and 37.5% HBV (n=33) patients, based on VCTE. Liver fibrosis stage in patients with ALD, NAFLD, Hepatitis B, and Hepatitis C are depicted in Figure 1.

Out of 129 patients with ALD, liver stiffness values corresponding to F4 liver disease stage was reported in 62.0% patients, followed by F0-F2 in 22.5%, F2 in 10.1%, and F3 in 5.4% patients. Out of 200 patients with NAFLD, liver stiffness corresponding towards the diagnosis of F4 liver disease stage was found in 46.0% patients, followed by F0-F2 in 22.5%.

**Table 4: Summary of patient disposition by zone**

<table>
<thead>
<tr>
<th>Zone</th>
<th>ALD n (%)</th>
<th>NAFLD n (%)</th>
<th>Hepatitis B n (%)</th>
<th>Hepatitis C n (%)</th>
<th>DILI n (%)</th>
<th>Others n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>East</td>
<td>34 (26.4%)</td>
<td>62 (31.0%)</td>
<td>15 (17.0%)</td>
<td>2 (50.0%)</td>
<td>1 (50.0%)</td>
<td>1 (51.1%)</td>
</tr>
<tr>
<td>North</td>
<td>61 (47.3%)</td>
<td>33 (16.5%)</td>
<td>32 (36.4%)</td>
<td>21 (52.5%)</td>
<td>-</td>
<td>17 (37.8%)</td>
</tr>
<tr>
<td>South</td>
<td>22 (17.1%)</td>
<td>57 (28.5%)</td>
<td>15 (17.0%)</td>
<td>1 (2.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>West</td>
<td>12 (9.3%)</td>
<td>48 (24.0%)</td>
<td>26 (29.5%)</td>
<td>16 (40.0%)</td>
<td>1 (50.0%)</td>
<td>23 (51.1%)</td>
</tr>
</tbody>
</table>

**Fig. 1: Liver fibrosis stage assessed by vibration-controlled transient elastography in patients with ALD/NAFLD/Hepatitis B/Hepatitis C**
Management of CLD patients

About 193 (38.3%) were on hepatoprotective drugs. Among hepatoprotective drugs, 120 (23.8%) patients were on ademetionine, 90 (17.9%) were on ursodeoxycholic acid, 57 (11.3%) on drugs of herbal origin (Achillea millefolium, Capparis spinosa, Cichorium intybus, Senna occidentalis, Solanum nigrum, Tamari gallica, Terminalia arjuna), 24 (4.8%) on ornithine aspartate, and 17 (3.4%) patients on Silybum marianum. Among other drugs, majority of patients were on diuretics (95 [18.8%]), followed by vitamins (89 [17.7%]), antivirals (75 [14.9%]), beta blocking agents (67 [13.3%]), anti-infectives and antinauseants (60 [11.9%]), drugs for acid related disorders (60 [11.9%]), drugs for constipations (53 [10.5%]), and drugs for functional gastrointestinal disorders (53 [10.5%]).

Safety

No adverse events were reported during the study.

Discussion

The present study indicated that NAFLD (39.7%) is the commonest emerging etiology of CLD in Indian real-world setting. This is followed by ALD (25.6%), HBV (17.5%), HCV (7.9%), autoimmune hepatitis (1.6%), cryptogenic cirrhosis (1.6%), DILI (0.4%), and Wilson disease (0.2%). Similar trend of high prevalence of NAFLD was noted amongst newly and previously diagnosed CLD cases.

However, a retrospective study on adults with CLD at the University of Calgary Liver Unit between 2008 and 2011 reported that majority of the enrolled patients had HCV (36%) or HBV (29%), while 7% had NAFLD, 5% had autoimmune liver disease, 3% had hemochromatosis, and 2% had ALD.2122 Velosa et al from Portugal in a study of 988 CLD patients found viral etiology in 82%, alcoholic in 11%, metabolic in 2%, biliary in 2%, idiopathic in 2% and autoimmune in 1.5% of the total cohort.23 Among viral group, HBV infection was reported in 65%, HCV in 26% and hepatitis D in 8% patients. Another prospective study from Pakistan in children (1-14 years) with suspected CLD demonstrated that 24% of the subjects had chronic HBV, 16% had autoimmune disease, and 16% had Wilson’s disease.25 However, the etiology was uncertain in 44% cases. No cases of NAFLD or ALD were observed in these children. Biopsy proven chronic hepatitis was found to be present in 354 patients out of 518 patients with CLD in a study reported by Khokhar in 2002. Out of these 86% had HCV, 10.7% HBV, 3.1% had both B and C.24 This difference in the prevalence rate between studies could be attributed to the observed differences in CLD prevalence across countries and the contributing risk factors, which may vary based on the geographical regions.

Further, our data denoted a significant regional difference in the predominant etiology within the country. HCV, ALD and HBV were the most common cause of CLD in the northern region of India. NAFLD was found to be predominant in the east and south zone. However, Jhajharia et al in 2014 reported a high prevalence of ALD (58%), followed by HBV (19.0%), HCV (3.7%), and others (22.0%), which included autoimmune, Wilson’s, NAFLD-related, and cryptogenic) in northern India. In addition, 11 patients (2.7%) had more than one etiology of CLD.25 Chandra et al had also showed that alcohol is the most common perpetrator for CLD in central India.26 Similarly, a study of 44 patients by Acharya et al reported that 50% of patients had chronic HBV, associated hepatitis D with HBV in 21%, HCV in 15%, and non-A, non-B other than HCV virus in 13%; 2% patients had autoimmune HBV.27 Nevertheless, in these studies from Indian subcontinent, majority of the patients belonged to low socio-economic status.

This etiological spectrum of CLD as indicated in this study highlights the epidemiological transition within the country. Further, higher proportion of NAFLD reported in our study could be attributed to the fact that majority of patients in this study population were educated, belonging to upper middle class, making them less susceptible to alcohol dependence and abuse,27 a factor contributing to ALD. Nevertheless, this raises concerns of access to available care for the rural, and illiterate patients, considering the Indian society as a whole.

The bidirectional association between NAFLD and components of metabolic syndrome has been strongly established.28 Hence, the increasing
prevalence of metabolic risk factors including diabetes mellitus, obesity, etc. in Indian setting could also be the contributing factor for this rapidly increasing prevalence of NAFLD in India. Considering the fact that metabolic risk factors are common in patients with NAFLD, it is postulated that NAFLD may actually be a hepatic manifestation of metabolic syndrome.\(^2\) Moreover, NAFLD has been observed to be consistently associated with obesity,\(^29\) type 2 diabetes mellitus,\(^30,31\) and dyslipidemia.\(^32\) In line with the above fact, our study also reported a high prevalence of associated comorbidities such as T2DM, hypertension, hypothyroidism, anxiety, dyslipidemia, coronary artery disease, depression and obesity.

Male predominance was observed in the present study, which is consistent to the results reported by Pal et al\(^22\) where 79% of patients were male and Chandra et al\(^26\) who had reported 80.6% males in the study. Jhajharia et al (2014) had also noted male predominance with a male to female ratio of 5.5:1.\(^23\) This indicate that males are more susceptible to CLD than females, suggesting high risk of exposure to causative factors. Further, it is noted from previous literatures that the risk of a liver disease increases with age. Our study recorded a mean age of 46.5 years for CLD diagnosis which is in agreement with the finding of Jhajharia et al where the mean age of presentation was 45.6 years.\(^25\)

Mode of presentation of patients with CLD was an important consideration taken in our study. Abdominal pain, fatigue, nausea, vomiting, ascites and decreased appetite were the major sign and symptoms associated with CLD patients in our study. These complications are markers of disease progression and depict diseases severity in its respective order. On the contrary, Pal et al has reported ascites in 52% of patients followed by jaundice in 40% and GI bleeding in 24% as the sign and symptoms associated with CLD.\(^30\)

Liver stiffness corresponding towards the diagnosis of F4 liver fibrosis stage was reported in 77.5% HCV, 62.0% ALD, 46.0% NAFLD and 37.5% HBV patients. Moreover, 12.5% of HCV, 8.0% of NAFLD, 5.4% of ALD, and 1.1% of HBV patients had liver stiffness corresponding towards the diagnosis of F3 liver fibrosis stage. This signifies that majority of patients diagnosed in clinics with CLD seem to have F3 or F4 fibrosis at presentation.

Child-Pugh score and class, a marker of extent of liver damage, was evaluated in this study. Laboratory results of hemoglobin count, platelets count, total white blood cells count, hematocrit, red blood cells count showed elevated levels in more than half of patients, signifying ongoing injury. In a study in 91 patients, Pal et al found that 51% of patients belonged to Child-Pugh class B, followed by class C in 35% and only 14% in class A.\(^23\) In another study by Chandra et al,\(^26\) it was found that Child-Pugh class B and C together constituted 81.7% of the patient, which is considered as fairly advanced liver disease. In our study, out of 68 patients whose Child Pugh’s scoring was done (~15% patients), approximately equal proportion of patients had Grade A and Grade B score. However, only 1 (0.2%) patient was in Grade C of Child-Pugh score. Among patients in whom USG findings were available, hepatic steatosis grade was mild, moderate and severe in 7.9%, 8.9%, and 0.8% patients, respectively. This indicate that almost half of patients of CLD were asymptomatic while remaining (constituted by Group Child-Pugh B & C) presented a remarkably advanced stage, or approached for medical care at an advanced stage. In the context of the resource restraint systems like India, this observation of a relatively late presentation of a fairly large segment of CLD patients is of particular concern. In view of this, screening and increasing awareness about liver diseases are of paramount importance. Improving liver disease awareness, risk factor detection and value-added patient education might all be considered important interventions to impact this scenario.

To the best of our knowledge, this is the first of its kind PAN-India study to report the prescribing pattern of drugs in the treatment of different etiologies of CLD. Hepatoprotective drugs were the most commonly prescribed category in our study (38.3%). Among them, ademetionine (23.8%), ursodeoxycholic acid (17.9%) and drugs of herbal origin (11.3%) were the commonly prescribed hepatoprotective drugs. Many studies have reported the effectiveness and tolerability of ademetionine in the symptomatic management of CLD.\(^35,36\) Ursodeoxycholic acid has also been effective in reducing biochemical markers of cholestasis in patients with CLD.\(^37,38\) Herbal medicines have also been in use in the treatment of liver diseases for a long time. As nutritional deficiency is very common in these patients, prescription of vitamin preparations was seen to be common in our study and overall they are one of the most commonly prescribed drugs after hepatoprotectives.

To conclude, this study indicate that NAFLD is emerging as an important etiology of CLD in Indian real-world setting, followed by ALD, HBV, HCV and others. Significant regional differences regarding predominant etiology within the country was also noted. CLD in India has a male preponderance, affecting mostly people of middle age group. Considerable percentage of the patients had advanced fibrosis, based on VCTE assessment. This study thus emphasizes the need for appropriate risk evaluation and early assessment of severity of liver disease, for adequate disease management. There is need for a consensus or guidelines for the management of all etiologies of CLD based on liver disease stages. However, as this was a cross-sectional study, the cause and effect of relationship could not be determined in this study. Hence further studies are warranted in larger and more representative samples to improve the generalizability of the findings to the country as a whole.

**Funding**

This study was funded by Abbott India Ltd.

**Conflict of interest**

Dr. Choudhuri and Dr. Chaudhari have received research funding from Abbott India Ltd as a consultant. Dr. Pawar and Dr. Roy are employees of Abbott India Ltd.

**Data Availability**

The data sets supporting the results of this article are included within the article.

**References**

3. Ray G. Trends of chronic liver disease in a tertiary care referral hospital in Eastern India. Indian J Public Health 2014; 58:186-


Early Detection of Right Ventricular Dysfunction in Chronic Obstructive Pulmonary Disease by Echocardiography

GD Ramchandani, Ravi Kumar Meena, BS Gupta, Sanjiv Maheshwari, Girish Mathur, KK Pareek

Abstract

**Objectives:** This study is designed to investigate the effects of pulmonary arterial hypertension on RV systolic and diastolic functions in cases of COPD and to correlate RV systolic and diastolic functions with pulmonary arterial pressure.

**Material and Methods:** 100 patients admitted in various medical wards of tertiary care Hospital and a primary care hospital with stable chronic obstructive pulmonary disease persons with age and sex-matched. 35 age and sex matched person without any associated and known disease were taken as control subjects. Selection of cases has been made on basis of detailed history, thorough clinical examination, electrocardiography, chest x-ray, pulmonary function tests.

**Observation:** RV Systolic function (RVEF and RVWT) are significantly abnormal in patients of stable compensated COPD and they are significantly correlated with PAP(p<0.002). RV diastolic function i.e., E/A ratio and PFR are altered in 60%(n-60) of patients of COPD studied against control subjects and significantly correlated with PAP(p<0.002).

**Conclusion:** Echocardiography is a non invasive method to detect changes of right ventricular dysfunctions in early stages with very good significant sensitivity and specificity.

Introduction

**C**hronic obstructive pulmonary diseases (COPD) is among the major causes of disability and mortality worldwide and recently its incidence is on an uphill. As the disease progresses, pulmonary arterial hypertension develops insidiously which leads to development of RV hypertrophy, dilatation and failure. Once Cor-pulmonale becomes evident, the prognosis is poor. Early detection and therapy can lead to a reduction of symptoms, as well as the rate of progression of the disease. Hypertrophy and/or dilatation of the right ventricle are the major factors which contribute to the consequences of the disease.

Various non-invasive techniques such as x-ray chest, electrocardiography, vector cardiography, Thallium 201 myocardial imaging and gated equilibrium blood pool imaging are available, but individually each of them has low sensitivity in detection of right ventricular function. Echocardiography offers promise in identifying clinically occult pulmonary arterial hypertension, right ventricular enlargement, hypertrophy and right ventricular systolic and diastolic functions in patients with COPD. RV diastolic properties can be evaluated with ease with the help of pulse Doppler echocardiography.

This study was designed to investigate the effects of pulmonary arterial hypertension on RV systolic and diastolic functions in cases of COPD and to correlate RV systolic and diastolic functions with pulmonary arterial pressure.

**Material and Methods**

100 patients admitted in various medical wards of tertiary care Hospital and a primary care hospital with stable chronic obstructive pulmonary disease persons with age and sex matched. 35 age and sex matched person without any associated and known disease were taken as control subjects.

Selection of cases has been made on following criteria:

1. **Clinical History:** According to American Thoracic Society on Diagnostic Standard for COPD, patients had to have history of cough with sputum for at least three consecutive months for each of two consecutive years or presence of breathlessness with radiological evidences of emphysema or both.

2. **X-ray Chest - Plain/Digital X-ray of the chest showing over-inflation with increased bronchovascular markings.** Chronic bronchitis cannot be diagnosed on the basis of radiological features which are helpful in the diagnosis of emphysema alone. Characteristic features of emphysema include depression and flattening of diaphragm, irregular radioluency of lung fields, increase in retrosternal space, long tubular heart. Attenuation of peripheral pulmonary vasculature, widening of intercostal spaces and prominence of main branches of pulmonary artery, emphysematous bullae etc.

3. **Electrocardiography:** evidences consistent with COPD and its sequelae like progressive right axis deviation of P wave and QRS, R:S ratio becomes less than 1 in lead V6 and increasing amplitude of P
wave in standard leads II, III and aVF.

4. Pulmonary function test: The diagnostic criteria for COPD are FEV1 less than 75% and FEV1/FVC ratio less than 80% of the value predicted from measurement of pulmonary function in asymptomatic non-smoker.

Such selected patients were subjected to echocardiographic examination with colour Doppler echocardiographic machine complete M-mode. 2-Dimensional and pulsed wave Doppler echocardiographic studies with other relevant parameters.

Statistical Methods and Analysis

Such collected data was tabulated and reported as mean value ± standard deviation. Student’s ‘t’ test was used to assess the significance of the difference in pulmonary function and echocardiographic data between the COPD and control subjects.

Correlation coefficients were obtained from standard regression equation between the PAP and various echocardiographic parameters. A ‘p’ value < 0.05 was considered statistically significant.

Observations

The present study consists of detection of RV systolic and diastolic dysfunction in patients of COPD by 2-dimensional echocardiography and its correlation with pulmonary artery pressure (PAP).

In the present study PAP and following systolic and diastolic functions in patients of COPD were measured and correlated with control group. The mean ± SD value of PAP in COPD and control subjects was 29.520 ± 7.180 and 14.820 ± 2.680 respectively. The ‘t’ value was 6.546 and p value was significant (p< 0.01). The RVWTd in both subjects was 0.970±0.226 and 0.550 ± 0.180 respectively. The ‘t’ value was 4.350 ± 0.711 and 6.060 ± 0.843 respectively. The ‘t’ value was -6.288 and p value was significant (p< 0.01). The RVEF in both subjects was 0.980 ± 0.152 and 1.480 ± 0.345 respectively. The ‘t’ value was -6.044 and ‘p’ value was significant (p< 0.01) (Table 1).

To study the diastolic functions following echocardiographic parameters were measured in control and COPD subjects. E’ wave, ‘A’ wave, E/A ratio and peak filling rates. The ‘E’ wave in both subjects was 0.540 ± 0.068 and 0.550 ± 0.090 respectively. ‘t’ value was 0.484 and ‘p’ value was insignificant. The ‘A’ wave in both subjects was 0.550 ± 0.073 and 0.580±0.071 respectively. ‘t’ value and ‘p’ values in both subjects was insignificant. E/A ratio in COPD and control subjects was 0.980 ± 0.152 and 1.480 ± 0.345 respectively. The ‘t’ value was -6.044 and ‘p’ value was significant (p< 0.01) (Table 1).

PAP has a strong negative linear correlation with RVWTd (r=-0.92, p<0.002), E/A (r=-0.74, p<0.002) and PFR (r=-0.75, p<0.002) (Table 2).

PAP has a strong linear correlation with RVWTd (r=0.83, p<0.002) (Table 2).

Discussion

Because of high compliance of RV, the ability of the RV to increase wall tension and systolic ejection pressure is limited. An absolute rise in RV afterload increases RVEDP and decreases RVEF and may lead to a fall in RV output. When pulmonary hypertension develops gradually as in patients with COPD, the RV is able to adapt to the increase in workload. As PVR rises, there is an increase in the density and the number of mitochondria in the myocytes of the RV free wall. In early stages, hypertrophied RV becomes less compliant and wall tension and contractility increases. The structural and functional adaptation of the RV to increase in afterload caused by disorders of the respiratory systems and commonly referred to as cor-pulmonale.

The prevalence of RV dysfunction increases with severity of pulmonary artery hypertension. As PAP increases, RVEF falls and ratio of early/late peak atrial filling is reduced.

