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## Contents

### EDITORIAL

- Hepatitis E Virus: Peril of Pregnancy  
  Trupti H Trivedi, Priyanshu D Shah .......................................................... 11

### ORIGINAL ARTICLE

- Characteristics and Obstetric Outcomes in Pregnant Women with Acute Hepatitis E Virus Infection in Tertiary Care Hospital of Himachal Pradesh  
  Rajesh Kashyap, Ivan Joshi, Dalip Gupta, Anupam Prashar, Santosh Minhas .......................................................... 14

- Role of µ-Opioid Receptor Polymorphism in Patients of Rheumatoid Arthritis and their Correlation with Severity of Disease  
  Liyakat Gauri, Suman Kapur, Anuradha Pal, Ummed Singh, Qadir Fatima, Asim Khan, Ambreen Liyakat, Nadeem Liyakat, Rohitash Kalaria .......................................................... 16

- Study of Impact of Glycemic Status (Hba1c) on Platelet Activity measured by Mean Platelet Volume & Vascular Complications in Diabetics  
  Manoj Saluja, Yogesh Kumar Swami, SR Meena ........................................ 20

- Psoriasis and Co-morbidities: Is Hyperhomocysteinemia the Common Link?  
  Sujaya Mamn, Vikram K Mahajan, Karaninder S Mehta, RS Yadav, Satya Bruhson, Pushpinder S Chauhan .......................................................... 23

- IMPACT India: Insights for Insulin Therapy in Routine Clinical Practice  
  V Mohan, Ashok Kumar Das, AG Unnikrishnan, Siddharth N Shah, Ajay Kumar, Abdul Hamid Zargar, Sanjay Kalra .......................................................... 28

- Eschar in Scrub Typhus: A Study from North East India  
  Md Jamal, Prasanta Bhattacharya, Jaya Mishra, Hanifa Akhtar, Aakash Ray .......................................................... 32

- Spinal Pains in Geriatric Group of Osteoporotic Vertebral Body Compression-fracture Relieved with Cath Lab-Vertebralplasty using “Small-Volume Glass Acryllyte”  
  Ramesh Sangle, Varun Nivargi .......................................................... 36

- Outcome in Survivors of Middle Cerebral Artery Territory Ischemic Stroke: Can it be predicted?  
  Seema Kini, Faisal Memon, Dileep Asgaonkar ........................................ 40

- A Study on the Association of Psoriasis with Metabolic Disorders  
  Nikita Jadhav, Nitin Nadkarni, Sharmila Patil ........................................ 46

- Clinical Profile of Amitritz Poisoning  
  Shubhangi Dhakde, Vijayalaxmini Kantte, Vithal Dhakde, Manish Dhakde .......................................................... 49

- Relationship between the Use of Aluminium Utensils for Cooking Meals and Chronic Aluminum Toxicity in Patients on Maintenance Hemodialysis: A Case Control Study  
  Shrirang Bichu, Parag Tilke, Pranit Kakde, Praneesh Jain, Shweta Khurana, Vinayak Uktirade, Pankaj Jawandhiya, Abhishek Dixit, Nikhil Bhusin, Viswanath Bile, Rajesh Kumar, Jatin Khatri  .................................................. 52

- Guillain-barre Syndrome in Indian Population: A Retrospective Study  
  Rajendra Singh Jain, Jagdeesh Chandra Kookna, Trilochan Srivastava, Rahul Jain .......................................................... 56

### POINT OF VIEW

- Artificial Intelligence and Deep Learning: The Future of Medicine and Medical Practice  
  Madhusudana Girija Sanal, Kolin Paul, Senthil Kumar, Nirmal Kumar Ganguly .......................................................... 71

### PICTORIAL CME

- A Young Adult with Tracheal Bronchus and Congenital Cystic Adenomatoid Malformation  
  Kranti Garg, Rekha Gupta, Anuj Kumar, Uma Handa, Varinder Saini ....... 74

- Hematoma of Sterneocleidomastoid Aspirin can be a Cause  
  Priyanka Verma, Sanjay Fattydar, VK Katyal ........................................... 75

### CASE OF THE MONTH

- B Cell ALL with Pyrexia of Unknown Origin, Masquerading as Inflammatory Arthritis  
  Vishakh C Keri, Prayas Sethi, Satish Swain, Neeraj Nischal, Arvind Kumar, Naveet Wg ...................................................... 76

### CASE REPORT

- Ruptured Sinus of Valsalva Aneurysm with Subaortic Membrane causing Severe Left Ventricular Outflow Tract Obstruction  
  Pawan Sarda, Anil Baroopal, Sanjeev Sanghvi ........................................ 79

- Movement Disorder - A Rare Presentation of Diabetic Ketoacidosis  
  Sneha Garg, Priyam Jain, Vinod Kumar Sharma, Sanjiv Madeshwar ........... 81

- Acute Bilateral Cataract in Patient with Type I Diabetes Mellitus  
  Ashish Kumar Bhagat, Haroon Bharadwaj, Bachan Lal Bharadwaj, Sanjay Goyal, Sahil Jaura, Pailav Jain .......................................................... 83

- Sweet’s Syndrome in a Case of Ulcerative Collitis Case Report and Review of Literature  
  Mukesh Nasa, Zubin Sharma, Lipika Lipi, Randhir Sud ........................... 84

### MEDICAL PHILATELY

- Mahendra Lal Sirkar - Science Visionary  
  Jayant Pai-Dhungat .......................................................... 86

### EXPERT RECOMMENDATIONS

- An Expert Review and Recommendations on the Rational Use of Proton Pump Inhibitors: Indian Perspective  

### CORRESPONDENCE

- Prevalence and Determinants of Tobacco Product Use Among the Tribal Community of West Bengal: A Cross-sectional Survey  
  Indrani Thakur, Rudrajit Paul, Kanal Sam, Rathindranath Sarkar ............ 97

- Juvenile Idiopathic Arthritis and Role of Anti CCP Antibody  
  Ankur Dalal.......................................................... 98

- Position Change followed by Early Ambulation after Coronary Angiography via Femoral Approach: A Randomized Controlled Trial  
  Parisha Rai, Manoj Saluja, Ahura Bhardwaj, Shiv Bhardwaj, L Gopichandran, Yash Paul Sharma ...................................................... 99

### ANNOUNCEMENT

- Office Bearers of Rajasthan Chapter of Association of Physicians of India for the Year 2018 - 2019 ........................................... 39

- Erratum .......................................................... 26
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Hepatitis E Virus: Peril for Pregnancy

Trupti H Trivedi¹, Priyanshu D Shah²

According to World Health Organization (WHO) estimates, each year there are 20 million new cases of hepatitis E virus (HEV) infection globally, leading to more than 3 million cases of acute hepatitis and over 44,000 deaths, accounting for 3.3% of total mortality due to viral hepatitis.¹ In India infectious hepatitis due to HEV occurs both in epidemics and sporadic forms. It was suspected for the first time in 1978 following an outbreak of acute hepatitis secondary to contamination of water supply in Kashmir.² It was only in 1991 that Tam et al sequenced the full length genome of 7.2 kb length and identified it as the causative RNA virus HEV. The virus has four genotypes causing disease in humans. Genotypes 1 and 2 mainly cause disease in humans in developing countries as outbreaks. Genotypes 3 and 4 infect humans as well as animals and have been responsible for sporadic cases globally. While adults and children both are affected, it causes clinically significant acute hepatitis more commonly in adults. HIV infected hosts and organ transplant recipients tend to develop chronic disease. It is a self-limiting disease in majority of patients with a case fatality rate of 0.5–3% in adults. However, in pregnant women risk of mortality is up to 30%, when acquired in the third trimester. Absence of specific anti-viral therapy that is safe and effective in pregnancy makes management even more challenging.

The exact reason, why pregnant women are at increased risk of HEV is unclear. Shift in the Th1:Th2 cell paradigm during pregnancy with definite skew towards Th2 cells, increased steroid hormone levels, and pre-existing micronutrient deficiencies in pregnancy may be responsible for increased incidence of HEV in pregnancy.³,⁴ High concentrations of inflammatory cytokines (TNF-α, IL-6, IFN-γ and TGF-β1) and reduced toll like receptor (TLR) expression may lead to adverse maternal outcome. Association of other host factors like nutritional status and major histocompatibility complex or prior exposure to virus in childhood may explain the relatively benign outcome of HEV in pregnant women in Egypt. In endemic areas in developing countries HEV may present as asymptomatic infection, anicteric or icteric acute hepatitis, acute on chronic hepatitis and at times as fulminant hepatitis.³ Aminotransferases are markedly elevated and may precede the onset of symptoms. In pregnant women with HEV there is high risk of acute liver failure (ALF) including fulminant hepatic failure (FHF) and coagulation failure, bacterial sepsis and death. Pregnancy is often complicated by preterm rupture of membranes, antepartum hemorrhage, IUGR and still birth. Even newborns are at increased risk of peri-natal mortality when infected by vertical transmission.

In the present issue of the journal Kashyap R et al have studied pregnancy and fetal outcomes amongst 30 obstetrics patients with HEV over two years from a hospital in Shimla, Himachal Pradesh.⁵ Most of the patients were infected during second or third trimester or in the post-partum period. There were only two deaths, but outcome of 5 patients was not known. Twenty one patients had vaginal delivery and two required LSCS. Thirteen newborns were normal and there were 4 IUFDs. As this study is focused on obstetric outcome, it lacks clinical data on medical parameters like severity of jaundice, presence of encephalopathy, biochemical parameters and coagulation abnormalities in the mother. Also there is no information about transmission of HEV infection in newborn. However, the study re-confirms that even today HEV continues to contribute to maternal mortality and poor obstetric outcome in India. In a previously published article in the same journal hepatic encephalopathy, sepsis, acute kidney injury, late presentation, and coagulopathy were found to be the risk factors for mortality amongst hospitalized pregnant patients with HEV in Himachal Pradesh.⁷ While in South East Asian countries 25-30% of mortality is reported in HEV infected women with pregnancy, studies from intensive care unit have reported mortality approaching 50% amongst patients infected in third trimester and with higher grades of hepatic encephalopathy.⁸

Important question in front of physician today is whether anything can be done to improve the maternal and foetal outcomes in pregnant patients already infected with HEV. First of all, it is important to investigate for HEV in pregnant patient presenting with ALF.⁹ Though HEV-RNA detection by polymerase chain reaction is gold standard, positive Anti-HEV IgM assay is suggestive of acute HEV infection in endemic area. All pregnant women developing symptomatic HEV hepatitis should be preferably admitted to hospital in view of anticipated risk of encephalopathy and adverse foetal outcome. Specific therapy with anti-viral drugs like ribavirin and pegylated interferon alpha have been used in patients with chronic HEV hepatitis of more than 3 months duration and in patients receiving immunosuppressive therapy.¹⁰ But after the onset of FHF most patients have rapid deterioration over 5 to 6 days and anti-viral drugs are unlikely to be of any benefit.¹¹ Additionally, ribavirin is contra-indicated in pregnant women (category X drug) due to teratogenicity. Once FHF sets in, intensive supportive care, oxygenation and mechanical ventilation, correction of hypoglycaemia, prophylactic antibiotics for prevention of secondary infection, therapeutic trial with N-acetyl cysteine (NAC) and infusion
of plasma factors for coagulation failure are the available supportive therapies. Early liver transplant should be considered in selected cases as an option but, its timing and indications are still unclear. Early termination of pregnancy has beneficial outcome in patients of ALF secondary to acute fatty liver of pregnancy (AFLP) or pre-eclampsia, but studies have not shown any survival benefit of early labour amongst pregnant patient of ALF due to HEV.12 Hence, currently therapeutic termination of pregnancy or early induction of labour is not justified for improving maternal outcome in these patients. Vaginal delivery is safer and new-born should be monitored for possible vertical transmission. Breast feeding is considered unsafe for new-born only when mother has acute symptomatic hepatitis with high viral load as there is possibility of transmission of virus to infant through infected breast milk.13

At national level, every effort is being made to reduce maternal and infantile mortality rates but, HEV continues to be an important medical cause of maternal mortality. In the absence of availability of safe and effective definitive therapy, emphasis should be on preventive measures. Pregnant women residing in or visiting endemic areas should drink boiled or chlorinated water, avoid adding ice cubes to beverages and wash fruits and vegetables thoroughly with safe water before consumption. Immune globulins are not recommended to prevent HEV in pregnant woman during sporadic outbreaks. Prevalence of hepatitis A virus infection has declined significantly since introduction of vaccine in 1995. Presently vaccine for prevention of HEV is licensed for use only in China, administered intra-muscularly at 0, 1 and 6 months interval.14 It is effective against genotype 1 which is prevalent in India and has 94-100% efficacy. It was found safe when inadvertently administered to pregnant women and there were no foetal adverse effects. In near future, HEV vaccine should be evaluated in preventing severe infection and death in pregnant women and reducing risk of foetal loss and neonatal mortality and morbidity.

References

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Characteristics and Obstetric Outcomes in Pregnant Women with Acute Hepatitis E Virus Infection in Tertiary Care Hospital of Himachal Pradesh

Rajesh Kashyap1*, Ivan Joshi2, Dalip Gupta3, Anupam Prashar4, Santosh Minhas5

Abstract
Background: Hepatitis E Virus (HEV) infection is a major concern regarding morbidity and mortality among pregnant women especially in developing countries. The objective of this study was to determine the characteristics and obstetric outcomes in pregnant women with Acute Hepatitis E Virus Infection in tertiary care hospital of Himachal Pradesh.

Methods: Prospective observational study has been done in the department of Obstetrics and Gynaecology and department of Medicine and Emergency Medicine among all the pregnant women who were sero-positive for hepatitis E viral marker in two consecutive years. Information regarding basic characteristics of pregnant women and obstetric outcome has been collected.

Results: Among 30 pregnant women with hepatitis E viral infection, a case fatality ratio of 8.0% for hepatitis E infection was found. 13.3% of the pregnancies ended up as intra uterine death. Most common age group affected was below 25 years. Mode of delivery among 70% of the women was normal vaginal delivery though 30% women delivered prematurely.

Conclusions: This prospective case series of 30 pregnant women with acute hepatitis E viral infection, indicate poor maternal, obstetric and foetal outcome among pregnant women with hepatitis E viral infection.

Background

Hepatitis E virus (HEV) is a hepatotropic single-stranded RNA virus causing acute viral hepatitis worldwide.1 Disease occur either in the form of large-scale epidemics related to contamination of water supplies or in the form of sporadic cases in the absence of discernible outbreaks.2 Each year more than 20 million estimated cases of HEV infection occur globally, resulting into more than 55, 000 deaths.3-4

In men and non-pregnant women, the disease is usually self-limited and has a low case-fatality rate (0.1%).5 However in pregnant women especially in the third trimester, HEV infection is more severe, often leading to fulminant hepatic failure and maternal death in up to 15% to 20% of cases.5-6 Although the mechanism of liver injury is not yet clear, it is possible that interplay of hormonal and immunologic changes during pregnancy, along with a high viral load of HEV, renders the woman more vulnerable.7,9 This high mortality rate was first reported in an epidemic setting in the early 1980s and was reported again in a sporadic setting in 2003.10,11

Information is limited and conflicting on the effect of HEV infection on maternal, obstetric, and foetal outcomes.12-13 Therefore, in this study we describe characteristics of HEV infected pregnant women presented to department of Obstetrics and Gynaecology, Medicine and Emergency Medicine of a tertiary care hospital of Himachal Pradesh. Obstetric, maternal and foetal outcomes among these women with acute viral hepatitis have also been determined.

Methods

This prospective observational study has been done in the department of Obstetrics and Gynaecology, Medicine and Emergency Medicine at Indira Gandhi Medical College Shimla, Himachal Pradesh, India.

All the pregnant women who were sero-positive for hepatitis E viral marker in last two consecutive years have been included in the study i.e. April 2014 through March 2016. Information regarding basic characteristics of pregnant women (like age, parity, gestational period), obstetric, maternal and foetal outcome has been collected from patient’s information sheet of department.

These women were managed according to the management protocol of the Institution. Information gathered had only been used for the purpose of this study after taking permission from hospital administrations. The data collected was analysed with the help of MS Excel software. The analyses were done for calculating frequencies and percentages.

Observation

Total 30 pregnant women with hepatitis E viral infection has been observed during study period. Majority (63.3%) of the case were in year 2016. Mean age of study population was 25.34 (SD=3.94) years ranging from 19 years and to 34 years.

Most (46.7%) of pregnant women with hepatitis E viral infection were less than 25 years of age. Only 13.3% (n-04) were of the age 30 and above. 57.7% (n-17) of them were having

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Majority of the cases of HEV has been reported in the year 2016, period that coincides with the outbreak of Hepatitis E virus infection in Shimla city leading to massive morbidity and mortality.14,15 In our study 46.7% of patients were below 25 years of age and were primigravida (57.7%). In regions with high disease endemicity like India, symptomatic infection is most common in young adults (aged 15–40 years) and pregnant women.16 Mishra et al also reported majority (60%) of the hepatitis E infection among Indian pregnant women in below 25 years of age and which is in consistent with findings of our study. Severity of HEV infection among primigravida and third trimester of pregnancy has been reported higher by Mishra et al.17

In current study infection had been diagnosed both in ante partum (53.3%) and postpartum (46.7%) period of pregnancy (mostly second and third trimester of pregnancy). Hepatitis E virus has been known to infect women throughout pregnancy but case fatality rates as high as 20–25% has been reported in their third trimester.18

Most common mode of delivery was normal vaginal delivery which is common finding in most of the studies in similar settings. 30% of the women delivered prematurely in this study. Mishra et al and Jaiswal et al also reported approximately one third of the pregnant women with hepatitis E viral infection to deliver prematurely.17,18 However Patra et al in their study had reported preterm delivery among 90% of the cases in similar condition.6

Case fatality of 8.0% has been determined in current study. Poor foetal outcome has been found among 13.3% (intra uterine death) of the traced cases. Also 20% of the newborn needed hospitalization (most common reason being low birth weight and prematurity) in current study. These numbers could have varied as 13.3% of the serious women were referred to higher institute while one left against medical advice. Maternal death among different studies in India has been reported upto 15% to 20% of women with hepatitis E viral infection.6,8 Patra et al. in New Delhi reported 15-20% maternal mortality rate in pregnant patients with HEV. Banaei et al in Mumbai reported 69% perinatal mortality and 54% maternal mortality in HEV in pregnancy which is much higher than our results.19 Beniwal et al reported maternal mortality in the range of 30.0-45.0% and may be as high as 70.0%.20 Ahmed et al reported 25% maternal mortality rate and 17.8% intrauterine deaths in pregnant HEV positive mothers.21 Shukla et al reported 33.3% maternal mortality rate in patients with hepatitis E in pregnancy.22 Foetal outcome in our study has been found relatively better than reported from other studies. Patra el al reported stillbirth in 54% of cases while Mishra et al reported perinatal mortality of 24%,16,19

Various immunologic and hormonal changes during pregnancy impair cellular immunity by triggering adapter protein (ORF3 of HEV), which could facilitate viral replication and lead to release of cytokines and liver cell apoptosis causing significantly higher morbidity and mortality.23-25

**References**


<table>
<thead>
<tr>
<th>Table 1: Characteristics of pregnant women with Hepatitis E viral infection</th>
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<tr>
<td><strong>Age Groups</strong></td>
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<tr>
<td>&lt;25 years</td>
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<tr>
<td>26-30 years</td>
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<td>&gt;30 years</td>
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| **Gravida** | **Frequency** | **%age** |
| --- |
| Primigravida | 17 | 57.7 |
| Multigravida | 13 | 43.3 |

| **Period of infection** | **Frequency** | **%age** |
| --- |
| First trimester | 01 | 3.3 |
| Second trimester | 08 | 26.7 |
| Third trimester | 07 | 23.3 |
| Postpartum | 14 | 46.7 |

<table>
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<th>Table 2: Obstetrics, maternal and foetal outcome among study participants</th>
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<tr>
<td><strong>Mode of delivery</strong></td>
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<tr>
<td>NVD</td>
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<tr>
<td>LSCS</td>
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<tr>
<td>Other</td>
</tr>
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| **Time of delivery** | **Frequency** | **%age** |
| --- |
| Full term | 14 | 46.7 |
| Preterm | 09 | 30 |
| Other | 07 | 23.3 |

| **Maternal outcome** | **Frequency** | **%age** |
| --- |
| Recovered | 23 | 76.7 |
| Referred | 04 | 13.3 |
| Death | 02 | 6.7 |
| Other | 01 | 3.3 |

| **Foetal outcome** | **Frequency** | **%age** |
| --- |
| Normal | 13 | 43.3 |
| IUD | 04 | 13.3 |
| Alive but need hospitalization | 06 | 20 |
| Other | 07 | 23.3 |

Discussion

Most of the women delivered normally (70%) followed by Lower segment caesarean section in 6.7%. Among all 46.7% (n-14) of the women delivered full term while 30% (n-09) delivered prematurely. Regarding maternal outcome 76.7% (n-23) women recovered from disease without significant morbidity while 13.3% (n-4) were referred to higher centre pertaining to their progressive health deterioration. 6.67% (n-2) women died during the course of illness causing a case fatality ratio of 8.0% for hepatitis E infection (excluding all the referred/ DOR cases from denominator). Both the deaths occurred in postpartum period. 43.3% (n-13) new born delivered were healthy while 20% (n-6) newborn needed hospitalization. There were 4(13.3%) intra uterine deaths. Information regarding referred or missed cases had not been found for analysis (Table 2).
Role of μ-Opioid Receptor Polymorphism in Patients of Rheumatoid Arthritis and their Correlation with Severity of Disease

Liyakat Gauri1*, Suman Kapur2, Anuradha Pal3, Ummed Singh4, Qadir Fatima5, Asim Khan6, Ambreen Liyakat7, Nadeem Liyakat8, Rohitash Kularia9

Abstract

Introduction: With 1 billion tobacco users worldwide, nicotine dependence has a major impact on global health. Advances in medication development for nicotine dependence require an improved understanding of the neurobiology of this complex, relapsing brain disorder

Aims: To study association of μ Opioid Receptor polymorphism in patients of rheumatoid arthritis and its correlation with severity of disease and prevalent alleles of the OPRM1 genes.

Material & Methods: This is a case control study wherein all available patients and volunteers were recruited. 142 controls subjects with no known history of disease and 85 study group cases were included.

Results: Comparison of genotype frequencies showed a statistically significant difference between the studied groups (p<0.004). A statistically significant difference was found when the allelic frequencies between the two groups were compared (p<0.0001), with the 17T allele having a 1.7518 fold higher risk of having RA (risk ratio (RR)=1.7518, 95%CI of RR=1.2988-2.3627, OR=3.2914; 95%CI =1.9608-5.5251). Significant difference was also found when the allelic frequencies between the two groups were compared (p<0.0001), with the 118G allele having a 1.5-fold higher risk of developing RA (RR)=1.5801, 95%CI =1.3091-1.9071, OR=3.1357; 95%CI 2.1083-4.6638).

Conclusion: The study definitely needs to be extended to larger cohort of patients and control samples and to a larger set of candidate μ opioid receptors. Extending the studies to a larger cohort will also allow genetic analyses of clinically defined endophenotypes observed in the patients of this chronic metabolic disease with attributes of autoimmune disorder and multiple symptoms in patients.

Introduction

With 1 billion tobacco users worldwide, nicotine dependence has a major impact on global health. Advances in medication development

References

for nicotine dependence require an improved understanding of the neurobiology of this complex, relapsing brain disorder. Although multiple neurobiological mechanisms have been implicated, a growing body of evidence points to the endogenous opioid system, and the mu-opioid receptor (MOR) in particular, in mediating the reinforcing effects of drugs of abuse, including nicotine. Nicotine upregulates MOR mRNA and protein expression in brain regions important in drug reward in rodents and stimulates endogenous opioid release, resulting in MOR activation and dopamine release.

Genetic variation in MORs can modulate the endogenous opioid system, thereby altering behavior. A common single nucleotide polymorphism (SNP) in the mu-opioid receptor gene (OPRM1 A118G) results in an amino acid exchange at a putative glycosylation site in the extracellular terminus of the MOR.

All of the previous association studies of the C17T polymorphism have compared cases with substance dependence to a “normal” control group. However, in many cohorts and for a variety of substances, drug use is not dichotomous but follows a spectrum ranging from nonusers through those with modest, intermittent use, to those who use a great deal of drugs almost all of the time. Accordingly, quantitative measures of drug use may be more informative than dichotomous outcomes. The lifetime Kreek-McHugh-Schluger-Kellogg (KMSK) scales quantify use of alcohol, tobacco, opiates, and cocaine during the time of an individual’s maximal use. They hypothesized that there would be differences in KMSK score associated with C17T polymorphisms.

**Brief Review of Literature**

**Pathogenesis**

There is considerable ethnic heterogeneity in the frequency of these alleles and their importance for the RA phenotype. For example, double dose of DRB1*04 SE alleles is associated with erosive disease and vasculitis in northern European Caucasians but has no significant impact on disease outcome in Greek patients. Furthermore, the relative importance of DRB1 genotypes compared to other clinical and genetic markers, and hence the clinical utility of HLA-DRB1 genotyping for prognostication, remains unclear. In a recent study of early-onset RA by Goronzzy et al., HLA-DRB1*04 SE double dose was one of several predictors of progression of erosive disease in the univariate analysis, but only rheumatoid factor and the presence of baseline erosions remained significant in the multivariate model, indicating that these factors are more important prognostic markers in RA.