The pathogenesis of RV dysfunction in COPD is multifactorial but studies demonstrating a close inverse correlation between PaO2 and mean PAP indicate that hypoxic pulmonary vasoconstriction (HPV) and subsequent remodelling of the pulmonary vascular bed undoubtedly play the greatest role. Normally HPV diverts blood flow from areas of regional alveolar hypoxia to better ventilated areas of the lung, thereby optimizing ventilation perfusion relationship. When alveolar hypoxia involves the entire lung, however as occurs during hypoventilation or exposure to high altitude, HPV results in increased PAP and PVR. In COPD, HPV is followed by medial hypertrophy of muscular pulmonary arteries and proliferation of vascular smooth muscle into normally non-muscular vessels of the pulmonary circulation. This remodelling of the vascular bed rises PVR and contributes to the development of PHT.

COPD affects RV functions through mechanisms other than HPV and vascular remodelling. Destruction of lung parenchyma decreases the cross sectional area of the pulmonary capillary bed. Patients with COPD may have increased serum viscosity from secondary polycythaemia and prove to develop chronic pulmonary thromboembolic disease. Finally, increased intrathoracic pressure related to air trapping in the lower lobe may

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Table 1: Right ventricular functions measured by 2D echocardiography of controls and cases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Mean ± SD</th>
<th>Controls Mean ± SD</th>
<th>Student's t test</th>
<th>D.F.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFR (mm)</td>
<td>29.520 ±7.180</td>
<td>14.820 ±2.680</td>
<td>6.546</td>
<td>34</td>
<td>0.01</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>39.760 ±6.670</td>
<td>57.820 ±3.950</td>
<td>-8.324</td>
<td>34</td>
<td>0.01</td>
</tr>
<tr>
<td>RVWTd (mm)</td>
<td>0.970 ±0.226</td>
<td>0.550 ±0.180</td>
<td>-5.390</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>“E” Wave (mm)</td>
<td>0.540 ±0.068</td>
<td>0.550 ±0.090</td>
<td>-0.448</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>“A” Wave (mm)</td>
<td>0.550 ±0.073</td>
<td>0.580 ±0.071</td>
<td>-0.493</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>0.980 ±0.152</td>
<td>1.480 ±0.345</td>
<td>-6.044</td>
<td>34</td>
<td>0.01</td>
</tr>
<tr>
<td>PFR (mm)</td>
<td>4.350 ±0.711</td>
<td>6.060 ±0.843</td>
<td>-6.288</td>
<td>34</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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Table 2: Correlation between PAP and right ventricular systolic and diastolic dysfunctions measured by 2D ECHO

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Variables</th>
<th>Correlation coefficients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>135 (100+35)</td>
<td>PAP and RVWTd</td>
<td>-0.92</td>
<td>0.002</td>
</tr>
<tr>
<td>135 (100+35)</td>
<td>PAP and E/A</td>
<td>0.83</td>
<td>0.002</td>
</tr>
<tr>
<td>135 (100+35)</td>
<td>PAP and PFR</td>
<td>-0.75</td>
<td>0.002</td>
</tr>
</tbody>
</table>
increase RV afterload by compressing pulmonary vessels. Determinants of right ventricular systolic functions based on the concept that ventricular functions are determined by preload, afterload and contractility. A physiologically correct definition for afterload is systolic wall tension. Component of afterload are PAP, total pulmonary resistance, RV wall thickness and ventricular volume.

Correlation of RVEF and PAP: Our data showed a strong negative linear correlation (r=-0.92, p<0.002) between pulmonary artery pressure and RVEF that closely parallels the findings of other recent observations of RV functions. Steven M. Kawut et al 2009 found RVEF was inversely correlated with pulmonary vascular resistance (r = -0.51; p < 0.001). Schuler et al, conducted a study in 1978, and obtained a comparable correlation (r=0.75) between RVEF and PAP. Similarly, Ellis et al observed a significant decrease in PAP and a concomitant increase in RVEF after low flow oxygen therapy. Similarly, Korr K. K. etal in 1981, conducted a study and observed a significant negative linear correlation between RVEF and mean PAP (r=-0.82).

Correlation of PAP and RVWT: RVWT was significantly higher (0.970±0.226) in patients COPD and it was significantly correlated with PAP (r = 0.83, p<0.002). In COPD when PAP and PVR rises it leads to increase afterload on the RV, this chamber dilates and hypertrophies. To maintain cardiac output, the RV, by Frank starling mechanism, enlarges and hypertrophy develops. Our study closely parallels the study conducted by Cacho A. et al who concluded that 2D ECHO is useful in diagnosing RVH.

The mechanisms for the abnormalities of RV diastolic filling in COPD have not been clearly delineated. In patients with normal to mild increased in Right ventricular free wall thickness (RVFWT), the relaxation process may be altered to affect calcium fluxes or to cause non uniformity between contraction and relaxation of myocardial cells , resulting in delayed early ventricular filling and prominent filling with atrial contraction as a compensatory mechanism in contrast to patients with moderate to severe increase in RVFWT leads to firm, poorly compliant Right ventricle, resulting to rapid early filling and then subsequent restriction to filling.

This study shows that RV diastolic function in altered in stable moderate to severe COPD. Peak filling rate was lower (4.350±0.711) which indicates prolonged myocardial relaxation (mishimura RA et al 1989). Increase in peak velocity of atrial filling and reversal of E/A ratio in 15 patients (60%) indicates increased atrial contribution to ventricular filling. These parameters show that RV diastolic function is altered and is compensated by atrial filling.

Pulmonary artery pressure has a strong negative linear Correlation with E/A (r= 0.74, p <0.002) and PFR (r =-0.75, p < 0.002).

Summary and Conclusion

RV Systolic function (RVEF and RVWT) are significantly abnormal in patients of stable compensated COPD and they are significantly correlated with PAP.

RV diastolic function i.e., E/A ratio and PFR are altered in 60% of patients of COPD studied against control subjects and significantly correlated with PAP.

References


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Emerging Landscape of Antibiotic Resistance and Use of Endoscopic Injection in Vesicoureteral Reflux

Pooja Roy¹, Ramesh S², Rajan Mittal³, Suyog Mehta⁴

Abstract
Vesicoureteral reflux (VUR) in children is often treated with antimicrobials for prolonged durations, which often leads to antimicrobial resistance. In this context, this review article discusses the use of endoscopic injection in VUR as a safe and efficacious option for these children.

The literature pertaining to VUR- its clinical manifestation and management, antibiotic resistance- with special reference to management of VUR, and endoscopic dextranomer/hyaluronic acid gel injection for management of VUR was reviewed by identifying key words in a PubMed search.

Vesicoureteral reflux is managed using antibiotic prophylaxis, urotherapy, or surgical correction (open, endoscopic injection therapy, or laparoscopic). Continuous antibiotic prophylaxis for urinary tract infections in VUR can lead to antibiotic resistance. Urotherapy cures about 75% of cases with dysfunctional voiding and the rest have to be managed at specialized centers. While open surgery provides relief of VUR and related complications in majority, it requires hospitalization. Endoscopic injection of dextranomer/hyaluronic acid gel into the submucosa of bladder or ureter near ureteral orifice increases the tissue bulk and creates a valve function. Various studies show the efficacy and safety of endoscopic injection of dextranomer/hyaluronic acid gel in VUR. The use of endoscopic injection being a non-invasive modality, can be performed in children with VUR in the outpatient department, precluding hospitalization.

In view of the threat of developing antimicrobial resistance and also realising the need for definitive treatment of VUR, endoscopic injection is an efficacious and safe option in primary VUR.

Introduction

Antimicrobial therapy has become one of the pillars of modern medicine over the last 60 years. The fear of death due to microbial infection is now almost obsolete in the developed world due to availability of various antimicrobial agents, but on the other side, this is threatened by the development of resistance to antimicrobials. The arrival of these antimicrobial agents marked the beginning of an era of optimism and enthusiasm regarding conquest over infectious diseases. This optimism started fading with the development of resistance to these agents in bacteria. This is particularly a major problem in developing countries where the burden of infections is very high and cost constrains the replacement of older antimicrobial agents. The infectious disease burden in India is one of the highest in the world; therefore, antimicrobial agents have a role to play in limiting morbidity and mortality in India.

Primarily, drug resistance has been recognized as a medical problem. When antimicrobial agents are used either in human beings or animals, there is always a risk of the development and spread of antibiotic resistance in bacteria. Therefore, there is need of each country to adopt strategies fit to its own condition.

Antimicrobial Resistance – A Global Threat

Antimicrobial resistance is a major problem that strikes at the centre of infectious disease control. Antimicrobial resistance and its global spread threaten the continued effectiveness of antimicrobials and also risks global health security.

Infections caused by multidrug-resistant (MDR) bacteria are often associated with prolonged and expensive hospitalization. The most important factor behind the evolution of drug resistance in bacteria is the drug selection pressure, which involves use of drugs in both human and animals.

In many cases, these infections lead to higher morbidity and mortality. Multi-drug resistant organisms have been an epidemiological concern as they may spread locally, regionally or globally through individual contacts, poor sanitation, travel or food chain.

For antimicrobial resistance to become a clinical problem, three events must occur.

1. First, an individual pathogenic bacterium must acquire resistance to the antimicrobial agent in question. This could occur by a spontaneous mutation in one of its genes, which might make a target protein less susceptible to the antibiotic by modification of the antibiotic binding site. Alternatively, the bacterium could gain a gene encoding antimicrobial resistance via horizontal transfer of deoxyribonucleic acid from a different bacterial strain.

2. Second, the newly resistant bacterium must multiply in such a fashion that its resistance-encoding gene spreads in the local bacterial...
population and cannot be wiped out through fluctuations in the number of organisms carrying this gene.

3. Third, the resistant bacterial strain must spread beyond the local bacterial population where it originated, until it infects a significant number of humans and becomes clinically significant.

Currently although antimicrobial resistance is a grave threat in many places in India, the problem remains largely unrecognized mainly because there are not many studies published and also because the surveillance system in India does not match up the magnitude of the problem. The threat of antimicrobial resistance came into light in a big way only when the New Delhi metallo-β-lactamase-1 (NDM1) was first reported in 2009. New Delhi metallo-β-lactamase-1 is an enzyme produced by the gene blaNDM1, carried on plasmids which could be transferred to many bacterial species, for example Klebsiella pneumoniae and Escherichia coli, thereby conferring resistance to multiple antibiotics, including carbapenems.

The first epidemic reported to be caused by an antibiotic-resistant bacterial strain was by chloramphenicol resistant Salmonella typhi in 1972 in Mexico. Subsequent outbreak was reported by the chloramphenicol-resistant S. typhi strains in Kerala, India. Since then, MDR S. typhi strains showing resistance to chloramphenicol, ampicillin, and trimethoprim have been reported in the Indian subcontinent, Southeast Asia, and Africa.

New Delhi metallo-β-lactamase-1, a metallo-beta-lactamase (MBL), belonging to the family of carbapenemases, was first identified in isolates of K. pneumoniae and E. coli, both recovered from a patient in Sweden after his treatment in a hospital in New Delhi, India. Thereafter, studies reported NDM1 from a tertiary centre in Mumbai, following isolation of MDR Enterobacteriaceae in other cities.

Thereafter, resistance to a further wide range of antibiotics has been reported among hospital-acquired gram-negative organisms (Acinetobacter, Pseudomonas, Klebsiella, E. coli, Salmonella, Neisseria gonorrhoeae). The prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae is increasing worldwide and infections with ESBL producing E. coli are posing major threat in many countries including India.

Immediate strategies to combat such emerging landscape of antibiotic resistance should include rational use of antimicrobial agents, public health education, behavioural change and communication strategies.

Several disease conditions characterised by infections are treated with the use of antibiotics. However, injudicious use of antibiotics in these disease conditions leads to development of antibiotic resistance in these patients. One such condition is vesicoureteral reflux (VUR) in which patients suffer from urinary tract infections (UTIs).

Vesicoureteral Reflux and its Clinical Manifestations

Vesicoureteral reflux is characterized by the retrograde flow of urine from the bladder to the upper urinary tract.

The prevalence of VUR is estimated to be around 0.4% to 1.8%. The prevalence of VUR is higher in siblings of patients with VUR (46%), children with recurrent UTI (30%), infants with prenatal hydronephrosis (16%), and the presence of congenital anomalies of the urinary tract such as posterior urethral valves (60%), cloaca (60%), and duplex kidney (46%).

Children, who present with hydronephrosis in intrauterine life, identified prenatally via ultrasonography; often present with clinical UTI in early years of life.

The diagnosis of UTI in children can be difficult. Children often present with nonspecific clinical features. Pyelonephritis in young children usually manifest with abdominal discomfort rather than with the classic flank pain and tenderness observed in adults.

Globally, VUR is considered a crucial etiological factor for post-UTI renal scarring in children. Vesicoureteral reflux predisposes children to UTI and pyelonephritis, and both are associated with significant renal scarring.

Management of VUR

The goals of management of VUR include the prevention of reflux and prevention of pyelonephritis, reflux nephropathy, and other complications of reflux. The various treatment strategies include antibiotic prophylaxis, urotherapy (correction of voiding dysfunction), and surgical correction (open, endoscopic injection therapy, or laparoscopic).

Antibiotic prophylaxis

The knowledge of the relationship between renal scarring, UTI, and VUR paved the path for the emergence of the clinical use of prophylactic antibiotics in the early 1970s. This was largely due to the work of Normand and Smellie, who had shown a decrease in the incidence of UTI in children with VUR on Continuous Antibiotic Prophylaxis (CAP). As a clinical strategy, CAP became the recommendation of the American Urological Association guideline in 1997.

However, the patients suffering from primary VUR generally belong to the paediatric age group and injudicious and long-term usage of antibiotics for prevention and/or treatment of these UTIs often is associated with the risk of onset of antibiotic resistance in these patients.

Concern is growing among medical practitioners about the long-term use of CAP in VUR patients. Poor compliance to antibiotic regime is also common. These facts against long-term antibiotic use have led to a rethinking about the use of CAP in these children.

Urotherapy or bladder training

It is a non-surgical, non-pharmacological treatment of lower urinary tract symptoms of neurogenic and non-neurogenic bladders. It mainly includes - pelvic floor training and biofeedback. Urotherapy cures about 75% of children with overactive bladder and dysfunctional voiding. Non-responders should be referred to specialized centres for further urodynamical investigations.

Surgery

Decisions for surgery are based on numerous factors like patient’s age, health, grade of reflux, clinical course of the disease, compliance to antibiotics, presence of renal scarring, and parental preference. Prevention of febrile UTI or pyelonephritis is one of the major goals of surgical management. Surgical treatment of VUR reduces the occurrence of pyelonephritis. Patients with recurrent UTI and/or persistent reflux benefit most from surgery.
increasing the length of the intravesical ureter and thereby facilitating compression of the ureter against the detrusor muscle during the urinary bladder filling. In endoscopic repair, the dextranomer/hyaluronic acid gel is injected into the submucosa of either the bladder or the ureter near the ureteral orifice. As a result, the ureteral orifice closes because of the increase in tissue bulk, creating a valve function. This allows coaptation of the ureter during filling and contraction of the bladder, making it more difficult for urine to reflux, or flow, back into the ureter.

Open surgery generally requires hospitalization for management of post-operative pain as well as for temporary urinary catheter drainage whereas the endoscopic repair is an outpatient procedure (some surgeons even prefer the minor operation theatre) with minimal post-operative pain and no need for urinary catheter.25

**Antibiotic Prophylaxis in Vesicoureteral Reflux and Development of Antibiotic Resistance**

There has been strong evidence for overuse of antibiotics in children suffering from paediatric urological disorders. Febrile UTI is one of the most serious bacterial infections in the paediatric age group because of the involved risk of renal scarring with permanent damage to the kidneys in about 5%.16

As reinfection in these children is very common, physicians prescribe daily low-dose antibiotic prophylaxis to prevent further UTIs in these children especially those with VUR and prenatal hydronephrosis.17

In 2010, a Cochrane Review studied the efficacy and safety of long-term chemoprophylaxis to prevent recurrent UTIs in the paediatric age group. The Cochrane Review concluded that even though long-term chemoprophylaxis reduces the risk of recurrent UTIs in children, there is a simultaneous highly increased risk of microbial resistance.18

The choice of antibiotic for chemoprophylaxis is also very crucial. Cheng (2008) found that children receiving cephalosporins for prophylaxis tend to develop ESBL-producing bacteria or MDR bacteria for breakthrough UTIs; therefore, it was suggested that these antibiotics are not suitable for prophylactic use in patients with VUR.19

Also compliance with chemoprophylaxis is often poor, particularly in the lower socioeconomic strata and poor compliance leads to increased risk for antibiotic resistance. Younger age, recurrent hospitalizations, and visits to the physicians have been observed to be associated with improved compliance, suggesting that probably compliance to chemoprophylaxis may be improved through increased patient contact with the healthcare system.

Appropriate prescribing of antibiotics is necessary to improve patient outcomes and to help prevent the emergence of antibiotic resistance. Although there has been a reduction in use of antibiotics in the United States by 17% in the last few years, there is still evidence of antibiotic overuse and misuse (The Center for Disease Dynamics, Economics and Policy, 2013).20

With respect to paediatric urology, the resistance pattern of uropathogens has been constantly evolving. When compared with the years 2002-2004, in 2009 the resistance rates of trimethoprim/sulfamethoxazole (TMP/SMX) for *E. coli* paediatric urinary tract infections (UTIs) increased in both boys (from 23% up to 31%) and girls (from 20% up to 23%). Also a ten-time increase in *E. coli* resistance to ciprofloxacin in boys (from 1% in 2002-2004 to 10% in 2009) and girls (from 0.6% to 4%) in paediatric UTIs was reported.21 Moreover, paediatric hospitalizations for pyelonephritis in California increased from 17 per 100,000 children in 1985 to 31 per 100,000 children in 2006.22

There is often misuse of certain antibiotics in the outpatient treatment of paediatric UTIs. There has been a strong shift towards using the newer antibiotic classes, including macrolides and fluoroquinolones. There were fewer overall prescriptions for antibiotics in 2010 as compared to 1999, but the prescription for macrolides increased from 22% to 27%; similarly, the prescription for quinolones increased from 9% to 12%. Increased use of an antibiotic class can markedly accelerate the rise of bacterial resistance.23

Irrational empirical antibiotic therapy may contribute to increased morbidity and increased expenses due to the long durations of the antibiotic treatment and recurrent hospital admissions.24 Based on clinical and in vitro studies, TMP/SMX should not be used empirically. However, data from the National Ambulatory Medical Care Survey suggests that around 50% of children were prescribed TMP/SMX for paediatric UTIs even though recent data suggests that most regions in the United States have resistance rates to TMP/SMX that exceed the approved levels for prescribing this antibiotic empirically.25

Recent examination of UTI resistance patterns has demonstrated that most UTIs are sensitive to narrow spectrum antibiotics, such as first-generation cephalosporins and urinary antinefectives (nitrofurantoin). These underutilized antibiotics have demonstrated significantly low resistance rates over time.26

**Endoscopic Injection in Vesicoureteral Reflux**

It is in the view of the strong yet fearful risk of development of antibiotic resistance which strongly increases the incidence of mortality and patients dying due to infections worldwide, that the question and the concept of an alternative mode of intervention (ie, surgical) arises in the patients with VUR. The various surgical options are – open surgery, laparoscopic and endoscopic injection at the ureteric orifice. With all of them, the underlying anomaly at the vesicoureteric junction is corrected. However, the endoscopic injection has certain advantages over the open surgery.

Surgical cure of VUR reduces the occurrence of pyelonephritis, though it has not been proven to reduce the existing renal injury. Patients with recurrent pyelonephritis and/or persistent reflux benefit most from surgery.27

The various theoretical advantages of laparoscopic approach to reflux repair include decreased hospital stay, decreased postoperative pain, smaller incisions, and faster recovery. It has efficacy similar to open surgery, with success rates of 88% to 100%, but technical difficulty, longer durations during the procedure and the probable risk of higher rate of complications including ureteral injury/obstruction, urine leak, and fistula, have prevented its widespread adoption.28
Endoscopic injection techniques prevent reflux by injecting a bulking substance to allow elevation and coaptation of the ureteral orifice. The various benefits of the endoscopic technique over open surgery are - outpatient procedure and in case of hospital admission, minimal duration of hospital stays, non-invasive and reduced patient morbidity.

An ideal injectable material must have the following characteristics - durable, effective, safe, inert, easily injectable, stable with time and must not migrate, biocompatible, non-antigenic and non-carcinogenic. Dextranomer/hyaluronic acid (Dx/HA or Deflux®) was approved by the United States Food and Drug Administration in 2001 for the treatment of VUR Grades II to IV. Dextranomer/hyaluronic acid copolymer is a viscous gel consisting of two sugar-based molecules. The microspheres are suspended in non-animal stabilized hyaluronic acid. The microspheres are large in size (80–250 µm) and therefore less likely to embolize or migrate.29

In one of the earliest studies conducted by Stenberg (1995) in Sweden, the authors investigated conducted by Stenberg (1995) in Sweden, the authors investigated retrospectively examined and analyzed 419 ureters of 243 patients. These patients underwent Deflux® injection therapy between September 2004 and September 2014. It was found that the Deflux® injection was highly efficacious with almost no complication for the anti-reflux procedure in children. The complete cure rates at three months, one year, and three years follow-up in the patients were 70.8%, 64.3%, and 65.6%, respectively. There was an extremely low recurrence rate of UTI and high probability of no VUR at three years if no VUR occurred at 1 year.32

Beetz (2002) evaluated the ongoing risk of UTIs in long-term follow-up of 158 young adults surgically treated for VUR in childhood. It was observed that in the entire long-term follow-up period, episodes of UTI developed in 66% of all patients, including 74% of female patients. Out of 46 pregnancies, symptomatic UTIs were observed in eight cases.33

Mor (2003) also reviewed patients who had surgical correction of VUR by ureteric reimplantation during childhood, and thus assessed their long-term outcome. In the 1970s, 322 children underwent surgical correction of VUR; these patients were followed-up for a long duration of 20 years. The follow-up focused on the incidence of UTIs, current renal function tests, complications during pregnancy, and the incidence of development of hypertension at least 20 years after surgery. In the study group, 49% had long-term urological complications. The incidence of UTIs was 43% in women and 24% in men, respectively. The onset of hypertension was detected in 6% of the patients during follow-up. There was development of renal scars, despite surgery, in 20% of the patients. Among 47 females who became pregnant, 28% reported UTIs during pregnancy. Thus, this study showed that even patients who were treated successfully by open surgery during their early life were prone to develop UTIs, progressive renal scarring, hypertension, and complications during pregnancy. The authors realized and emphasized that there is a need to establish a protocol for the long-term follow-up of such patients.34

Kim (2015) in their article relating to long-term follow-up in children treated with endoscopic injection open surgery for VUR in childhood are not free from complications in later life. However, longer term follow-up after endoscopic injection in VUR shows almost no complications and an extremely low rate of recurrence of UTI.32

In a systematic review to identify the role of Dextranomer/hyaluronic acid for paediatric VUR, the authors searched the Cochrane Controlled Trials Register and other databases from 1990 to 2008 and found that the overall success rate with Deflux® injection was 77% after 3 months with variations existing among studies. It was also observed that increased VUR grade negatively affected success rates.35

**Conclusion**

In view of the emerging landscape of antibiotic resistance in VUR in children, it would definitely not be recommended to prescribe long-term or repeated chemoprophylaxis in children. Among surgical options, endoscopic injection in these children is an option with minimum hospital stay, non-invasive nature and reliable success rates when injected appropriately. Thus, an increased use of the endoscopic injection (Deflux®) should be encouraged in children suffering from Grades II to IV VUR.

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**References**

Neurological Emergencies in Pregnancy

Koushik Pan¹, Shyamal Kumar Das²

Abstract
On one side, pregnancy is a bliss, a beautiful journey for most women while on other, it increases the risk of several diseases which may cause considerable morbidity and mortality in young women in the most productive period of their lives. Neurological emergencies in pregnancy often have grave prognosis and so, must be promptly diagnosed and treated. This article reviews the clinical features and management of some of the common severe neurological emergencies in pregnancy.

Introduction
Neurological complications of pregnancy may turn out emergent.¹ However, several diseases have increased prevalence during pregnancy

Table 1: Neurological emergencies in pregnancy

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorder</th>
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<tbody>
<tr>
<td>Headache</td>
<td>Migraine</td>
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<tr>
<td>Vascular</td>
<td>Posterior reversible encephalopathy syndrome</td>
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<tr>
<td></td>
<td>Reversible cerebral vasocnstriction syndrome</td>
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<td></td>
<td>Stroke</td>
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<tr>
<td>Neuromuscular</td>
<td>Post partum neuropathy</td>
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<td></td>
<td>Guillain-Barre syndrome</td>
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<tr>
<td></td>
<td>Myasthenia gravis</td>
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<tr>
<td>Cranial neuropathy</td>
<td>Bell’s Palsy</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Pituitary apoplexy</td>
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<tr>
<td>Movement disorder</td>
<td>Chorea gravidanum</td>
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<tr>
<td>Encephalopathy</td>
<td>Wernicke’s encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Eclampsia</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Seizure</td>
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</tbody>
</table>


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fibrinogen levels and factors VIII, IX and X. Fibrinolytic activity is decreased with a reduction in the levels of endogenous anticoagulants, like protein S and antithrombin III. These changes persist into the early postpartum period. Consequently, majority of the ischemic strokes occur late in pregnancy and particularly in the postpartum period. Hypertension, which is associated with ischemic as well as hemorrhagic strokes, is a primary feature of preeclampsia. Pregnancy, in itself, is a state of induced hypercoagulability which may facilitate the development of venous thromboemboli in a susceptible individual. Paradoxical embolism related to the presence of a patent foramen ovale (PFO) sometimes gets triggered by both the coagulation profile and by the hemodynamic changes such as increased venous stasis, Peripartum cardiomyopathy is a rare complication of pregnancy but may cause cardioembolic stroke and severe progressive cardiac failure requiring transplant. Etiologies of stroke unique to pregnancy include choriocarcinoma, postpartum cerebral angiopathy and postpartum cardiomyopathy. Stroke during labor or soon after vaginal delivery may result from an amniotic fluid embolus. Abortions and obstetric procedures performed outside medical standards may cause vaginal air insufflations, thus resulting air embolus to the heart, with subsequent generalized and focal cerebral ischemia.

Stroke patients usually present with abrupt onset of focal neurological deficits (hemiparesis, hemianesthesia, ataxia, blindness). However, at times, patients may present with non-focal symptoms like headache, seizures and altered consciousness. These symptoms are more frequently observed in patients with venous thrombosis and resulting venous infarctions.

The primary treatment for acute ischemic stroke is intravenous thrombolysis with tissue plasminogen activator (tPA). However, pregnant patients were not included in tPA clinical trials. There have been concerns regarding the adverse effects of tPA on the pregnant mother and fetus like placental abruption, abortion, uterine hemorrhage and preterm delivery as well as hemorrhage including intracerebral hemorrhage. However, with scientific data available, preterm delivery and fetal loss are infrequent.

Hemorrhagic stroke is of lower incidence in pregnancy as compared to ischemic stroke and occurs mostly during late pregnancy and the puerperium. Intracerebral hemorrhage has a higher maternal mortality rate, nearly accounting for 5% to 12% of overall maternal mortality in pregnancy. Hemorrhage is often associated with preeclampsia / eclampsia, arteriovenous malformations (AVM,) and aneurysmal rupture. In case of an unruptured AVM, risk of first hemorrhagic event during pregnancy is about 3.5%, no higher than over a similar period outside pregnancy. Aneurysmal rupture is more likely in the second and third trimesters (30% and 55% of ruptures respectively), as compared with first trimester or puerperium (6% and 9% respectively). The possible etiology for the heightened risk of intracerebral hemorrhage (ICH) during pregnancy may relate to the physiological changes of pregnancy including increased blood volume, rising blood pressure, and changes in vascular tone. The physical stress of delivery and labor may also contribute to the risk of aneurysmal rupture, and patients with known aneurysms and AVMs are often delivered by scheduled C-section. Treatment include antihypertensives and antiseizure medications including magnesium, with close monitoring.

Eclampsia

Worldwide, the incidence of eclampsia ranges between 2% and 10% of pregnancies. The incidence of preeclampsia, the precursor to eclampsia, varies greatly worldwide. WHO estimates the incidence of preeclampsia to be seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%). Preeclampsia is defined by proteinuria and gestational hypertension which usually occurs after the 20th week of pregnancy. Severe cases may manifest with headache, visual changes, other signs of raised intracranial pressure and reduced fetal growth. The underlying etiology for preeclampsia and eclampsia remain unknown, but abnormal immunological interactions between foetal and maternal tissues appear to be involved.

Eclampsia may complicate with diffuse cerebral oedema, subarachnoid haemorrhage, cerebral haemorrhage and microinfarctions.

Eclampsia is conventionally characterized by the new onset seizures and/or coma during the pregnancy, labor, or puerperium in the background of preeclampsia.

Recently researchers found favor with the opinion that seizures usually occur without the pre-existing setting of preeclampsia, particularly in late postpartum eclampsia.

In severe pre-eclampsia and eclampsia, prompt delivery is the immediate goal. Thus, treatment strategies include control of arterial blood pressure, reduction of cerebral oedema, and rapid control and prevention of seizures. Magnesium sulphate is being commonly used in pre-eclampsia and eclampsia. Ongoing seizures should be aborted with intravenous diazepam 5-10 mg or lorazepam 2-4 mg given as slow intravenous bolus, while phenytoin may prevent recurrent seizures. Chlormethiazole is not commonly used nowadays.

Myasthenia Gravis

Myasthenia gravis (MG) is a chronic disease which affects the neuromuscular transmission resulting in fatigable weakness of the skeletal muscles. Women are more commonly affected with the disorder (2:1). The course of MG during pregnancy is variable and varies with subsequent pregnancies. Exacerbations occur in nearly 40% of pregnancies with the remainder of patients having stable disease or remission of symptoms. The neuromuscular blockade occurs due to an autoimmune mechanism, and anti-acetylcholine receptor (AChR) antibody is detectable in 90% of affected patients. Antistriated muscle antibody is often associated with an underlying thymoma.

In the pre-thymectomy era, one third of myasthenic patients deteriorated during their pregnancies, one third had their health unchanged, and one third improved.

Thymectomy is indicated for thymoma and is recommended in all young myasthenic patients who have a deteriorating response to an anticholinesterase drug. The thymoma should be resected prior to a planned pregnancy;
Steroid-sparing immunosuppressant drugs such as azathioprine should be discontinued prior to pregnancy owing to the risk of teratogenicity.\textsuperscript{35} Corticosteroid therapy also poses a risk to the mother and the foetus. The oral or intramuscular administration of pyridostigmine and neostigmine is safe as there is little passage through the placenta. Azathioprine can induce fetal leukopenia but is often maintained for severe disease.

The management of preeclampsia in myasthenic patients presents a challenge as magnesium sulfate is contraindicated. Phenytoin can be a suitable alternative to manage seizures.\textsuperscript{31} Vaginal delivery is not contraindicated but a myasthenic patient may not be able to tolerate full labor due to fatigue.\textsuperscript{31} Following the delivery, infant must be evaluated for neonatal MG which may occur in nearly 10\% to 20\% of deliveries via placental transmission of acetylcholine antibodies.\textsuperscript{36} Neonatal MG responds well to anticholinesterase medications.\textsuperscript{37} Pregnancy does not worsen the long-term prognosis of MG.\textsuperscript{31}

**Guillain-Barre syndrome (GBS)**

GBS represents a heterogeneous group of immune mediated peripheral neuropathies. GBS must be kept under consideration in any pregnant woman complaining of muscle weakness, tingling of the fingers, and difficulty in breathing.\textsuperscript{37,38}

Presentation: Rapidly progressive symmetric areflexic weakness.

Timing: Any trimester and postpartum period but is more frequent in third trimester and initial 2 weeks after delivery.

Course: Worsen in post partum period due to delayed type of hypersensitivity.\textsuperscript{39} Nearly 20\% disability and a maternal mortality of approximately 7\% has been documented while GBS without pregnancy has a mortality rate of less than 5\%.\textsuperscript{40}

Treatment: Intravenous immunoglobulins (IVIG) or plasmapheresis, along with ventilatory support whenever needed. Plasmapheresis and IVIG significantly improve patients’ outcome with complete recovery in almost 70-80\% of the cases.\textsuperscript{36,41}

Obstetric Precaution: Delivery must be actively coordinated with anesthesiologist as autonomic instability in some patients may complicate anesthetic care.\textsuperscript{42} Additionally, there are reports of succinylcholine administration precipitating hyperkalemia and use should be avoided.\textsuperscript{42,43}

**Idiopathic Facial Nerve Palsy**

Bell’s palsy occur in approximately 17/100,000 women of child bearing age per year.\textsuperscript{44} Overall, Bell’s palsy is more frequent in females (2-4:1) and incidence may rise up to 6 times more in pregnancy as compared to non-pregnant women, although some of the studies have found no increase in incidence.\textsuperscript{45,46} Bell’s palsy presents mostly during the third trimester and peripartum.\textsuperscript{46,47} There appears to be an association with pre-eclampsia.\textsuperscript{47,48} Almost 15\% of pregnant women with acute lower motor neuron facial paralysis may have secondary etiologies.\textsuperscript{49} Plasma volume expansion in pregnancy may result in increased intracellular fluid which may lead to mechanical compression of the facial nerve in fallopian canal. Based on this hypothesis, Bell’s palsy apparently has maximum incidence in third trimester because of the peak increase in intracellular fluid volume during third trimester.\textsuperscript{30,50} Besides, some researchers have proposed another hypothesis that hypercoagulable state in pregnancy may predispose to thrombosis of vasa nervosum of the facial nerve, thus leading to devascularization and ischemic nerve injury.\textsuperscript{51}

**Neuropathies**

Postpartum neuropathies are relatively uncommon. Intrinsic obstetric palsies may result from delivery or labor process, the most commonly occurring of which is lateral femoral neuropathy. Other neuropathies known to occur are femoral, obturator, sciatic, common peroneal nerve, and lumbosacral plexus in descending order of frequency.\textsuperscript{52} The most apparent cause of these neuropathies is mechanical stretch in dorsal lithotomy position. However, nulliparity and prolonged second stage of labor have been reported as important risk factors.\textsuperscript{53}

**Cerebral Venous Thrombosis**

A rare cause of stroke overall, cerebral venous thrombosis (CVT) is an important consideration in pregnancy and postpartum state.\textsuperscript{54-57} A spike in incidence in the first trimester might be attributable to women who become pregnant with an underlying thrombophilia.\textsuperscript{59} However, more than 75\% of cases of CVT are post partum.\textsuperscript{59} The main risk factors are caesarean section, traumatic delivery, dehydration, anaemia, increased serum homocysteine and low CSF pressure due to dural puncture from a neuraxial anaesthetic.\textsuperscript{59,60} Pregnancy in itself is a hypercoagulable state, and thus a risk factor for thrombotic events.\textsuperscript{11,13} Other genetic causes of hypercoagulability including antiphospholipid syndrome, prothrombin gene mutations, and factor V Leiden / MHTFR deficiency are predisposing factors for the development of CVT.\textsuperscript{61} Oral contraceptive pills (OCP) use is often associated with CVT and must be enquired for, especially in young women presenting with acute headache and visual changes.\textsuperscript{62}

Superior sagittal and transverse sinuses are most commonly involved and may manifest with headache, seizures, papilledema and other signs of raised intracranial tension. The cavernous sinus is infrequently involved and when thrombosed, may present with proptosis, cranial nerve deficits and painful ophthalmoplegia due to raised pressure inside the sinus and orbit. CT of brain is often negative, but 30\% of cases might show a clot or signs of infarction.\textsuperscript{53} Ischaemic infarcts often undergo haemorrhagic transformation. MR venography along with gradient echo (GRE) sequences is usually diagnostic and often, the imaging study of choice.\textsuperscript{53}

Anticoagulation with warfarin is generally avoided in pregnancy complicated with CVT, especially in first trimester due to risk of teratogenicity. However, the American Heart Association (AHA) recommendations say that warfarin therapy is safe in second and third trimester while it should be discontinued in later stage of pregnancy.\textsuperscript{64} Low-dose aspirin is felt to be safe, particularly after the first trimester, according to the American College of Chest Physicians 2008 guidelines.\textsuperscript{65} Additionally, both groups suggest that unfractionated heparin or low-molecular weight heparin can be utilized in pregnancy either as a bridge to warfarin therapy or as a stand-alone treatment.\textsuperscript{64,65} Following delivery, warfarin can be utilized for anticoagulation which is generally continued for a 3- to 6-month period.
with repeat imaging.

Seizures

Seizures in pregnant or post-partum stage can be classified into three categories: first, and most common, are women with established epilepsy prior to pregnancy;6 second group comprises of non-pregnancy related seizures, like new onset seizure from an structural brain lesions or hypoglycemia; and lastly, the third group comprises of pregnancy related new onset seizures (caused by eclampsia, cerebral venous thrombosis, reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome, intracerebral hemorrhage or thrombotic thrombocytopenic purpura).