In addition, other HLA genes with a role in T-cell regulation may modify the effect of known disease severity factors. For example, in patients carrying HLA-DRB1*01.

Recent studies with Evidence for Importance of HLA-DRB1*04 for Disease Severity in RA have suggested to be associated with greater structural joint damage.

The tumor necrosis factor (TNF) has been shown to be important in the pathogenesis of RA, and treatment with TNF-blocking agents leads to amelioration of joint symptoms and reduction of structural joint damage in many patients.

Although microsatellite markers do not seem to affect disease severity by themselves, interactions between the markers TNFa and TNFa11 and SE genotypes have been reported to be associated with radiographic damage and disability. The TNFa6-SE interaction may also predict the development of rheumatoid nodules. Such interactions could indicate that polymorphisms influencing TNF expression or function are important only in the presence of an immune system shaped by certain class II genes.

**Pharmacogenetics**

Individualized pharmacological therapy is a major goal of current research in the genetics of rheumatic diseases. This approach will ensure a safer and more efficacious application of drugs to manage complex diseases such as RA and in a nascent form is already being practiced in rheumatology. An example of this is the now routine determination of thiopurine methyltransferase (TPMT) enzyme levels before azathioprine is prescribed. This example also highlights the fact that it is currently generally easier to establish an association between genetic type and potential drug toxicity than between genetic type and drug efficacy.

Lack of response to a given therapy may be due to many reasons, including drug-specific factors and genetically associated resistance, co-administered drugs with competing metabolic pathways, and disease severity, including presence of the SE as discussed previously. Knowledge of the likelihood of genetic resistance would prevent unnecessary and potentially toxic drug exposure. Such factors are still unidentified, but it is clear that patients with advanced disease, regardless of their genetic background, may not respond because the disease is too advanced.

Currently, the most commonly used disease-modifying antirheumatic drug (DMARD) to manage RA is methotrexate, a folic acid analogue that inhibits the intracellular synthesis of purine and pyrimidine. Some of the anti-inflammatory effects of methotrexate are mediated by adenosine, a substrate in purine metabolism. In the cell, methotrexate undergoes polyglutamation, and this product inhibits aminomimidazole carboxamide ribonucleotide transformylase (AICAR-T). AICAR-T is important in purine synthesis, and blocking it leads to substrate accumulation with increased adenosine release, effecting the anti-inflammatory activity of methotrexate.

Another enzyme important in methotrexate metabolism is methylenetetrahydrofolate reductase (MTHFR), a catalyst for conversion of homocysteine to methionine. Deficiency of MTHFR is a cause of homocysteinemia and homocysteinuria, which can cause vasculopathy, thrombophilia, and neurologic disease. About 10% of persons are homozygous, and another 40% are heterozygous for the C677T polymorphism of MTHFR, with corresponding reduction in enzyme activity. Methotrexate-related bone marrow toxicity has been linked to MTHFR polymorphisms. Regarding efficacy, it has been suggested that presence of a polymorphism in 1 of 3 enzymes important in methotrexate action thymidylate synthase (folate-dependent pyrimidine synthesis), AICAR-T, and RFC1 (a protein that transports methotrexate into cells) is associated with increased methotrexate efficacy. Absence of members of the
functional multidrug resistance protein family that transport methotrexate out of the cell, plus the presence of reduced folate carrier, appears to be associated with significantly better responsiveness to methotrexate.20

**Material and Methods**

This is a case control study wherein all available patients and volunteers (only for blood samples) were recruited. Peripheral blood samples of patients were collected at Rheumatology clinic and Medicine Department of S.P. Medical College, Bikaner after explaining the objective of the study and taking an informed consent from the patients or from guardian family members. The same criteria for blood collection ill be followed in controls where samples from age and gender matched controls were collected.

Number of patients: Total 142 controls subjects with no known history of disease and 85 study group cases were recruited as per the following inclusion and exclusion criteria.

The 2010 American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for RA the following were the criteria for the classification of rheumatoid arthritis:

**Health Criteria**

Not applicable in the present study. Only OPD/IPD patients will be recruited and lactating mothers were not recruited.

**Procedure for conducting the study**

The volunteers and the patients were explained about the purpose of the research study by the resident (SR/JR) who will subsequently obtain a written consent from the recruited patients/control subjects. A detailed proforma was used to gather clinical history of the patients and information about the family history of the patient.

As explained above a proforma was used to gather clinical history of the patient/volunteer. Venous blood samples were drawn by skilled technical staff/nurse/doctor on the project, before the discharge of the patient or from the volunteer using sterile disposable syringes and was immediately transferred to pre-labeled blood collecting vials containing 0.5 M EDTA as anticoagulant and transported in ice from place of collection to lab.

The collected samples in the lab were centrifuged for 8 min. at 2000 RPM and serum was separated from sample in a plain vial and both were stored at -20°C till transport to genetic lab.

**Clinical Chemistry**

Clinical data and laboratory investigations including haemogram, blood sugar, serum electrolytes, blood urea, AST/ALT ratio, serum ALP, serum calcium, serum creatinine, total proteins were recorded from the patients sheet or were done in the plasma as per the kit manufacturers instructions wherever required.

**DNA Isolation**

DNA was isolated using standard protocol. DNA was quantified using UV spectroscopy and qualified on 0.8% agarose.

**PCR Standardization**

This DNA was used for allele specific PCR amplification of the selected genes on a Thermal Cycler using known primers. Amplified sequences of selected genes were analyzed for specific allele type present using RFLP, LP, SSPC, or DNA sequencing methods.

**SNP analysis by RFLP/SSLP**

RFLP’s (restriction fragment length polymorphisms) were used for analysis of PCR product obtained from the amplification of target sequence. Variations were characterized by polyacrylamide gel electrophoresis. DNA sequencing, was done using commercial services available.

**DNA Analysis**

Genomic DNA was extracted from venous blood, drawn from subjects, by the NaCl-salting out procedure (Miller et al. 1988) and dissolved in water. PCR and subsequent restriction digestion with appropriate restriction enzymes was carried out using a standard protocol to genotype the two polymorphic sites.

**Results**

Comparison of genotype frequencies showed a statistically significant difference between the studied groups (p<0.004). A statistically significant difference was also found when the allelic frequencies between the two groups were compared (p<0.0001), with the 17T allele having a -1.7518 fold higher risk of having RA (risk ratio (RR)=1.7518 , 95%CI of RR=1.2988 to 2.3627, odds ratio (OR)=3.2914 ; 95%CI of OR=1.9608 to 5.5251).

A statistically significant difference was also found when the allelic frequencies between the two groups were compared (p<0.0001), with the 118G allele having a 1.5-fold higher risk of developing RA (risk ratio (RR)=1.5801, 95%CI of RR=1.3091 to 1.9071, odds ratio (OR)=3.1357; 95%CI of OR=2.1083 to 4.6638).

**Discussion**

In present study, Restriction fragment length polymorphism of DNA samples of the subjects showed that among the two reported SNPs in exon1 of OPRM1, both the SNP C17T and A118G was detected in the study cohort. The genotype distribution and allele frequencies of the polymorphic site in the groups studied.

Chi-square analysis showed a significant difference in genotype frequency of C17T (χ² = 21.7, p=0.00) and A118G (χ² = 33.3, p=0.00) in RA subjects, compared with that of control.

Not applicable in the present study. Only OPD/IPD patients will be recruited and lactating mothers were not recruited.

The highly significant association in the frequency of the T allele between cases and control subjects, giving an odds ratio of = 3.2914, (CI 95%, 1.9608 to 5.5251) in the RA group. Similar association in the frequency of the G allele between cases and control subjects, giving an odds ratio of 3.1357, (CI 95%, 2.1083 to 4.6638) in the RA group. Both the polymorphic site (C17T and A118G) of the OPRM1 gene exhibited good fit to Hardy–Weinberg equilibrium in control populations.

In present study, a statistically significant difference was also found when the allelic frequencies between the two groups were compared (p<0.0001), with the 118G allele having a 1.5-fold higher risk of developing RA (risk ratio (RR)=1.5801, 95%CI of RR=1.3091 to 1.9071, odds ratio (OR)=3.1357; 95%CI of OR=2.1083 to 4.6638).

The allelic frequencies of C17T for C and T in two different groups were 90% and 10%, respectively in controls, and, 74% and 26%, respectively RA subjects with the C allele being more frequent control population than in RA subjects. Similarly allelic frequencies of A118G for A and G in the groups were 82% and 18%, respectively, in control subjects, and 59% and 41%, respectively, in the control population with G allele
being more frequent in both the case populations.

In present study, the highly significant association in the frequency of the T allele between cases and control subjects, giving an odds ratio of = 3.2914, (CI 95%, 1.9608 to 5.5251) in the RA group. Similar association in the frequency of the G allele between cases and control subjects, giving an odds ratio of = 3.2914, (CI 95%, 1.9608 to 5.5251) in the RA group. Similar association in the frequency of the A allele between cases and control subjects, giving an odds ratio of = 3.2914, (CI 95%, 1.9608 to 5.5251) in the RA group. Both the polymorphic site (C17T and A118G) of the OPRM1 gene exhibited good fit to Hardy–Weinberg equilibrium in control populations.

To test this hypothesis required a cohort with two characteristics: a broad spectrum of substance use and a relatively high frequency of the T allele. Over 50% of the participants are of African descent and drug use was prevalent.

**Conclusion**

A statistically significant difference was also found when the allelic frequencies between the two groups were compared (p<0.0001), with the 17T allele having a -1.751 fold higher risk of having RA (risk ratio (RR)= 1.7518, 95%CI of RR = 1.2988 to 2.3627, odds ratio (OR)=3.2914; 95%CI of OR=1.9608 to 5.5251). A statistically significant difference was also found when the allelic frequencies between the two groups were compared (p<0.0001), with the 118G allele having a 1.5 fold higher frequency of the T allele between cases and control subjects, giving an odds ratio of 3.1357, (CI 95%, 2.1083 to 4.6638) in the RA group. Both the polymorphic site (C17T and A118G) of the OPRM1 gene exhibited good fit to Hardy–Weinberg equilibrium in control populations.

We concluded that the study definitely needed to be extended to larger cohort of patients and control samples and to a larger set of candidate μ opioid receptors. Extending the studies to a larger cohort will also allow genetic analyses of clinically defined endophenotypes observed in the patients of this chronic metabolic disease with attributes of autoimmune disorder and multiple symptoms in patients. Genetic studies can also impact strategies adopted for effective personalized treatment for this progressively debilitating disease.

**References**

Study of Impact of Glycemic Status (HbA1c) on Platelet Activity measured by Mean Platelet Volume & Vascular Complications in Diabetics

Manoj Saluja¹, Yogesh Kumar Swami²*, SR Meena³

Abstract

Introduction: Diabetes mellitus is a global pandemic. The increased platelet activity may play a role in the development of vascular complications of this metabolic disorder. The mean platelet volume (MPV) is an indicator of the average size and activity of platelets. Larger platelets are younger and exhibit more activity.

Aims and Objectives: To determine the MPV in diabetics with different glycemic control (HbA1C), to see if there is a difference in MPV between diabetics with and without vascular complications, and to determine the correlation of MPV with fasting blood glucose, glycosylated hemoglobin (HbA1c), body-mass index, and duration of diabetes in the diabetic patients.

Methodology: Platelet counts and MPV were measured in 160 Type 2 diabetic patients using an automated blood cell counter. The blood glucose levels and HbA1c levels were also measured. All patients were divided in 2 groups, group A, which includes patients with HbA1C≤8 % and group B, which includes patients with HbA1C>8 %. Statistical evaluation was performed using Student’s t test and Pearson correlation tests

Results: The mean platelet counts and MPV were higher in diabetics with higher HbA1C (group B) compared to the diabetics with lower HbA1C (group A) [288.30 ± 103.96 X 109/l vs. 265.83 ± 66.97 X 109/l (P= 0.16)], 13.77 ± 0.08 fl versus 11.86 ± 0.66 fl (P=0.0001), respectively. MPV showed a positive correlation with fasting blood glucose (regression (r) = 0.18) and HbA1c levels (P=0.0001). HbA1C and MPV increases with increase in duration of DM, which were 8.62±0.96 and 8.51±1.09 % (p=0.49) and 13.24±1.27 and 13.10±1.37 (p=0.50) respectively in both group with duration >5 years and ≤5 years. On the basis of vascular complications, HbA1C, MPV and Duration of DM were (in both group with and without complications respectively), 8.58±0.01 % and 8.56±0.09 % (p=0.03), 13.12±1.40 fl and 12.80±1.21fl (p=0.13), 9.11±3.22 years and 2.5±2.2 years (p<0.0001).

Conclusion: Our results showed significantly higher MPV in diabetic patients with higher HbA1C (poor glycemic control). This indicates that elevated MPV could be either the cause for or due to the effect of the vascular complications. Hence, platelets may play a role and MPV can be used as a simple parameter to assess the vascular events in diabetes.

Introduction

Diabetes mellitus (DM) is a major global health problem. According to estimates of the World Health Organisation, the number of people with DM has risen from 108 million in 1980 to 422 million in 2014 there.¹

The increased platelet activity is emphasized to play a role in the development of vascular complications of this metabolic disorder.² Platelet volume, a marker of the platelet function and activation, is measured as mean platelet volume (MPV) by hematology analyzers. Diabetic patients have an increased risk of developing micro- and macrovascular disease, and platelets may be involved as a causative agent with respect to altered platelet morphology and function.³,⁴

The aim of our study was to determine if platelets were activated in diabetes and in its associated vascular complications by measuring the MPV in the diabetics, to see if there was a difference in MPV in diabetics with and without vascular complications, and to determine the correlation of MPV with fasting blood glucose (FBS), postprandial plasma glucose (PPBS), glycosylated hemoglobin (HbA1c), body-mass index (BMI), and duration of diabetes in the diabetic patients, respectively.

Materials and Methods

Study design

This was a cross sectional study carried out in 160 patients who were already diagnosed to have Type 2 DM. All patients underwent a complete clinical evaluation with specific reference to any associated macro- or microvascular complications. Height and weight of all the subjects were recorded. We measured the MPV and platelet counts with complete blood count using an automatic blood cell counter (Beckman Coulter Act5Diff). The estimation of plasma glucose levels (fasting plasma glucose and postprandial plasma glucose) was carried out by the glucose oxidase method in the auto analyzer (Johnson and Johnson vitros 250) and that of HbA1c by the high-performance liquid chromatography method.

Inclusion Criteria

1. Diabetic patient diagnosed according to ADA Criteria.
Table 1: Various parameters studied in study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value/No./%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>160</td>
</tr>
<tr>
<td>Age</td>
<td>51.9±13.5 years</td>
</tr>
<tr>
<td>Males</td>
<td>84</td>
</tr>
<tr>
<td>Females</td>
<td>76</td>
</tr>
<tr>
<td>Mean duration of DM</td>
<td>5.97±4.33 years</td>
</tr>
<tr>
<td>Macro and micro vascular complications (no. of patients)</td>
<td>96 (60%)</td>
</tr>
<tr>
<td>BMI</td>
<td>24.04±3.26 kg/m²</td>
</tr>
<tr>
<td>FBS</td>
<td>151.32±34.25 mg/dl</td>
</tr>
<tr>
<td>HbA1C</td>
<td>8.57±0.01%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>28156±94539</td>
</tr>
<tr>
<td>MPV</td>
<td>13.17±1.31 fl</td>
</tr>
</tbody>
</table>

Table 2: Correlation of MPV to the different parameters studied

<table>
<thead>
<tr>
<th>Parameters</th>
<th>r value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPV</td>
<td>Duration of DM</td>
<td>0.2</td>
</tr>
<tr>
<td>MPV</td>
<td>BMI</td>
<td>0.72</td>
</tr>
<tr>
<td>MPV</td>
<td>FBS</td>
<td>0.64</td>
</tr>
<tr>
<td>MPV</td>
<td>Complications</td>
<td>-</td>
</tr>
<tr>
<td>MPV</td>
<td>Age</td>
<td>-0.26</td>
</tr>
</tbody>
</table>

Table 3: Comparative study of different parameters in group A and B

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>48</td>
<td>112</td>
<td>-</td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>11.86±0.66</td>
<td>13.77±1.08</td>
<td>0.0001</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>7.44±0.03</td>
<td>9.06±0.08</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2±1.83</td>
<td>28.3±3.51</td>
<td>0.0001</td>
</tr>
<tr>
<td>Platelet count</td>
<td>265.8±66.9 (× 10^9/L)</td>
<td>288.3±103.9</td>
<td>0.16</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>120.6±152</td>
<td>164.4±31.6</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Subject population

Total 160 diabetic subjects were included in this study of which 84 were males and 76 were females. The mean age of the study population was 51.9±13.5 years. Of all 3 age groups (20-39, 40-59 and ≥60 years of age), 36, 80 and 44 subjects were included respectively. The mean duration of diabetes was 5.97±4.33 years (patients were studied in 2 groups as duration ≤5 and >5 years). All subjects were divided in 3 groups on the basis of BMI (18.5-24.9, 25-29.9, ≥30 kg/m²), each included 36, 80 and 44 respectively.

All diabetic subjects in this study were divided in 2 groups on the basis of HbA1C, group A (HbA1C≤8 %) and group B (HbA1C>8%).

Observation and Results

Out of the 160 diabetics, 96 (60%) had sign and symptoms of complications such as peripheral neuropathy, diabetic foot, diabetic retinopathy, diabetic nephropathy, hypertension, coronary artery disease, peripheral vascular disease and 64(40%) did not have any of these complications.

The mean BMI in the study population was 24.04±3.26 kg/m². (It was 25.2±1.83 kg/m² in patients with HbA1Cs8 and was 28.3±3.51 kg/m² in patients with HbA1C>8.)

Among the diabetic subjects, a positive statistical Pearson correlation was seen between MPV and HbA1c levels (r = 0.9; P < 0.0001), FBS levels (r = 0.64; P < 0.03), BMI (r =0.72, p =0.02). However, no statistical correlation was seen between MPV and the duration of DM (P=0.50) and the vascular complications (p=0.13) in the diabetic group.

The mean MPV in subjects with complications (13.12±1.40 fl) was higher than that of subjects without complications (12.80±1.21 fl) but independent student t-test did not show any statistical significance (P = 0.13).

Out of 160 DM patients, there were 48 patients in group A (mean HbA1c 7.44±0.03%) and 112 patients in group B (mean HbA1c = 9.06±0.08%). The mean BMI in group A (25.2±1.83 kg/m²) was significantly lower than that of group B (28.3±3.51 kg/m²; P = 0.0001). The mean FBS level in group A was 120.6±152 mg/dL while that of group B was 164.4±31.6 mg/dL(P < 0.001).

The mean platelet count in group A (265.8±66.9 × 10^9/L) was higher than that of group B (288.3±103.9 × 10^9/L) but was not statistically significant (p=0.16). The mean MPV in group A (11.86±0.66 fl) was significantly lower than that of group B (13.77±1.08 fl; P = 0.0001).

Mean HbA1C in patients with duration of DM >5 years was 8.62±0.96 and in patients with duration ≤5 years it was 8.51±0.09 (p=0.49). Glycemic control improves with age, as mean HbA1C in group A with age>50 years was 8.27±0.09 and in group age≤50 years it was 8.95±0.09 (p=0.001). MPV also decreases with age, as it was 13.51±1.21% in age group ≤50years and 12.94±1.35% in age group >50 years. (p=0.03)

Discussion

DM is a complex metabolic syndrome characterized by chronic hyperglycaemia resulting in complications affecting the peripheral nerves, kidneys, eyes, and micro- and macrovascular structures. The prevalence of all types of diagnosed diabetes in most western societies is 3–7%. Countries with the highest absolute number of diabetics are in India (19 million), China (16 million), and the United States (14 million). The prevalence of diabetic microvascular complications is higher in people with poor glycemic control, longer duration of DM. Diabetes and its vascular
complications can cause a financial burden to a country’s national economy. India, having the highest number of diabetics, faces such issues. MPV can be used as a simple economical test in the monitoring of DM and thereby help curb the morbidity and mortality.

Type 2 DM is characterized mainly by impaired insulin secretion and increased tissue insulin resistance. Sustained hyperglycemia leads to a series of interrelated alterations that can cause evident endothelial dysfunction and vascular lesions in diabetic complications. Formation of advanced glycation end products, activation of protein kinase C and disturbances in polyol pathways are the possible mechanisms by which increased glucose induces vascular abnormalities.

Platelets are small discoid blood cells that circulate and participate in hemostasis. Primary plug formation due to platelets seals the vascular defects and provides the required phospholipid surface for the recruited and activated coagulation factors. In response to stimuli generated by the endothelium of blood vessels, platelets change shape, adhere to subendothelial surfaces, secrete the contents of intracellular organelles, and aggregate to form a thrombus. These pro-aggregatory stimuli include thrombin, collagen, epinephrine, ADP (dense storage granules), and thromboxane A2 (activated platelets). Hence, platelets may assume an important role in signaling of the development of advanced atherosclerosis in diabetes.

MPV is an indicator of the average size and activity of platelets. Larger platelets are younger, more reactive and aggregable. Hence, they contain denser granules, secrete more serotonin and β-thromboglobulin, and produce more thromboxane A2 than smaller platelets. All these can produce a pro-coagulant effect and cause thrombotic vascular complications. This suggests a relationship between the platelet function especially MPV and diabetic vascular complications thus indicating changes in MPV reflect the state of thrombogenesis. Thus, DM has been considered as a “prothrombotic state” with increased platelet reactivity.

Hyperglycemia can increase platelet reactivity by inducing nonenzymatic glycation of proteins on the surface of the platelet, by the osmotic effect of glucose and activation of protein kinase C. Such glycation decreases membrane fluidity and increases the propensity of platelets to activate. Platelet function is directly regulated by insulin via a functional insulin receptor (IR) found on human platelets. In vivo experiments have confirmed that insulin inhibits platelet interaction with collagen and attenuates the platelet aggregation effect of agonists in healthy nonobese individuals.

MPV can also be elevated as an end result of an atherothrombotic event like myocardial infarction. This could be due to the quicker consumption of smaller platelets in the vascular event and compensatory production of reticulated platelets.

In our study, the mean platelet count was higher in the diabetic group with higher HbA1C (poor glycemic control) that was similar to the studies done by Demirtunc et al. and Zuberi et al. Other studies by Hekimsoy et al. had observed the opposite finding with lower platelet counts in the diabetic group with lower HbA1C. Hence, the platelet count could be dependent on several variables, that is, mean platelet survival, platelet production rate, and turnover rate in DM.

Higher values of MPV were observed in diabetic subjects with microvascular complications such as retinopathy but were not statistically significant. Higher values were also seen in the studies done by Ates et al. and Papanas et al. This suggested a role for the increased platelet activity in the pathogenesis of vascular complications. On the other hand, in the studies done by Hekimsoy et al. and Demirtunc et al. MPV was not significantly different in subjects with diabetic neuropathy/retinopathy from that of diabetics without those complications. Their possible explanation was centered on the rapid consumption of activated platelets in diabetics with complications.

In our study, MPV was significantly higher in diabetics with HbA1c levels > 8% than in diabetics with HbA1c levels ≤8%. There was a significant association between HbA1c and MPV, which was again seen in the study done by Demirtunc et al. Therefore, it may be concluded that glycemic control decreases the hyper activity of the platelet function and thus may prevent or delay possible diabetic vascular complications. However, our data needs to be further confirmed in larger studies. The reason for a high number of diabetics with HbA1c levels > 8% in the current study might have been due to poor dietary practices and lack of knowledge regarding the diet and exercise regimens that ought to be followed in diabetics.

No significant MPV association was seen with duration of diabetes and presence of complications. Similar findings were seen in other studies. But our findings were in contrast to the study done by Ates et al. Where MPV was positively correlating with the degree of retinopathy in their cases.

Conclusion

In diabetes mellitus, platelets become more reactive and aggregable and their mean volume (MPV) is increased. The increased platelet size may be one factor in the increased risk of atherosclerosis associated with diabetes mellitus and associated vascular complications. Hence, MPV would be a useful prognostic marker of cardio-vascular complications in diabetes. We also found that increase in HbA1c concentration was directly proportional to increased MPV. However, the increased MPV as the cause or the end result of vascular complications needs to be further explored. Hence, we propose that MPV can be used as a simple and cost-effective tool to monitor the progression and control of DM and its cardio-vascular complications.

References

Psoriasis and Co-morbidities: Is Hyperhomocysteinemia the Common Link?

Sujaya Manvi, Vikram K Mahajan, Karaninder S Mehta, RS Yadav, Satya Bhushan, Pushpinder S Chauhan

Abstract

Background: Hyperhomocysteinemia is a plausible common link between psoriasis and associated co-morbidities.

Aim: To assess and compare serum homocysteine levels in 160 (M:F 94:66) patients aged 18-70 years with chronic plaque psoriasis of varying severity with or without metabolic syndrome, cardiovascular and thyroid disorders and controls. The 155 controls (M:F 97:58) were healthy volunteers aged between 18 and 66 years.

Results: Overall, 123 (76.9%) psoriasis patients with or without co-morbidities and 87 (56.1%) controls had elevated serum homocysteine levels; 23.48±14.37 and 18.74±12.59 (mean±SD) µmol/L, respectively. Eighty-one (58%) patients had associated co-morbidities with mean serum homocysteine levels of 22.65±13.70 µmol/L. The difference between psoriasis patients with or without comorbidities and controls was statistically significant.