Maternal seizures and antiepileptic drugs can accentuate the risk of fetal malformation approximately two to three times. The conventional anticonvulsants drugs (phenytoin, valproate, and carbamazepine) carry almost similar overall risk. Valproate and Carbamazepine are associated with a higher risk of spina bifida (about 1% for carbamazepine and 2% for valproate).67,68 Polytherapy appears to increase the risk of fetal malformations.69,70 Folate supplementation is vital to reduce the risk of spina bifida.

Generalised tonic-clonic seizures can lead to profound fetal bradycardia.71,72

Status epilepticus may be associated with poor prognosis and death of the child or mother, have both been reported as a consequence. Treatment protocol for status epilepticus in pregnancy remains the same as in general cases.73 Mothers who are kept on antiepileptic enzyme inducing drugs should be given 20 mg oral vitamin K1 daily for a week prior to delivery. If the exact date of delivery is not known in advance which is a usual situation, it seems sensible to start K1 a month before the expected delivery.74 Alternatively, the mother can be given 10 mg K1 parenterally during labour. Administration of vitamin K1 to the newborn is recommended in these circumstances. Most of the anticonvulsants drugs apparently pass into breast milk, albeit in very low concentrations, which is not likely to have any adverse effect on infant.75 Breast feeding can therefore be encouraged.

Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by abrupt onset of thunderclap headaches and multifocal, reversible cerebral vasoconstriction.76

Timing: Within 1 week of a normal delivery associated with a normal pregnancy.76

Clinical Features: Recurring daily thunderclap headaches in several weeks after a single thunderclap headache are nearly pathognomonic.76-78 Headache episodes are often associated with vomiting, confusion, photophobia, and blurred vision. When seizures or focal neurological deficits develop, they nearly always follow the headache.

Course: Symptoms usually subside over 2-3 months.76,77,79

Complications: Cerebral infarction, edema, and death.76,77

Association: Cervicocranial arterial dissections.

CSF Study: Normal but can show small numbers of lymphocytes and a mild rise in protein concentrations.76,80

CT Scan: Normal if there is no associated hemorrhage.

Angiography: Multifocal segmental arterial constriction and can detect arterial dissections.81

Treatment: Analgesics including opiates. Glucocorticoids, magnesium sulfate, calcium channel blockers and cytotoxic agents have tried to boost patient’s recovery.24 Steroids and immunosuppressive agents are considered in cases of suspected underlying vasculitis or inflammatory process.

Differential: Aneurysmal subarachnoid hemorrhage (SAH), pituitary apoplexy, ICH and venous sinus thrombosis

Posterior Reversible Encephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome (PRES) commonly presents with headache, seizures, encephalopathy, and visual disturbances.

Clinical Setting: Acute hypertension, pre-eclampsia or eclampsia, renal disease, sepsis, and other conditions and in those exposed to immunosuppressant and other drugs.92-94

Clinical Features: Nearly 90% of seizures might be focal to start along with secondary generalization, and generally precede visual changes or headache, which is generally dull, bilateral, and not thunderclap. Confusion is common and may progress to more significant degrees of altered awareness including stupor or coma.85 40% of cases have visual symptoms such as visual hallucinations, blurred vision, scotomata, and diplopia.86 Nearly, 1-15% of patients have transient cortical blindness.

Etiopathogenesis: Impairment in underlying cerebral autoregulation and/or endothelial dysfunction.82

Course: Symptoms often develop without a prodrome and progress rapidly over 12-48 hours. Visual symptoms often resolve completely in hours to days while the resolution of oedema on imaging lags behind.87,88

CT Finding: Vasogenic oedema mostly involves occipital lobe

MRI Finding: Focal oedema, in the parieto-occipital lobes. Unlike posterior cerebral artery lesions, the occipital lesions spare the medial occipital lobe and calcarine cortex.

Treatment: Emergent delivery if feasible and appropriate. Magnesium sulfate is commonly used for seizure control.23

Differential Diagnosis: The distribution of the lesions usually involves multiple vascular territories that help to distinguish the changes from ischemic stroke.

Conclusions

Pregnant and post-partum patients who present with new acute neurological symptoms need a thorough diagnostic evaluation that targets a range of pathological conditions that are either unique to or arise more frequently in this population. Appropriate management, preferably under the joint care of obstetricians, neurologists, neurosurgeons, and paediatricians in established centres, will ensure successful foetal and maternal outcomes.

References

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For the use of a registered medical practitioner or a pharmacist only.
A 76 years old male, non smoker, non alcoholic, was diagnosed as psoriatic arthritis 3 years back on the basis of psoriatic skin rash, asymmetrical polyarthritis including distal interphalangeal joints and asymmetric sacroilitis with raised inflammatory markers. He was allergic to sulphasalazine and intolerant to methotrexate. He was given leflunomide 20 mg daily but he did not responded well to it and therefore anti-TNF agent subcutaneous injection etanercept 50 mg weekly was added to it. He responded well and remains stable for about 2.5 years but any attempt to taper anti TNF resulted in recurrence of symptoms and signs, so patient was continued on same dose.

Inspite of regular and adequate dose of etanercept and leflunomide, patient developed skin rash on dorsum of both hands associated with gradually increasing inflammatory type of low back pain and polyarthalgia from last 3 months. On examination his tender joint count (TJC) was 15/68, swollen joint count (SJC) was 0/66,without any deformity, Patient’s pain score was 6/10 score, patient global assessment score was 8/10, with increase in CRP-32 mg/L, ESR-41 mm/h, Disease Activity in PSoriatic Arthritis (DAPSA)-32.2(High activity). Secondary anti-TNF Failure was considered and etanercept was stopped. Patient was shifted to subcutaneous injection Secukinumab 300 mg every weekly for 4 weeks than monthly , he responded very well within one month, with disappearance of rash and improvement in back pain without any side effect. His DAPSA score significantly improved from 32.2 (high activity) to 2.3 (remission) with marked dermatological improvement (Figures 1, 2, 3).

Secukinumab is a fully human monoclonal antibody that selectively neutralizes circulating IL-17a. Research suggests that IL-17a may play an important role in driving the body’s immune response in psoriasis, psoriatic arthritis and ankylosing spondylitis. Even though many patients with psoriatic arthritis benefit from anti-TNF therapy but many do not respond to Anti-TNF agents, therefore unmet needs remain, including an unacceptable side-effect, lack of primary efficacy (primary failure), loss of efficacy (secondary failure), and immunogenicity with these agents in some patients.

Secukinumab showed efficacy among patients who had received previous anti-TNF therapy and especially in above mentioned situations.

References
A 27-year-old male presented with multiple, itchy, erythematous, concentric plaques over the groins since 3 months. The patient consulted a physician (non-dermatologist) and was prescribed topical preparation containing potent topical corticosteroids (clobetasol) in combination with clotrimazole. Initially, there was a quick response in itching which prompted him to apply the product continuously for a few weeks. After application of topical steroids, the morphology of the lesion changed from annular to concentric plaques. We performed potassium hydroxide mount which showed hyphae and on culture, *Trichophyton rubrum* was grown.

These days dermatologists across India have been seeing such cases in dermatology outdoor on a very regular basis. This condition is named as Tinea pseudoimbricata, which is essentially a form of tinea incognito characterised by presence of multiple concentric rings within a lesion of dermatophytosis. It resembles tinea imbricata caused by *Trichophyton concentricum,* but latter has many more concentric circles and is usually generalized. Injudicious use of topical steroids is probably the major reason for development of this distinct clinical presentation of tinea. Such cases are resistant to conventional treatment and often require prolonged therapy with systemic antifungals like Itraconazole. As many of these cases of tinea initially present to general physicians, we want to share this case to make them aware of pitfalls of use of topical corticosteroids and combination products (antifungal with steroids) in cases of tinea.

**References**

1. Verma S. Tinea pseudoimbricata. *Indian J Dermatol Venereol Leprol* 2017; 83:344-5
Hypereosinophilia with Multi-organ Dysfunction - A Diagnostic Conundrum

Ankit Mittal¹, Animesh Ray², Ranveer Singh Jadon², Smita Manchanda³, Shivdas Rajaram Naik¹, Komal Singh¹, Piyush Ranjan⁴, Naval K Vikram⁵

Abstract

Eosinophils are predominantly tissue-dwelling cells (spleen, lymph nodes, thymus, digestive tract) and counts <500/mm³ in the peripheral blood are considered to be normal. The functions of eosinophils are not completely understood, however there can be a significant rise in their levels in the peripheral blood and/or tissues in a variety of disease states. Hypereosinophilic syndromes (HES) are a group of disorders characterised by blood eosinophilia greater than 1500/mm³ on at least two occasions and eosinophilic infiltration and damage to multiple organs. Eosinophils on activation release substances that can lead to tissue damage. However, it is important to note that the degree of tissue damage is not directly proportional to the level of eosinophilia. A significant number of cases of HES are commonly missed and therefore a systematic approach is necessary for all such patients. Through our case, we have tried to summarise how to systematically approach a case of HES and manage it.

Our case was a 35 year old male, resident of Bihar, India, who presented to us with complaints of on and off fever, generalised rash, shortness of breath and loose stools for the last 3-4 years.

The patient was apparently well till around 4 years back when he started having fever; which was intermittent, low-moderate in intensity, without any recognizable pattern, associated with chills but no rigors and responded to anti-pyretics. For this complaint he had consulted local doctors and was prescribed multiple courses of antibiotics for the same, however 3 months after onset of fever, the patient also developed generalised maculo-papular rashes over body and extremities, which were mildly itchy but not associated with scaling or any serous/purulent discharge. The rashes used to come in crops, responded to anti-histaminics and usually healed with hyperpigmentation.

At around the same time of development of rash, the patient also developed complaints of shortness of breath which was insidious in onset and gradually progressive. It was associated with wheezing and was worse early in the morning and during the winters. It was also associated with cough and scanty mucoid expectoration. There was however, no history suggestive of paroxysmal nocturnal dyspnea, orthopnea, exertional chest pain, palpitations or syncope.

Around 1 week after developing rash and shortness of breath, he also developed complaints of loose stools which were of large volume, watery in consistency, without pus or blood or mucus. The frequency was around 3-4 times/day. There was mild diffuse abdominal pain, loss of appetite without any no history of vomiting. He had also attributed to worm infestation and was treated with albendazole on multiple occasions. However, 3 months after onset of fever, the patient also developed generalised maculo-papular rashes over body and extremities, which were of large volume, watery in consistency, without pus or blood or mucus. The frequency was around 3-4 times/day. There was mild diffuse abdominal pain, loss of appetite without any history of vomiting.

Table 2: Causes of eosinophilia

<table>
<thead>
<tr>
<th>Allergic disorders</th>
<th>Infectious causes</th>
</tr>
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<tbody>
<tr>
<td>Asthma</td>
<td>Parasites</td>
</tr>
<tr>
<td>Drug/ Food allergy</td>
<td>Toxocariasis</td>
</tr>
<tr>
<td>DRESS syndrome</td>
<td>Strongyloidesi</td>
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<tr>
<td>Allergic bronchopulmonary Aspergillosis (ABPA)</td>
<td>Ascarisiasis</td>
</tr>
<tr>
<td>Hyper-eosinophilic Syndrome (HES)</td>
<td>Filarisiasis</td>
</tr>
<tr>
<td>Mastocytosis</td>
<td>Trichinellosis</td>
</tr>
<tr>
<td>Hematological diseases</td>
<td>Fungi (Coccidioidomyces, Basidiobolomycosis)</td>
</tr>
<tr>
<td>Leukemias (CML, CEL)</td>
<td>HIV, HTLV</td>
</tr>
<tr>
<td>Hyper-eosinophilic Syndrome (HES)</td>
<td>Hematological diseases</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Immune reaction</td>
</tr>
<tr>
<td>Hypoadrenalinism</td>
<td>Transplant rejection</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>Autoimmune diseases</td>
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<tr>
<td>Churg Strauss Syndrome</td>
<td>Churg Strauss Syndrome</td>
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<tr>
<td>Autoimmune lymphoproliferative syndrome (ALPS)</td>
<td>Autoimmune lymphoproliferative syndrome (ALPS)</td>
</tr>
<tr>
<td>Gleich syndrome</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Acute Interstitial Nephritis</td>
<td>Acute Interstitial Nephritis</td>
</tr>
<tr>
<td>Cholesterol embolisation</td>
<td>Cholesterol embolisation</td>
</tr>
<tr>
<td>Hyper IgE syndrome</td>
<td>Miscellaneous</td>
</tr>
</tbody>
</table>

Table 1: Common drugs associated with eosinophilia

- Non-steroidal anti-inflammatory drugs (NSAID)
- Penicillins, sulphonamides, tetracyclines, nitrofurantoin
- Ranitidine
- Allopurinol
- Phenytoin, carbamazepine

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lost significant body weight (around 18 kgs) in the last 4 years. There was no history of intake of drugs that are commonly associated with eosinophilia (Table 1).¹

On examination, the patient was conscious and oriented. He was hemodynamically stable without any respiratory distress at rest. No orthostatic hypotension was present. Mild pallor was present. There were few hyperpigmented macular lesions all over his body; however, there was no generalised hyperpigmentation. Mid and lower jugular lymph nodes approximately 1 cm x 1.5 cm were palpable bilaterally. The patient was febrile to touch. The ear-nose-throat examination was unremarkable. Respiratory system examination revealed bilateral diffuse ronchi with prolonged expiration and occasional crepitations. There was diffuse tenderness all over the abdomen. Liver was enlarged and the splenic tip was palpable. Cardiovascular and nervous system examination was normal.

With this clinical picture and a background of persistently elevated eosinophil counts, differential diagnoses of persistent parasitic infestation, Churg-Strauss syndrome, hemotological malignancies and hyper-eosinophilic syndrome (HES) amongst any major illness in the past except for occasional allergic rhinitis, otitis media or sinusitis. There was no history of similar illness in his family. He was married with one child and had no addictions. He had also availed of alternative medications occasionally since there was no improvement in his clinical condition over these many years. There was no history of intake of drugs that are commonly associated with eosinophilia (Table 1).¹

On examination, the patient was conscious and oriented. He was hemodynamically stable without any respiratory distress at rest. No orthostatic hypotension was present. Mild pallor was present. There were few hyperpigmented macular lesions all over his body; however, there was no generalised hyperpigmentation. Mid and lower jugular lymph nodes approximately 1 cm x 1.5 cm were palpable bilaterally. The patient was febrile to touch. The ear-nose-throat examination was unremarkable. Respiratory system examination revealed bilateral diffuse ronchi with prolonged expiration and occasional crepitations. There was diffuse tenderness all over the abdomen. Liver was enlarged and the splenic tip was palpable. Cardiovascular and nervous system examination was normal.

With this clinical picture and a background of persistently elevated eosinophil counts, differential diagnoses of persistent parasitic infestation, Churg-Strauss syndrome, hemotological malignancies and hyper-eosinophilic syndrome (HES) amongst

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¹ Please refer to the original document for Table 1 and other references.
others (Table 2) were kept.²⁴

Initial investigations included a complete blood count which revealed a total leucocyte count of 23000 cells/mm³ with 37% eosinophils. Peripheral blood smear showed no atypical cells or parasites but microcytic hypochromic anemia was present. ESR and CRP were mildly elevated. The renal and liver function tests were normal. Urine examination did not reveal any proteinuria or any active sediments. Stool examination showed few pus cells without any blood and culture was negative. AFB smear of sputum was negative.

His CT chest showed mild bilateral bronchiectasis with bronchial wall thickening; patchy ground glass opacities and peripheral consolidation (Figure 1). CT of the abdomen revealed hepatosplenomegaly with multiple non necrotic lymph nodes. Since the patient had pulmonary infiltrates with eosinophilia the following causes were considered (Table 3).³⁷

His ANCA was negative and Nerve conduction studies were normal. There was only mild bilateral maxillary sinusitis on CT of para nasal sinuses. No active skin lesion, suggestive of vasculitis was present. Work up for Allergic Bronchopulmonary Aspergillosis (ABPA) was negative.

Since the primary work up for the common causes was negative, a bone marrow examination was done which revealed a cellular marrow with increased eosinophils and eosinophil precursors. He was further evaluated to look for the other causes of secondary HES. Since HES may be associated with myeloproliferative disorders, PDGFRA HES. Since HES may be associated with myeloproliferative disorders, PDGFRA kinase mutation studies were done, which were all negative. His vitamin B12 and serum tryptase levels, that are also strongly associated with myeloid variants of HES, were normal. The other possibility kept in was the lymphoid variant of HES; since skin manifestations were predominant, serum IgE levels were high and the causes associated with myeloid variants were ruled out. A peripheral blood flow cytometry was done to look for any T-cell abnormalities. The flow cytometry results came out to be normal. A transbronchial lung biopsy, from left upper lobe, was done which showed features suggestive of chronic interstitial pneumonia, eosinophilia and interstitial fibrosis (Figure 2). A duodenal biopsy was also done which showed chronic inflammatory changes with eosinophil infiltration. A summary of all the investigations has been listed in Table 4.

The patient fulfilled the criteria for and was finally labelled as a case of idiopathic HES (Table 5).³

HES can be of various types (Table 6) and an approach to a case of HES is summarised in Figure 3. Identification of the underlying condition is important as it significantly changes the treatment strategy and the prognosis of the patients.

An extensive review of literature confirmed that the available options for the same in eosinophilia were limited (Figure 4).³⁻¹¹ The patient was started on prednisone at 1mg/kg/day in view of persistent eosinophilia and organ involvement. The patient became afebrile on the next day and eosinophilia rapidly declined to 2700/mm³ from 8510/mm³ in 24 hours. Eosinophil counts completely normalised in 5 days. His shortness of breath, gastro-intestinal complaints and skin rash also resolved. The patient was discharged on prednisone. Oral iron supplementation was done for iron
**Fig. 4: Algorithm for the management of HES**

**Table 6: Types of HES**

<table>
<thead>
<tr>
<th>Variants of HES</th>
<th>Important features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloid variant</td>
<td>Often associated with PDGFRB and FGFR1 rearrangements. Usually associated with cytopenias and organomegaly.</td>
</tr>
<tr>
<td>T cell lymphocytic variant</td>
<td>Due to IL-5 producing T cells. Skin findings (plaque, erythroderma etc) can predominate. Can be associated with polyclonal hypergammaglobulinemia.</td>
</tr>
<tr>
<td>Familial HES</td>
<td>Autosomal dominant form. Eosinophilia from birth which is usually asymptomatic.</td>
</tr>
<tr>
<td>Organ–restricted HES</td>
<td>Along with peripheral eosinophilia there is eosinophilic infiltration and associated symptoms/signs in a single organ</td>
</tr>
<tr>
<td>Idiopathic HES</td>
<td>Multi-system involvement with myriad manifestations</td>
</tr>
<tr>
<td>Specific syndromes associated with hypereosinophilia</td>
<td>e.g. Eosinophilic granulomatosis with polyangiitis</td>
</tr>
</tbody>
</table>

deficiency anaemia.

The patient is on regular follow up and doing well at a maintenance dose of 10mg of prednisolone per day.

**Conclusion**

It is important to systematically approach a case of eosinophilia to establish the proper etiological diagnosis. Idiopathic hypereosinophilic syndrome is diagnosed after ruling out the other common causes and its mainstay of treatment is steroids.

**References**

46 XX, SRY Negative Ovotesticular DSD

Prashant Kaduskar¹, KM Suryanarayana², Prakash Babu³, Vijaya Mysorekar⁴

Abstract
46 XX ovotesticular DSD is a rare disorder. It presents with cryptorchidism, hypospadias or ambiguous genitalia at birth, gynaecomastia in adolescent stage or infertility in adult age. We report here a 20 year old phenotypically male who presented with gynaecomastia and found to have testis on right side and left inguinoscrotal swelling consisting of ovary, uterus and fallopian tubes. Evaluation revealed SRY negative 46 XX karyotype. He underwent surgical removal of ovary and Mullerian structures. The highlight of case is development of testicular tissue in absence of SRY gene.

Introduction
Ovotesticular DSD (Disordered sexual differentiation) is an uncommon disorder of sexual development and approximately 500 cases have been reported world-wide in literature.¹ The diagnosis of this disorder requires presence of ovarian and testicular tissue in same or opposite gonad. Differentiation of genital tract and development of secondary sex characters vary in different individuals but usually follows the gonad which is dominant. Hemi uterus or rudimentary uterus is often present on side of the ovary or ovotestis. In addition breast development, cryptorchidism and hypospadias are common manifestations.

Case Report
A 20 year old patient reared as a male presented to endocrinology OPD with history of left inguinoscrotal swelling of 1 month duration and gynaecomastia (Figure 1) of 6 months duration. At the age of 2 years, patient’s mother had noticed two streams of urine. He undertook two corrective surgical procedures, between 8 and 10 years of age following which he became asymptomatic. There was no significant contributory family history. Due to poor scholastic performance he discontinued studies after class 7. His gender identity, role and sexual orientation were like a male. There was no history nocturnal penile tumescence.

On examination: Vitals were normal. Height: 175 cm, Arm span: 184 cm, Upper segment: 86 cm, Lower segment: 89 cm, US: LS: 0.87, Weight: 60 kgs, BMI: 19.60 kg/m². SPL – 8 cm, 2 opening visible on ventral aspect, right testicular volume – 8 ml. Left inguinoscrotal swelling: Two separate swellings palpable-Upper swelling 2 x 2 cm, soft, non-tender, extending from left inguinal region up to base of scrotum with positive cough impulse. Lower swelling 1x1 cm, fluctuating, non-tender. His SMR A3, P4. He had grade 4 gynaecomastia (Figures 1 and 2). Systemic examination was within normal limits.

Investigations
CBC : Hb : 12.4 gm/dl, TLC : 9610 (4000-11,000), DLC : Normal ESR : 23 mm at the end of 1 hour (0-20), Platelet count : 3,24,000 /mm³ (1,50,000-4,00,000), FBS : 80 mg/dl (70-110) PPBS : 85 mg/dl (70-140)

Hormonal profile : T3 : 1.32 ng / dl (1.23-3.23), T4 : 87.63 ug / dl (59-135), TSH : 0.899 uIU / ml (0.5-4.3), FSH : 10 mIU/ ml (1.5 – 12.4 ), LH : 12.06 mIU/ml (1.7 – 8.6 ), Testosterone : 3.85 ng /ml (1.8 – 7.63), Estradiol : 40.49 pg / ml (< 39.8 )

USG pelvis: Well-defined hypoechoic area measuring 31 x 15 mm in left scrotum suggestive of ovary, Right scrotal sac shows testis measuring 25 x 11 mm. A well-defined cystic area adjacent to ovary measuring 11 mm.

MRI pelvis: Testes is seen in the scrotal sac on right side, inguinal hernia on left side with herniation of structure that looks like ovary. Inferiorly loculated fluid collection that measures 19 X 20 X 12 mm suggestive of encysted hydrocele. Uterus not identified; prostate not visualized (Figures 3 and 4).

Chromosomal and FISH analysis: Chromosomal analysis of cultured peripheral blood from male patient revealed female 46 XX chromosome complement (Figure 5). Patient sample confirmed presence of two X chromosomes and absence of SRY (Sex determining Region on Y chromosome) – Negative for SRY gene

Patient underwent surgery for left inguinoscrotal swelling. Surgical repair of hernia was done. Hernial sac examination revealed uterus, fallopian tube and ovary (Figure 6). He has been advised reduction mammoplasty for gynaecomastia.

Histopathology
Gross examination: Uterus with ovary with fallopian tube were seen. Uterus measured 5 x 2 x 2 cm; endometrial thickness was 1 mm; Left ovary measured : 3.5 x 1.5 x 1 cm; fallopian tube was measuring 2 cm.

Microscopic examination: Sections from the uterus showed tubular endometrial glands. Sections from the ovary showed predominantly showed fibrotic areas. The fallopian tube showed mucosal plicae.

Discussion
Ovotesticular DSD is rare disorder. It has 3 types: 1. Lateral-(20%) have a testis on one side and an ovary on the other 2. Bilateral - (30%) have testicular

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and ovarian tissue present bilaterally, usually as ovotestes. 3. Unilateral- (50%) have an ovotestis present on one side and an ovary or testis on the other. It is a rare condition, with a frequency of 1:20,000-25,000 male newborns and was first described by La Chapelle and cols. in 1964. 2 On basis of the analysis and detection of SRY gene, 46, XX male patients can be clinically divided into SRY-positive and the SRY-negative group. SRY region was thought to be necessary for determining maleness. However, presence of normal males without SRY region on X chromosome proves that other factors apart from SRY also contribute to maleness of a person.

SRY-positive individuals: 90% of 46 XX ovotesticular DSD are SRY positive. Patients in this group have normal male genitalia, small azoospermic testes and hypergonadotropic hypogonadism. 3 Most carry the SRY gene translocated to X chromosome. 4 Diagnosis is achieved in adulthood during infertility investigation.

SRY-negative individuals – 10 % of 46 XX ovotesticular XX DSD are SRY negative. This group includes patients with ovotesticular DSD : presence of both testicular and ovarian tissue in the gonads of the same individual in the absence of SRY on X chromosome. 5 Development of the testis and normal male genitals in SRY-negative 46,XX males suggests existence of other autosomal or X-linked genes in the sex-determining pathway. The maleness in the absence of SRY gene is explained by several mechanisms. The up-regulation or super-expression of some members of SOX family (SRY-related HMG-box) has been proposed as one of the mechanisms. McElreavey et al. (1993) proposed that SRY acts by inhibiting a regulatory autosomal recessive gene, termed ‘Z’, whose product normally inhibits the male pathway. 6 Two different studies have shown the duplication of a region of the long arm of chromosome 22 in a XX true hermaphrodite. 7

In this particular case, the diagnosis was done only when patient had inguinoscrotal swelling and gynecomastia at an adult age. In a recent case series of ovotesticular DSD from India 8 inguinoscrotal swelling and genital ambiguity before puberty and gynecomastia and cyclical hematuria after puberty were common presentations in ovotesticular DSD cases. Ovotesticular DSD should be considered as one of the differential diagnoses in any case of ambiguous genitalia with nonpalpable or asymmetrical gonads, pubertal gynecomastia, and cyclical hematuria.

Conclusion
46 XX ovotesticular DSD is a rare case. Such patients need timely diagnosis and management by a multidisciplinary team consisting of endocrinologist, pathologist, urologist, surgeon, psychiatrist and geneticist for better health.

Acknowledgements
We are sincerely grateful to Dr. K. M. Suryanarayana, Senior Professor and Head of Department of Endocrinology for evaluating this case.

References
Recurrent Prosthetic Pulmonary Valve Endocarditis in Repaired Tetralogy of Fallot

Himanshu Arora¹, Rajat Mohan², Deepak Agrawal¹, Prashant Wankhide¹, Sangeeta Sachdeva², Payal Nindra³

Abstract

25 year old male who was a known case of repaired Tetralogy of Fallot with history of early prosthetic pulmonary valve fungal endocarditis in 2012 presented in 2016 with history of prolonged fever. On subsequent work up, he was diagnosed to have recurrent fungal prosthetic pulmonary valve endocarditis.

Introduction

Clinical diagnosis of prosthetic valve endocarditis is guided by the modified Duke criteria¹. Mostly prosthetic valve endocarditis in adults has been frequently described with prosthetic aortic or mitral valve. There is a paucity of data on prosthetic pulmonary valve endocarditis. We are presenting a case of recurrent fungal endocarditis of a Bioprosthetic pulmonary valve in an adult male who had a total correction of tetralogy of Fallot earlier in 1993. Cases of Prosthetic pulmonary valve endocarditis are increasing nowadays because of growing number of prosthetic valves being placed in repaired tetralogy of Fallot.

Case Report

25 year old male, presented to the Sir Ganga Ram hospital with One month history of Fever associated with 15 days history of Vomiting and pain abdomen. On examination there was presence of Pansystolic murmur in Tricuspid area with ejection Systolic Murmur and early Diastolic murmur in pulmonary area with splenomegaly.

He was a known case of Cyanotic congenital heart disease (Tetralogy of Fallot) which got total correction done in 1993. Patient had undergone Pulmonary valve replacement (Bioprosthetic) in 2012 due to development of free pulmonary regurgitation. Subsequently He developed early prosthetic valve fungal endocarditis. He was managed with I/V antifungals and fever subsided. Patient underwent echocardiographic examination which revealed vegetation attached to prosthetic pulmonary valve (Figure 1) and pulmonary regurgitation (Figure 2). Blood culture was positive for fungus Candida Albicans. Diagnosis of the prosthetic pulmonary valve endocarditis was made.

Discussion

Infective endocarditis means the infection of the cardiac valve or endothelium, which can be seen as vegetations. The common congenital heart anomalies predisposing to infective endocarditis are bicuspid aortic valve, Patent ductus arteriosus, Ventricular septal defect, Coarctation of the aorta, Tetralogy of Fallot etc.

Prosthetic valve endocarditis accounts for about 10% to 20% of all cases of infective endocarditis. The greatest risk of infection is in the first 6 months after valve implantation and appears to be similar in mechanical and bioprosthetic valves.

Fungi account for 10% to 15% of late prosthetic valve endocarditis cases and are associated with a higher mortality rate.² Prosthetic pulmonary valve endocarditis is a rare entity. In a large multicenter prospective 5 year observational study by Wang et al,³ 556 cases of prosthetic endocarditis were reported, out of which only 31(5.5%) cases had prosthetic pulmonary valve involvement. However, the increased number of cardiac surgeries followed by prosthetic valve implantation has led to their increasing incidence.

Conclusion

Prosthetic pulmonary valve endocarditis is a rare entity with an increasing incidence in the current era. High index of suspicion should be maintained for detecting it.

References


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An Unusual Site of Infective Endocarditis after Surgical Trauma-Evaluated by Three Dimensional Echocardiography

Prem Ratan1, Prashant Dwivedi1, Rajiv Kharwar2, Parveen Kumar1

Introduction

Infective endocarditis (IE) is an inflammation of endocardium and heart valves, associated with high risk of morbidity and mortality, prompt and early diagnosis and early treatment is essential. The age-specific incidence of endocarditis is 5 cases per 100,000 person-years among persons younger than 50 years to 15 to 30 cases per 100,000 person-years in the sixth to eighth decades of life.1 Ventricle septal defect (VSD), patent ductus arteriosus (PDA) and bicuspid aortic valve (BAV) are common predisposing lesion for IE in adults. Isolated Atrial septal defect (ASD) associated with IE not reported in literature yet. We are reporting a rare case ASD associated with IE.

Case Report

A 43 year non diabetic, non-hypertensive, post-surgical closure of atrial septal (ASD) female patient presented with high grade fever from last one month. Her blood pressure was 130/86 mm of mercury and pulse rate was 104 minute, chest bilateral clear, no murmur, Abdomen and nervous system examination was normal. No significant abnormality detected in x ray chest PA view, total leucocyte count was 18000/cm3, 90 % neutrophil. All blood culture were negative. All other parameters were normal. Evaluation with two dimensional echocardiography (2D ECHO) reveals oscillating mass seen in right atrium (Figure 1A) attached to interatrial septum. which was not present in previous 2D ECHO before surgical closure. Trans esophageal echocardiography confirmed oscillating mass attached to opening of superior vena cava (Figure 1B) which was further confirmed by three dimensional echocardiography (Figure 1 C, D).

Discussion

Intact cardiac endothelium is resistant to bacterial invasion, damaged cardiac endocardium is strong stimulator for bacterial attachment leading to infective endocarditis. In VSD, PDA, BAV high velocity blood stream jet cause damage to endothelium in adult leading to IE. In literature most common site IE is valves (native or prosthetic), interventricular septum and intra-cardiac devices.2 IE after surgery first reported by Taussig and associates in patients tetralogy of Fallot, assumed that unhealed suture line was the potential source of IE.3 Various case reports also described IE after surgical mitral commissurotomy.4-6 Hurst, Jones and Scott reported case of IE after PDA surgery.7-9 Uncomplicated ASD in adult never been reported in literature as associated with IE. But after surgical closure of ASD, normal endothelium could be receptive for bacterial adhesion due to unusual site surgical trauma, could be a source of prolonged fever. Prompt and early recognition and treatment result in excellent patient recovery.

Conclusion

Surgical trauma, could be a unusual site of infective endocarditis. Awareness of unusual site of infective endocarditis and early recognition result in excellent patient recovery.

References

3. Hurst, Jones and Scott reported case of IE after PDA surgery.7-9
4. Uncomplicated ASD in adult never been reported in literature as associated with IE. But after surgical closure of ASD, normal endothelium could be receptive for bacterial adhesion due to unusual site surgical trauma, could be a source of prolonged fever. Prompt and early recognition and treatment result in excellent patient recovery.

Fig. 1: (A) Two-dimensional TEE at 45° angle showing a vegetation near the aortic valve in RA. (B) Two-dimensional TEE at 115° angle clearly delineating the vegetation attached to SVC opening. (C and D) 3D TEE showing Vegetation attached to SVC. TEE=Transesophageal echocardiography, RA= Right atrium, SVC = Superior vena cava, 3D=Three dimensional
Myocardial Infarction following Organophosphorus Compound Poisoning

Puvanalingam Ayyadurai¹, Gopalakrishnan Subbiah², Venkatesan Selvaraj¹

Abstract

We report a 22 year old male who was admitted to our hospital with alleged history of consumption of monocrotophos poison and had presented with chest pain. His electrocardiogram (ECG) had showed ST segment elevation myocardial infarction and troponins were elevated. He also had low cholinesterase levels and was treated with pralidoxime and atropine and his condition improved. Cardiac catheterization showed patent coronaries. Acute coronary syndrome is a rare manifestation of organophosphorus compound (OPC) poisoning. The current case and subsequent review of literature tells us the need for close cardiac monitoring of all patients with OPC poisoning.

Introduction

OPC poisoning is very common in India where farmers form a significant proportion of the population who commonly use it as insecticides. OPC poisoning can cause cholinergic symptoms like salivation, lacrimation, urination and defecation. Nicotinic symptoms like neck muscle weakness, ocular weakness, proximal muscle weakness and respiratory muscle weakness can occur as a part of intermediate syndrome. ECG changes like transient ST-T wave changes, QT prolongation, atrial and ventricular arrhythmias can occur¹. Few cases of myocardial infarction (MI) after OPC poisoning has been reported. We report a young man who developed myocardial infarction after OPC (monocrotophos) poisoning.

Case

22 year old young man got admitted in our toxicology ward with alleged history of consumption of 15 ml of monocrotophos poison in his house. He was initially taken to the nearby private hospital where gastric lavage and activated charcoal was given. He had presented to the hospital with complaints of chest pain. Chest pain was left sided and diffuse and 8/10 in intensity. He also had shortness of breath at the time of presentation. No palpitation or syncope was noted. He also had increased salivation. Review of system was negative for other complaints. He had no significant past medical history. He was a nonsmoker and did not drink alcohol. He was not allergic to any medications. Physical examination revealed a moderate build male. Cardiopulmonary examination was clinically normal. Abdomen was soft and he had bilateral constricted pupils on neurological examination.

Fig. 1: ECG of the patient showing ST-elevation in lead 2, 3 and AVF— Inferior wall myocardial infarction

Fig. 2: Coronary angiogram of the patient which reveals patent coronary vessels

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ECG which was taken revealed ST elevation in leads II, III, AVF (Figure 1). His vitals were stable. He was then referred to the government general hospital, Chennai. In our center, serum CPK-MB, troponins were immediately done which were elevated. Echocardiogram was done which showed regional wall motion abnormality in the inferior wall of the left ventricle. Serum cholinesterase levels were 1172 IU/dl which is low. Serum homocysteine levels, PT/INR, APTT, antithrombin, lupus anticoagulant and anticardiolipin antibodies were within normal limits. On the next day serum pro-NT BNP levels was done which was elevated. Patient was treated with pralidoxime, atropine, anticoagulant and antiplatelet drugs. Following this treatment, the patient’s serum cholinesterase levels improved, chest pain recovered. Coronary angiogram (Figure 2) was done the next day which was found to be normal. Patient’s medical condition improved and he was discharged.

**Discussion**

Cardiac complications often accompany poisoning with OPC. These may be serious and often fatal, being represented by cardiac arrhythmias, electrocardiographic abnormalities and conduction defects, as well as MI, a rarely reported complication of OPC poisoning. The extent and pathogenesis of cardiac toxicity from these compounds is not yet clearly defined. In literature we had few cases of MI occurring after OPC poisoning. Lionte C et al reported a 57 year old woman who developed anteroseptal MI and succumbed to death. Kiss Z et al reviewed 168 cases of OPC poisonings with special respect to frequent arrhythmias. In five patients a transient picture of MI was seen. Dayton S.B et al reported increased risk of MI among farm women exposed to pesticides. A rare case of MI due to parathion poisoning was reported by Yajneesh kidiyoor et al. The affected patient was a farmer from rural India who had succumbed to the complications of MI. Madhu Pankaj et al reported a 30 year old male who had taken chlorpyrifos and had presented with anterior wall myocardial infarction. Edibe Karasu et al also reported a 52 year old patient who had presented with inferior wall myocardial infarction after parathion ingestion. In patients with angiographically smooth coronary arteries, acetylcholine has been reported to produce both vasodilation and constriction. The development of vasoconstriction is likely to be an abnormality of endothelial function that precedes atherosclerosis or an early marker of atherosclerosis not detectable by angiography. This is a likely mechanism in our patient. Coronary vasoconstriction response in isolated perfused heart mediated by M 3 receptor has been reported in rats. The cardiovascular manifestations also reflect mixed effects on the autonomic nervous system. Increased sympathetic tone is often initially present and most patients manifest as sinus tachycardia and sometimes hypertension. As toxicity becomes more severe, bradycardia with a prolonged PR interval and atrio-ventricular blocks of various degrees occur because of excessive parasympathetic tone and possibly because of reduced coronary blood flow.