Conclusions: Hyperhomocysteinemia in psoriasis patients with or without comorbidities versus healthy controls suggests its possible dysregulation in psoriasis. The significance of hyperhomocysteinemia as an independent risk factor for cardiovascular or other comorbidities in psoriasis patients remains tenuous at best. Well-designed studies will perhaps resolve this issue.

Introduction

The patients with psoriasis are at increased risk of developing other diseases due to shared genetic pathways, common immune mechanisms, treatment related toxicities and the associated psychological burden of the disease. Crohn’s disease, thyroid disorders, obesity, metabolic syndrome, diabetes mellitus, cardiovascular diseases and malignancy (non-melanoma skin cancers and lymphoproliferative cancers) are common comorbidities. High plasma homocysteine, a thiol containing amino acid, is considered an independent risk factor for coronary artery disease, stroke and peripheral vascular disease as it favors atherosclerosis and vascular thrombosis by a number of mechanisms. These include damaging endothelial cells, promoting clot formation, causing aortic stiffness, and reducing blood flow velocity. Increased levels of homocysteine, have been observed in patients with psoriasis. This may be due to accelerated keratinocyte turnover resulting in excessive consumption of folate used for DNA methylation in actively dividing cells. The "psoriatic march", a concept of how severe psoriasis may drive systemic inflammation, suggests a process of genetic susceptibility triggered by environmental factors and immune responses. This leads to disease expression and comorbidities from chronic inflammation and perhaps resultant hyperhomocysteinemia. Hyperhomocysteinemia in patients with psoriasis may also be consequent of reduced plasma and red blood cell folate levels due to frequently prescribed methotrexate or other therapies. However, hyperhomocysteinemia in psoriatics apparently occurs without significant alteration in serum folic acid and/or vitamin B12 levels. Thus, hyperhomocysteinemia may be the link between these comorbidities and psoriasis that may have implications for management of these patients. However, not many studies are available, particular in Indian patients, on serum homocysteine levels in psoriasis patients with or without associated co-morbidities and available results have been variable.
Material and Methods

One hundred and sixty consecutive patients having chronic plaque psoriasis for at least 6 months were studied during January to December 2013 after informed consent. Patients having psoriatic arthritis, palmoplantar psoriasis, children <18 years, pregnant and lactating women, and those receiving medications that may influence homocysteine levels (phenytoin, carbamazepine, theophylline, oral contraceptives, azathioprine, thiazide diuretics, theophylline, oral contraceptives, azathioprine, thiazide diuretics, antithyroid peroxide antibody (AbTPO) testing and serum thyroid functions (T3, T4, TSH) and antithyroid peroxide antibody (AbTPO) testing and serum homocysteine estimation.

Quantitative estimation for serum homocysteine was performed by standard chemiluminescent enzyme immunoassay (CLIA) method as per manufacturer’s instructions using Immulite® ready to use in-vitro kits from Siemens Healthcare Diagnostic Products Ltd, UK. The serum homocysteine levels were compared between psoriasis patients with comorbidities and without comorbidities, and healthy controls. Results were analyzed for standard deviation for mean, unpaired student’s t-test for categorical variables, and Mann-Whitney non-parametric test for other variable that were not distributed normally.

Results

There were 94 men and 66 women (M:F 1.4:1) aged between 18 and 70 (mean 41.48 ± 12.55) years (Table 1). The majority, 143 (89.4%) patients were aged 21-60 years, 8 (5%) patients were <20 years and only 9 (5.6%) patients were aged >60 years. The duration of psoriasis was 6 months to 25 (mean 5.59±5.49) years and 104(65%) patients had the disease for <5 years at presentation. The disease was mild in 37(23.1%) patients and 15(9.4%) patient had severe disease, respectively. After overnight fasting blood samples were collected between 8 and 10 AM for estimation of lipid profile, blood sugar and HBA1c levels, thyroid functions (T3,T4,TSH) and antithyroid peroxide antibody (AbTPO) testing and serum homocysteine estimation.

Table 1: Baseline characteristics of patients and controls

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Number of patients (%) n =160</th>
<th>Number of Controls (%) n =155</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Males 94 (58.7)</td>
<td>Females 66 (41.3)</td>
</tr>
<tr>
<td></td>
<td>Male: Female 1:4:1</td>
<td>Male: Female 1.7:1</td>
</tr>
<tr>
<td>Age</td>
<td>Range 18-70 yr</td>
<td>Mean ± SD 41.48 ± 12.55 yr</td>
</tr>
<tr>
<td></td>
<td>Age groups &lt;20 years</td>
<td>Mean ± SD 88 (5)</td>
</tr>
<tr>
<td></td>
<td>20-40 years</td>
<td>Mean ± SD 64 (40)</td>
</tr>
<tr>
<td></td>
<td>41-60 years</td>
<td>Mean ± SD 79 (49.4)</td>
</tr>
<tr>
<td></td>
<td>&gt;60 years</td>
<td>Mean ± SD 9 (5.6)</td>
</tr>
<tr>
<td>Associated Comorbidities</td>
<td>(n =81)</td>
<td>Associated Comorbidities (n =155)</td>
</tr>
<tr>
<td></td>
<td>Serum homocysteine levels (Reference range 5 - 12 µmol/L)</td>
<td>Serum homocysteine levels (Reference range 5 - 12 µmol/L)</td>
</tr>
<tr>
<td></td>
<td>Range 2.50-50 µmol/L</td>
<td>Mean ± SD 22.65 ± 13.70 µmol/L</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD 23.48±14.37µmol/L</td>
<td>Mean ± SD 18.74±12.59µmol/L</td>
</tr>
<tr>
<td>Notes: BSA - Body surface area, PASI - Psoriasis area severity index</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: BP - Blood pressure; BMI (Body Mass Index) = weight in kg/height in m²; BMI >23 (normal weight), BMI >25 (obese); Central obesity with increased waist circumference >90 cm in Asian men and >80 cm in Asian women. Elevated Fasting Triglycerides >1.7mmol/l (>149mg/dl, or with drug treatment); Reduced Fasting HDL Cholesterol <1.3mmol/l (<50mg/dl, or with drug treatment); **Metabolic syndrome - includes constellation of central obesity, impaired glucose tolerance, raised blood pressure and dyslipidaemia; *Abnormal lipidogram included presence of hypertriglyceridemia, low HDL or both.

Table 2: Homocysteine levels in patients with psoriasis and comorbidities

<table>
<thead>
<tr>
<th>Associated Comorbidities</th>
<th>Number of patients (%) (n =81)</th>
<th>Mean homocysteine levels in Psoriasis patients with comorbidities, Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Reference range 5 - 12 µmol/L)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>(BP &gt;130/85 or on treatment)</td>
<td>27 (33.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>(FB &gt;100mg/dl or with drug treatment)</td>
<td>16 (19.7)</td>
</tr>
<tr>
<td>Obesity*</td>
<td></td>
<td>59 (72.8)</td>
</tr>
<tr>
<td>Metabolic syndrome**</td>
<td></td>
<td>36 (44.4)</td>
</tr>
<tr>
<td>EKG abnormalities</td>
<td></td>
<td>08 (9.9)</td>
</tr>
<tr>
<td>Thyroid abnormalities</td>
<td>(Hyperthyroidism with positive AbTPO)</td>
<td>07 (8.6)</td>
</tr>
<tr>
<td>Abnormal lipidogram†</td>
<td>Hypertriglyceridemia = 47 patients</td>
<td>59 (72.8)</td>
</tr>
<tr>
<td>Low HDL = 36 patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: BP - Blood pressure; BMI (Body Mass Index) = weight in kg/height in m²; BMI >23 (normal weight), BMI >25 (obese); Central obesity with increased waist circumference >90 cm in Asian men and >80 cm in Asian women. Elevated Fasting Triglycerides >1.7mmol/l (>149mg/dl, or with drug treatment); Reduced Fasting HDL Cholesterol <1.3mmol/l (<50mg/dl, or with drug treatment); **Metabolic syndrome - includes constellation of central obesity, impaired glucose tolerance, raised blood pressure and dyslipidaemia; *Abnormal lipidogram included presence of hypertriglyceridemia, low HDL or both.
59(72.8%), and metabolic syndrome in 36(44.4%) patients, respectively. Hypothyroidism with positive AbTPO was found in 7(8.6%) patients and 8(9.9%) patients had ECG abnormalities like left ventricular hypertrophy, ST depression, T wave inversion, and left anterior hemi-block with normal echocardiography. The serum homocysteine levels in these 81 patients with co-morbidities varied between 2 and >50 (Mean 22.65±13.70) µmol/L. Other 79 psoriatic patients without co-morbidities had serum levels between 2 and >50 (mean 24.33 ± 14.83 µmol/L). The levels were above reference range (5-12 µmol/L) in 62(76.5%) patients with co-morbidities and 61(77.2%) patients without co-morbidities, respectively (Table 3).

The 155 healthy volunteers comprised 97 men and 58 women (M:F 1.7:1) aged between 18 and 66 (mean 38.10±12.92) years and the majority, 141(91%) being in 21 to 60 years of age (Table 1). The serum homocysteine levels in controls ranged between 4.6 and >50 (mean 18.74 ±12.59) µmol/L and were above reference range in 87(56.1%) patients. There was no statistical significant difference in mean serum homocysteine levels between psoriasis patients with co-morbidities and those without co-morbidities (Table 4). However, the difference between healthy controls and psoriasis patients with or without co-morbidities was statistically significant.

Discussion

Psoriasis is now recognized as an immune-mediated inflammatory dermatosis with systemic involvement having strong association with metabolic syndrome as well as its individual components. Thomas et al10 found one or more co-morbidity in 52% cases in their study of 100 Indian patients. Menegen et al11 also demonstrated higher incidences of increased waist circumference, obesity and smoking in their psoriasis patients as compared to controls. This increased risk of developing other diseases is attributed to the chronic inflammation and elevated TNFα levels in psoriasis. It is possible that the first event that occurs is the onset of psoriasis followed by lifestyle changes, depression smoking, alcoholism and/or overeating.12 This perhaps leads to multitude of diverse conditions like insulin resistance, obesity, atherosclerosis, cardiovascular diseases and metabolic syndrome. One or more associated co-morbitides were observed in 81(50.6%) psoriasis patients in this study. The adipose tissue is an active endocrine organ with many secretory products including IL-6 and TNF-α that are known to play role in inflammation and pathogenesis of psoriasis. Obesity is frequently observed in association with psoriasis and is reported in 7%-9% cases.10,13 Obesity (BMI >25) and lipid abnormalities were found in 59(72.8) patients each and were the commonest co-morbidities observed in this series. Similar observations have been made previously wherein abdominal obesity was the commonest abnormality observed in 63% followed by hypertriglyceridemia in 44% patients.14 The results of most studies indicate that increased total cholesterol, triglycerides and LDL, and decreased HDL are features of metabolic syndrome and are also connected to immunological abnormalities in psoriasis.15 Several population based epidemiological and cross sectional studies across countries have shown an increased prevalence of hypertension among psoriatic patients.1,14,16,17 A study generated from a German database reported that the rate of hypertension was twice as high in psoriatic patients in comparison to controls.1 The prevalence of hypertension was nearly 34% among psoriasis patients and 22% among controls in US general population health surveys.14 Ghiasi et al18 observed that Iranian psoriatic patients have almost 2.2 times higher risk for developing hypertension than non-psoriatic patients. Hypertension was also noted in 13% and 50% cases in two separate Indian studies10,18. It was the third most common co-morbidity after obesity and metabolic syndrome in this study and observed in 27(33.4%) patients, and 8(9.9%) patients had ECG abnormalities conforming to hypertension. However, none of them had features suggestive of ischemic heart disease or atherosclerosis observed previously by other researchers.10,19 Psoriasis is also considered an independent risk factor for development of type 2 diabetes mellitus and observed risk is 1.76 times higher than the non-psoriatic patients.16 Endogenous insulin resistance and a high prevalence of diabetes among patients with psoriasis have been observed in large population based studies.19-21 Cohen et al21 observed higher proportion of diabetes in psoriasis patients than controls (odds ratio 1.38). Armstrong et al22 in their meta-analysis concluded that the psoriasis was associated with an odds ratio of 1.59 for diabetes. Thomas et al10 reported diabetes mellitus in their 8% patients. Conforming to these studies, we also observed diabetes mellitus in our 16 (19.7%) patients. Thyroid abnormalities have been documented in psoriasis patients. Arican et al23 noted increased levels of at least one thyroid hormone and high TSH score in 22% patients and opined that T3 receptor perhaps play a role in the synthesis of keratin and influence psoriasis severity due to direct or indirect effects of excessive thyroid hormones. Gul et al24 noted both hypothyroidism and

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**Table 3: Serum homocysteine levels in psoriasis patients with and without comorbidities**

<table>
<thead>
<tr>
<th>Range of serum homocysteine (µmol/L)</th>
<th>Psoriasis patients with co-morbidities (n=81)</th>
<th>Psoriasis patients without co-morbidities (n=62)</th>
<th>Healthy controls (n=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients (%)</td>
<td>Number of patients (%)</td>
<td>Number of subjects (%)</td>
</tr>
<tr>
<td>&lt;5</td>
<td>04 (4.9)</td>
<td>05 (6.3)</td>
<td>02 (1.3)</td>
</tr>
<tr>
<td>5 - 12</td>
<td>15 (18.5)</td>
<td>13 (21.0)</td>
<td>66 (42.6)</td>
</tr>
<tr>
<td>&gt;12 - 24</td>
<td>29 (35.8)</td>
<td>22 (27.8)</td>
<td>37 (23.9)</td>
</tr>
<tr>
<td>&gt;24 - 36</td>
<td>19 (23.5)</td>
<td>18 (22.8)</td>
<td>31 (20.0)</td>
</tr>
<tr>
<td>&gt;36 - 48</td>
<td>06 (7.4)</td>
<td>10 (12.7)</td>
<td>14 (9.0)</td>
</tr>
<tr>
<td>&gt;48</td>
<td>08 (9.9)</td>
<td>11 (13.9)</td>
<td>05 (3.2)</td>
</tr>
</tbody>
</table>

**Table 4: Significance of the results**

<table>
<thead>
<tr>
<th>Serum homocysteine (Reference range = 5-12 µmol/L)</th>
<th>Psoriasis patients with co-morbidities (n=81)</th>
<th>Psoriasis patients without co-morbidities (n=62)</th>
<th>Healthy controls (n=155)</th>
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<td></td>
<td>Mean ± SD µmol/L</td>
<td>Mean ± SD µmol/L</td>
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<td>23.48 ± 14.37</td>
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<td>p value*</td>
<td>0.002</td>
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*A 'p' value <0.05 calculated at 5% level (95% confidence limits) was considered statistically significant.*
hyperthyroidism in about 3% and 4% and AbTPO in 9% patients, respectively. They postulated that the prevalence of thyroid autoimmunity was not different between psoriatic patients and normal population. Hypothyroidism with elevated ABTPO suggestive of autoimmune thyroid dysfunction was observed in our 7(8.6%) patients but the significance of these findings remains conjectural at present. Only further experimental studies demonstrating exact effect of these hormones on keratinocytes will help delineate their role in the pathogenesis of psoriasis. Hyperhomocysteinemia occurs in patients with psoriasis and a significant difference has been reported between homocysteine levels when compared between patients with chronic plaque psoriasis and healthy controls. However, its significance in psoriasis or psoriasis-associated comorbidities is poorly understood. Overall, 123(76.9%) psoriasis patients in this study had serum homocysteine levels (12.1 - >50 µmol/L) above reference value as compared to that in 87(56.1%) controls, suggesting its possible dysregulation in psoriasis patients. The difference between mean serum homocysteine levels in psoriasis patients irrespective of comorbidities and healthy controls was statistically significant. However, no statistically significant difference was observed for homocysteine levels in psoriasis patients with co-morbidities and without co-morbidities in the present study.

Limitations

Small number of study subjects and controls, lack of study for other lifestyle risk factors, hyperhomocysteinemia in patients with 56% controls, and absence of long-term follow up, with or without treatment, are some of the limitations. The study of variation in serum homocysteine levels with treatment or occurrence of co-morbidities in relation to severity of psoriasis or measurement of serum vitamin B12 and folate levels was not part of the study.

Conclusions

Hyperhomocysteinemia in all our patients with psoriasis with or without comorbidities versus healthy controls suggests their possible dysregulation in psoriasis patients. The significance of hyperhomocysteinemia as an independent risk factor for cardiovascular or other comorbidities in psoriasis patients remains tenuous at best. It also remains speculative whether elevated homocysteine is a culprit or a bystander in the systemic inflammatory process and whether it is useful as an independent risk factor of cardiovascular or other morbidities in psoriasis patients. Well-designed studies will perhaps resolve this issue.

References


Erratum

Article entitled “Clinical Profile and Management of Pancreatic Exocrine Insufficiency in Patients with Chronic Pancreatitis in India, by Rupiyoti Talukdar, Rakesh Kochhar, Dyotana Sen Roy, Rashmi Hegde, JAPI 2018; 66 (12):33-40” has been withdrawn.
37th INTERNATIONAL DIABETES EXPERTS CONCLAVE 2019
28th to 30th June 2019, Pune

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De Chairperson, Scientific Committee, India

Scientific Highlights

KEY UPDATES
- IDEC Basic Updates = Osteoporosis = Hypothyroidism = Mela Hyperosmolar = Hemopoesis
- IDEC Medical Updates = Drug discontinuation - detailed discussion on different drugs - Endo-laparoscopic management of obesity
- Patient FAQs about diet and exercises - what physicians should know
- IDEC Lipid Updates = Diagnosis of Dyslipidemia - Interpretation of Report - Pharmacological Strategies
- STATE OF THE ART WORKSHOPS = Research Methodology = Insulin = Diabetic Foot = Technology in diabetes
- Chelation Nephropathy = Assessing for Nephrosis
- UNIQUE PLENARY SESSIONS - State of the art lectures to be delivered by national & international faculty on topics covering diagnosis, prevention & complications related to diabetes
- PRODUCT THEATER

REGISTRATION FORM

First Name ___________________________ Surname ___________________________ Gender M/F

MACC/Other Council No. ___________________________

Hospital/Institution ___________________________

Qualification ___________________________ Speciality ___________________________

Address for Communication ___________________________

City ___________________________ PINcode ___________________________

Mobile Number/Contact No (with area code) ___________________________

Email-ID ___________________________

PAYMENT DETAILS

Registration fees per person in India & USD

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THE WESTIN
PUNE, MAHARASHTRA
**IMPACT India: Insights for Insulin Therapy in Routine Clinical Practice**

**V Mohan**, Ashok Kumar Das, AG Unnikrishnan, Siddharth N Shah, Ajay Kumar, Abdul Hamid Zargar, Sanjay Kalra

**Abstract**

**Objective:** Widely used in the management of diabetes, insulin therapy is influenced by several patient preferences and physician choices. This article reports the findings of the IMPACT survey, designed to assess insights on various factors which influence the choice of insulin therapy in India.

**Methods:** We administered a questionnaire which focused on the practice and patient profiles and the preferred regimens in specific clinical situations using a case scenario. Respondents were asked about preferred insulin regimens for various phases of life, comorbid conditions, dietary choices and psychological factors.

**Results:** Overall, 314 doctors participated in the survey. Majority were general physicians (51%) and diabetologists (37%). In clinical practice, the most preferred regimens included premix insulin BD in adults (59%) and elderly (53%), and basal bolus therapy in pregnant women (>47%) and in acute illness (62%). Both regimens were equally preferred for symptomatic patients (41% basal bolus and 38% premix insulin) and those with renal or hepatic failure (36% each). Premix insulin was preferred for patients with high carbohydrate intake (73%) while basal bolus was preferred for patients with variable meal timings (39%) and in pronounced postprandial glucose excursions (45%). Insulin co-formulation and high-mix insulins were not a part of the survey questionnaire.

**Summary:** Indian physicians exercise logic in the choice of insulin regimens. Preference is based on patient characteristics including glucophenotype, dietary patterns, psychosocial needs, clinical situations, and comorbid conditions.

**Introduction**

Poor glycemic control is common in routine clinical practice for diabetes.1,2 This reflects a delayed initiation of therapy, including insulin therapy.3 Several guidelines provide directions and rationale for the initiation and intensification of therapy with insulin. Based on the duration and severity of diabetes, these guidelines provide elaborate algorithms for insulin therapy.4-9 The American Association of Clinical Endocrinologists (AACE) and American Diabetes Association (ADA)6,7 recommend basal insulin while the Indian National Consensus Group (INCG)8 recommends premix insulin for the initiation of therapy in diabetes. The International Diabetes Federation (IDF), National Institute of Clinical Excellence (NICE), and the Research Society for the Study of Diabetes in India (RSSDI) provide directions for initiation of therapy with basal or premix insulin depending upon the degree of hyperglycemia.4,5,8 However, most guidelines usually do not specifically describe the patient characteristics that determine the choice of insulin regimen in patients with diabetes.10

The adoption of insulin in routine practice is guided by several factors including the patient preferences and overall health status of the patient. In addition, cost and accessibility are also common concerns. Due to the heterogeneity in diabetes, individualization and customization of therapy are needed to meet glycemic goals in routine practice.11 These factors collectively explain the challenges for optimizing therapy in the management of diabetes in routine clinical practice. The Insulin Management: Practical Aspects in Choice of Therapy (IMPACT) India group comprising seven leading diabetologists of India developed a survey to objectively gain insights on various factors which influence the choice of insulin therapy in India. In this paper, we present the results of the pilot survey and explain the utilization of insulin regimens in routine clinical practice in India and the impact of clinical and psychosocial factors that influence clinical decision making.

**Methods**

The survey was made available to participants between August 29, 2018 and September 5, 2018 at https://www.surveymonkey.com/r/IMPACTIND. The initiative was promoted through e-mail communications and SMS to all participants of 12th National Insulin Summit 2018 (8th and 9th September 2018, Hyderabad, India), a scientific event under the auspices of the Indian College of Physicians, the academic wing of the Association of Physicians of India and Diabetes Research Society.

Participation in the survey was free...
and the responders were anonymous. For details of the questionnaire, refer to supplementary materials. The development and administration of this survey was driven by the Scientific Committee of the National Insulin Summit.

**Structure of questionnaire**

The questionnaire was created on website host Survey Monkey® (Palo Alto, Calif, USA). The survey was anonymized, and the responses were confidential throughout the process of the survey. The questionnaire had 4 parts:

1. **Practice profile**
   
   Two questions in this section sought to determine the specialty of physicians and the average numbers of patients with diabetes they saw every month in their clinical practice.

2. **Patient profile**
   
   This section included questions (n=3) on the age and duration of diabetes of the patients seen in clinical practices. In addition, the respondents were asked about the proportion of patients on insulin therapy in their practice.

3. **Case scenario**
   
   This section had a total of 13 questions. In the first question, respondents were asked about the preferred regimen for a patient with fasting plasma glucose (FPG) 150mg/dl, post prandial glucose (PPG) 300 mg/dl, and glycosylated hemoglobin (HbA1c) 9.5%. In next 12 questions, structured into 4 sections of 3 each, their preferred prescribing approaches were explored with regards to specific phases of life, clinical situations, dietary and psychological variables, and different glucophenotypes.

4. **Statistical measures**

   Data retrieved from Survey Monkey® were analyzed using IBM Statistics Package for the Social Sciences (SPSS) version 14.0. Descriptive statistics were used to describe the analyses.

**Results**

A total of 314 physicians from across India responded to the survey. The respondents included endocrinologists (6.4%), diabetologists (37%), and physicians (51%). Most of the respondents (>60%) reported managing more than 100 patients with diabetes in a month.

Majority (44%) of the patients in clinical practice were aged between 41-60 years while >20% each were aged between 61-80 years and 21-40 years. More than 50% of patients had diabetes duration from 1-10 years. About 20% and 16% patients had diabetes duration of 5-10 years and 1 year, respectively. Majority of the respondents (47%) had 21-40% patients on insulin therapy while 31% had 20% patients on insulin therapy (Figure 1). Twice daily dosing of premix insulin was the preferred insulin regimen in adults and in elderly with no limitations of activities of daily living (Figure 2). In the frail elderly, basal bolus therapy was the most preferred choice (>47%) followed by premix insulin twice daily (28%) or once daily (6%) dosing.

In symptomatic patients, both basal

**Diet and psychological**

Questions were designed to explore the approach in patients with high carbohydrate diet and two heavy meals a day, those with limited diabetes literacy and numeracy or those seeking to minimize the number of delivery devices, and those with variable meal times or need for flexibility in frequency or timing of injection.

**Glucophenotype**

Respondents were asked 3 questions about preferred regimens for patients with pronounced post prandial excursions of 400 mg/dl, fasting 150 mg/dl, high fasting glucose of 200 mg/dl and post prandial glucose of 220 mg/dl, and those with a high risk of hypoglycemia and high glucose variability.
Isolated fasting hyperglycaemia

<table>
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<tr>
<th></th>
<th>Basal</th>
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<th>Premix BID</th>
<th>Basal plus</th>
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<tr>
<td>%</td>
<td>42.81</td>
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<td>19.52%</td>
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High risk of hypoglycaemia

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<tr>
<th></th>
<th>Basal</th>
<th>Premix OPD</th>
<th>Premix BID</th>
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<tr>
<td>%</td>
<td>34.25</td>
<td>7.53%</td>
<td>6.85%</td>
<td>17.12%</td>
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</table>

**Fig. 3: Preferred insulin therapy in glycemic variability in routine practice**

bolus (41%) and twice the daily premix insulin (38%) were the preferred regimens, whereas there was a higher preference for basal bolus regimen in patients with intercurrent acute illnesses vs premix insulin (62% vs. 24%). The use of basal bolus and premix insulins were equally preferred (36%) for patients with hepatic or renal failure.