**Conclusion**

Cardiac complications often accompany poisoning with OPC, particularly during the first few hours. Hypoxemia, acidosis, and electrolyte derangements are major predisposing factors. Close monitoring in intensive or coronary care facilities with administration of antidotes in adequate doses early in the course of the illness will improve the outcome.

**Conflict of interest**

The authors of the paper declare that there is no conflict of interests involved regarding the publication of this paper.

**Acknowledgement**

We thank all the faculty of Institute of Internal Medicine, Madras Medical College for their kind help rendered in the evaluation of this case report.

**References**

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DNA is probably the most famous molecule in the world. Its double helix shape is the single most familiar image from biology and chemistry. Apart from unraveling the mechanism of inheritance it has made possible new medical treatments, screening for genetic diseases, DNA fingerprinting, controversial technique of genetic engineering, and cloning. Science of molecular biology - a fusion of biology, chemistry and physics started with DNA.

By 1944, biochemists were coming to realize that nucleic acids rather than proteins were instruments responsible for characteristics inherited and it was deoxyribonucleic acid (DNA) of the chromosomes, that were key chemicals of life to carry the information. Whereby physical characteristics were inherited and it was deoxyribonucleic acid of the chromosomes that were key chemicals of life to carry information.

One method of studying internal structure of large molecules like proteins is X-ray diffraction. Maurice Wilkins (1916-2004) who obtained his Ph.D. in physics from Cambridge studied DNA in this manner and by 1953, his data yielded specific information on the type of regularities regarding nucleotides that were to be found. Problem was how best to interpret those regularities in atomic terms. Within the molecule of nucleic acid there was a definite relationship among nitrogenous bases. There were four such bases in the DNA molecule- adenine, guanine (purines), thymine and cytosine (pyrimidines). Number of adenine units was always roughly equal to number of thymine units, while that of guanine was equal to cytosine.

Francis Crick (1916-2004), educated at University College in London had obtained his PhD in physics. He turned to biochemistry or rather molecular biology and moved to Cavendish laboratory to study proteins. Young American James Dewey Watson (b. 1928) while studying for his PhD at Indiana University (USA), became interested in genetics, and involved himself in X-ray diffraction crystallography. Best work in the field at the time was done in England, so he set off to learn more, ending up in Cavendish lab at Cambridge, where he met Crick. Two became firm friends and shared an office together. They considered analyzing Wilkins X-ray diffraction data on DNA, but the work was hampered by poor quality films. Watson made models of possible structures that would accommodate what was known of DNA molecule at that time.

Second British group worked on the problem at Kings College laboratory, London. The team consisted of Maurice Wilkins (b.1916- 2004) and Rosalind Franklin (1920-1958) who after her degree in Cambridge went to Paris to learn more about X-ray crystallography; on her return she joined Wilkins to work at Kings College laboratory but, unlike Watson-Crick their relations soured. Rosalind’s X-ray photographs taken at Kings College were brilliant. Unfortunately her role in the studies was constantly underplayed partly due to ant-feminist attitude at the time.

Crick and Watson made use of the key photograph taken by Rosalind Franklin, apparently without her permission and came with the revolutionary model of the nucleic acid molecule. The model represented it not merely as helix but as a double helix. Two sugar phosphate backbones winding like a double railed spiral staircase up the same vertical axis. From each sugar phosphate are held at the same distance apart by pairs of nucleotide bases interlocking in the centre acting like steps of a ladder. The bases are always paired in the same way adenine with thymine and guanine with cytosine. Structure of DNA so revealed, did indeed show how it works. Each strand works as a template- where adenine appears, a thymine must be added opposite it and so on. As cells divide to multiply, DNA is copied exactly into each new cell. The work was accepted immediately. Crick and Watson received the 1962 Medicine or physiology Nobel Prize with Rosalind Franklin for her work. Since she died before Nobel Prizes were given, portion of the prize was awarded to Maurice Wilkins along with Crick and Watson.
Uttar Pradesh Association of Physicians of India Position Statement: Betel Quid (Paan) and Diabetes

Yatan Pal Singh Balhara¹, Sanjay Kalra², Sarita Bajaj³, Pooja Patnaik Kuppili⁴, D Himanshu⁵, Veerendra Atam⁶, Kauser Usman⁶, Veerendra Singh⁶, Shyam Chand Chaudhary⁶, S Chakravorty⁷, Anupam Wakhlu¹¹, Jalees Fatma¹², Sanjay Tandon¹³, Anuj Maheshwari¹⁴, Abha Gupta¹⁵, Anjum Parvez¹⁶, Jaya Chakravarty¹⁷, RR Chaudhary¹⁸, AK Singh¹⁹, KK Sawlani²⁰, Manoj Mathur²¹, NK Soni²², Om Kumari Gupta²³, Madhukar Rai²⁴, Sudhir Agarwal²⁵

Abstract
Betel quid (paan) chewing is common in India, especially in Uttar Pradesh. Betel quid has multifaceted relationship with health, including metabolic and psychosocial health. The current recommendations have been released keeping in view the public health and clinical importance of this addictive behavior. The objective of this document is to offer clinical guidance for screening, diagnosis and management of co-occurring betel quid chewing among persons with Diabetes Mellitus (DM). The document aims to provide education and guidance to clinicians engaged in care and management of persons with DM, and improve access to treatment for co-occurring betel quid chewing among persons with DM. The current recommendation grades are based on published evidence, and categorized as strong, intermediate, weak and no evidence. The strength of these recommendations is based on the level of evidence.

Scope and Purpose
Betel quid (paan) chewing is common in India, especially in Uttar Pradesh. Betel quid (paan) has multifaceted relationship with health, including metabolic and psychosocial health. The Indian College of Physicians Position Statement on Addictive disorders among persons with diabetes (2017)¹¹ have addressed this important aspect of health and clearly advise against betel quid (paan)-chewing. A grade 3B evidence/ recommendation is given to this statement.

The current recommendations have been released keeping in view the public health and clinical importance of this addictive behavior. The objective of this document is to offer clinical guidance for screening, diagnosis and management of co-occurring betel quid (paan) chewing among persons with Diabetes Mellitus (DM). The document aims to provide education and guidance to clinicians engaged in care and management of persons with DM, and improve access to treatment for co-occurring betel quid chewing among persons with DM.

Grading of Evidence
The current recommendation grades are based on published evidence, and categorized as strong, intermediate, weak and no evidence. The strength of these recommendations is based on the level of evidence. The categories of the level of evidence and strength of recommendation are listed in Tables 1 and 2, respectively.¹³

Table 1: Evidence level used for rating various recommendations

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Evidence rating</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Strong</td>
<td>Meta-analysis of randomized controlled trials</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate</td>
<td>Meta-analysis of non randomized prospective or case-controlled trials, systemic literature review</td>
</tr>
<tr>
<td>3</td>
<td>Weak</td>
<td>Cross-sectional study, Surveillance study, Consecutive case series, Single case reports, observational study, pilot study</td>
</tr>
<tr>
<td>4</td>
<td>No evidence</td>
<td>Theory, opinion, consensus, review or pre-clinical study</td>
</tr>
</tbody>
</table>

¹¹Associate Professor of Psychiatry, National Drug Dependence Treatment Center and Department of Psychiatry, AIIMS, Delhi; ¹²Consultant, Department of Endocrinology, Bharti Hospital and BRIDE, Karnal, Haryana; ¹³Consultant Endocrinologist, Director-Professor and Head, Dept of Medicine, MLN Medical College, Allahabad, Uttar Pradesh; ¹⁴Senior Resident, Department of Psychiatry, JIPMER, Puducherry; ¹⁵Professor, Dept. of Medicine, KGMU, Lucknow, Uttar Pradesh; ¹⁶Professor, Dept. of Medicine, KGMU, Lucknow, Uttar Pradesh; ¹⁷Professor, Department of Medicine, KGMU, Lucknow, Uttar Pradesh; ¹⁸Senior Consultant Physician, Faizabad, Uttar Pradesh; ¹⁹Additional Professor, Dept of Medicine, KGMU, Lucknow, Uttar Pradesh; ²⁰Sr. Consultant Physician and Unit Head, Department of Internal Medicine, Diabetology and Critical Care, Metro Multispeciality Hospital, Noida, Uttar Pradesh; ²¹Professor, Department of Rheumatology, KGMU, Lucknow, Uttar Pradesh; ²²Professor and Head, Department of Medicine, Era’s Lucknow Medical College, Lucknow, Uttar Pradesh; ²³Diabetologist and Metabolic Physician, Professor and Head in Internal Medicine, BBDCODS, BBD University, Lucknow, Uttar Pradesh; ²⁴Consultant Physician, Former Associate Prof and Head, Dept. of Medicine, AIIMS, Lucknow, Uttar Pradesh; ²⁵Professor, Dept. of Medicine, JN Medical College, AMR, Aligarh, Uttar Pradesh; ²⁶Professor, Dept. of Medicine, IMS, BHU, Varanasi, Uttar Pradesh; ²⁷Senior Consultant Physician & Geriatrician, S.S.P. G Divisional District Hospital, Varanasi, Uttar Pradesh; ²⁸Associate Professor, Department of Medicine, MLN Medical College, Allahabad, Uttar Pradesh; ²⁹Consultant Physician, Ghaziabad, Uttar Pradesh; ³⁰Sr. Consultant and Clinical Hematologist, Metro Heart and Research Institute, Noida, Uttar Pradesh; ³¹Consultant Physician, Saharanpur, Uttar Pradesh

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Association of Clinical Endocrinologists has used such an approach previously. Most recommendations are extrapolated from literature on substance use disorder, as limited literature exists about DM comorbid with addictive (substance use) disorders. It must be noted that different evidence levels can be mapped to the same recommendation grade by ‘adjusting up’ or ‘adjusting down’ depending on the importance and relevance based on expert opinion.

**Epidemiology**

Betel quid is perhaps the fourth most popular psychoactive substance in the world, after caffeine, nicotine and alcohol. At least 600 million people worldwide chew betel quid. Uttar Pradesh reports a high consumption rate of betel quid chewing, especially in studies on persons with oral malignancy.

Betel quid has a few core constituents (areca nut (supari), betel leaf (paan ka patta), slaked lime (chunna) and tobacco), though other ingredients may be added as per preference. These include aniseed, cardamom, rose petal preserve and catechu (katha) (Table 1). The term ‘sweet paan’ or ‘meetha paan’ is used to describe a tobacco-less variant of betel quid, in which the sweet flavor is derived from these spices. However, it does contain other ingredients including areca nut (commonly called geele supari).

**Betel Quid Dependence**

Betel quid use can be associated with a level of addiction or dependence that is similar to that of other psychoactive substances. Tobacco (smokeless form) present in betel quid is a psychoactive substance with well-accepted addictive properties. Apart from and independent of presence of tobacco, betel quid does have psychoactive properties owing to the presence of areca nut. It has clearly been shown that addictive potential of areca nut is not based upon simultaneous use of tobacco in the mixture. Additionally, areca nut has been established as a proven carcinogen.

Areca contains 4 main alkaloids: arecoline, arecaidine, guvacine, and guvacoline. These alkaloids create a sense of alertness and wellbeing, by binding to GABA receptors.

The Betel Quid Dependence Scale, developed and tested in Taiwan and Guam, has been validated to measure betel quid dependence. It assesses three domains: ‘physical and psychological urgent need (7 item) ‘increasing dose (5 items), and ‘maladaptive use’ (4 items). Persons who practiced addition of tobacco to the betel quid mixture, and who reported a greater frequency of chewing, or a longer period of chewing, were found to have greater dependence on betel quid.

**Adverse Effects**

**Cancer**

Betel quid has been classified as a Group I carcinogen by the International Agency for Research on Cancer. It is linked to cancer of oral cavity, pharynx, esophagus, liver, biliary tract and uterus.

**Metabolic Syndrome**

Betel quid has adverse effects on metabolic health. Betel nut contains nitrosated derivatives of arecal alkaloids. Apart from their psychoactive and tumorigenic effects, they are shown to have diabetogenic and obesogenic effects in animal as well as clinical studies.

The Taiwan Longitudinal Survey on Aging has shown that past betel quid chewing is positively associated with new onset diabetes in Taiwanese adults aged 53 years or more. In a community-based study of 993 ‘healthy’ Bangladesis living in east London, betel nut consumption was associated with increased waist size in both men and women; and increased glucose levels in women. A met analysis of 17 Asian studies (5 cohort studies, 12 case control studies), including 388134 participants has shown an increased risk of obesity (adjusted relative risk [aRR] 1047; p < 0.001); metabolic syndrome (aRR 1051, p=0.01), diabetes (aRR 1.47, p < 0.001), hypertension (aRR 1.45, p= 0.06), cardiovascular disease (aRR 1.2, p= 0.02), and all-cause mortality (aRR 1.21, p=0.02), with betel quid chewing. Various mechanisms of action have been proposed to explain the metabolic effects of betel quid. These are listed in Table 3.

**Renal Disorders**

A small study of eight patients proposed that betel quid chewing may predispose to urinary stone disease, perhaps because of the high intake of slaked lime. A prospective review of charts of Taiwanese 3264 men has shown a higher prevalence of chronic kidney disease in betel nut users (adjusted odds ratio 2.572, 95% CI 1.917-3.451). This association is independent of other factors including smoking, alcohol use, and diabetes.

**Vitamin D Levels**

Betel nut chewing may contribute to hypovitaminosis D. In a pilot study conducted among 33 healthy British Bangladesis, serum 25 dihydroxy vitamin D showed an inverse correlation with betel quid chewing. Betel chewing, therefore, could aggravate the metabolic effects of vitamin D deficiency.

**Infectious Disease**

In Cambodia, Betel quid use is associated with an increase in risk of infectious disease, including HIV/AIDS, dengue fever, tuberculosis and typhoid, especially in women. It is postulated that betel quid chewing may increase propensity to infection by immunosuppression, injury to the oral mucosa (facilitating oral entry pathogens) or faeco-oral contamination of its ingredients.

**Mortality**

A Bangladeshi cohort study-carried

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**Table 2: Grading of strength of recommendations**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strength of recommendations</th>
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<tbody>
<tr>
<td>A</td>
<td>Strong</td>
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<tr>
<td>B</td>
<td>Intermediate</td>
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<tr>
<td>C</td>
<td>Weak</td>
</tr>
<tr>
<td>D</td>
<td>Not evidence based</td>
</tr>
</tbody>
</table>

**Table 3: Proposed Mechanism of Action**

| Release of pro-inflammatory mediation | Prostanoids, interleukin-6, tumor necrosis factor –α |
| Reactive oxygen species               | Arecoline-induced adipocyte dysfunction               |
| Inhibition of adipogenic differentiation | Induction of adenylyl cyclase-dependent lipolysis   |
| Induction of insulin-induced glucose uptake | In brain, leading to increased appetite |
| Arecoline-induced competitive inhibition of γ-aminobutyric receptors | In pancreas, altering insulin secretion |
| Autonomic effect | Central sympathetic effect |
| Tachycardia | Parasympathetic effect |
| Coronary artery spasm | Vitamin D deficiency |

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**Table 1.** The term ‘sweet paan’ or ‘meetha paan’ is used to describe a tobacco-less variant of betel quid, in which the sweet flavor is derived from these spices. However, it does contain other ingredients including areca nut (commonly called geele supari).
out among 20033 adults living in Araihazar, over 10 years, has shown a greater risk of all-cause mortality and cancer-related mortality (HR 1.55, 95% CI hazard ratio (HR) 1.26; 95% confidence interval (CI) 1.09-1.44) (1.09-2.22), with betel quid chewing. There was no correlation of betel quid chewing with cardiovascular disease (HR 1:16; 95% CI 0.93-1.43). The duration and intensity of betel quid use demonstrated a dose-response relationship with all-cause mortality. The population attributable fraction for betel use was 14.1% for all-cause mortality and 24.2% for cancer.24

Transgenerational Impact

There is evidence that betel nut consumption during pregnancy may have adverse effects on birth weight, newborn neurological status and pregnancy outcome.25 A community-based screening programme from Taiwan reports that longer duration and earlier onset of paternal betel chewing and smoking may increase the risk of metabolic syndrome in offspring, independent of each other.26

Uttar Pradesh (UP) Association of Physicians of India (API) Recommendations

Based upon the data presented above, the UP API suggests the following:

1. All persons with diabetes should be screened for betel quid use and dependence (Grade A, EL 2).
2. All persons using betel quid should be counselled to stop (Grade A, EL 2)
3. All persons not using betel quid should be counselled not to begin (Grade A, EL 2)
4. All persons dependent upon betel quid should be offered appropriate non-pharmacological therapy (Grade A, EL 4)
5. All persons dependent upon betel quid, especially with evidence of metabolic or health impairment due to this, should be referred to a qualified mental health specialist for further management (Grade A, EL 4)

6. All persons using betel quid, with comorbid conditions or complications, should be referred to appropriate health care providers (Grade A, EL 4)

7. Public health campaigns to limit the use of betel quid must be promoted and encouraged (Grade A, EL 4)

8. Research must be promoted to create validated betel quid dependence scales in Hindi and Urdu, and to assess various deaddiction strategies (Grade A, EL 4)

References

19. Balhara et al. Accepted in JIMA.
Indian Consensus on OPerational Treatment of Angina (OPTA)

Uday Jadhav¹, Brian Pinto², PB Jayagopal³, Tiny Nair⁴, Prabhat Kumar⁵, Prasant Kr Sahoo⁶, Arunangshu Ganguly⁷, Sameer Srivastava⁸, Sunil Kapoor⁹, Deepak Davidson¹⁰, RC Ahuja¹¹, Anirudh Dharamadhikari¹², Ashutosh Singh¹³

Introduction

Coronary artery disease or coronary heart disease (CHD) is a condition wherein the atherosclerotic plaques or vasospasm leads to narrowing of the lumen, thereby resulting in an insufficient supply of oxygenated blood to the myocardium.¹ The reversible mismatch between the myocardial oxygen demand and supply causes myocardial ischemia or hypoxia, which is manifested as angina.