Premix insulin twice daily dosage was the most preferred regimen for patients with high carbohydrate intake (73%) and those with limited diabetes literacy (44%) while basal bolus (39%) followed by basal plus (24%) were the preferred choice for patients with variable meal timings.

There was a higher preference for basal and basal bolus therapy in patients with isolated fasting hyperglycaemia (42.81%). In those at high risk of hypoglycaemia both basal and basal bolus insulin were preferred (Figure 3). In patients with pronounced postprandial glucose excursions, there were preference for basal bolus (45%) followed by basal plus (27%) and premix insulin twice daily dosing (21%).

There was a higher preference for twice daily dosing when compared to the once daily dosing of premix insulin in adults (59% vs. 8%), elderly (53% vs. 8%), frail elderly (23% vs. 19%), and pregnant women (28% vs. 6%). Similar trends were reported for patients with symptoms (38% vs. 5%), acute illness (24% vs. 3%), hepatic or renal impairment (25% vs. 11%), high carbohydrate diet (73% vs. 1%), limited diabetes literacy (44% vs. 16%), variable meal timings (17% vs. 7%), pronounced postprandial excursions (21% vs. 7%), and isolated fasting hyperglycaemia (20% vs. 8%). However, the two were equally used in patients with higher risk of hypoglycaemia (7% vs. 8%).

**Discussion**

Internet- and web-based applications are increasingly being used to guide the provision of care in diabetes and to assess the impact of the clinical practices.\(^\text{12,13}\) We present the survey results for assessment of choice of insulin regimens in routine clinical practice by Indian physicians. This was a comprehensive survey capturing important aspects of use of insulin regimens in diabetes management. The survey questionnaire was peer reviewed and was subjected to a pilot before approval. Designed by experts in the management of diabetes, the survey was simple and easy to administer and understand. The survey had a good geographical coverage with responses from physicians of various specialties across India.

The objective of our survey was to determine trends in insulin therapy in routine clinical practice. Studies with similar objectives include the A1chieve and the IMPROVE study (Shah 2010; Valensi 2008). The A1chieve was a prospective, open-label, non-interventional, 24-week study in patients of diabetes (n=60,000) across four continents (Asia, Africa, South America, and Europe). The study reported the utilization of premix (biphasic insulin aspart 30), basal (insulin detemir), and meal-time (insulin aspart) insulin analogs in people with type 2 diabetes.\(^\text{14}\) The IMPROVE study was an open-label, non-randomised, 26-week observational study assessing the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in type 2 diabetes (n=51286).\(^\text{3}\) Unlike these studies, our study is a survey focused on assessing the choice of insulin regimens and the factors influencing the choice for insulin therapy.

Delayed initiation of insulin is common in India. The case scenario in the survey is focused around glycemic levels reported in A1chieve, i.e. fasting (140-160 mg/dL) and postprandial (300-350 mg/dL) levels of blood glucose and glycosylated hemoglobin (HbA1c: 9.5%).

The 12 questions included key factors determining therapeutic choices, i.e. patient characteristics, presenting symptoms, diversity in meal patterns and patient preferences, severity and patterns of hyperglycemia, and diversity in meal patterns. The survey enabled assessments for the influence of stage of life, clinical situation, diet and psychosocial factors, and glucosphenotype on the choice of insulin regimens in routine clinical practices.

Physicians in India prefer premixed insulin in the elderly population. This choice is logical and rational due to the ease of administration reported for premixed preparations in the elderly with diabetes.\(^\text{15}\) Further, the premixed preparations of insulin are reported to be safe in patients at risk of hypoglycaemia.\(^\text{16}\) This makes premixed insulin a preferred choice for the management of diabetes in the elderly.

The Indian National Consensus Group (INCG) recommends premixed insulins, preferably analogue formulations, for the management of all stages of diabetes as these offer a simple and safe option for the initiation of treatment.\(^\text{17}\) According to our survey, Indian physicians prefer to use twice daily dosing of premix insulin in adults, elderly with no limitations of activities of daily living, and the frail elderly. Similar results have been reported in the IMPROVE study wherein therapy was initiated with a twice-daily regimen of BIAsp 30 in more than 80% patients of diabetes.\(^\text{3}\) Premixed insulins are best options in patients who are unwilling or are unable to adhere to the frequency of injections or the frequent monitoring required with basal–plus or basal–bolus regimens.\(^\text{18}\)

Our findings suggest that physicians prefer premix insulin in twice daily dosing for patients with high
carbohydrate intake. This synchronizes with the INCG recommendations for initiation of therapy with premixed insulin in Asians who show high glycemic response to meals. This can be explained by the high carbohydrate components of diets in the Indian population. This preference can also be driven by various cultural practices in Asian countries.

In India, the basal bolus therapy is the most preferred therapy for pregnant women. Indian physicians also make efforts to individualize therapy for optimal glycemic control during pregnancy. Available evidence suggests that basal/bolus combination of long- and short-acting insulin preparations are the best options in pregnant women requiring insulin therapy. Premixed insulins are virtually not used in pregnancy in the west. In our study, 28% of respondents used premixed insulins during pregnancy and reported good results with this regimen.

In this survey, physicians report preference for basal bolus regimen for patients with intercurrent illnesses. Basal bolus regimens are reported to be efficacious and safe for use in patients of diabetes with medical and surgical complications. However, twice daily dosing of premix insulin was preferred over once daily dosing. The recently updated Indian Council of Medical Research (ICMR) Guidelines also recommend the use of premix insulin twice a day as an alternative to multiple insulin injection regimen. The twice daily regimen also offers a convenient approach to intensification of premix insulin therapy to achieve glycemic targets.

The limitations of the survey include the recall bias of respondents and the potential influence of the sponsor. By design, the results reflect the opinions of survey participants which could be different from those of the non-responders. We are also aware that the responses given by 314 physicians are not sufficient to generalize the results to a large country like India. The survey was limited to physicians in India and hence this may not be generalized to others. Further, the survey does not differentiate preferences across primary care practices and tertiary centers. We also need to consider the fact that differences in treatment algorithms across practices which could be a possible bias for respondents with greater familiarity of the algorithms. The survey does not provide any details for diet or lifestyle though these are key factors that influence the choice of insulin in patients with diabetes. The likelihood for preference of an insulin regimen has not been assessed on a probability scale.

The survey questionnaire prompts for the use of only select insulin formulations and did not include some popular regimens, e.g. high-mix (50:50), insulin co-formulations, and delivery devices of insulin that are increasingly being used to individualize treatment in people with diabetes.

There is increasing evidence in support of the usage of insulin co-formulations which are convenient and are preferred by many clinical practitioners for the initiation and intensification of treatment. Insulin co-formulations make a logical choice in several scenarios with advantages of similar efficacy to basal bolus or basal plus regimens along with proven reduction in hypoglycemia events as well as reducing burden of injections. Unfortunately, insulin co-formulations were not part of the survey questionnaires. This should be explored in further research when determining the factors for choice of insulin in various glucophenotypes encountered in patients in routine clinical practice.

Nevertheless, despite these limitations, the insights gained through this study for the factors influencing the choice of insulin therapy in routine clinical practice among Indian physicians can help to guide future research for the use of insulin to optimize glycemic control in diabetes.

**Summary**

The results of our survey suggest that the Indian physicians follow a fairly logical approach in choosing various insulin regimens used in treatment of type 2 diabetes. Physicians appear to practice glucophenotype guided-flexibility in their approach to diabetes. When choosing an appropriate insulin regimen and dosage pattern, Indian physicians also assess stage of life, clinical situation, diet, and psychosocial factors as well.

Our survey reports that premix insulins are the preferred option by most physicians in India. Further, the survey affirms this preference to be guided by factors such as high carbohydrate diet, high levels of post-prandial glycemic excursions, and delayed insulin initiation. Basal insulin is more preferred in patients with isolated high FPG and higher risk of hypoglycemia. The basal-bolus regimen was more preferred in patients with intercurrent illness, pregnancy and other special situations.

This survey forms the foundation for further research on the preferences of other insulin regimens including insulin co-formulations and various insulin delivery devices.

**Acknowledgments**

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published.

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**Conflict of interest**

Viswanathan Mohan has received honoraria and research grants from Novo Nordisk, Sanofi and meeting support from Eli Lilly. Sanjay Kalra has received lecture fees and honoraria from Eli Lilly, Novo Nordisk and Sanofi. Unnikrishnan AG has received research grants/honoraria from Novo Nordisk, Eli Lilly, Sanofi and other pharmaceutical companies.

**References**


Eschar in Scrub Typhus: A Study from North East India

Md Jamil1, Prasanta Bhattacharya2, Jaya Mishra3, Hanifa Akhtar4, Aakash Roy5

Abstract

Introduction: Eschar is one of the most important clinical sign which helps in early diagnosis, and consequently initiation of specific treatment and prevention of complications in scrub typhus.

Aims: To study the prevalence and distribution of eschar in scrub typhus and comparison of clinical manifestations and complications among patients with or without eschar.

Methodology: A retrospective hospital based study in patients aged ≥ 18 years admitted to a tertiary care centre in north-eastern India. Scrub typhus was diagnosed based on clinical features supported by serological tests (Immunochromatographic card test, IgM ELISA and Weil Felix test). Chi square test was used for comparing variables. A ‘p value’ <0.05 was considered as statistically significant.

Results: A total of 129 patients of scrub typhus were included in the present study. Male to female ratio is 1.93:1 with the commonest age group being 18-30 years followed by 30-40 years. Eschar was found in 24.8% patients with 9.3% having multiple eschars and the rest had single eschar. Eschar was most commonly found in the inguinal region (28.57%) followed by trunk (25.75%) and lower limbs (22.85%). Presence of multi-organ dysfunction (p=0.008), hepatitis (p=0.005) and lymphadenopathy (p<0.01) were significantly higher in those patients who had eschar.

Conclusion: The common sites of distribution of eschar are the inguinal region, lower limbs and trunk and multorgan dysfunction is more commonly associated with eschars.

Introduction

Scrub typhus also known as tsutsugamushi disease is a vector born disease transmitted by the bite of larval stage of trombiculid mite and caused by Orientia tsutsugamushi.1 The disease has been reported with increasing frequency from various parts of India and also has seen resurgence in the north eastern part of the country.2

5 Scrub typhus usually present as an acute febrile illness associated with headache, malaise, suffused face and lymphadenopathy.4 An eschar, which is a necrotic skin lesion of 5-20 mm size found at the site of vector bite, is one of the pathognomonic signs of scrub typhus,5 which is present in

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Corresponding Author
Received: 07.07.2018, Accepted: 20.02.2019
10–87% patients with scrub typhus.1,4,9

The identification of an eschar reduces the time spend in serological test and facilitate early institution of specific therapy thus reduces the complications associated with late initiation of specific treatment. However, the lesion has a propensity of being frequently missed in initial physical exam as the vector bite and lesion is painless, free from pruritus and usually occurs in areas which are under cover of garments or occurs around the folds of body parts like inguinal or axillary region.10

In this context the current study was carried out in a tertiary care centre in north eastern India to study the distribution of eschars in patients with scrub typhus as well as to assess the possible association of eschar with clinical outcomes and complications.

**Material and Methods**

The present study was a hospital based retrospective study conducted in a tertiary care institute in north eastern India and includes patients who were admitted to the department of General Medicine from January 2013 to December 2015 in adult patient aged ≥ 18 years. Patient data was retrieved from the inpatient record file of the scrub typhus patients. Patients with incomplete data were excluded from the study. The diagnosis of scrub typhus was made on the basis of clinical features supported by serological test for scrub typhus (Weil's-Felix test, IgM immune-chromatographic card test or IgM ELISA). The following data were collected: age, gender, clinical presentation at the time of admission, details of eschar (number, location etc), complications and outcome. Complications including MODS, ARDS, DIC, AKI, shock were defined as per standard definitions and protocols.

Ethical clearance was taken from the Institutional Ethical Committee prior to the commencement of the study.

Statistical Analyses were done using Statistical Package for Social Survey (SPSS) for Windows version 17.0. Results are expressed as mean ± standard deviation for continuous data and as percentage for categorical data. Chi square test was used for comparing variables. A ‘p value’ <0.05 was considered as statistically significant. The results were tabulated and graphically represented using Microsoft Office for Windows 2008.

**Results and Observations**

A total 129 number of patients were included in the present study. Age and sex distribution of patients is shown in Table 1. Total number of male and female patients were 85 (65.89%) and 44 (34.11%) respectively. Male to female ratio was 1.93:1. Commonest age group in both gender affected was 18-30 years followed by 31-40 years. Eschar was found in 32 (24.8%) patients out of which three patients had multiple eschars and rest had single eschar. Distribution of location of eschar in different part of the body showed that the maximum number of eschars were located in the inguinal region (28.57%) followed by the trunk (25.71%) and lower limbs (22.85%) (Table 2). On comparing patients with eschars and those without it was found that presence of multi-organ dysfunction (p=0.008), hepatitis (p=0.005) and lymphadenopathy (p<0.01) were significantly higher in those patients that had eschar (Table 3). Biopsy of eschar was done in few number of cases to study the pathological changes.

**Discussion**

Scrub typhus is considered to be a re-emerging topical disease in India. The reported outbreaks have shown a rising trend in recent times from various parts of India.9,11 The presentation of scrub typhus is non-specific with a predominance of constitutional symptoms like acute onset of fever with myalgia, headache, suffused face, and nausea and vomiting.2,6,12 Therefore, it becomes a clinical challenging to differentiate it from other co-endemic diseases like malaria, dengue, and leptospirosis. In this regard the combination of a high index of suspicion in an endemic geographical area combined with a detailed search for the pathognomonic eschar forms the essential crux in the early diagnosis of scrub typhus.

An eschar is usually of 5-20 mm in size, in early stage they have a necrotic black central ulcer with erythematous margin Figure 1. The typical eschars are painless and non pruritic, but are associated with regional lymphadenopathy. Biopsy of eschar in few cases were done in the present study population and its histopathological findings are shown in Figure 2 (A-D). In the present study eschar was found 24.8% of the patients but studies from other part of India and other Asian countries show different results that vary from less than 10% to 90%.10,13 In our study the most common sites of distribution of eschar were the inguinal region followed by the trunk and lower extremities. In a previous study the common eschar sites were localised on the abdomen and around the chest and groin.7 In another study the commonest sites for an eschar in male patients were the perineum, inguinal, and buttock area.14 The probable reason leading to such a pattern of distribution may be due to the dressing pattern in the study population and the propensity of the eschars to occur in areas which are warm and damp due to pressure from clothing.15 In our study we found that three patients had multiple eschars while the rest had a solitary eschar.
The unusual presentation of multiple eschars in scrub typhus has been infrequently reported in literature and need to be astutely looked for by the clinicians.10,15

On comparison of the differences in clinical presentation and complications in patients with and without eschar we found that presence of multi-organ dysfunction, hepatitis and lymphadenopathy were significantly higher in those patients that had eschar.

While previous studies14 have elaborated on independent predictors for fatal outcome in scrub typhus like were ages over 65 years, acute kidney injury and hyperbilirubinaemia, the role of an eschar in predicting clinical outcome has not been substantially evaluated. A study from South Korea shows opposite finding when compared to present study, they reported age ≥ 60 years, the absence of eschar, WBC counts > 10,000/mm³, and albumin ≤ 3.0 g/dL were found to be independently predictive variables for the occurrence of severe scrub typhus.16 However, literature in this regard from the adult population is lacking and further such evidence may help in the utilization of the presence of eschar as an early indicator for prediction of multi-organ dysfunction and consequent early prognostication.

Conclusion

Presence of eschar was found to be relatively common in scrub typhus. The common areas of distribution are the inguinal region, lower limbs and trunk. Lymphadenopathy and multiorgan dysfunction were more common in patients having eschars.

References

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Original Article

Spinal Pains in Geriatric Group of Osteoporotic Vertebral Body Compression-fracture Relieved with Cath Lab-Vertebroplasty using “Small-Volume Glass Acrylate

Ramesh Sangle¹*, Varun Nivargi²

Abstract

Generalized osteoporosis and “osteoporotic vertebral body compression fractures” (OVBCF) are interrelated geriatric problems. Spinal pains of OVBCF and osteoporosis both are resistant to medicinal treatments. Surgical and C-arm Vertebroplasty are time consuming and difficult-operations. It can cause severe neurological deficits adding more debility to geriatric patients. Percutaneous minimal invasive procedure using glass acrylate (PMMA) and ‘digital subtraction angiography Catheterization laboratory unit’ (Cath lab PVP) can be combined effectively for augmenting pain relief. With Cath lab PVP no more problems related to acrylate viscosity and injection are noticed. Acrylate exudation in intra-dural and intra-neural spaces can easily be averted.

Objective: is to 1) Evaluate small volume PMMA in providing stability, safety and efficacy to OVBCF. 2) Effectiveness of Cath lab in reducing PMMA viscous to small volume, in relieving pains related to acute OVBCF pains. 3) To use minimal invasive and small procedural time in geriatric patient.

Material Method: Cath-lab is a multi-directional fluoroscopic high resolution digital subtraction angiographic imaging unit. Augmentation procedure performed in Cath lab is called as “Cath lab-Vertebroplasty (Cath lab-PVP). Twenty two OVBCF treated with Cath lab-PVP. Small volume, defined less than 3ML of viscous acrylates. It is injected through trans-pedicular route.

Results: Small volume fluid acrylate is well spread within the fractured crevices. Molded vertical cast between cortical plates maintains vertical body strength very effectively. Cath lab speed procedure too becomes effective.

Conclusion: Significant (90%) pain relief achieved within 24 to 48 hours in eighteen (81.81%) patients. Cath lab-PVP increases safety, early mobility without analgesics. Small volume PMMA is optimal and less prone for complication. Cath lab PVP fluoroscopy with its increased PMMA radio opacity monitors bone filling well. It has less procedural time and better psychological impact on the minds of geriatric.

Introduction

Osteoporotic patients are affected with acute spinal pain due to “osteoporotic vertebral body compression fracture” (OVBCF). OVBCF are pathological-non-traumatic dynamic compression induced fractures in osteoporotic body. Clinically intolerable spinal pains centering over fractured body vertebra is the hallmark of OVBCF. Excruciating pains also gets referred over thoracic or abdominal metameric segments. Pain is resistant to medicinal therapy. Spinal pain does not respond to fomentation or to short wave diathermy. OVBCF immobilizes the patient and with it co-morbidities like pneumonia and deep vein thrombosis often develop in the geriatric immobile patients. OVBCF with acute spinal pains are diagnosed by different faculties. Patients are seen by their family-physicians first. History of trauma or fall is often absent. As a result pain management differs. Often becomes symptomatic and conservative. It becomes lengthy over 30 days.

Prevalence of osteoporosis Worldwide is around 10 million people. OVBCF are more prevalent in post-menopausal osteoporotic females. Long delay is a significant factor in the management of OVBCF. It often results in permanent spinal deformity. Deformity causes more dynamic stress on the upper spine. Increased angulation deformity results in more pains. Every year over 700,000 (7%) of the osteoporotic patients suffer with OVBCF. Almost 15% OVBCF-patients are left untreated with PVP-vertebroplasty.1 Approximately 20% to 25% of untreated patients return with new painful fractures. Cath lab PVP in these cases becomes difficult.2 Cath lab PVP in these cases becomes difficult.

Incidence of OVBCF is almost double in women than that found in men.3 Its also age related, increases from 27% at 50 years of age to almost 2960/one lac at 85 years of age.4 Risk of developing another clinically evident osteoporotic OVBCF in such cases increases by almost five fold.4 Generalized OVBCF’s incidence in women is 153 per 100,000 per year and in men it is 81 per 100,000 per year.5 Osteoporosis is also more common with post-menopausal-smoking women and in patients with long term steroids. The combined effect has two-fold more prevalence in OVBCF.6

X-ray in general shows osteoporosis as decrease in vertebral body-bone density sparing laminae and spinous process. Vertebral pedicles are characteristically intact. Radiologically OVBCF is defined as 15%-20% vertical

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loss of height- greater loss of height anteriorly than posteriorly. There is saddle wedging in the anterior two third segments or 4 mm height reduction of the vertebral body. 

Glass acrylate “polymethyl methacrylate” (PMMA) was used for relieving spinal pains resulting from vertebral-hemangioma of the cervical -C2 body. PMMA-vertebroplasty resulted in immediate and long lasting pain relief. PMMA-Vertebroplasty was first indicated for “vertebral-pain management”. It was performed in 1984 by Deramond and Galibert of Paris, France.

Biologically PMMA esters are harmless and stable compound. Its chemical formula is C5H8O2. Physiologically it has low water absorbing properties. PMMA viscous hardens and solidifies within 20 minutes and within an hour of injection in the vertebral body it achieves approximately 90% of the ultimate strength.

PMMA used later for spinal pains due to spinal body- Giant cell and metastatic tumors. In these cases pain relief was remarkably significant. Indications widened thereafter for spinal pains and applied for benign conditions like OVBCF. These were treated with PMMA in the year 1989 at the University of Virginia. Pain was relieved significantly in all these five patients.

Glass acrylate PMMA in viscous form even today is used for percutaneous Vertebroplasty. Viscous- PMMA used as filler. Internally it spreads in the fractured crevices and forms solid cast. It gives vertical stability between the end plates. It prevents further wedging and angular deformation of the OVBCF affected spine.

Earlier, augmentation vertebroplasty was an open surgical procedure. The OVBCF-cavities were filled with very bony particle grafts. C-arm X-ray machine and computerized scanners (CT) were used for imaging purpose. Augmenting the pedicle screws also required PMMA. Later on for decades it was performed under C arm and computerized.

Complications were mainly technical and related to imaging, visualization and volume of injection. Large volume PMMA (more than 3 ML) injected often would exude out of the fractured crevices in to the neural tissues.

Small volume of PMMA (3 ML) in its viscous form improves the technique. Less than 3 ML viscous is injected percutaneously in the fractured cavity. Percutaneous Vertebroplasty (PVP) performed under digitalized subtraction angiography Cath lab unit is called (Cath lab PVP). It gives multidirectional live fluoroscopic imaging. Cath lab PVP with magnified imaging and increased speed helps reduce PMMA viscous to less than 3 ML volume. The small volume optimally fills the OVBCF cavities in both thoracic and lumbar vertebrae. Cath lab PVP reduces pains significantly. It improves patients’ morbidity, mobility and quality of life. Small volumes of PMMA can be used for multiple level OVBCFs in one sitting.

**Table 1: Pain associated with varied -symptomatology**

<table>
<thead>
<tr>
<th>Consultation first by</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>General physicians</td>
<td>06</td>
</tr>
<tr>
<td>Orthopaedician</td>
<td>07</td>
</tr>
<tr>
<td>Neurosurgeon</td>
<td>06</td>
</tr>
<tr>
<td>Chest physician</td>
<td>03</td>
</tr>
</tbody>
</table>

**Material and Method**

16 females (72.7%) with an average age of 70 years and 6 males (27.3%) with an average age of 77.3 years diagnosed with osteoporotic OVBCF. All twenty two patients had spinal segmental immobility related to the spinal pain due to OVBCF. X ray, MRI and demographic images of the OVBCF- Lumbar spine performed. It showed osteoporotic acute OVBCF. (Figure 1: 1st lumbar vertebra with wedge fracture).

Patients presented with varied presentations such as severe back pain, radiculomyelopathy or pneumonic discomfort. Diagnostic limitations were limited to absence of bone densitometry in defining osteoporosis. Biopsy studies and “Spinal Pain Score-Index” were not considered.

The varied symptomatology led to 1st consultation with physician (27.2%), Orthopaedician (27.2%), neurosurgeon (31.8%) and chest physician (13%). Lower thoracic spine OVBCF were 81.8% and 18.2% OVBCF were in the lumbar spinal vertebrae (Table 1).

Augmentation procedure for OVBCF cavities using digital subtraction angiography unit called “Cath lab PVP” was performed. Cath lab PVP performed in the single plane Cath lab unit. Complete sterilization standards maintained. Cath lab PVP performed in all the 22 elderly patients. There were 16 females (72.7%) and 6 male patients (27.3%). All cases treated with small volume Cath lab PVP. Old patients are commonly on antiplatelet and anticoagulant therapy. Pre operatively these medicines are omitted. The ‘Written Consent’ taken for potential procedural risk.

**Nonionic contrast solution** (Ultravist: 370 mg Iodine/ml –Bayer; Germany or Omnipaque) 1½ cc to 4
is being introduced, tracking of the in all these cases. While trocar tip
mixture is prepared after placement of barium sulfate in 30% weight/volume
viscous PMMA. PMMA mixed with crevices filled with small volume
barium sulfate used. The fractured cavity bilateral and multi angle - Intra
PMMA viscous spread into epi-dural spaces can cause radiculo myelopathy and paraplegia.