Coronary artery disease (CAD) is a major health concern today and has assumed epidemic proportions worldwide. The prevalence of CAD has been steadily increasing, and India is no exception to this.² In the last three decades, the prevalence of CAD has significantly increased. The prevalence of CAD in urban areas was 2.5%–12.6% and in rural areas, it was 1.4%–4.6%.² The projected data show that from 1990 to 2020, there will be a 117% and 105% rise in mortality from CAD in men and women, respectively, in India.³ Further, CAD is known to be the leading cause of heart failure, arrhythmias, and sudden death.

Angina, the common initial manifestation of CAD, is responsible for a significant burden on Indian healthcare. Early identification of angina is important for the initiation of interventions to reduce the future risk of more serious cardiac events.³

Angina is classically described as substernal chest pain or discomfort which lasts for less than 10 minutes. Chest pain in case of stable angina is often provoked by emotional or physical stress or exercise and is relieved by rest or nitroglycerin.⁵ Stable angina consists of such transient episodes of chest pain over several weeks.⁶ The pain may be referred to the arms or jaw. Atypical presentation may include complaints of discomfort, dyspnea, and diaphoresis.

Angina may result due to different reasons listed herein (Figure 1):

- **Chronic stable angina** is precipitated by exercise-induced or emotional stress-induced ischemia in patients with coronary flow-limiting atherosclerotic stenosis in the large coronary arteries.
- In certain cases, the pain continues after revascularization/the coronary arteries appear normal or near normal on angiography. These cases may show a positive treadmill test. This entity is now termed as microvascular angina and is seen in nearly 40% of the cases of angina.
- One more entity with normal coronary arteries is vasospastic angina. This is seen in a minority of the condition. This form of angina presents with specific characteristics, that is, pain is not triggered by exercise but occurs at rest.⁷

**Need and Objectives of OPTA**

It is well known that risk factors for CAD, such as diabetes, hypertension,
dyslipidemia, and smoking/tobacco use, have a high prevalence among the Indian population; it results in higher CAD cases in India.\textsuperscript{3} It is estimated that 60% of the global cases of heart disease will occur in India by 2020.\textsuperscript{4} Most of these patients develop stable ischemic heart disease and would present clinically as stable angina.

Studies have demonstrated that individuals with baseline typical angina and exertional chest pain had a worse prognosis for the long-term coronary outcome than those with no baseline chest pain did.\textsuperscript{5} In such cases, early diagnosis and intervention is necessary to reduce the morbidity and mortality due to CAD.

Further, the Indian population displays a higher trend of presenting with atypical symptoms of angina, which may result in a missed diagnosis. Due to scarce resources, healthcare affordability and delivery, and other logistical difficulties, the optimal treatment may not be available to the Indian population.\textsuperscript{6}

Current guidelines recommend antianginal therapy even before revascularization is considered to aid in symptom control. The traditional approach has been to consider first-line and second-line therapy options, but most patients end up with multiagent therapy and in fact, there is stronger evidence supporting the use of “second-line therapy” currently. This brings up the question of whether the first-line/second-line approach is the right approach toward optimal management of stable angina.\textsuperscript{7} The appropriate pharmacotherapy will ensure the optimal use of resources to reduce the risk of future cardiac events.

Thus, the combined effect of increasing the burden of CAD among Indians and concerns regarding the delivery of optimum healthcare makes it imperative that healthcare professionals are equipped with enough understanding to recognize a patient of CAD who presents with chronic stable angina and be equipped to treat the condition. This led to the conception of OPTA or “Optimal Treatment of Angina.” OPTA is primarily intended to equip clinicians with the necessary expertise to ensure the following:

- To make an accurate and early diagnosis, which is the first step toward optimum management of chronic stable angina
- To enable risk stratification of patients with angina to ensure their optimum management
- To introduce an OPTA approach that is founded on the principles of individualizing therapy which takes into consideration the presence of comorbidities and the underlying pathology responsible for angina

OPTA was created to assist healthcare professionals with tools to ensure higher standards of care for angina patients that would result in better patient outcomes. Activities of OPTA are not limited to the development of this statement but extend further to involve cardiologists, family physicians, and patients to achieve the following four important goals of optimal treatment of stable angina:

1. Disease control
2. Relief from symptoms
3. Building of exercise capacity
4. Improvement of the quality of life

The tools planned for achieving these goals are as follows:

a. A diagnosis and treatment algorithm to manage chronic stable angina which is relevant for the Indian scenario
b. A clinical checklist for an early and accurate diagnosis of chronic stable angina
c. Understanding of symptoms and standard presentation of a patient with angina
d. A questionnaire to sensitize the physicians towards important goals of stable angina management
e. An OPTA approach toward optimal utilization of available pharmacotherapy by Indian clinicians

**Methodology**

With the above-mentioned objectives in mind, multiple meetings were held across India. These meetings were well attended by experts from the field of cardiology. During these meetings, there was a discussion regarding:

a. Current burden of the disease (CAD) in India
b. Common clinical presentation of a patient with chronic stable angina
c. Challenges faced in the diagnosis and management of the Indian population
d. Various pharmacotherapies available in India and their appropriate use

Intense discussions, an extensive literature review, and feedback from experts led to the development of the following OPTA tools which were finalized in National Steering Committee attended by eminent cardiologists of India:

I. A clinical checklist to enable the diagnosis of stable angina
II. A questionnaire to assist in risk stratification and planning of the management
III. An OPTA approach for the management of angina

These tools would enable clinicians in early diagnosis and appropriate management of their patients.

**Outcomes of the National Steering Committee Meeting**

The outcomes of the National Steering Committee Meeting can be categorized as those related to diagnosis, management, and prognosis.

**Diagnosis and Assessment: The First Step of Optimal Therapy in Stable Angina**

**Suggestions from the expert panel on the approach toward a suspected case of angina include the following:**

- A detailed history and physical examination
- Biochemical investigations, including cardiac biomarkers
- Electrocardiogram (ECG), both resting and with the treadmill test
- Echocardiography (commonly, at rest)
- Coronary angiography: CT and/or invasive
- Fractional flow reserve (FFR)/intravascular ultrasound (IVUS) [if necessary]
- Other less commonly performed procedures, including cardiac MRI, exercise echocardiography, and myocardial perfusion scintigraphy

**History**

History is the key to screen suspected cases of angina. The national committee of OPTA has developed a tool to screen cases of angina. This checklist provides specific questions that a clinician
Box 1: OPTA clinical checklist

If the answers to the following questions are “YES,” it most likely is stable angina.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Questions</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Is the pain diffused and cannot be pointed by one finger?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Is the chest pain or discomfort in the precordial region/radiates to the shoulder back/jaw/teeth/ear or upper abdomen (above umbilicus)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Does the pain appear on exertion/is associated with a triggering factor, like climbing stairs, walking on an inclined surface, or playing with kids/ cold weather/within half an hour post meals?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Does the pain relieve after stopping the activity/taking nitrate?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Is the pain associated with dizziness/diaphoresis/dyspepsia/palpitation?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Is the pain lasting for less than 10 minutes?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Does the pain occur at the same location always/mostly?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Is age of the patient &gt; 40 years (if male) or &gt; 45 years (if female)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Is there a history of exertional palpitation/dyspnea/discomfort?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Compared with the previous capacity, is the patient able to do the same level of physical activity?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If the answers to the following questions are “YES,” it most likely isn’t stable angina.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Questions</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Is the pain lasting for 20–30 seconds?</td>
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<td></td>
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<tr>
<td>2</td>
<td>Does the pain change with respiration?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Does the pain change with posture?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Does the pain get relieved with movements of the hand or trunk?</td>
<td></td>
<td></td>
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</tbody>
</table>

can ask a patient for selecting which patients are likely to have angina and identify the cases in which other causes of angina should be looked out for.

Furthermore, a detailed history leads to the information that can identify patients who require additional testing. The history also helps in identifying the risk factors and predictors of coronary heart disease that would give a more complete picture of CSA.

Physical examination

A systematic physical examination is a cornerstone of an accurate diagnosis. Although it is often normal in angina, it can aid in excluding other diagnoses and in identifying the risk factors for CAD, such as hyperlipidemia (xanthomas) or left ventricular failure (dependent edema and third heart sound).

Biochemical testing

Biochemical investigations help diagnose CAD, identify possible causes, and recognize the presence of risk factors. The Table 1 provides the list of tests which are commonly employed to provide the possible risk factors and cause of cardiac ischemia that has led to stable angina and also provides prognostic information.

Electrocardiogram

Mishra et al recommend that a resting ECG be recorded in all patients suspected of stable angina. The national committee at OPTA recommended that it is crucial to emphasize that a normal ECG does not rule out angina, while an abnormal ECG does not guarantee the presence of angina. There can be large variations in ECG reports.

Similarly, a treadmill test (stress test) should be performed whenever possible. Treadmill or bicycle exercise is recommended for patients with a normal resting ECG. All physicians should be aware of the indications and contraindications of such tests. According to the available literature, the mean sensitivity and specificity of the stress test for the diagnosis of CAD is 67% and 72%, respectively. However, a point to remember is that the results of a stress test are largely dependent on the pretest probability, and hence should be carried out in patients with a pre-test probability of 15%–65%, wherever feasible.

Pharmacologic (Dobutamine stress test) testing can be considered wherever the patient is unable to exercise. Apart from the diagnosis of ischemia, the test provides information on several parameters that have a prognostic significance.

Echocardiography at rest

The LVEF is an important determinant for risk stratification,
Fig.2: Management algorithm for chronic stable angina

In the era of coronary computed tomography angiography (coronary CTA), invasive angiography is more commonly indicated for risk stratification than for diagnosis. Coronary CTA can be considered as an alternative to stress imaging techniques and the expert recommendations from the national committee, Team OPTA has developed an algorithm for the diagnosis and management of chronic stable angina (Figure 2).

Although chest pain is a common presentation of stable angina, it is not the only possible diagnosis. It is important to know the common differential diagnoses of stable angina, so that they can be ruled out. This can aid in establishing a confirmed diagnosis with more certainty.

The common differential diagnoses include the following (Figure 3):7,11

Following the diagnosis, it is necessary to stratify the risk and accordingly plan the management. The optimal treatment of angina would aim to maintain the quality of life while preventing future adverse cardiac events. Thus, the OPTA goals of medical management of CAD were identified as follows:

- Disease control
- Relief from symptoms
- Build exercise capacity, and
- Improvement of quality of life

The expert panel of national committee developed the following OPTA questionnaire (Box 2). The objective of this questionnaire is to sensitize the clinicians toward the above mentioned four important goals of OPTA and assist in risk stratification and planning of further management in individual case.

Management

Management of chronic stable angina includes lifestyle modification, pharmacological therapy, and surgical intervention. The aim is to maintain quality of life while preventing future adverse cardiac events. Control of risk factors for coronary artery disease need lifestyle modification as well as pharmacotherapy.

Lifestyle modification

Management for event prevention includes lifestyle modification and control of risk factors which are described in Box 3.

Pharmacological management

Lifestyle management alone may not be adequate, and medical management would be necessary in most cases. The drugs that control the disease are (aspirin, statins, and angiotensin-converting-enzyme inhibitors) not
Box 2: OPTA questionnaire

1. Over the past 4 weeks, my day-to-day activities have been___________.
   - Extremely limited
   - Moderately limited
   - Not limited at all
   - Present

2. Over the past 4 weeks, I have had chest pain/tightness/discomfort/angina ____________.
   - Four or more times per week
   - Three or less times per week
   - Not at all
   - Present

3. Over the past 4 weeks, on average, how many times have you had to take short-acting nitrate for your chest pain, chest tightness, or angina? I have taken nitroglycerin...
   - Four or more times per week
   - Three or less times per week
   - Not at all
   - Present

4. Over the past 4 weeks, how much has your chest pain, chest tightness, or angina limited your enjoyment of life?
   - It has extremely limited my enjoyment of life
   - It has moderately limited my enjoyment of life
   - It has not limited my enjoyment of life at all
   - Present

5. If you had to spend the rest of your life with your chest pain, chest tightness or angina the way it is right now, how would you feel about this?
   - Not satisfied at all
   - Somewhat satisfied
   - Mostly satisfied
   - Present

Capable of alleviating anginal pain and likewise the antianginals control the symptoms but not the disease.

The European Society of Cardiology explains the multi-pronged approach toward management of angina, and the optimization of medical therapy to ensure successful outcomes.  

Antiplatelet drugs, statins, ACEI/ARB need to be considered for disease modulation. 

**Antiplatelet drugs**
- They prevent the development of thrombus by inhibiting platelet accumulation.
- Studies have shown that they reduce the recurrence of major adverse cardiac events.  
- Some evidence suggests that dual antiplatelet therapy should be preferred. However, a Cochrane review concluded that dual therapy should be used only post-stenting.

Aspirin is the prophylactic antiplatelet drug of choice in patients with cardiovascular disease.

**ACEI/ARB**
Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are known to reduce total mortality, MI, stroke, and heart failure in patients with CAD. An ACE inhibitor or ARB is recommended for patients with anterior MI or high risk diabetes/persistent hypertension, or if there is evidence of left ventricular dysfunction or heart failure. An ACE inhibitor is the first-

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Modification</th>
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</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>Complete cessation of tobacco intake in any form (including chewing, passive smoking, etc.)</td>
</tr>
<tr>
<td>Deranged lipid profile/Obesity</td>
<td>Modification of diet (diet rich in fruits and vegetables)</td>
</tr>
<tr>
<td></td>
<td>Diet intended for weight loss</td>
</tr>
<tr>
<td></td>
<td>Adequate intake of water</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>Regular physical activity</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Maintenance of optimum weight</td>
</tr>
<tr>
<td></td>
<td>Diet modification</td>
</tr>
<tr>
<td></td>
<td>Pharmacological management</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Systolic pressure should be maintained &lt; 140 mmHg, and diastolic pressure &lt; 90 mmHg</td>
</tr>
<tr>
<td></td>
<td>Salt restricted diet</td>
</tr>
<tr>
<td></td>
<td>Physical activity</td>
</tr>
<tr>
<td></td>
<td>Emotional state</td>
</tr>
<tr>
<td></td>
<td>Pharmacological therapy</td>
</tr>
</tbody>
</table>

**Statins**
- They are useful in angina due to their pleiotropic effects, which include improvement of endothelial function, enhancement of the ischemic vasodilatory response, modulation of inflammation, and protection from ischemia-reperfusion injury.
- Several studies have independently demonstrated the major impact of statins in primary prevention of CAD.
- They have also shown to reduce the occurrence of major adverse outcomes in known patients of CAD. It is thus recommended that irrespective of the lipid profile, statins should be prescribed to all patients with stable disease.
Other CCBs Reduce myocardial contractility and heart rate, leading to reduction in oxygen demand and in afterload

Nicorandil Increases coronary blood flow and vasodilatation

Ivabradine Reduces the heart rate Increases coronary flow reserve

Ranolazine Improves anaerobic metabolism under ischemic conditions Reduces in symptoms of chronic stable angina occurs without affecting heart rate, blood pressure, or myocardial perfusion

Trimetazidine Inhibits oxidation of free fatty acids and increases glucose utilization by ischemic myocardium

### Table 2: Antianginal drugs with their mechanism of action, adverse effects, and special consideration points

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
<th>Points to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>Vasodilators leading to reduction of afterload and preload</td>
<td>Headache, flushing, palpitations, phosphodiesterase 5 inhibitors potentiate the vasodilator effect of nitrates</td>
<td>Effective in microvascular and macrovascular angina Long-term use should be with caution</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Lower heart rate and reduce myocardial work and oxygen demand</td>
<td>Bradycardia, hypotension, bronchospasms</td>
<td>First choice drugs in chronic stable angina Preferred treatment if LVEF &lt; 40% Contraindicated in vasospastic angina</td>
</tr>
<tr>
<td>Dihydropyridine calcium-channel blockers (CCBs)</td>
<td>Vasodilator Reduce myocardial oxygen demand</td>
<td>Hypotension, flushing, palpitations, and leg edema</td>
<td>Useful for vasospastic angina No improvement in outcome of chronic stable angina Deleterious effect in heart failure</td>
</tr>
<tr>
<td>Other CCBs</td>
<td>Reduce myocardial contractility and heart rate, leading to reduction in oxygen demand and in afterload</td>
<td>Leg edema</td>
<td>Useful for vasospastic angina Avoid in combination with β-blocker due to the risk of bradycardia</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>Increases coronary blood flow and vasodilatation</td>
<td>Headache, reflux, tachycardia, hypotension</td>
<td>No improvement seen in chronic stable angina Improvement in effort tolerance and number of angina episodes Can be considered for second line therapy</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Reduces the heart rate Increases coronary flow reserve</td>
<td>Bradycardia, phosphenes</td>
<td>Effective in alleviating symptoms of chronic stable angina Contraindicated in hepatic dysfunction</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Improves anaerobic metabolism under ischemic conditions Reduces in symptoms of chronic stable angina occurs without affecting heart rate, blood pressure, or myocardial perfusion</td>
<td>Prolongation of QT interval</td>
<td>Effective in alleviating symptoms of chronic stable angina Contraindicated in hepatic dysfunction</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>Inhibits oxidation of free fatty acids and increases glucose utilization by ischemic myocardium</td>
<td>Nausea, vomiting, headaches</td>
<td>Decreases the frequency of angina, reduces the use of nitrates, and increases exercise duration Especially useful in diabetes Contraindicated in renal dysfunction</td>
</tr>
</tbody>
</table>

### ‘OPTA’ Approach

The OPTA approach differs from this traditional approach. In most cases of angina, more than one drug may be needed for optimal control of symptoms. Also, these individuals with angina have usually several associated comorbidities. Certain agents may have properties that could be useful depending on the comorbidities present and the mechanisms of angina, but the guidelines do not provide recommendations on the optimal combinations of these drugs.

In this consensus statement, we propose an individualized approach, the OPTA approach, for the management of angina, wherein the underlying pathology responsible for angina and the associated comorbidities are taken into consideration.

Based on the presence of comorbidity, the preferable and not preferable (less attractive) antianginals have been classified in the Table 3 given below.

There have been several recent reports of additive or synergistic effects of several antianginal drugs that can be administered in combination, especially in certain conditions.

The possible combinations of different classes of antianginal drugs.

The schematic diagram, shown as Figure 4, demonstrates useful combinations (green lines), combinations that are not recommended (red lines), possible combinations (blue solid lines), and drugs with similar action (blue dashed lines).