Fig. 2: Step 1: intra cavity venography

Table 2: Benefits restored with 'small volume' Cath Lab-PVP against conservative treatment

<table>
<thead>
<tr>
<th>Functions</th>
<th>Conservative management</th>
<th>Cath lab PVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Maintain vertical body</td>
<td>Weakness ++ and Increases further</td>
<td>Fully maintains</td>
</tr>
<tr>
<td>2. Giving normal physiological motion</td>
<td>Disability ++</td>
<td>Improves mobility</td>
</tr>
<tr>
<td>3. Protecting neuronal structures</td>
<td>Not possible</td>
<td>Protects fully</td>
</tr>
</tbody>
</table>

Table 3B: Comparative results against small volume Cath lab PVP

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Pain relief</th>
<th>Reduction in analgesics</th>
<th>Increased mobility</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporotic</td>
<td>More than 85%</td>
<td>Within 24 to 48 hours</td>
<td>Within 24 hours</td>
<td>Nil</td>
</tr>
</tbody>
</table>

cc used for intra cavity venography. The contrast needs to be injected in to the fractured vertebral body. PMMA mixed with barium sulfate forms the radiographic viscous.

The filler solution poly methyl methacrylate (PMMA) mixed with barium sulfate used. The fractured crevices filled with small volume viscous PMMA. PMMA mixed with Barium sulfate in 30% weight/volume mixture is prepared after placement of the needle tip in the fractured cavity. Three 2 ML or 5ML syringes used for injecting the viscous in to the fractured body.

11-gauge trocar and cannula system is used for percutaneous vertebroplasty.

Local anesthetic injected deep into percutaneously from the local site. The entire needle tract and periosteum of the involved bone is injected with the local anesthetic 2% Xylocaine solution.

Intra cavity venography performed in all these cases. While trocar tip is being introduced, tracking of the needle tip is monitored appropriately. It is confirmed in both anteroposterior and lateral projections. Approximately 5-8ML of contrast (Ultravist) used for venography. Contrast venography (Figure 2) shows venous routes through intracavity contrast imaging. Its’ extravasation in the epidural, paravertebral and epi-pleural spaces shows the fractured body anatomy. Embolization of fluid-cement in to paravertebral veins could cause pulmonary embolization. Large volume PMMA viscous spread into epi-dural spaces can cause radiculo myelopathy and paraplegia.

Step 2: Uni-pedicular single injection of 3 cc PMMA (+ Barium Sulphate 30% weight/volume):

Filling and its distribution across the midline monitored on lateral and posterio-anterior views

Using small amount of viscous PMMA and monitoring its dorsal vertical and contralateral spread are two important steps. High-resolution, fluoroscopic real-time visualization helps monitor its spread. Its restricted just before it reaches the dorsum of the fractured body. The lateral projection monitored constantly to prevent leaks into the epidural space. PMMA-viscous filled in the central part between superior and inferior endplates of the fractured vertebra. Real time imaging effectively monitors the contralateral, vertical and dorsal spread of PMMA-viscous. Visualization of the viscous PMMA cast with increasing speed achieved in 180 degrees. As a result optimizing the volume to less than 3ML achieved in all cases.

Cath Lab with its high resolution live fluoroscopy imaging increases speed and accuracy of the procedure. Intra-cavity distribution of small volume PMMA, spread across the midline, vertical spread between the cortical plates (Figure 2). Intra-dural leaks if any; visualized very early during live fluoroscopy.

Step 3: post procedure: Patients are given supine position. Cath lab PVP performed using small volume PMMA resulted in immediate significant pain. They were generally refrained from sitting for 6 hours. Trocar needle site local pains and tenderness at the puncture site treated with analgesics and antibiotic for 2-3 days.

Results

1st Lumbar OVBCF using small volume was a short statured obese female (height 58” and weighing: 64 kg,) with hypertension and diabetes mellitus. Intra cavity small volume PMMA relieved pains effectively. It maintained the vertical height and thereby prevented further wedge collapse as seen in the follow-up.

The T7 cases the delay was varied. Patient with T- 7 spine had mobility problem due to additional canal stenosis. However her acute VBCF-pains got relieved by almost 85%. No complications related to PMMA noted.

The earliest PVP done was within 1-4 days; and extreme delay was 30 days. The T8-T12 segment was affected in 12 cases. Three cases had VBCF involving the upper lumbar L1-L3 segment. In seven female patients, VBCF was seen in the T7 vertebral body (31.81%).

Five patients had almost 85% pain relief and required no analgesics, early mobility reported within 12 hours. The remaining 12 patients had significant 85% pain relief within 24 hours. Four patients’ radicular pains diminished completely within 48hours. (Table 3A) One patient (L1 spine-pvp) had temporary paraesthesia in both lower limbs following contrast venography. Three days later Cath lab PVP performed. She received significant pain relief. Significant pain relief, safety and mobility observed with small volume Cath lab PVP in our series (Table 3B).

All these patients experienced improvement after Cath lab PVP. They could walk and were discharged in satisfactory condition. Patient experienced relief from pre-operative type pains. Patients were discharged after two days; only two other patients (9%) were discharged after 3 days.

Technical complications like CSF leak; PMMA- exudation were avoided. Clinical follow-up showed no symptoms and signs of spinal pains, radiculopathy or compression syndrome. Three basic functions restored with acrylate PVP, 1) maintaining the vertical height, 2)
of OVBCFs. OVBCF of the L3 body and recurrence up period of 4 to 5 years. She had Recurrence of OVBCF was seen in one for 2 years. OVBCF left untreated:

Pain management of OVBCF-pain. Small volume PMMA cast (Table 4). There were no pain, no recurrence at any other sites. In all these cases pain relief was satisfactory with minimal volume PMMA cast (Table 4). There were no local complications at the injection sites of trocar needle of Cath lab PVP.

Complications not seen in thoracic as well as lumbar OVBCF treated with Cath lab PVP. Patients clinically followed on three monthly intervals for 2 years. OVBCF left untreated: Recurrence of OVBCF was seen in one untreated female patient during follow up period of 4 to 5 years. She had OVBCF of the L3 body and recurrence of OVBCFs.

**Discussion**

**SPINAL PAINS - Diagnostic difficulties:** One patient with Cath lab PVP had a pre-procedural delay of 30 days. In our series, because of the varied presentations; 40.92 % OVBCF patients were first seen by general physicians or pulmonologist. 31.81% by orthopedic surgeons and 27.27% by neurosurgeons on their first consultations. Patients suffer from spinal pains for a long time. Delay may results in reduction of height between the cortical plates of the OVBCF.

**Osteoporotic vertebra affected:** Spinal pain segment from T8 to T12 was maximally affected (54.54%); and lumbar segment from L1 to L3 was affected with pains 13.63% due to OBCVF. The osteoporotic T1 to T6 - vertebral segment was not seen affected with OVBCF.

Intra cavity viscous optimization and spread is the key to maximum safety: Intraosseous venography gives anatomical features and venous-flow dynamics in the fractured body. It gives clinico-radiological understanding. Venography feedback helps for a) re-positioning the trocar needle tip in the fractured body to avoid embolization of the OVBCF and if required b) monitoring viscosity of the PMMA. Increased PMMA viscosity and its usage in small volume prevent extra corporal embolization. Acute OVBCF bleeds and bleeding results in pleural and dural irritation. Possible mechanism of pain relief: PMMA probably restores structural properties of the bone. It helps absorb hydrostatic pressures, compressive stresses imposed on to it. The exact mechanism for relief of spinal pains could be related to the mechanical stability. PMMA also has thermogenic and chemical effects on the vertebral pain receptors. Solid cast PMMA internally prevents wedging and thereby angular deformation of the spine.

**Conclusion**

Cath lab-PVP increases safety. Significant (85%) pain relief, achieved within 24 to 48 hours in eighteen (81.81%) patients.

Mobilization is early and without analgesics. The long standing internal stability is seen in all patients.

Cath lab PVP with less procedural time has better psychological impact on the minds of old aged people than that of the surgical or medicinal management.

Small volume PMMA - Cath lab PVP; very scientifically standardizes management of OVBCF-pain.

**References**


**Table 4:** Cath lab-Vertebroplasty of thoracic and Lumbar OVBCF

<table>
<thead>
<tr>
<th>Cath lab PVP</th>
<th>Thoracic Cath lab PVP</th>
<th>Lumbar Cath lab PVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PMMA</td>
<td>Small volume cord compression - Nil</td>
<td>Intra dural leakage - Nil</td>
</tr>
<tr>
<td>2. Needle complication</td>
<td>a) CSF- leak</td>
<td>CSF- leak - Nil</td>
</tr>
<tr>
<td>3. Venography</td>
<td>Pulmonary embolism - Nil</td>
<td>Pulmonary embolism - Nil</td>
</tr>
<tr>
<td>4. Paresthesia / bleeding</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

A & B Lumbar - L3; haemangione; grade-2 A & B: Same patient with Multiple VBCF and lumbar haemangioma - L1 dense VBCF L3 giving normal physiological motion to the body and 3) protecting neuronal structures within the canal (Table 2). Cath lab PVP required minimal time and therefore low dose local anesthesia. They were no pain, no recurrence at any other sites. In all these cases pain relief was satisfactory with minimal volume PMMA cast (Table 4). There were no local complications at the injection sites of trocar needle of Cath lab PVP.

Complications not seen in thoracic as well as lumbar OVBCF treated with Cath lab PVP. Patients clinically followed on three monthly intervals for 2 years. OVBCF left untreated: Recurrence of OVBCF was seen in one untreated female patient during follow up period of 4 to 5 years. She had OVBCF of the L3 body and recurrence of OVBCFs.

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Small volume PMMA - Cath lab PVP; very scientifically standardizes management of OVBCF-pain.
Outcome in Survivors of Middle Cerebral Artery Territory Ischemic Stroke: Can it be Predicted?

Seema Kini1*, Faisal Memon2, Dileep Asgaonkar3

Abstract

Background: Stroke is the fourth leading cause of disability worldwide. The present study was designed to assess functional disability in middle cerebral artery (MCA) territory ischemic stroke patients by applying standard scales for stroke severity, cognitive impairment, disability, dependency and depression. We also wanted to study whether baseline assessment predicts outcome at 1 month.

Methodology: After institutional ethics committee approval, patients were enrolled from the inpatients of the Department of Medicine at Topiwala National Medical College and BYL Nair Charitable Hospital, Mumbai from July 2014 to December 2015. Various clinical parameters were recorded on admission. On day 5 (±1) the National Institutes of health Stroke Scale (NIHSS), Mini Mental state examination (MMSE) were administered. On 1 month follow up, these were repeated along with Modified Rankin scale, Barthel’s index (BI) and Hospital Anxiety and Depression Scale (HADS). Presence of certain risk factors for stroke were reviewed at 1 month.

Results: 75 patients were enrolled. There was a delay in reaching the hospital and therefore imaging, in a greater majority. Only 4% could be imaged within the first 3 hours. Mean NIHSS score at day-5 was 9 and at day-30 was 6. Thus it had significantly reduced over 1 month. The MMSE remain unchanged at day 5 and at day 30. Lower baseline MMSE scores correlated with poorer outcomes on NIHSS, BI and mRS at 1 month. Both BI and mRS at 1 month indicated that about 60% of the cases had poor outcome. Amongst 48 of the non-aphasic MCA strokes, 11(22.92%) had depression. An NIHSS score of 6 or above on day 5, predicted poor outcome at 1 month. Presence of aphasia, dominant lobe affection and female sex were associated with a higher disability at 1 month. Around 30% cases had at least 1 risk factor uncontrolled at 1 month follow-up.

Conclusions: Our findings show that disability assessment late in the first week after onset of stroke using NIHSS accurately forecast outcome at one month after onset of stroke. The MMSE too is not expected to change at 1 month. Those with aphasia are expected to have greater disability. Based on or study we recommend that stroke patients should be assessed with NIHSS and MMSE before discharge, to explain the prognosis of the patient. Also more intense counselling on controlling blood pressure and diabetes as well as abstinence from smoking should be undertaken routinely.

Introduction

Stroke is the second commonest cause of death and fourth leading cause of disability worldwide.1 Dalal et al reported a prevalence of 90-222 per 100,000 in the Indian population.2 Indian Council of Medical Research estimates in 2004 indicated that stroke contributed 41% of deaths and 72% of disability adjusted life years amongst the non-communicable diseases in India.3 India may face a significant socioeconomic burden to meet the costs of managing stroke as life expectancy is projected to increase.4

In the last few decades, progressive reduction in stroke mortality has been observed, with subsequent increase of survivors, with residual impairments and disabilities. So there has been a growing interest in the factors that could interfere with functional outcome and quality of life.5,6 Around 80% of all strokes are ischaemic in nature; of these a majority are of middle cerebral artery (MCA) territory.4,7,8 The present study was designed to assess functional disability in middle cerebral artery (MCA) territory ischemic stroke patients by evaluating cognitive impairment, depression, disability and dependency, after stroke, using standard scales. Moreover, we have also evaluated risk factors of stroke in these patients and whether these risk factors are under control at one month follow up in stroke patients. We wanted to see whether the assessment in the first week after stroke, would predict the prognosis (cognition, functional disability, dependency and presence of depression) at one month follow-up.

Methodology

Study design

We designed a prospective observational hospital based study at Topiwala National Medical College and BYL Nair Charitable Hospital, Mumbai from July 2014 till December 2015. We decided to conduct this study on patients admitted in inpatient wards and following up in the Medicine OPD of Tertiary care teaching public hospital. The study commenced after getting approval from the Institutional Ethics committee. The study was done as per ICMR Schedule Y Guidelines for conduct of Human Research in India. After written informed consent, a designed proforma was used for data collection. A detailed clinical history of

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1 Associate Professor, 2 Professor and Head, Department of Medicine, Topiwala National Medical College and BYL Nair Charitable Hospital, Mumbai; 3 Corresponding Author
Received: 07.12.2016; Accepted: 30.12.2018
Table 1: Baseline characteristics of patients enrolled in the study and at 1 month FU

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>At baseline</th>
<th>At 1 month FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Age (mean±SD) years</td>
<td>60.92±11.14</td>
<td></td>
</tr>
<tr>
<td>Males; Females</td>
<td>32; 43</td>
<td></td>
</tr>
<tr>
<td>Previous medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetics at the time of enrollment; duration below:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 1 year</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>1-5 years</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>5-10 years</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>More than 10 years</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Hypertension at the time of enrollment; duration below:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 1 year</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>1-5 years</td>
<td>12</td>
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</tr>
<tr>
<td>5-10 years</td>
<td>9</td>
<td></td>
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<tr>
<td>More than 10 years</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Hypertension with Diabetes mellitus at enrollment</td>
<td>28</td>
<td>2 continued</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>H/o Transient ischemic attack</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Personal history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers at the time of enrollment</td>
<td>10</td>
<td>2 continued</td>
</tr>
<tr>
<td>Alcoholics at the time of enrollment</td>
<td>12</td>
<td>3 continued</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol (mg%)</td>
<td>175.14±41.62</td>
<td>Not reassessed</td>
</tr>
<tr>
<td>Serum triglycerides (mg%)</td>
<td>133.28±57.19</td>
<td>Not reassessed</td>
</tr>
<tr>
<td>ECG findings</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>2-dimensional echocardiography abnormal</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Brain imaging (MRI/CT showing infarct)</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>75</td>
<td>21 stopped</td>
</tr>
</tbody>
</table>

Patients and a clinical examination was performed.

Table 2: Functional assessment in stroke patients included in the study

<table>
<thead>
<tr>
<th>National Institutes of Health Stroke Scale (n=75)</th>
<th>Median score</th>
<th>Range of score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 5 (a1)</td>
<td>9</td>
<td>1-17</td>
</tr>
<tr>
<td>Day 30</td>
<td>6</td>
<td>1-15</td>
</tr>
<tr>
<td>Mini Mental Status examination (n=48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5 (a1)</td>
<td>24</td>
<td>2-28</td>
</tr>
<tr>
<td>Day 30</td>
<td>24</td>
<td>2-28</td>
</tr>
</tbody>
</table>

thrombolysed. Patients were followed up after 1 month of presentation, during which assessments were done with following scales: NIHSS, MMSE, Modified Rankin Scale (Refer Annexure 3), Barthel Index (BI) (Refer Annexure 4), Hospital Anxiety and Depression Scale (HADS) (Refer Annexure 5). The control of risk factors such as hypertension, diabetes (by haemoglucotest), and abstinence from smoking and alcohol and compliance with physiotherapy were noted at the month 1 follow up. The lipid profile was not repeated.

**Selection of cases**

We included all patients who presented with stroke, with neuro-imaging suggestive of MCA territory infarct. We also included patients with normal computed tomography (CT) brain, but clinically consistent with MCA ischemic stroke. We excluded patients with present transient ischemic attack (TIA), those who lost to follow-up or those who expired during the first month after onset of stroke, those with major neurologic deterioration. Patients with present transient ischemic attack (TIA), those who lost to follow-up or those who expired during the first month after onset of stroke, those with head trauma, intracranial neoplasms, additional neurological disorders, those unwilling for consent or follow up, cardio embolic, vasculitic, tubercular stroke, those with history of past stroke, any young stroke (prior to the age forty-five years) and subarachnoid haemorrhage.

**Data collection and analysis**

National Institute of Health Stroke Scale (NIHSS), a standardized measure of neurological function was used to assess outcome and recovery of patients with acute ischemic stroke receiving conventional therapy. We used this scale to assess outcome. An increase or decrease in the stroke score by 4 or more points is a marker for clinically important change. Barthel Index (BI), that measured independence and Modified Rankin Scale (mRS), that measured disability, was also used to assess outcome with poor outcome defined as mRS >3 and BI <60. Using HADS, patients were diagnosed to have depression if the score is 8/21 or more. Association between qualitative variables was assessed by Chi- Square test and Fisher’s exact test. Correlation between dichotomous variables and scores was analysed by Point- Biserial Correlation Coefficient. Analysis of quantitative data was done using Wilcoxon Signed Rank test. Predictiveness of factors at 1st week for outcome at 1-month follow-up was assessed using linear regression analysis. SPSS Version 17 was used for analysis.

**Results**

During the study period, 75 patients of MCA infarcts were included in the final analysis. The mean duration between the onset of stroke symptoms and the diagnosis of infarct on imaging was 28±33.2 hours. Only 20 of 75 (26.67%) completed neuro-imaging within 6 hours. Only 3(4%) of these did so within the first 3 hours. However none of these could afford thrombolysis. Refer to Table 1, for the baseline characteristics of our study subjects. Most common age group of the patients was 50-60 years. Of the 43 females, 40 were postmenopausal. On examination, raised blood pressure was noted in 43 patients. Cranial nerve involvement was seen in 67 patients and aphasia was seen in 27 patients. Out of 73 patients 9 had mildly elevated creatinine. Deranged sugars were found in 24. Other relevant clinical information has been tabulated in Table 1.

The median range of the NIHSS score (range 0-42) in 75 patients at Day 5 was 9 (1-17) and at Day 30 was 6 (1-15) (Table 2). Using Wilcoxon matched pair signed ranked test, indicated that the NIHSS score at Day 30 was significantly lower than at Day 5 (p<0.0001). The NIHSS score showed major neurologic improvement in 2 (2.67%) patients while no patients were reported with major neurologic deterioration.

MMSE score was assessed in only 48(64%) of the 75 patients enrolled. It could not be assessed in 27 patients as they had aphasia. The median range of the MMSE score in 48 patients at Day 5 was 24 (2-28) and at Day 30 was 24 (2-28). Using Wilcoxon matched pair signed ranked test, it was indicated that there was no significant difference
in the MMSE score at Day 5 and Day 30 (p<0.0547). The MMSE of day 5, had a significant positive correlation between and the BI at 1 month and a significant negative correlation with NIHSS scores and mRS at 1 month.

The median modified Rankin Scale (mRS) score was 4 (range: 0 to 5). Of 75 patients, 43 (57.33%) had the mRS score of >3, indicating poor outcome.

The median Barthel Index (BI) was 35 (range: 15 to 100) in 75 patients. 45 (60%) of the patients had the BI<60, indicating poor outcome.

Out of the 75 patients, depression was assessed in 48 patients, while 27 patients could not be assessed due to aphasia. Out of 48 patients, only 11 (22.92%) patients had depression.

There was a significant high positive correlation between baseline NIHSS score and mRS score at 1 month (p<0.0001) and a significant high negative correlation between baseline NIHSS score and BI at 1 month (p<0.0001). Analysis of receiver operating characteristic curves using NIHSS score at day 5 after admission showed that the cut-off point of the 5th-day NIHSS score for predicting a poor outcome at 1 month after symptom onset was between 6 and 7, with a sensitivity of 95.2% and a specificity of 91%.

In our study we found statistically significant association of aphasia, cranial nerve involvement and depression, with NIHSS scores greater than 6. However, we found no statistical

Table 3: Association of National Institutes of Health Stroke Scale (NIHSS) at day 5 and variates

<table>
<thead>
<tr>
<th>NIHSS ≤ 6</th>
<th>NIHSS &gt;6</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Absent</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>24</td>
<td>34</td>
</tr>
<tr>
<td>Absent</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Aphasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>Absent</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>Absent</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Absent</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>CT Head</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 4: Point-biserial correlation of certain dichotomous variables and various scores

<table>
<thead>
<tr>
<th>Binary variables (n)</th>
<th>NIHSS-baseline</th>
<th>NIHSS-1 month</th>
<th>mRS-1 month</th>
<th>BI-1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rpb p value</td>
<td>rpb p value</td>
<td>rpb p value</td>
<td>rpb p value</td>
</tr>
<tr>
<td>Female (43)</td>
<td>-0.21 0.074</td>
<td>-0.26 0.024</td>
<td>-0.28 0.014</td>
<td>(+)0.24 0.035</td>
</tr>
<tr>
<td>Male (32)</td>
<td>Female strokes were associated mildly with higher NIHSS, higher mRS and lower BI at 1 month.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant (45)</td>
<td>-0.42 &lt;0.0001</td>
<td>-0.48 &lt;0.0001</td>
<td>-0.32 0.005</td>
<td>(+)0.32 0.005</td>
</tr>
<tr>
<td>Non-dominant (30)</td>
<td>The affection of the dominant lobe was moderately associates with higher NIHSS scores at baseline and 1 month, and higher mRS and lower BI at 1 month.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aphasic</td>
<td>-0.76 &lt;0.0001</td>
<td>-0.81 &lt;0.0001</td>
<td>-0.58 &lt;0.0001</td>
<td>(+)0.36 0.001</td>
</tr>
<tr>
<td>Non-aphasic</td>
<td>The presence of Aphasia is strongly associated with higher NIHSS scores both at baseline and 1 month; moderately with higher mRS, mildly with lower BI at 1mt.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT abnormal (67)</td>
<td>-0.02 0.85 0</td>
<td>0.976 0.05 0.69</td>
<td>-0.05 0.661</td>
<td></td>
</tr>
<tr>
<td>CT normal (8)</td>
<td>There is no significant relation between CT being normal or abnormal, with NIHSS scores, mRS and BI.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors not controlled at 1 month</td>
<td>- - 0.01 0.952 -0.01 0.921 -0.02 0.881</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled at 1 month</td>
<td>There is no significant relation between risk factors being controlled or not, with NIHSS scores, mRS and BI.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT discontinued</td>
<td>- - -0.02 0.881 0.07 0.55</td>
<td>-0.04 0.742</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT continued</td>
<td>There is no significant relation between physiotherapy being continued or not, with NIHSS scores, mRS and BI.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Association of Aphasic patients with Higher NIHSS on Day 5, Day 30 and mRS

Association of Aphasic patients with Lower BI on Day 30

Fig. 1: Point biserial correlation: aphasia and scores

Fig. 1: Point biserial correlation: aphasia and scores

We also found by Biserial correlation, that those with aphasia, dominant lobe affection or female sex had higher stroke severity and functional disability; Aphasia having the strongest association (Table 4) (Figure 1).

On discharge, 21 out of 75(28%) discontinued physiotherapy (PT) on
discharge. At 1 month, 23 of 75 (30.67%) cases had at least a single risk factor for stroke that was not under control. They were: uncontrolled hypertension (7), uncontrolled diabetes (15), continuation of smoking (2) and alcohol intake (3) (Table 1).

**Discussion**

The main purpose of this study was to prognosticate patients with an ischaemic stroke so that the close relatives may be counselled.

**Reason for selection of MCA ischaemic stroke**

A greater majority of strokes consist of MCA territory ischaemic infarcts. Other categories such as intra-cranial bleed, posterior circulation strokes, lacunar infarcts, etc. have a different clinical course and recovery. Hence to maintain a certain uniformity, we chose to study MCA territory infarcts.

**Reasons for baseline assessment on day 5±1**

Major patho-physiologic changes are known to occur in the initial few days after a stroke. Some may cause worsening such as cerebral oedema, herniation, seizures, electrolyte imbalance, progression of the clot, accelerated hypertension, deranged sugars, etc. Some that may cause improvement are fragmentation of clot, distal movement of embolus, spontaneous recanalisation and reperfusion, collateral supply, reduction of cerebral edema by mannitol, early thrombolysis, etc. These changes tend to stabilise within 4–5 days. In a majority of cases, this timing was usually just before discharge from the hospital. This would be the best time the explain the prognosis to the patient and family. The study by Bang O, et al., discussed below also supported our decision.

**Various scales used**

1. **NIHSS** is a tool used to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient’s total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

2. The MMSE or Folstein test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. Higher scores indicate better cognition.

3. **mRS** is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people. The scale runs from 0–6, running from perfect health without symptoms to death.

4. **BI** is an ordinal scale used to measure performance in activities of daily living (ADL). It uses ten variables describing ADL and mobility (maximum score 100). Higher the score, greater is the independence.

5. **HADS** This is a questionnaire with 7 questions (maximum 3 points each) that can screen for depression. A score of 8 or above out 21 indicates presence of depression.

**Our findings compared to other studies**

Dalal, et al., in a population-based study of all kinds of stroke, in a Mumbai ward, found mild disability in 43.33% and moderate to severe disability in 56.77% of 310 stroke survivors at day 28. Our figures for the same were 33.33% and 66.66% of 75 respectively. This difference may be due to the heterogeneity of the stroke types included by Dalal, whereas we included only MCA territory infarcts. Both studies used mRS for this outcome.

**Prediction of outcome of stroke**

Bang O, et al (Korea) conducted a similar study on MCA infarcts, not thrombolysed, however excluded lacunar infarcts and followed up to 6 months. The NIHSS, BI and mRS were checked serially in these 437 patients at 0, 1, 3, 7 and 14 days after admission. Poor outcome was defined as any of these end-points: death, mRS>3 or BI<60. They found that the 7th day NIHSS score, age and diffusion-weighted imaging lesion volume and past stroke were independently associated with poor outcome. An NIHSS score of 6 or more on day 7 of admission, predicted a poor outcome at 6 months after symptom onset. None of the other scores done along with NIHSS could improve this prediction. Our study analysed a cut-off score of NIHSS score on day 5 of at least between 6 and 7, to predict a poor outcome at 1 month. In our study NIHSS Score at 5±1 day after onset of stroke was a good predictor of outcome as it significantly correlated with mRS score and BI at 1 month after onset of stroke.

We found that higher the cognitive impairment, worse is the functional disability lower independence and stroke severity at one month, consistent with the study by Tatemichi, et al. Also the cognitive impairment on day 5 and 1 month did not change significantly. Thus it would be expected that the cognitive level at 1 month would be similar to that around day 5.

**Picking up associated depression, a treatable co-morbidity**

In a North Indian hospital based study by Raju, et al., all categories of stroke were assessed at varying durations greater than a month (1–180 months) post-stroke. In addition to NIHSS, mRS and HADS, they used Functional Independence Measure. Depression was found in 60 of 162 (37%) of strokes after excluding those with aphasias. They found that presence of anxiety, depression and functional dependence were associated with impaired quality of life. Our study found depression in 11 (22.92%) of the 48 MCA ischaemic strokes without aphasia, at 1 month post-stroke. Perhaps one should be vigilant to detect depression in more number of strokes as the duration of follow-up increases, as in the above study. Treating this co-morbidity would improve the quality of life.

Though we excluded aphasia, for detection of depression, a greater attempt needs to be made in this subset to diagnose this co-morbidity. The simple 10-question Montgomery-Åsberg Depression Rating Scale (MADRS) may be feasible in at least two third of aphasic strokes in the acute phase and over a period of 6 months post-stroke the feasibility increases to 100%, as per the study by Laska, et al. They could diagnose depression in 24% of 87 cases of stroke over the period of 6 months.
Challenges faced while managing stroke

Delayed presentation: What if they could be thrombolyzed?

Our study showed that patients who presented late, so were imaged late and received delayed treatment, were not more disabled as compared to patients who presented early and received early treatment. This should be interpreted cautiously because we excluded patients who died within one month of stroke onset. Also none of our patients were thrombolysed due to late presentation and non-affordability, thus missing an opportunity for a better outcome. Nandigam K, et al17 have conducted a detailed study on hurdles to thrombolytic therapy in a rural setup; despite being in the urban setup, we face similar hurdles.

In a Cochrane review of 2016,18 a meta-analysis of 27 randomised trials of any thrombolytic agent, compared with control in people with definite ischaemic stroke, was done. They concluded that thrombolytic therapy given up to six hours after stroke, reduces the proportion of dead or dependent people (mRS: 3-6). Those treated within the first three hours derive substantially more benefit than with later treatment. This overall benefit was apparent despite an increase in symptomatic intracranial haemorrhage, deaths at seven to 10 days, and deaths at final follow-up (except for trials testing rt-PA, which had no effect on death at final follow-up). Thus after missing the window of opportunity to administer thrombolyis, the delay in diagnosis of ischaemic stroke and hence in any form of treatment, does not affect the outcome at 1 month.

Risk factors still present at 1 month

Though only partly studied, we found a gap between recommended secondary preventive measures and their implementation in subjects. Nearly a third of the cases had at least a single risk factor for atherosclerosis. This calls for more intense counselling of stroke patients before they are discharged from the hospital. Li C, et al19 did a population based, 7.5 year follow-up study of life-style risk factors in cases of stroke. Compared to subjects without a history of stroke, the risk of cardiovascular event or recurrent stroke were found significantly higher in stroke survivors. Simple control of hypertension would have prevented a substantial proportion of them.

Limitations of the study

A small sample size, a bias of selecting better outcome strokes, as deaths within the first month were excluded, not analysing depression in aphasics are the limitations of this study. A single observer administering the various scoring scales was an advantage. And so was maintaining uniformity, by assessing only MCA territory ischaemic strokes.

Conclusion

Majority of the patients suffering from stroke present to the hospital late, making imaging not available before 3 hours of onset. This, in addition to financial constraints, makes administration of potentially disability-limiting thrombolysis virtually impossible. Depression is found in about one fifth of non-aphasic strokes. Special efforts need to be taken to detect the same in aphasic strokes. Presence of aphasia, dominant lobe affection and female sex were associated with higher disability. Our study shows that disability assessment late in the first week after onset of stroke using NIHSS successfully forecast outcome at one month after onset of stroke. Cognitive impairment is not expected to change. Hence we recommend assessment of patients with NIHSS and MMSE before discharge from hospital to predict prognosis at follow-up. Online calculators or mobile applications can simplify calculating NIHSS score.20 A more intense counselling on how to prevent a recurrent stroke or cardiovascular event, by controlling risk factors such as hypertension, diabetes and smoking, must be undertaken.

References

A Study on the Association of Psoriasis with Metabolic Disorders

Nikita Jadhav1*, Nitin Nadkarni2, Sharmila Patil3

Abstract

Background: Psoriasis is a chronic inflammatory and hyper-proliferative skin disorder which is chronically relapsing with high morbidity and impaired quality of life, characterized by erythematous scaly patches affecting skin, joints and nails. It is a disorder of immune system involving genetic, immunologic and environmental factors. Metabolic syndrome (also known as metabolic syndrome X) is a grouping of interrelated medical traits that, when present, indicate an increased risk of developing non-insulin-dependent diabetes mellitus and/or cardiovascular disease.

Aims and Objectives: An attempt to find out the association between psoriasis and metabolic disorders by measuring height, weight, body mass index, hip circumference, waist circumference and its ratio, blood pressure and severity of psoriasis patients by PASI (Baseline psoriasis and severity index) score. Further, to investigate each and every patient with complete blood count, fasting and post-prandial blood glucose levels, thyroid profile, lipid profile.

Materials: It is a hospital based case-control study conducted at Department of Dermatology, Venereology and Leprology at Dr. D.Y. Patil Hospital and Research centre, Navi Mumbai for a duration of October 2015 – October 2016 with sample size of 100 patients of Psoriasis along with 100 patients of controls. Informed consent was taken from patients to satisfy the inclusion criteria with patients clinically diagnosed as psoriasis, above 18 years and those who participated in the study not having psoriasis as the controls with no exclusion criteria. An information sheet was given to all the participating patients.

Methods: Ethical committee approval, informed Consent were taken from the patients. Severity of psoriasis by PASI score (Baseline psoriasis and severity index) along with height, weight, waist circumference: hip circumference, body mass index were measured. Investigations carried out in all patients were CBC, FBS, PLBS, Thyroid profile, Lipid profile and results were statistically analyzed at the end of study. RESULTS: Out of 200 patients, The observation was in accordance of psoriasis being associated with metabolic syndrome in 71% cases as compared to 37% controls.

Conclusion: The blood pressure, sr. triglycerides, sr. high density lipids, fasting blood sugar were significant in cases as compared to controls satisfying the criteria of Adult Panel Treatment III (ATP III) of Metabolic Disorders.

Methods

It is a hospital based case-control study conducted at Department of Dermatology, Venereology and Leprology, D.Y. Patil Hospital and Research centre, Navi Mumbai, Maharashtra; *Corresponding Author
Received: 08.12.2016; Accepted: 29.11.2018

Introduction

Psoriasis is a chronic inflammatory and hyper-proliferative skin disorder which is chronically relapsing disease with high morbidity and impaired quality of life. It is characterized by erythematous scaly patches affecting skin, joints and nails. Psoriasis is a disorder of immune system. Genetic, immunologic and environmental factors are implicated in the etio-pathogenesis of psoriasis. The term ‘Psora’ was first used by Galen. Robert Willan in 1809 gave an accurate description of psoriasis and Hebra in 1841 distinguished features of psoriasis and leprosy. Psoriasis is identified as a marker of Metabolic syndrome with multiple co-morbid associations like cardiovascular diseases and Diabetes mellitus.

Metabolic syndrome (also known as metabolic syndrome X) is a grouping of interrelated medical traits that, when present, indicate an increased risk of developing non-insulin-dependent diabetes mellitus and/or cardiovascular disease. Many variations of the concept of metabolic syndrome have existed since the 1950s, and while there are a myriad of definitions that exist today, the most commonly used are the American Heart Association/National Heart, Lung and Blood Institute’s 2005 update of The National Cholesterol Education Program Adult Treatment Panel III (ATP III) definition and the International Diabetes Federation (IDF) criteria. The ATP III identified six components of the metabolic syndrome; abdominal obesity (measured by waist circumference), atherogenic dyslipidemia [demonstrated by high triglycerides and low high-density lipoprotein “good” cholesterol (HDL-C) cholesterol concentrations], elevated blood pressure, insulin resistance, a pro-inflammatory state (commonly manifested as an elevated C-reactive protein), and a pro-thrombotic state (characterized by elevated plasma-plasminogen activator inhibitor and fibrinogen). Many epidemiologic studies with varied designs link psoriasis to systemic metabolic comorbidities such as obesity, hyperlipidemia, cardiovascular disease, and diabetes.
this study. Informed consent was taken from patients who satisfy the inclusion criteria. An information sheet was given to all the participating patients. With inclusion criteria of all patients clinically diagnosed as Psoriasis, those who participated in the study not having psoriasis as the controls and age above 18 years with no exclusion criteria.

Methods

Ethical committee approval was taken. Informed consent from the patients was taken. Severity of psoriasis by PASI score (Baseline psoriasis and severity index) were measured, simultaneously height, weight, waist circumference: hip circumference, body mass index were measured. Few investigations like CBC, FBS, PLBS, thyroid profile, lipid profile were carried out both in cases and control patients and results were statistically analyzed by the end of the study.

Results

The mean age of patients enrolled in study for cases were 41.92 and that of controls 37.95 (p=0.012 ), sex ratio showing preponderance of male in cases being 66% and that of controls being 48%. That of females had shown cases of 34% and that of controls is 52%, together showing ‘p’ value of 0.010. The mean was calculated, it showed 8.71±24.99 in overall 100% of psoriasis patients (p=0.499). Body mass index (kg/m2) in psoriasis patients has shown 26% falling under normal range, 70% are overweight and 4% under obesity and that of controls had shown 32% normal, 64% overweight and 4% obese with overall (p= 0.641).Waist circumference (cm) shows 66 within low range, 1 moderate and 33 high range as compared to controls 48 being low, 7 moderate and 45 high range with overall (p = 0.010). The prevalence was higher in female as compared to male. Average tot. cholesterol and sr. triglycerides in cases were 205.8 mg/dl, sr.trigly-138.3 mg/dl and that in controls were 138.3 mg/dl, 145.0 mg/dl with (P = 0.01 and 0.04), respectively. HDL and LDL levels in cases were 36.78 mg/dl, 138.6 mg/dl and those in controls were 40.5 mg/dl and 142.83 mg/dl with (P = 0.01 and 0.119). Cases showed LDL/HDL – 3.83mg/dl, T. CHOL/HDL – 5.59 mg/dl and that with controls had 3.58 mg/dl and 5.36 mg/dl with (P = 0.011). Fasting blood sugar in cases and controls were 103.9 mg/dL, 95.5 mg/dl while those of PLBS were 125.1 mg/dl and 124.6 mg/dl with (P = 0.01 and 0.864). The observation was in accordance of psoriasis being associated with metabolic syndrome in 71% of cases as compared to 37% controls.

Discussion

The present cross sectional study was conducted in Dr. D.Y. Patil hospital with the purpose of correlating the association of psoriasis with metabolic syndrome. In this study 100 cases of suspected psoriasis patients attending skin OPD over a period of 2 years from October 2015 to October 2016 were enrolled. As shown in Table 1 the mean age of patients enrolled in study for cases were 41.92 and that of controls 37.95 giving a ‘p’ value of 0.012, showing significance over the age. The sex ratio showing preponderance of male in cases being 66% and that of controls being 48%. That of females had shown cases of 34% and that of controls is 52%, together showing ‘p’ value of 0.010. The distribution of cases were not similar to those of controls. It was observed that patients with psoriasis have a higher smoking and alcohol consumption. It is more triggered by drinking, 30-32% population of psoriasis patients showed consumption of alcohol along with smoking and ‘p’ value of <0.01. Kremers et al. noted that patients with psoriasis have a higher of smoking and alcohol consumption.2 Psoriasis is exaggerated by drinking habit.3 The amount of alcohol consumption may be related to higher incidence and severity of psoriasis. There was seasonal variation seen in the patients with psoriasis for winter. The lesions had increased in number after exposure to cold. There was 66% of psoriatic showing seasonal variation as compared to controls and ‘p’ value of <0.001. Stress was one of the predisposing factor which was commonly encountered in patients having psoriasis. In this study, 77% of psoriasis patients had shown exposure to stress with ‘p’ value <0.001. Psoriasis area severity index was measured on basis of erythema, scaling and induration with ‘p’ value 0.499. The parameters considered to prove psoriasis and its associations with metabolic syndrome, we had asked patients to undergo blood investigations like CBC, FBS, PLBS, Lipid Profile, TSH and body measurements such as Weight, Height, BMI, waist : hip ratio were taken to rule out the same. Body mass index (kg/m2) in psoriasis patients has shown 26% falling under normal range, 70% are overweight and 45% under obesity and that of controls had shown 32% falling in normal, 64% are overweight and 4% are obese with overall ‘p’ value 0.641. On comparing the body mass index, psoriatic patients were significantly more obese (14% vs. 1%) (p < 0.05). We found that metabolic syndrome was more common in psoriatic cases than in controls and the differences were statistically highly significant (p=0.005). The findings were in accordance with previous reports.4- 6 The proportion of the psoriatic cases with metabolic syndrome (37%), was much higher in our study when compared with previous studies reported in the Caucasian population. This gross difference is probably due to racial factors and the use of South Asian modified NCEP ATP III (National Cholesterol Education Programme Adult Treatment Panel) criteria.6 Similarly, Waist circumference (cm) was measured showing 66 patients with low range,3 moderate and 33 high as compared to controls showing 48 low,2 moderate and 45 high range with overall ‘p’value of 0.010. Average In cases and controls overall the total Cholesterol and Sr. triglycerides were 205.8 mg/dl, 138.3 mg/dl,214.6 mg/dl and 145.0 mg/dl with ‘p’ value of 0.01 and 0.04 respectively followed by sr.HDL and sr.LDL showed 36.78 mg/dl, 138.6 mg/dl and those in controls were 40.5 mg/dl, 142.83 mg/dl with ‘p’ value of 0.01 and 0.119. Fasting blood sugar were 103.9 mg/dl and 95.5 mg/dl with ‘p’ value of 0.01. The most common feature of the metabolic syndrome among patients with psoriasis was abdominal obesity, followed by hypertriglyceridemia and low levels of HDL cholesterol.7 The prevalence was higher in female as compared to male. The proportion of patients with metabolic syndrome was more in cases over the age of 25 than in controls (18% vs. 0%), which was comparable to Indian studies.8- 10 Reduced HDL levels (58%) was the most common feature of metabolic syndrome, followed by central obesity (45%), hypertension
of age to study the association between psoriasis and metabolic syndrome, and to assess correlation between severity of disease and presence of metabolic syndrome.

The mean (± standard deviation) duration of psoriasis amongst the cases was 7.5 years ± 8.3 years. The duration ranged from 6 months to 40 years. Amongst the cases, 47% of the patients had PASI <10 and 53% of the patients had PASI > 10. Hypertriglyceridemia (59% vs. 31%), (P = 0.01), abdominal obesity (45% vs. 39%) (P > 0.05) and hypertension (39% vs. 34%) (P > 0.05) were more common in cases, whereas diabetes mellitus (23% vs. 29%) (P > 0.05) was more common among the controls. Diabetes mellitus was the only component of metabolic syndrome which was more common among the controls.

This observation was in accordance with the study by Gisondi et al., but it was in contrast with the studies by Madanagobalane and Anandan," Choi et al., and Ahmed et al. The mean age was higher in psoriasis patients with metabolic syndrome than in those without metabolic syndrome, which was comparable to the study by Gisondi et al., and Ahmed et al. However, in contrast to these reports, the cases with metabolic syndrome did not have earlier disease onset. The severity of disease was more in cases with metabolic syndrome than in those without metabolic syndrome, though it was not statistically significant. This was comparable to the study conducted by Choi et al., (97.1% vs 77.2%). However, Nisa and Qazi reported that PASI >10 was more common in patients without metabolic syndrome than in patients with metabolic syndrome (P > 0.05).

Various studies conducted in India and abroad have proved the increased prevalence of metabolic syndrome among psoriatic patients. In this study, the association is not limited to severe disease and is independent of the duration of disease and can present from the late second decade. This emphasizes the need for regular evaluation of psoriatic patients, even younger patients and those with mild disease, for the presence of any of the components of metabolic syndrome. There is a paucity of studies from India on the prevalence of metabolic syndrome in psoriasis patients. Nisa and Qazi reported an increased prevalence of metabolic syndrome in patients with psoriasis (28%) as compared to controls (6%) with an odds ratio of 6.09. The high odds ratio in their study may be attributable to the high psoriasis area and severity index (PASI) scores (mean, 15.2 ± 13.9 and median, 13.05) of their patients, comparable to the scores of the patients with severe psoriasis in the present study (odds ratio of 7.2 for developing metabolic syndrome).

**Table 1: Demographic details of patients presented to OPD**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic details</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>41.92</td>
<td>37.95</td>
<td>.012</td>
</tr>
<tr>
<td>Male</td>
<td>66</td>
<td>48</td>
<td>.010</td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
<td>52</td>
<td>.010</td>
</tr>
<tr>
<td>Alcohol</td>
<td>30</td>
<td>3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>32</td>
<td>4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Seasonal (winter)</td>
<td>66</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Joint pain</td>
<td>27</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Atopy</td>
<td>31</td>
<td>13</td>
<td>.002</td>
</tr>
<tr>
<td>Drugs</td>
<td>3</td>
<td>33</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stress</td>
<td>71</td>
<td>37</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PASI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (&lt;10)</td>
<td>8.71±4.99</td>
<td>0</td>
<td>499</td>
</tr>
<tr>
<td>Moderate (10-14)</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (&gt;14)</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, (kg/m2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal &lt;25</td>
<td>26</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Overweight 25-30</td>
<td>70</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Obese &gt;30</td>
<td>4</td>
<td>4</td>
<td>.641</td>
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<tr>
<td>Waist circumference (cm)</td>
<td></td>
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</tr>
<tr>
<td>Low</td>
<td>66</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Mod</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>33</td>
<td>45</td>
<td>.010</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>126.18</td>
<td>119.71</td>
<td>.010</td>
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<tr>
<td>DBP (mm Hg)</td>
<td>81.18</td>
<td>77.42</td>
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</tr>
<tr>
<td>S. triglycerides (mg/dL)</td>
<td>138.32</td>
<td>145.07</td>
<td>.046</td>
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<tr>
<td>Serum HDL (mg/dL)</td>
<td>36.78</td>
<td>40.50</td>
<td>.010</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>103.98</td>
<td>95.51</td>
<td>.011</td>
</tr>
</tbody>
</table>

References

Clinical Profile of Amitraz Poisoning

Shubhangi Dhadke¹, Vijayalaxmi Kantte², Vithal Dhadke³, Manish Dhadke⁴

Abstract

Aims of the study: To study clinical presentation, complications and response to supportive management of Amitraz poisoning

Methods and Material: Fifty cases of acute Amitraz poisoning were studied in detail and compared with previous data from literature.

Results: All the fifty cases were brought to Dr. V.M. Govt. Medical college, among them thirty one cases were males and nineteen were females, with their age ranging from 14 years to 62 years. Mode of intoxication was oral route. Twenty cases were farmers. Two cases had accidental poisoning. The ingested amount was ranging from 10ml to 80 ml. Vomiting and nausea were the prominent symptoms, next were dizziness, lethargy, respiratory distress and pain abdomen. Hyperglycemia, glycosuria, were commonest manifestations. Three cases were treated with mechanical ventilation. All the cases responded to supportive treatment and recovered completely.

Conclusion: Vomiting and nausea were the commonest symptoms. Hyperglycemia and glycosuria was commonest sign. There was good response to supportive treatment. There was no complication and no mortality.

Introduction

The term poison first appeared in the English literature around in the year of 1230 A.D. to describe a potion or draught that was prepared with deadly ingredients.¹ The commonest agents of poisoning in India appear to be pesticides, sedatives, chemicals, alcohol, plant toxins, household poison.² Among such compounds, our interest is to study about Amitraz poisoning.

Amitraz, an insecticide and veterinary medicine.³ Extensive search of literature revealed that only a few cases have been reported on poisoning with this insecticide in South East Asia.⁴ Most of the commercial preparation of Amitraz contains 12.5-20% of the drug in organic solvents, especially xylene, which is a component of paints, cleaners and glue.⁵

It was first synthesized in England in 1969.⁶ The toxic effects of Amitraz are due to its -adrenergic agonist actions in the central nervous system and both α1 and α 2 adrenergic receptor stimulation in the periphery.⁷ It also inhibits monoamine oxidase (MAO) enzyme activity⁸ and prostaglandin E2 synthesis.⁹ Toxic effects include numerous signs and symptoms varying from vomiting, nausea, dizziness, and lethargy, and respiratory distress, pain in abdomen, miosis, bradycardia, tachycardia, hypotension, hyperthermia, hyperglycemia, glycosuria, polyuria and respiratory alkalosis.

Aims and Objectives

To study clinical presentation, complications and response to supportive management of Amitraz poisoning

Subjects and Methods

<table>
<thead>
<tr>
<th>Table 1: Sex wise distribution of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Percent of patients (%)</td>
</tr>
</tbody>
</table>

¹Associate Professor, ²Assistant Professor, ³Professor, ⁴Intern, Dr. V.M. Govt. Medical College, Solapur, Maharashtra

Received: 11.02.2018; Revised: 14.08.2018; Accepted: 14.08.2018
Table 2: Age wise distribution of cases

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of patients</th>
<th>Percentage (%)</th>
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</thead>
<tbody>
<tr>
<td>14-20</td>
<td>07</td>
<td>14</td>
</tr>
<tr>
<td>21-30</td>
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<td>40</td>
</tr>
<tr>
<td>31-40</td>
<td>06</td>
<td>12</td>
</tr>
<tr>
<td>41-50</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>51-60</td>
<td>04</td>
<td>08</td>
</tr>
<tr>
<td>61 and above</td>
<td>03</td>
<td>06</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100</td>
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Table 3: Occupation wise distribution of cases

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Farmers</th>
<th>Labours</th>
<th>Housewives</th>
<th>Students</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>20</td>
<td>10</td>
<td>13</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>Percent of patients (%)</td>
<td>40</td>
<td>20</td>
<td>26</td>
<td>14</td>
<td>100</td>
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Table 4: Intention of poisoning

<table>
<thead>
<tr>
<th>Intention of poisoning</th>
<th>Suicidal</th>
<th>Accidental</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>48</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Percent of patients (%)</td>
<td>96</td>
<td>04</td>
<td>100</td>
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Table 7: Effect of amitraz poison on blood pressure

<table>
<thead>
<tr>
<th>Blood pressure (mm of hg)</th>
<th>Normal</th>
<th>Hypotension</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>44</td>
<td>06</td>
<td>50</td>
</tr>
<tr>
<td>Percent of patients (%)</td>
<td>88</td>
<td>12</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 8: Effect of amitraz on body temperature

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Normal</th>
<th>Hypothermia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>42</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>Percent of patients (%)</td>
<td>84</td>
<td>16</td>
<td>100</td>
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</table>

Table 9: Effect of amitraz on the size of the pupils

<table>
<thead>
<tr>
<th>Size of pupils</th>
<th>Normal</th>
<th>Miosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>44</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>Percent of patients (%)</td>
<td>88</td>
<td>12</td>
<td>100</td>
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</tbody>
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Table 10: Effect of amitraz on urine output

<table>
<thead>
<tr>
<th>Urine output</th>
<th>Normal</th>
<th>Polyuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>Percent of patients (%)</td>
<td>64</td>
<td>36</td>
</tr>
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</table>

Table 11: Effect of amitraz on blood sugar level

<table>
<thead>
<tr>
<th>Blood sugar</th>
<th>Normal</th>
<th>Hyperglycemia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14</td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td>Percent of patients (%)</td>
<td>28</td>
<td>72</td>
<td>100</td>
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</table>

Table 12: Effect of amitraz on urine sugar level

<table>
<thead>
<tr>
<th>Urine sugar</th>
<th>Normal</th>
<th>Glycosuria</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14</td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td>Percent of patients (%)</td>
<td>28</td>
<td>72</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 13: Effect of amitraz on arterial blood gas analysis

<table>
<thead>
<tr>
<th>ABGA</th>
<th>Normal</th>
<th>Respiratory alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>46</td>
<td>04</td>
</tr>
<tr>
<td>Percent of patients (%)</td>
<td>92</td>
<td>08</td>
</tr>
</tbody>
</table>

In present study of 50 cases, 8(16%) patients had hypothermia. Maximum number of patients had normal blood pressure 44 (88%). Present study correlates with following studies:

Avsarogullari L et al\textsuperscript{10} in their study of 23 patients, bradycardia was present in 2 (8.7%) patients. Remaining 21 (91.3%) patients had normal heart rate.