### Combinations that are beneficial

- β-blockers are often combined with dihydropyridine calcium-channel blockers to enhance their anti-ischemic effect.
- Combining nitrates with β-blockers can be useful to block tachycardia, leading to a synergistic anti-ischemic effect.
- The synergistic effect between...
Table 3: Choice of antianginals based on the presence of associated co-morbidity with angina

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Preferable antianginal</th>
<th>Less preferred choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on heart rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High heart rate</td>
<td>β-blockers, nonhydroydryidine calcium-channel blockers, diltiazem and verapamil</td>
<td>Calcium-channel blockers and nitrates may further increase the heart rate.</td>
</tr>
<tr>
<td>Low heart rate</td>
<td>Dihydropyridine</td>
<td>Calcium-channel blockers and nitrates, and β-blockers as they would further decrease the BP</td>
</tr>
<tr>
<td>Based on blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>β-blockers and dihydropyridine calcium-channel blockers</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>Ranolazine or trimetazidine</td>
<td>Calcium-channel blockers, nitrates, and β-blockers as they would further decrease the BP</td>
</tr>
<tr>
<td>Based on the underlying pathology of angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microvascular angina</td>
<td>β-blockers</td>
<td></td>
</tr>
<tr>
<td>Vasospastic angina</td>
<td>CCN and long-acting nitrates</td>
<td>β-blockers can precipitate spasm</td>
</tr>
<tr>
<td>Based on rhythm disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defects in AV conduction</td>
<td>Antianginals other than β-blockers and nonhydroydryidine calcium-channel blockers</td>
<td>β-blockers and nondihydropyridine calcium-channel blockers</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>β-blockers and nondihydropyridine calcium-channel blockers</td>
<td></td>
</tr>
<tr>
<td>Based on LVEF</td>
<td>β-blocker</td>
<td>Diltiazem and verapamil can worsen LV dysfunction</td>
</tr>
<tr>
<td>Heart failure and left ventricular dysfunction</td>
<td>If HR remains high in spite of use of β-blocker, ivabradine may be added</td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>Trametazidine</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Nonselective β-blockers (propranolol)</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>Bisoprolol</td>
<td>β-blockers except bisoprolol</td>
</tr>
<tr>
<td></td>
<td>For reduction of heart rate, ivabradine, diltiazem or verapamil</td>
<td></td>
</tr>
</tbody>
</table>

- β-blockers and ivabradine suggests that in patients receiving treatment with β-blockers who are still symptomatic, adding ivabradine is more efficient than up-titration of β-blockers.
- Calcium-channel blockers are effective, alone or in combination with nitrates, in the treatment of vasospastic angina.

Combinations that must be avoided
- β-blockers should not be combined with verapamil, and only with caution with diltiazem because of the risk of bradycardia or atrioventricular block.
- Diltiazem and verapamil should not be used in combination with ivabradine owing to the risk of severe bradycardia.
- The concomitant use of nicorandil with aspirin might increase the risk of gastrointestinal ulcers, perforations, and hemorrhage.
- Ranolazine increases digoxin concentration and should be used with caution in patients taking digoxin.7

Thus, considering that the efficacy of all antianginal agents is nearly similar for symptomatic relief and without any advantage over survival, barring a few, it may now be said that the traditional approach needs a rethink and the new OPTA approach may be adopted. OPTA approach is based on individualization of therapy, taking into consideration the pathophysiology of angina and the associated co-morbidities. A significant number of patients with angina due to CAD will undergo revascularization procedure. But, antianginals may be needed even in these cases until the procedure actually takes place. Further, some patient may continue to be symptomatic even after the revascularization; in such cases, antianginals are needed for control of symptoms and improvement in the quality of life.45

Revascularization

Patients of CAD with significant stenosis (≥ 50% in left main, ≥ 70% in other coronary arteries) should be referred for revascularization procedures. However, the decision to revascularize should be taken after weighing in all the factors, and should be individualized.

Most of the patients with chronic stable angina can be managed with optimal medical treatment. Experts from the field recommend medical therapy for stable angina for following reasons:
- Patients with diffuse disease
- Elderly patients (Age: ≥ 80 Yrs)
- Patients who had incomplete vascularization
- Patients who developed restenosis
- Patients who are awaiting interventions

Procedures such as PCI or CABG for revascularization are reserved for patients who have:
- Uncontrolled symptoms despite being on medical treatment
- Severe angina of class III or IV
- Large area of myocardium at jeopardy
- Left main coronary artery obstruction or proximal LAD
Nitrates, Nicorandil
Calcium-channel blockers
Trimetazidine
Ranolazine
Ivabradine
Dilitiazem, Verapamil

Fig. 4: OPTA approach- The schematic presentation shows useful combinations (green lines), combinations that are not recommended (red lines), possible combinations (blue solid lines), and drugs with similar actions (blue dashed lines)

OPTA APPROACH

Nitrates, Nicorandil
Calcium-channel blockers
Trimetazidine
Ranolazine
Ivabradine
Dilitiazem, Verapamil
β-Blockers

β-Blockers
Ivabradine
Trimetazidine
Dilitiazem, Verapamil
Ranolazine
Calcium-channel blockers

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Mobile Phone Involvement and Dependence among College Students

Indranil Saha¹, Tapas Kumar Som², Sreemedha Choudhury¹, Gautam Ghose³, Manas Patra⁴

¹Professor, ²Assistant Professor, Community Medicine, ³Intern, ⁴Professor and HOD, Community Medicine, IQ City Medical College, Durgapur, West Bengal; ⁵Demonstrator, Community Medicine, Midnapore Medical College, Midnapore, West Bengal

Sir,

India has emerged as the second largest market for mobile phones after China. There’s no doubt that mobile phones are attractive and efficient tools for communication and interpersonal interaction, but there have been many reports in the recent past regarding the adverse effects of mobile phones in our daily lives; which many of us choose to ignore so easily. Face-to-face conversations have been replaced by online chats, reading books is now almost out of ‘fashion’ after the advent of e-books and so on. People have become so involved and dependent on mobile phones that it seems that they have become prisoners to their own phones. No wonder these gadgets are called ‘CELL PHONES’!

Nowadays, the term ‘Overuse’ is being used by many to refer to the ‘Dependence Syndrome’; which is the term used by the World Health Organization to replace addiction or habituation. Some mobile phone ‘over-users’ exhibit problematic behaviours similar to the behaviour shown by people suffering from substance use disorders; such as preoccupation with mobile communication, excessive money or time spent on mobile phones, increased time on mobile communication, and anxiety if separated from a mobile phone. Though addiction-like behaviour to mobile phones is not recognized as a diagnostic category at this time in DSM-IV but it has been seen that addictive people tend to feel depressed, lost, and isolated without mobile phone.

Various scales have been in use to assess problematic use of mobile phones. Out of those, Mobile Phone Dependence Questionnaire (MPDQ) and Mobile Phone Involvement Questionnaire (MPIQ) are used most commonly.¹ ² MPIQ assesses participants’ cognitive and behavioural association with their mobile phone consists of a 7 point Likert scale. Participants who scored 5 or higher out of a possible seven on the MPIQ were classified as being highly involved with their mobile phone, whilst participants who scored less than 3 were not. There are 8 domains in MPIQ scale like Domain 1 (Cognitive Salience) signifies how much the activity dominates the person’s thinking, Domain 2 (Behavioural Salience) signifies how much the activity dominates the person’s life, Domain 3 (Interpersonal Conflict) signifies how much of the performance of the activity leads to conflicts with other people, Domain 4 (Conflict with other activities) signifies how much of the performance of the activity leads to conflicts with other aspects of a person’s life, Domain 5 (Euphoria) signifies whether positive emotions arise from engaging in the activity, Domain 6 (Loss of control) signifies whether the person loses on the extent of performing the activity as the behaviour needs to be engaged in at a greater extent to experience euphoria, Domain 7 (Withdrawal) signifies whether unpleasant emotions are experienced when the person is unable to perform the activity, and Domain 8 (Relapse and reinstatement) signifies whether the activity is resumed at the same level following attempts to reduce it. MPDQ is used to assess dependence consisting of 20 items. Likert scores are calculated for each item to provide a quantitative overall mobile phone dependence score. Subjects exceeding the mean + 1 SD were put in the high-dependence category.

Mobile phone dependence has become an emerging public health problem. Different studies have found out relationship between mobile phone dependence and involvement with gender, duration of mobile phone use, recharge amount, per capita monthly income, high ended gadgets etc. Nomophobia, ringxiety, behavioural problems, headache are also found to be associated with high mobile phone dependence and involvement by different researchers.¹ ² ³ Thus to identify the students having high involvement and dependence, so as to generate adequate awareness and plan educational or treatment interventions is the need of the hour.

References


Subdural Haemorrhage Presenting with Isolated Unilateral 3rd Cranial Nerve Palsy

Rudrajit Paul¹, Biplab Gayen², Rathindranath Sarkar³

¹Associate Professor, ²Assistant Professor, Dept. of Medicine, Midnapore Medical College, Medinipur, West Bengal; ³Ex-HOD, Department of Medicine, Medical College, Kolkata, West Bengal

Sir,

Subdural hematoma (SDH) is a type of intracranial haemorrhage that can have varied presentations.¹ It is usually more common in the elderly but younger persons may also be affected. It can be completely asymptomatic for a long time or it may present with non-specific symptoms like headache, seizure or delirium.² Focal clinical signs like cranial nerve palsy are rare manifestations of SDH. We here present

![Subdural Haemorrhage Presenting with Isolated Unilateral 3rd Cranial Nerve Palsy](image_url)

Fig. 1: Left sided 3rd cranial nerve palsy in our patient
A 45 year old male presented to the outdoor clinic with drooping of left eyelid for two days. He was a known alcoholic with recent history of binge drinking. He was twice found in unconscious state at the roadside after the binges. However, there was no external sign of head injury. The patient was not on any anti-coagulant or anti-platelet drugs. On examination, the patient was alert and oriented but there was some difficulty in answering questions due to slurring of speech. He did not complain of any headache. The only complaint was an inability to open the left eye. On examination, complete ptosis of the left eye was present, along with outward deviation of the eye and dilated pupil. There was present, along with outward deviation of the eye and dilated pupil. There was no sensory symptoms. Regarding cortical, as in our case, or other atypical locations like tentorial. Rarely other intracranial hemorrhages like epidural hematoma can also present with isolated oculomotor palsy. Usually, the 3rd nerve palsy is reversible with surgical evacuation of the hematoma.2,4

We present this extremely rare case to highlight a rare association of intracranial hematoma. Thus, there should be a low threshold for neuroimaging in cases of isolated complete 3rd cranial nerve palsy. Unless timely treatment is instituted, the SDH may progress with eventual fatal consequences.

References


Post Malaria
Neurological Syndrome and Vivax Malaria

Khichar Shubhakaran
Professor Neurology, Dr. S. N. Medical College, Jodhpur, Rajasthan

I read an interesting case report of post malaria neurological syndrome (PMNS), in form of seizure, even after adequate treatment of P. vivax malaria entitled as “an unusual sequelae of uncomplicated vivax malaria” by Bhatt and colleagues.1 It is worth appreciation and I would like to share my experience and views-

1. Neurological complications or sequel earlier described in falciparum malaria are now known to occur in P. vivax malaria as well, of course with not equal potential.2 Malaria being a common problem in tropical countries even a rarest of rare complication or squeal is important.
2. Earlier also such cases are being reported of course not as PMNS, but with other grave complications.3
3. As observed in an earlier study, seizures may play an important role in pathogenesis of coma in
childhood cerebral malaria.4

4. Similarly we have reported a case of ADEM which was earlier reported with falciparum malaria.5

The aim of this correspondence is to further carry forward the message of the eminent authors1 with some additional information, so as to further enhance the relevance of such mini but otherwise quite informative articles. As PMNS being a self-limiting complication or sequelae it is more important to know it so as to avoid costly investigations, drug treatment and, avoidance of side effects of anti-epileptics in case of seizures.

References


Reply from Author

Manavsuvi Bhatt1, Manish Soneja2, Neeraj Nischal1

1Junior Resident, 2Associate Professor, Department of Medicine, All India Institute of Medical Sciences, New Delhi

Sir,

We appreciate the views regarding the uncommon manifestations of central nervous system involvement seen with both falciparum and vivax malaria. It is very aptly said that “malaria being a common problem in tropical countries even a rarest of rare complication or sequel is important”, and indeed sharing such relevant information through a widely read journal is useful for the readers. We have described a case of vivax malaria followed by post-malaria neurological syndrome (PMNS), who although initially had difficult to control seizures, recovered completely later on. It has hitherto been reported as an uncommon manifestation in falciparum malaria, we observed the same in vivax malaria. This adds to the list of complications which although classically described with Plasmodium falciparum is now increasingly being reported with Plasmodium vivax. We fully endorse the views expressed that PMNS is a self-limiting complication, and increased awareness among physicians will avoid costly investigations and help in better patient management.

Topiramate Use and Angle Closure Glaucoma

Khichar Subhakaran

Professor Neurology, Dr. N. Medical College, Jodhpur, Rajasthan

Sir,

I read an interesting correspondence by Patel and colleagues published in June 2018 issue of our esteemed journal (JAPI Vol. 66, 2018; page No.111). The authors have very well revised the side effects mainly the ocular ones and the doses with which they occur. Here I would like to share my experience and views as under-

1. The eminent authors have said that the ocular side effects are not mentioned in the standard text books of medicine and pharmacology. I do not agree with this statement as the side effects are very well mentioned in standard text books.1 2 Moreover The USFDA after it’s approval of topiramate use in 1996, has issued the warning of ocular side effect in 2001.3 4

2. I am using topiramate for more than a decade, of course in low doses mostly and found the side effects in only 2 patients, in one with a very low dose that is 12.5 mg alternate dosing schedule4 in which the patient developed side effect in form of angle closure glaucoma with second dose; and in another one with 25 mg per day with side effect occurring on 8th day of therapy. Both of my patients were females. As per author review, case studies and my experience, I think the Indian population may be more vulnerable to these side effects at lower doses. As with authors case series of 4 patients, my 2 patients were also females so it require further studies that whether females are predisposed or there is more use of topiramate in females. The incidence which is mentioned in standard texts may be more in comparison to my experience; the one explanation for that may be use of lower doses by me in my clinical experience.

3. As the drug has an excellent profile specially in obese patients, so it is of immense worth in headache, seizure, bipolar disorders, drug abstinence etc., so it may be worthwhile to observe such side effects with patient counselling, close observation and screening by means of optical coherence tomography (OCT).3 4 which is widely available now a days.

References


Reply from Author

Mukundkumar V Patel

Consultant Physician, Dhiraj Healthcare Multispeciality Hospital, Ahmedabad, Gujarat

Sir,

It’s my great pleasure to respond Dr. Khichar Subhakaran’s comments of our article “Topiramate Induced Serious Ocular Side Effects”. I am thankful to Dr. Khichar Subhakaran, senior eminent neurology professor of our country for reviewing our article.

1. We have referred latest edition of pharmacology and general medicine text books. I agree with his comment, but unfortunately, we have not referred neurology books he has suggested. Harrison’s principle of internal medicine latest edition has mentioned “topiramate should be used with caution in patients susceptible to glaucoma and renal stone diseases”, 1 but ocular side effects in-depth are not described.

2. Dr. Khichar sir’s vast experience of topiramate side effects is matching with our study. It occurs at lower dose and females are more vulnerable in India. This consensus requires large scale study and it is
possible by inviting “topiramate ocular side effect” cases from our esteem members through JAPI in specific format. Glaucoma at lowest 12.5 mg dose in one of his patient suggest idiosyncratic reaction of the drug.

3. Topiramate is a drug of choice in certain profile patients in many indications. Our aim of present article was to motivate physicians regarding counselling of ocular side effects of the drug and to start with lower dose. Dr Khichar has suggested OCT screening for glaucoma, but is it practical to do in all patients before prescribing topiramate? The drug also can cuase other ocular side effects like palinopsia, Allice in wonderland syndrome (AIWS). In my opinion detail ocular side effect counselling is enough to pick up them early.

Table 1: Parameters and characteristics of patients observed

<table>
<thead>
<tr>
<th>Parameters of patients</th>
<th>Characteristics of observation</th>
</tr>
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<tbody>
<tr>
<td>Total number</td>
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<tr>
<td>Male: Female</td>
<td>2:1</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>40 years</td>
</tr>
<tr>
<td>Disease duration (mean)</td>
<td>07 years</td>
</tr>
<tr>
<td>Duration of dyspeptic</td>
<td>03 months</td>
</tr>
<tr>
<td>symptoms (mean)</td>
<td></td>
</tr>
<tr>
<td>Disease activity by DAS</td>
<td>Moderate in 2 and high in 1</td>
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<tr>
<td>Ongoing treatment</td>
<td>MTX 20 mg/week</td>
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<tr>
<td></td>
<td>HCQ 200 mg/day</td>
</tr>
<tr>
<td></td>
<td>FA supplementation</td>
</tr>
<tr>
<td></td>
<td>NSAIDs as required</td>
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</tbody>
</table>

Dyspepsia Refractory to Conventional Measures in Patients with Rheumatoid Arthritis: Don’t forget Helicobacter Pylori

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

Sir,

Gastrointestinal tract (GIT) manifestations may be the initial or late presentation of systemic autoimmune disorders, but they may also be the complication of treatment. Rheumatoid arthritis (RA) does not affect the GIT directly but decreased lower oesophageal sphincter tone, hiatus hernia, chronic atrophic gastritis, collagenous colitis, amyloidosis (secondary) of the GIT, and mesenteric vasculitis were reported.

I would like to share my experience of three patients with RA encountered in recent past. The patients developed gradual onset of dyspepsia, leading to self-reduction of treatment in two and discontinuation of treatment in one of them. The parameters of patients are mentioned in Table 1.

All possible conventional measures like proton pump inhibitor (PPI) in maximum dose, change of methotrexate (MTX) to subcutaneous route, increase in dose of folic acid, trial of glucocorticoids before MTX, splitting the dose of MTX and use of cox-2 selective molecule were tried. However, during 6 weeks period even after all measures patients’ dyspeptic symptoms were not improved. So, patients were advised upper GIT endoscopy, which showed severe pan-gastritis in all 3 with Los Angeles grade-A esophagitis in 1 patient. All patients were rapid urease test (RUT) positive for Helicobacter pylori (HP) and given HP kit for 14 days. They were improved dramatically and dyspeptic symptoms almost subsided. Now they were able to tolerate oral treatment. All patients showed improvement in disease activity from moderate to mild after 12 weeks.

HP colonize the stomachs of over half of the world’s human population throughout their lifetimes and is the main risk factor for various gastrointestinal diseases, ranging from chronic active gastritis without clinical symptoms to peptic ulcer disease (PUD), gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. Disease outcome is the result of the complex interplay between the bacterium, host and environment.

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