Effect of amitraz poison on blood pressure (Table 7)

In present study 6 (12%) patients of poisoning had hypotension. Maximum number of patients had normal blood pressure 44 (88%). Present study correlates with following studies:

Hasan et al\textsuperscript{12} mentioned, in their study of 7 cases, 1(14.33%) patients had hypotension. Normal blood pressure was present in 6(85.66%) patients. Central α2 adrenergic receptor agonist stimulates pre synaptic receptors and causes hypotension, and diminishes peripheral sympathetic tone, lowering the blood pressure with augmentation by the depressive effects of xylene.\textsuperscript{13}

Effect of amitraz on body temperature (Table 8)

Discussion

Present study ‘Clinical Profile Of Amitraz Poisoning’ an observational study was conducted in Dr. V. M. Government Medical College, Solapur, from September 2013 to December 2016. In this study period 50 cases of Amitraz poisoning were evaluated for their clinical presentation, management and outcome.

Effect of Amitraz Poison on Heart Rate (Table 6)

In present study 39 (78%) patients had normal heart rate. Bradycardia was seen in 6 (12%) patients. Present study correlates with following studies:

Ertekin v et al\textsuperscript{8} mentioned, in their...
study of 21 cases of amitraz poisoning, 2 (9.53%) patients had hypothermia. The remaining 19 (90.66%) had normal body temperature. Alpha-adrenergic agonists are known to affect the thermoregulation centre at the hypothalamus. Amitraz due to its α-agonist action decreases body temperature. This action has also been reported for other α-agonists such as xylene and detomidine.

**Effect of Amitraz on Size of the Pupils (Table 9)**

In present study of 50 patients 6 (12%) patients were having miosis. Normal sized pupils was present in 44 (88%) patients. Present study correlates with following studies:

Avsarogullari L et al 10 studied 23 patients of amitraz poisoning. In their study there miosis was present in 6 (26.08%) patients and 14 (60.86%) patients had normal sized pupils. Low doses of α2 adrenergic agonists induces miosis by its pre synaptic effect and at higher doses it is known to cause mydriasis11 due to its post synaptic effect.

**Effect of Amitraz on Urine Output (Table 10)**

Out of 50 patients, 18 (36%) patients had polyuria followed by 32 (64%) patients had normal urine output. Present study correlates with following studies:

Sezgin Ulukaya et al 11 in their study of 5 cases, polyuria was present in 3 (60%) patient. 2 (40%) patients presented with normal urine output. The stimulation of α2 adrenergic receptor decreases the production of antidiuretic hormone and renin secretion. This inhibition of antidiuretic hormone leads to enhanced diuresis.

**Effect of Amitraz on Blood Sugar Level (Table 11)**

In present study of 50 amitraz poisoning 36 (72%) patients were having hyperglycemia. The left out 14 (28%) patients were having normal blood sugar levels. Our study correlates with following studies:

Avsarogullari L et al 10 in their study of 23 patients, mentioned hyperglycemia in 14 (60.86%) patients. Normal blood sugar was present in 9 (39.13%) patients. The reason for hyperglycemia in these patients is, α2 adrenergic receptor stimulation. Which ultimately reduces insulin secretion.

**Effect of Amitraz on Urine Sugar Level (Table 12)**

In present study of 50 cases 36 (72%) patients were having glycosuria and the remaining 14 (28%) patients were having normal urine findings. Present study correlates with following studies:

Hasan et al 12 in their study reported 3 (42.85%) cases were having glycosuria. The remaining 4 (57.14%) cases were having nil urine sugar.

Glycosuria was present in all those patients who had hyperglycemia suggesting it was secondary to raised serum blood sugar.

**Distribution of Patients According to Management (Table 14)**

In present study 4 (08%) patients were treated with ventilatory support. The remaining 46 (92%) patients were treated with supportive measures. Present study correlates with following studies:

Veale DJ et al 14 mentioned, in their study of 15.26% patients were treated with ventilatory support. The remaining 84.74% were treated with supportive measures.

Presence of respiratory distress and inability to maintain oxygen saturation were the indications for ventilatory support in present study. These patients were gradually weaned from ventilator and they recovered completely.

**Treatment and Outcome**

The main approach while treating the patients of amitraz intoxication includes hemodynamic stabilization by proper hydration, maintaining airway, oxygen administration, reduce absorption of poison and measure to improve elimination of the toxin from the body. In decontamination, although the effects of activated charcoal have not been studied, but may still be considered for treatment. 25 Nasogastric aspiration of the stomach contents should be done. Patient with respiratory distress can be treated with ventilatory support.

As there is no specific antidote for amitraz poisoning the medical management is essentially symptomatic and supportive. 13 In spite of the severe life threatening clinical features, all cases may recover completely. In present study we would like to emphasize that the incidence of amitraz intoxication is day by day increasing due to its worldwide use in veterinary medicine. In order to decrease the incidence of amitraz poisoning, public health education should be given as primary prevention of poisoning and besides, drug producing company should redesign containers to prevent intoxication in children.

**Duration of Hospital Stay (Table 15)**

In present study maximum duration for which patients stayed in hospital was 6 days and they were (4 (08%) patients.

Ertekine V et al 19 mentioned that, in their study of 21 cases of acute amitraz poisoning, the maximum duration of hospital stay was 5 days and minimum duration of hospital stay was 1 day.

**Conclusion**

Vomiting and nausea were the commonest symptoms. Hyperglycemia and glycosuria was commonest sign. There was good response to supportive treatment. There was no complication and no mortality.

**References**

Relationship between the Use of Aluminum Utensils for Cooking Meals and Chronic Aluminum Toxicity in Patients on Maintenance Hemodialysis: A Case Control Study


Abstract
Background: Chronic aluminum toxicity (CAT) in end stage kidney disease (ESKD) patients is now a rare clinical disorder, unlike in the past, because of improvements in hemodialysis water purification systems and discontinuation of use of aluminum hydroxide as a phosphate binder. The use of aluminum utensils for cooking could be an unrecognized cause of the CAT.
Objective: To assess the association between aluminum kitchen utensils used for cooking meals and chronic aluminum toxicity (CAT) in patients on maintenance hemodialysis (MHD)
Material and Methods: In this case control study, a total of 31 (cases n=10; controls n=21) patients on MHD for more than one year were included. Cases were defined as patients with clinical manifestations (including laboratory parameters) of CAT and high (>200 mcg/L) serum aluminum levels. Control group was chosen from the same hemodialysis facilities. Association between use of aluminum utensils for cooking and occurrence of CAT was assessed.
Results: The mean age of patients in the cases and the control group was 52.90 and 52.95 years respectively with no significant difference (p=0.99). There was no difference in mean duration of dialysis (p=0.78), serum calcium level (p=0.06), serum phosphate level (p=0.19), serum albumin level (p=0.06), history of hypertension (p=1.00) and history of diabetes (n=0.12) between two groups. Mean haemoglobin (p<0.05) and mean iPTH (p<0.05) was significantly lower in the cases as compared to control group. Thirteen patients had history of use of aluminum utensils [cases 10 (76.90%) and control 3 (23.10%); p<0.05]. All patients as compared to control group. Thirteen patients had history of use of aluminum utensils [cases 10 (76.90%) and control 3 (23.10%); p<0.05]. All cases i.e. 10 (100%) had exposure to aluminum utensils whereas three (14.3%) patients in the control group had exposure to aluminum utensils whereas 18 (85.7%) patients had no exposure. The relative risk of having CAT because of use of aluminum utensils compared to not using was 28.46 (1.81 to 445.3) and the odd’s ratio estimated was 120 (5.45 to 2642).
Conclusion: Use of aluminum utensils for cooking meals is associated with CAT. Larger studies are required to confirm these findings.

Introduction
Chronic aluminum toxicity (CAT) is a debilitating disorder seen in patients with end stage kidney disease (ESKD) on maintenance hemodialysis (MHD). With CAT, patients develop bone and muscle pain, proximal muscle weakness, joint pain, hypercalcemia, iron and erythropoietin resistant microcytic anaemia, osteomalacia and fractures, hypercalcemia and slowly progressive dementia.1 Acute aluminum toxicity (AAT) occurs with sudden exposure to very high concentrations of aluminum resulting in life threatening acute encephalopathy manifested as altered consciousness, seizures and coma.2 Major sources of aluminum are water used for making dialysate and oral aluminum hydroxide which was widely used as a phosphate binder in chronic kidney disease (CKD) patients in the past. Unlike two decades ago, with the advent of modern water purification systems for making dialysate and availability of newer non-aluminum phosphate binders, CAT is now very uncommon.3 In fact, some authors have questioned the utility of routinely measuring serum aluminum levels in patients on MHD.4–6 However, clusters of cases of AAT caused by defects in the water purification or distribution system are occasionally reported.2,5 We diagnosed a few patients with CAT which was confirmed by very high serum aluminum levels (>200 mcg/L). None of these patients was on aluminum hydroxide and the aluminum levels in the treated water in the two dialysis facilities where the patients received MHD treatment were confirming to the Association for the Advancement of Medical Instrumentation (AAMI) hemodialysis standard.6 A review of clinical history revealed that all these patients were using aluminum utensils for cooking all their meals. Aluminum utensils are commonly used particularly in developing nations. However, there is no published data on association between the use of aluminum utensils and CAT in MHD patients. Hence, we decided to conduct this study.

Objective
To assess the association between...
use of aluminum utensils for cooking and CAT in patients on MHD. To look for other factors influencing serum aluminium levels in patients on MHD.

**Materials and Methods**

In this non-interventional, observational, case control study, 10 cases of CAT and 21 controls were included. Cases were retrospectively enrolled, and controls were enrolled prospectively. All cases were on MHD at two busy dialysis facilities in South Mumbai, each conducting around 2000 hemodialysis sessions a month. One is a part of a tertiary care hospital and the other is a stand-alone dialysis facility. Controls were selected from the same two hemodialysis facilities.

Cases were defined as those patients on MHD having any or all the following three clinical manifestations – a. chronic persistent bone pain, proximal muscle weakness and joint pain, b. microcytic anaemia and c. memory disturbance and cognitive impairment.

Other causes for all these three manifestations were ruled out. Patients were diagnosed to have low turnover bone disease based on low serum intact parathyroid hormone (iPTH) and alkaline phosphatase levels and X-Ray findings. Although diagnostic, bone biopsy was not done as this requires special equipment and expertise which were not available. Patients with a haemoglobin persistently below 10 gm/dl despite adequate doses of erythropoietin and normal iron stores, had a peripheral blood smear, reticulocyte count, serum haptoglobin, serum LDH, serum vitamin B12 and folic acid levels, to rule out other causes of anaemia. Stool was screened for occult blood. Patients with memory impairment and cognitive disturbance underwent thyroid function tests, vitamin B12 level, biochemistry, brain imaging and a neurology consultation.

In addition to the clinical manifestations, an elevated serum aluminum level of over 200 mcg/L was a mandatory criterion to confirm CAT.

For the controls, the inclusion and exclusion criteria were as follows -

**Inclusion criteria**

1. Patients from the same two dialysis centres as the cases.
2. Patients on hemodialysis for more than one year.
3. Patients receiving thrice a week, low flux dialysis.
4. Patients who consented for participation in the study.
5. Patients having serum aluminum levels of less than 60 mcg/L.

**Exclusion criteria**

1. Patients on hemodialysis for less than one year.
2. Patients who were not willing to give consent or not capable of giving consent.
3. Patients with noncompliance with dialysis treatment.
4. Patients receiving less than or more than three times a week dialysis.
5. Patients receiving high flux dialysis.
6. Patients with aluminum containing prosthetic devices like metallic valves or joints.
7. Patients who have received aluminum hydroxide in the last 12 months.
8. Patients who had undergone iodine contrast study in the past 3 months.
9. Patients who have serum aluminum levels of more than 60 mcg/L.

All cases and controls were receiving three times a week hemodialysis with low flux dialysers. All received unfractionated heparin during dialysis. All cases and controls received erythropoietin and intravenous iron supplemenations as guided by haematocrit, serum ferritin and serum transferrin saturation. None of the cases or controls received oral aluminum hydroxide and none had aluminum containing prosthetic devices like valves or joints. All patients and controls were on dialysis for more than one year.

All cases and controls were questioned about the history of use of aluminum utensils for cooking meals. The number of utensils used, and the duration of use was documented along with what food was cooked or stored. All controls were questioned about the symptoms of CAT.

Cases were compared with controls for the following parameters – age, gender, dialysis vintage, medications, symptoms of CAT and laboratory parameters (haemoglobin, serum calcium, serum albumin, serum phosphorus, serum iPTH, alkaline phosphatase and serum aluminum level).

Serum aluminum was analysed by inductively coupled plasma – mass spectrometry (ICP-MS) technology. Treated water for hemodialysis was checked for aluminum content as per the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines and the results were conforming to the AAMI standard.

**Statistical methods**

Data was entered in Microsoft excel® and then imported to SPSS for analysis (version 16). For the quantitative variables such as age, calcium level, iPTH level, duration of dialysis, serum phosphate, serum albumin, etc., descriptive statistics was calculated. The difference between the mean of these variables, between cases and controls was compared by unpaired t test. The frequency base variables such as gender, chronic aluminium toxicity, use of drugs, hypertension and diabetes, descriptive statistics proportion or percentages were calculated and difference between proportions (for cases and control) were compared by Fisher exact test. Risk of CAT due to use of aluminum utensils was estimated by means of statistical measure like relative risk and odd’s ratio value.

**Results**

A total of 31 patients were included in the study. The enrolled patients were divided into two groups; cases (n=10) and controls (n=21). Baseline characteristics in patients in case and control groups are shown in table 1. The mean age of patients in the cases and the control group was 52.90 and 52.95 years respectively. There was no difference in the age (p=0.99), mean duration of dialysis (p=0.78), serum calcium level (p=0.06), serum phosphate level (p=0.19), serum albumin level (p=0.06), history of hypertension (p=1.00) and history of diabetes (n=0.12) between two groups (Table 1). Mean haemoglobin (p<0.05) and mean iPTH (p<0.05) was significantly lower in the cases compared to control group (Table 1).

There was no significant difference in the use of calcium carbonate (p=0.51), calcitriol (p=0.09) and insulin (n=0.35) between cases and control group (Table
Table 1: Baseline characteristics of patients in the case and control groups

<table>
<thead>
<tr>
<th>Cause of Chronic Kidney Disease</th>
<th>Cases (n=10)</th>
<th>Control (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic glomerulonephritis</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>CTID</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>3</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Renal calculi disease/obstructive Nephropathy</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Hemoglobin, serum calcium, phosphorus, albumin and iPTH – mean(±SD): Cause of CKD - number of patients.

2). Association between use of aluminum utensils for cooking and CAT –

The relative risk of having CAT by using aluminum utensils compared to not using was 28.46 (1.81 to 445.3) and the odd’s ratio estimated was 120 (5.45 to 2642). A correction factor of 0.5 was used as there was not a single patient without a history of use of aluminum utensils in the case group. A total of 13 patients from both the groups had history of use of aluminum utensils. Among these 10 (76.90%) and three (23.10%) were from the cases and control group respectively. This difference was statistically significant (p<0.05). All cases i.e. 10 (100%) had a history of use of aluminum utensils whereas three (14.3%) patients in the control group had a history of use of aluminum utensils.

There was no significant difference between the serum aluminum levels of patients not exposed to aluminum utensils, who received calcium carbonate (p=0.41), calcitriol (p=0.99) or insulin (p=0.96) and who did not (Table 3).

Discussion

World Health Organization states that the provisional tolerable weekly intake of aluminum for people with normal kidney function is 2 mgs per kg body weight. Most healthy adults tolerate larger daily oral aluminum exposures without any adverse effect. However susceptible population like pre-term infants, children and patients with renal insufficiency can be at risk of CAT even at lower doses (8). Aluminum being a ubiquitous element and as its use in industry and daily life is rising, exposure to aluminum sources is unavoidable for patients on MHD.

In the past, two major sources of aluminum in patients on MHD were the water needed for making dialysate and oral aluminum hydroxide prescribed as a phosphate binder. Some other medications used in ESKD patients such as erythropoietin, intravenous iron preparations, oral iron sulphate, calcitriol, calcium carbonate and insulin contain minute amounts of aluminum. Many studies have documented leaching of aluminum into food while cooking in aluminum utensils. In one study the mean exposure estimate for aluminum was 125 mg per serving, more than six times the World Health Organization’s provisional tolerable daily intake of 20 mg/day for a 70 years old person with normal kidney function.

Since the last 2 decades CAT in patients with MHD has become a rare clinical entity because of major improvements in the water purification and distribution systems and use of non-aluminum phosphate binders. Hence, when we encountered a few cases with CAT with a history of use of aluminum utensils for cooking, a case-control study was designed to ascertain the relative risk of CAT with the use of aluminum utensils in patients with ESKD on MHD.

Of the 10 cases of CAT, all had musculoskeletal manifestations and anemia. The mean haemoglobin (p<0.05) and the mean iPTH (p<0.05) were significantly lower in the cases as compared to the control group. Four cases had minor memory disturbances and three had cognitive disturbance out of which one had an episode of unexplained encephalopathy which resolved with supportive care.

Confounding factors were matched in both groups. The control group (n=21) and case group (n=10) had no statistically significant difference in mean age (p = 0.99) and duration on MHD (p=0.779). All cases and controls were from same ethnic background and cooking customs. Dialysis water quality was matched as the patients in both the groups were from the same two dialysis facilities. None from both groups was prescribed aluminum hydroxide in the past. All patients in both groups received low flux dialysis three times a week. Of the medications that contain aluminum, all received intravenous iron preparation and erythropoietin. There was no statistically significant difference in patients receiving other preparations like calcium carbonate (p=0.51), calcitriol (p=0.092) and insulin (p=0.35) in the two groups. None of the patients in both groups received oral iron sulphate or ferric citrate (as phosphate binder).

All cases had a serum aluminum level of >200 mcg/L. A mean could not be calculated as the laboratory does not routinely report the exact values above 200 mcg/L. As the cases were enrolled retrospectively, exact values could not be obtained on request. In the control group the mean aluminum level was 24.84 (±9.59) mcg/L.

Table 2: Comparison of use of aluminum containing drugs in cases and controls

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cases (n=10)</th>
<th>Control (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>4 (40%)</td>
<td>7 (33.3%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>2 (20%)</td>
<td>11 (52.4%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Insulin</td>
<td>1 (10%)</td>
<td>5 (23.8%)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Table 3: Effect of aluminum containing drugs on serum aluminum levels of patients not using aluminum utensils

<table>
<thead>
<tr>
<th>Drug</th>
<th>Yes</th>
<th>No</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>25.16 (9.93)</td>
<td>21.61 (7.66)</td>
<td>0.41</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>23.44 (8.57)</td>
<td>23.36 (9.19)</td>
<td>0.99</td>
</tr>
<tr>
<td>Insulin</td>
<td>23.14 (10.04)</td>
<td>23.44 (8.89)</td>
<td>0.96</td>
</tr>
</tbody>
</table>
All cases had a history of aluminum utensils usage for a minimum of more than ten years. Aluminum utensils were used to cook all the meals. 3 (14.28%) of the 21 patients, in the control group used aluminum utensils in a limited way i.e. only for boiling milk, making tea, coffee, curds and butter milk and for steam pressured cooking (“pressure-cooker”). For cooking all other meals, stainless steel utensils were used by these patients. These three patients in control group too used aluminum utensils for a minimum of more than ten years.

The relative risk of having CAT because of use of aluminum utensils compared to not using was 28.46 (1.81 to 445.3) and the odd’s ratio estimated was 120 (5.45 to 2642). Of all the patients (n=31) included in the study, 13 (41.9%) used aluminum utensils. Of these 10 (76.9%) had CAT whereas 3 (23.1%) did not have CAT. This difference is statistically significant (p<0.05). Of all the patients included in the study, 18 (58.1%) did not use aluminum utensils. Of these none had CAT (p<0.05). A Taiwanese study looked at the effect of aluminum utensils in CKD patients not yet on dialysis and found that replacing aluminum utensils by stainless steel ones significantly decreased serum aluminum levels.27 Results of the current study suggest a strong association between use of aluminum utensils and CAT in patients on MHD. Observations from the current study and the Taiwanese study suggest that aluminum kitchen utensils is a significant source of aluminum in patients with renal insufficiency.

In patients not using aluminum utensils (n=18), the effect of use of aluminum containing medications on serum aluminum levels was studied. In this group there was no significant difference in serum aluminum levels in patients taking or not taking calcitriol (p=0.47), calcium carbonate (p=0.99) or insulin (p=0.96). Intravenous iron and erythropoietin were used by all patients and oral iron preparation was used by none. A Spanish study found significantly higher aluminum levels in those consuming anti-anemics (p=0.007), anti-hyperphosphatemics (p=0.021) or hypercalceemics (p=0.012).18 Another study found significant higher aluminum levels (22.1 ± 9.0 mcg/L versus 6.7 ± 2.4 mcg/L, P<0.05) in those on intravenous iron, erythropoietin and insulin.12

According to the KDOQI guidelines the serum aluminum level in patients on MHD should be maintained below 20mcg/L.19 This is an opinion and not based on evidence. The mean serum aluminum levels amongst nonusers of aluminum utensils in the current study was 23.39 (± 8.77). In a study from the United States which looked at serum aluminum levels of 755 patients, done routinely, the mean value was 11.05 (± 8.07) which is significantly lower (p<0.05) than that in the nonusers of aluminum utensils in the current study.13 However, in a Spanish study which looked at serum aluminum levels of 116 patients, done routinely, the mean value was 39.9 (±23.1) which is significantly higher (p=0.004) than that in the nonusers of aluminum utensils in the current study.14 The reason for these differences is not clear. Whether these are related to differences in the amount of aluminum contaminants in medications mentioned above or there are any unknown sources of aluminum or there are any geographical differences leading to this observation needs to be studied in larger prospective studies.

KDOQI guidelines recommend monitoring serum aluminum level once a year in all patients on MHD.19 Several large studies from the United States have questioned this as only about 2 to 3 percent of the patients on MHD have a level above 20mcg/L in these studies.3,4 Indian Society of Nephrology guidelines on hemodialysis do not have a mention on monitoring serum aluminum levels probably considering these studies.30 However, the current study and the Spanish study bring forth the need for a larger prospective study from India to make a recommendation.18

The limitation of this study is its retrospective nature and the small number of cases and controls.

Conclusion
Use of aluminum utensils is very common in India and developing world. Use of aluminum utensils for cooking food is associated with CAT in patients on MHD. Patients on MHD should be counselled to stop using aluminum utensils and to replace them with stainless steel ones. This simple measure will help prevent this debilitating clinical disorder which is difficult to treat and cure.

A significant higher level of serum aluminum in patients not using aluminum utensils in the current study, highlights the pressing need for a large prospective trial from this region to confirm this observation and find the cause or recommend a higher acceptable value.

CAT, although reportedly rare, should be ruled out in all ESKD patients who use aluminum utensils and present with persistent bone and joint pains, unexplained anaemia or memory disturbances. Eliciting history of use of aluminum utensils should be routinely practised.

Acknowledgements
We thank the Apex Kidney Foundation for funding this study and trustees of Lalbagha Raja Sarvarajnik Utasav Mandal for permitting us to enrol some of the cases and controls from the dialysis facility owned by them and managed by Apex Kidney Care. We thank Dr Varun Marewadp, Apex Kidney Care for data collection and Dr Pradeep Jadhav, Asst Prof, Statistics and Demography, KEM hospital for the statistical analysis.

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Guillain-barre Syndrome in Indian Population: A Retrospective Study
Rajendra Singh Jain1, Jagdeesh Chandra Kookna2, Trilochan Srivastva3, Rahul Jain2

Abstract
Objectives: To study clinical characteristics of various forms of Guillain-Barre syndrome in Indian adults.
Material and Methods: The epidemiological, clinical, cerebrospinal fluid and electrophysiological data of 65 patients of Guillain-Barre syndrome (GBS) were reviewed in a retrospective study.
Results: Analysis of age distribution disclosed a high incidence (36.92%) in young adults between 18 to 29 years of age. Seasonal preponderance in winter and summer was found. Preceding events were identified in 22 (33.84%) cases. Motor weakness, areflexia, and facial weakness were the most common clinical features. Cerebrospinal fluid albuminocytological dissociation was present in 80% of patients. Utilising clinical and electrophysiological data, these 65 patients with Guillain-Barre syndrome were subclassified as acute demyelinating polyradiculoneuropathy 17 (26.15%), axonal form 17 (26.15%), Fisher’s syndrome 2 (3.07%) and ataxic variant 1 (1.53%). The remaining 28 (43.07%) patients were unclassified. 9 (13.8%) patients had recurrent GBS. Only 5 (7.7%) patients required mechanical ventilation. Follow up available on 47 patients disclosed that all of them recovered satisfactorily. No patient was persistently disabled and no mortality occurred during hospitalization.
Conclusions: GBS in Indian population from northwest India showed peculiar age, seasonal distribution and high frequency of both AIDP and axonal subtypes. Both, axonal and demyelinating subtypes shared common clinical features and had good prognosis.

Introduction
Guillain-Barre syndrome (GBS) is an acute, monophasic, symmetrically progressive, ascending demyelinating polyneuropathy characterized by rapidly evolving symmetrical limb weakness, areflexia, absent or mild sensory signs, and variable autonomic disturbances. It is the major cause of acute neuromuscular paralysis, with an annual incidence of 1.3-2 per 100,000 worldwide.1

GBS can be sub grouped into acute inflammatory demyelinating neuropathy (AIDP), Fisher syndrome (FS) and axonal forms (acute motor axonal neuropathy [AMAN], acute sensorimotor axonal neuropathy [AMSAN]).2

The purpose of this study was to review cases of GBS to study their epidemiological, clinical, cerebrospinal fluid and electrophysiological profile.

Materials and Methods
We reviewed the medical records of all adult GBS patients admitted to Neurology Department, SMS Medical College Hospital Jaipur, India, a teaching hospital located in northwest India and also a tertiary referring medical centre for the region, from January 2013 to May 2015. Asbury and Cornblath’s clinical diagnostic criteria for GBS were used for clinical diagnosis.3 We recorded data on age, sex, preceding events, date of onset of disease, clinical manifestations including initial symptoms, and neurological findings, results of cerebrospinal fluid (CSF) study, and specific treatments including steroids(methyl prednisolone), plasmapheresis, and intravenous immunoglobulin (IVIg). We also registered the findings of electrophysiological studies, including distal motor, sensory and F wave...
latencies, amplitudes of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs), and motor and sensory conduction velocities.

At the time of their maximal deficit during admission to the hospital, patients were graded using a disability scale (Hughes et al).⁴ Based on initial electrophysiological findings, patients were classified as having AIDP according to Albers and Kelly 1989 criteria⁵ and having axonal forms of GBS (AMAN or AMSAN) if there was no electrophysiological evidence of demyelination as defined above, together with a decrease of CMAP or SNAP amplitudes to less than 80% of lower limit of normal in at least two tested nerves.⁶ Patients were considered unclassified if data did not confirm to either category. A diagnosis of Fisher syndrome (FS) was made in patients who presented with triad of ataxia, areflexia, and ophthalmoplegia.

### Results

During the study period, 65 patients who fulfilled the diagnostic criteria for GBS were identified. According to the clinical and electrophysiological findings, 17 (26.15%) patients had AIDP, 17 (26.15%) had axonal forms of GBS (11 AMAN, 6 AMSAN), 2 (3.07%) had FS, 1 (1.53%) had ataxic variant, however 28 (43.07%) patients remained unclassified in our study (Figure 1).

#### Age, Sex and Seasonal Distributions

The age of all 65 patients ranged from 6 to 75 years (mean 37.9 years) with the highest frequency (40%) in adults between the ages of 18 to 29 years (Figure 2). A total of 47 (72.3%) were male and 18 (27.69%) were female (Table 1). Seasonal preponderance was found in cases of GBS, overall 24 (36.9%) of all patients were admitted in winter (October-January) and 23 (35.38%) of all cases were admitted in summer (April-June) (Figure 2) while 18 (27.69%) patients were admitted in other season.

### Preceding Events

Various preceding events before onset of illness were noted in 22 (33.84%) patients. The interval between the onset of preceding events and the onset of symptoms ranged from 11 days to 45 days. All events were infectious diseases (Table 1), mostly nonspecific febrile illness (12 patients), acute gastroenteritis in (5 patients) and upper respiratory tract infection (3 patients). Identifiable viral infections included chicken pox in 1 patient and acute viral hepatitis A in 1 patient.

#### Clinical Features

The most frequent initial symptoms in overall GBS patients were limb weakness in 62 (95.38%), sensory symptoms in form of paresthesias, muscle pain and back pain in 20 (30.7%) patients, facial weakness in 14 (21.53%), and bulbar dysfunction in 8 (12.3%).

Table 2 summarises the clinical features during the course of disease.

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2, 15 (23.07%) grade 3, 19 (29.23%) grade 4 and 4 (6.10%) grade 5.

**Cerebrospinal Fluid Studies**

Lumbar puncture was performed in 39 patients. The CSF protein concentration was raised (≥ 45 mg/dl) in 33 (84.61%) cases. The frequency of raised CSF protein concentration was 76.9% in first week, 85.7% in second week and 100% beyond second week. The CSF cell count was normal (< 10 cells/mm³) in all 39 (100%) patients. In total, 39 (84.61%) patients showed albuminocytological dissociation on CSF examination. One patient had cell count 103 on 4th day of IVIg therapy (aseptic meningitis).

Data for CSF were available in 10 with axonal forms, 9 patients with AIDP, 2 with FS, 1 with ataxic variant, and 17 with unclassified group. In these subgroups raised protein concentration was found in 6 (60%), 8 (88.8%), 2 (100%), 1 (100%) and 16 (94.11%) respectively.

CSF proteins were raised in 2 out of 2 (100%) patients with grade 1 disability score, 12 (60%) patients out of 17 with grade 2 disability score and 19 (95%) patients out of 20 with grade ≥3 disability score.

**Specific Treatments, Outcomes and Prognostic Factors**

The average duration of admission to hospital for all patients was 12.05 days (range 3 to 90 days). In addition to general medical management, 43 (66.15%) patients received specific treatments: 25 (38.46%) IVIg alone, 16 (24.61%) steroids alone, and in 2 (3.07%) patient plasmapheresis was done. All 65 patients discharged from hospital after improvement of at least one grade from their maximal deficit. No patient died during hospitalization.

5 (7.6%) patients required mechanical ventilation. Mean duration of stay in hospital in these five patients was 48.6 days (range 19 to 90 days). Follow up at 3 months to 1 year was possible in 47 patients. A good outcome with normal functional life was noted in all patients.

**Recurrent Guillain-barre Syndrome**

9 (13.84%) patients out of total 65 cases had history of similar illness in past. Male to female ratio was 8:1 and their age ranged from 23 to 57 years. Interval between present and past episode was >5 years in all patients. Preceding event in the form of nonspecific febrile illness was present in 4 out of 9 patients with recurrent GBS. Among the subgroups 3 out of 9 were unclassified, 3 had axonal forms, 1 patient had ataxic variant and 1 patient had recurrent FS. All 6 patients from unclassified and axonal subgroups had symmetrical motor weakness of extremities, generalized areflexia and 2 patients had bulbar and respiratory involvement. Lumbar puncture was performed in 6 patients out of whom 5 showed albuminocytological dissociation. One patient required mechanical ventilation.

**GBS Variants**

Recognized variants like AMAN (11 patients), AMSAN (6 patients), and MFS (2 patient) were observed in our patients. Apart from this, only lower limb weakness (paraparesis) was present in 8 patients (3 from AIDP subgroup, 1 from axonal subgroup and 4 from unclassified subgroup). Out of all 65 patients, 3 patients had preserved deep tendon reflexes.

Of special note are 2 patients; first was a 25 years old student who developed asymmetric proximal weakness of both upper limbs (bibrachial) preceded by jaundice 8 days prior to onset of weakness. He had positive titre for anti hepatitis A antibody, normal CSF protein and demyelinating polyneuropathy in electrophysiological studies.

Second patient was a 49 year old female who presented with 4 days history of progressive ascending symmetrical quadriplegia preceded by febrile illness 1 week prior to onset of weakness. Additional features on examination were bilateral external ophthalmoplegia, ptosis, facial weakness, bulbar weakness and generalized areflexia. Her MRI brain was normal, CSF showed albuminocytological dissociation and electrophysiological studies revealed nonrecordable SNAPs and normal motor conduction. She responded promptly to IVig.

**Discussion**

The classical presentation, progressive areflexic motor weakness and albuminocytological dissociation are the most reliable criteria for the diagnosis of GBS. Electrophysiological studies have a crucial role in confirming the diagnosis and distinguishing various subtypes. Most of the electrophysiological criteria are from western studies where AIDP is more prevalent and hence, most criteria addressed the diagnosis of AIDP. There is paucity of data from the Indian subcontinent and the available data suggests AIDP as the most common subtype. There has been considerable variation in the yield of AIDP when different sets of criteria were applied to patients. Alum et al found 21% to 72% patients belonging to AIDP variant applying six available criteria sets. Alexander et al identified 23% to 67% having AIDP using six different criteria. Furthermore, importance of serial electrophysiological studies for better characterization of GBS subgroups has been highlighted in previous studies. In our study 28 (43.07%) patients were categorized in unclassified group. This high percentage of unclassified patients probably reflects the low yield of Albers and Kelly 1989 criteria for AIDP, early timing and single electrophysiological study in our patients, and presence of variant GBS patients.

Of 65 patients with clinically defined GBS, only 2 (3.07%) had FS. This low frequency of FS is similar to its low frequency of 2% to 7% in series from western world. Axonal forms of GBS, including AMAN and AMSAN occurred in 30.7% of our patients. In North America and Europe, around 5% of patients with GBS have the axonal subtypes, whereas in Central and South America, Japan and China axonal subtypes account for 30-47% of cases. Increases in rates were observed in most studies of people aged 50 years or more. In our series GBS patients showed a pattern with maximum number of patients in 18-29 years age group (figure 2).

The issue of seasonal variation in incidence was raised in some studies. Some found more cases in colder months although cluster of cases were reported in spring and summer in Brazil, during winter and June in Netherlands and during autumn in Sweden. In studies from northern China, a striking seasonal preponderance was found in summer months. In our series, there was a seasonal clustering in winter (October-January) and summer (April-June).

Preceding events were detectable in 33.84% of our patients. In most series
reporting this information, 40-70% of cases recorded an infection prior to onset. In our study nonspecific febrile illness was the most common preceding event in 12 (54%) patients, followed by acute gastrointestinal illness, which occurred in 5 (22.72%) patients and URI in 3 (13.6%) patients (Table 1).

Recurrent GBS was present in 9 (13.84%) patients in our study. The epidemiological, clinical, cerebrospinal fluid and electrophysiological characteristics of these patients were similar to those with monophasic illness.

Common variants of GBS in form of AMAN, AMSAN, ataxic variant and MFS all were present in our study. Apart from these, variants with regional affection in form of paraparesis were found in 8 (12.30%) patients and asymmetrical bifibrachial weakness was present in 1 patient who was recovering from acute viral hepatitis (hepatitis A virus). Association of GBS and hepatitis A infection has been reported earlier in virus). Association of GBS and hepatitis A virus) and hepatitis A infection was the most common preceding event.

One patient of “overlapping GBS” had features of oculofaciobulbar weakness and flaccid quadriparesis. Overlapping GBS with similar features have been previously described in literature in relation to Bickerstaff’s brainstem encephalitis.16

Follow up studies showed that most of our patients recovered without appreciable neurological sequelae and resumed a normal life. There was no mortality in our series. Indefinite confinement to bed or wheelchair or prolonged mechanical ventilator dependence was not found in our patients. These results indicate that GBS in Indian adults is a disease with good prognosis in patients who survive acute stages. In addition, considerable clinical improvement shortly after initiation of specific therapies was found in most of our patients.

To conclude, GBS in Indian population from northwest India showed peculiar age and seasonal distribution and high frequency of both AIDP and axonal subtypes. Both axonal and demyelinating subtypes shared common clinical features and had good prognosis. Therefore treating clinicians should remain cautious but need not be unnecessarily over apprehensive while dealing with GBS.

References

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Abstract

Background: The current study investigates the efficacy of Jalra-M in improving glycemic control and reducing complications in patients with Type 2 Diabetes Mellitus (T2DM).

Methods: A prospective, randomized, controlled trial was conducted involving 100 patients with T2DM. The patients were randomized into two groups: the intervention group received Jalra-M, while the control group continued with their usual treatment. Blood glucose levels, hemoglobin A1c (HbA1c), and other relevant parameters were monitored at baseline and post-treatment.

Results: The results showed a significant reduction in HbA1c levels in the intervention group compared to the control group. There was also a decrease in the incidence of complications such as cardiovascular events.

Conclusion: Jalra-M is an effective and safe treatment option for improving glycemic control and reducing complications in patients with Type 2 Diabetes Mellitus.
Targeting Glycemic Level in Gestational Diabetes Mellitus to that of Normal Pregnancy would result in a better Maternal-Fetal Outcome

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Abstract

Women with a history of Gestational Diabetes Mellitus (GDM) are at increased risk of future diabetes and related Non-Communicable Diseases (NCD) as are their offspring. “Transgenerational transmission occurs”: Independent of genetic risk, offspring of hyperglycaemic pregnancies are at increased risk of early onset type 2 diabetes mellitus (Type 2 DM) and obesity. Differences exist in offspring risk of diabetes and obesity based on time and type of diabetes exposure in utero. There is a risk gradient, wherein type 2 DM exposure confers greater risk and reduces time to development of type 2 DM in the offspring compared to exposure to GDM and no diabetes exposure. These data suggest, glucose dose dependence in risk transmission. Given that the age of onset of prediabetes and type 2 DM is declining many reproductive age women may have undiagnosed diabetes or dysglycaemia when they become pregnant. This has great public health significance and it has become imperative that all pregnant women should be screened for hyperglycemia even if they have no symptoms. Ministry of Health, Government of India has developed the national guidelines for testing, diagnosis and management of hyperglycemia in pregnancy. These guidelines recommend early testing at booking, to be repeated again between 24-28 weeks if negative at first testing. The guideline also recommends that GDM can be diagnosed if the 2 hr PG is ≥140mg/dl after 75 gm of oral glucose administration without regard to the time of the last meal (i.e., fasting or non-fasting). This approach has also been endorsed by International Diabetes Federation (IDF), World Health Organization (WHO) and International Federation of Gynaecology and Obstetrics (FIGO) for resource constrained settings.

The aim should be to target new born baby’s birth weight, appropriate for gestational age (2.5 to 3.5 kg) to prevent the offspring developing NCD in the future. For this to happen early diagnosis and tight maternal glucose control during pregnancy similar to glycaemic level in the normal pregnancy, (FPG between 80 and 90 mg, 2 hr. post prandial between 110 and 120 mg) is necessary.

Introduction

The IDF Diabetes Atlas 8th edition published in 20171 revealed an alarming 180% increase in the prevalence of diabetes in the world from 151 million in 2000 to 425 million in 2017. How can we arrest or slow down this rising trend and what should be the focus of public health policy? These are questions that need serious consideration. While several reasons are ascribed for this rising trend including aging population, urbanization, nutrition and lifestyle transition, genetic predisposition etc., one factor that has not received adequate attention is the concept of intrauterine programming.

David Barker’s, “Fetal Origin of Adult Diseases theory” conceptualized that the body’s susceptibility to “lifestyle” diseases was programmed in the intrauterine period. Intrauterine programming is a process whereby stimuli or stresses occurring at critical or sensitive periods of fetal development permanently change structure, physiology, and metabolism, thereby predisposing individuals to disease in adult life.

If the stimulus happens to be hyperglycemia in pregnancy (HIP), the consequent abnormal maternal metabolic environment affects the developing fetal tissues, organs and control systems in complex ways which eventually lead to permanent functional changes in adult life. The quantum of hyperglycemic exposure in terms of duration and degree are relevant, as is the timing of the onset of exposure in the course of pregnancy. Early exposure during fetal organogenesis and placental development has relatively more severe and lasting consequences then later exposure. Depending upon the timing and quantum of exposure to the aberrant fuel mixture (embryonic-fetal), different effects may occur including abortion, congenital anomalies, macrosomia and large of gestational age (LGA), intrauterine growth restriction (IUGR) and small for gestational age (SGA), intrauterine death and still births etc. In addition, independent of genetic risk, offspring of hyperglycaemic pregnancies are at increased risk of early onset type 2 DM and obesity. Differences exist in offspring risk of diabetes and obesity based on time and type of diabetes exposure in utero. There is a risk gradient wherein intrauterine type 2 diabetes exposure confers relatively greater risk and reduces time to development of type 2 diabetes in offspring compared to exposure to GDM and no diabetes exposure. These data suggest that there is glucose dose...
dependence not only in the immediate poor pregnancy outcomes but even in transmission of risks for future type 2 DM. As offspring of mothers with HIP are at a heightened risk of early-onset obesity, pre-diabetes, and T2DM, female offspring of mothers with HIP also are highly vulnerable to hyperglycaemia during pregnancy thus creating a multigenerational impact. Pregnancy maybe considered a multiplier of the unfolding pandemic of diabetes, obesity and cardiovascular diseases.

A negative correlation has also been shown between severity of maternal hyperglycaemia and offspring performance on various neurodevelopmental and behavioral tests. Compared with children unexposed to diabetes in utero, children exposed to diabetes have been reported to be at higher risk for Attention Deficit Hyperactivity Disorders (ADHD), Autism Spectrum Disorders (ASD) and intellectual disabilities (IDs). A more marked effect has been reported with combined exposure to maternal pre-pregnancy obesity and diabetes.

Additionally women with GDM have a high vulnerability for future Type 2 DM and GDM is considered the most reliable marker for it and cardio metabolic disorders in women; with a proven possibility for prevention or delaying onset through appropriate post-partum lifestyle interventions.

**Maternal Glucose Level and Fetal Growth**

Higher glucose transfer as a consequence of maternal hyperglycaemia stimulates the developing fetal pancreatic β-cells to start secreting insulin earlier and in higher quantity resulting in fetal hyperinsulinemia which in turn increases fetal glucose utilization and fat deposition with resultant macrosomia. Once initiated fetal hyperinsulinemia becomes self-perpetuating. By improving glucose utilization in the fetal compartment it increases the glucose concentration gradient across the placenta, further increasing glucose flux to the fetus requiring more fetal insulin secretion. This may sometimes help lower maternal glucose level as well, but favors a persistently high glucose flux even when maternal blood glucose is not very high. This phenomenon is called the “fetal glucose steal” syndrome; wherein, a hyperinsulinemic macrosomic fetus apparently helps to attenuate and “normalize” maternal glucose despite poor maternal metabolic control. It provides an explanation for why some mothers with fetuses with all the characteristics of diabetic fetopathy have apparently “good” glucose control. Conversely, maternal hyperglycaemia through its effect on poor placentation may cause IUGR. Compared to GDM, pre pregnancy diabetes (PDM) both type 1 and 2 is relatively more likely to be associated with poor placentation and SGA babies.

Postprandial hyperglycaemia plays a more important role in causing fetal overgrowth. Data suggests that postprandial glucose levels more closely relate to macrosomia risk compared to fasting glucose levels. Based on studies in preterm births renal threshold for glucose in the fetus is probably <110 mg/dl. When maternal glucose level is >110 mg/dl, the fetal blood glucose load causes fetal glycosuria and consequently a glucose-enriched amniotic fluid. After 20 weeks of gestation, the fetus begins to swallow the amniotic fluid. In addition to the placental transfer of glucose, ingested high glucose amniotic fluid also stimulates insulin secretion. Thus, even transient elevations of blood glucose on the maternal side not only result in elevations of blood glucose on the fetal side but also provide for glucose ingestion by the fetus for many hours. Thus, post prandial hyperglycaemia for <1 h once a day in the mother may produce fetal insulin stimulus, through the oral route for hours. Elevations of maternal glucose levels more frequently (after every meal, for example) may produce a more prolonged oral glucose load for the fetus resulting in an overfed fat fetus.

**Implications for public health policy**

**Whom to test?**

Women with a history of GDM are at increased risk of future obesity, type 2 diabetes and cardio metabolic disorders, as are their children. Thus, GDM may play crucial role in the increasing prevalence of diabetes and cardio metabolic diseases. One of the highest prevalence of HIP is highest in South Asia (26.6%). It is obvious that all pregnant women should be screened for hyperglycaemia even if they have no symptoms.

**How to test?**

Given the load of testing over 30 million pregnant women in India what should be the best testing strategy? Some organizations and countries while accepting universal testing recommend a two-step approach – a 50 g non fasting glucose challenge test (GCT) followed by a 75 g OGTT in women who test positive on initial screening. This reduces the number of OGTTs and ensures that women diagnosed with GDM have ‘significant glucose intolerance’. However, it does not take into account that the GCT also misses around 25% of cases with OGTT abnormalities and in particular fails to identify women manifesting only fasting hyperglycaemia as they do not qualify for the OGTT. Moreover, a significant proportion of women fail to complete the evaluation as they do not turn up for the OGTT. This approach therefore may miss many women with HIP.

There is also the issue of one abnormal reading versus two abnormal readings as required by some guidelines (Carpenter and Coustan and NDDG). All dysglycaemic states (diabetes, IFG, IGT) are diagnosed based on single abnormal values. Surely, pregnancy where any degree of dysglycaemia has multi-generational consequences should be taken more seriously!

International Association of Diabetes in Pregnancy Study Group (IADPSG) guideline while recommending universal testing using a one step procedure and one abnormal value as being diagnostic may still not be relevant and applicable everywhere, and in particular countries like India. For sake of uniformity while it would be desirable to have uniform global diagnostic cut off values, in view of the continuous linear association between maternal glycaemia and perinatal outcomes any set of diagnostic criteria proposed will need to evolve from a consensus approach, balancing risks and benefits in particular social, ethnic, economic and clinical contexts. The IADPSG 2 hr cut off value is based on the 1.75 odds ratio for macrosomia of the HAPO cohort (Caucasian population) and it may not be as efficient in identifying women
at risk for fetal overgrowth as those identified by having a 2-h glucose corresponding to a slightly lower odds ratio, e.g. 1.5. The latter corresponds to the older WHO criteria 2 h. value of 7.8 mmol/L or 140 mg/dl. This maybe of importance in the developing countries particularly in South Asia where women are relatively small and a larger baby may pose greater obstetric risk 28 as well as be a marker for higher future diabetes risk. IADPSG guideline validity has become questionable as one of the authors of IADPSG guideline has recently commented that “even at centers”, that accepted IADPSG recommendation, the approach varies and needs revision for standardization of the strategy for diagnosing GDM. 24 South Asian population phenotype is different, one size does not fit all, and where possible, diagnostic threshold should be adapted using local data. 20, 23

The guideline and diagnostic criteria should be simple and feasible on the ground particularly when applied on a large scale at a public health program level. 26

WHO while endorsing the IADPSG criteria described the quality of evidence for its recommendation as “very low” and the strength of its recommendation is “weak”. “WHO made a few important and pertinent observations with regard to GDM testing. OGTT is resource scarce and not able to routinely perform OGTTs in pregnant women. In these circumstances, many health services do not test for hyperglycemia in pregnancy. For a pregnant woman, the request to attend fasting for a blood test may not be realistic because of the long travel distance to the clinic in many parts of the world, and increased tendency to nausea in the fasting state. Consequently, non-fasting testing may be the only practical option. 28

Diabetes in Pregnancy Study Group India (DIPS) and South Asian Initiative for Diabetes in Pregnancy (SAIDIP) recommend “a single step procedure” for diagnosing GDM using a single 2 h PG value ≥ 140 mg/dl after 75g oral glucose administration without regard to the time of the last meal (i.e., fasting or non-fasting). 29

DIPSI guideline is evidence based. In an RCT by Wahi et al 30 to test the validity of the DIPSI guideline 272 pregnant women were studied. Of these 140 were normal glucose tolerant (Group 1), 70 women with GDM received treatment (Group 2) and 62 women declined treatment (Group 3). The incidence of macrosomia and preterm birth was 1.4% and 2.8% in Group 1, 2.1% and 4.2% in Group 2 and 9.6% and 16.1% in Group 3. The prevalence of large babies > 4 kg was significantly higher in GDM without treatment group (p =0.02, c2 = 5.19) when compared to GDM with treatment. The study demonstrated that compared to normal glucose tolerant Indian women, those diagnosed with GDM using DIPSI guideline and not receiving standard treatment were at much higher risk of macrosomia and preterm birth, whereas the risk of these complications were considerably reduced among women with GDM who received treatment. The study concluded that the use of DIPSI guideline to diagnose and manage GDM has a significantly positive effect on pregnancy outcome (Table 1). In another study Balaji et al included 1267 pregnant women who had normal glucose tolerance (NGT) and 196 with GDM diagnosed using DIPSI guideline and who received treatment. Follow up, showed that the birth weight distribution between NGT and GDM women was similar because the GDM status was corrected by treatment 31 (Figure 1). It can be concluded from the above and other published studies 31, 32 that the diagnosis of GDM with 2-h PG ≥ 140 mg/dl and treatment is worthwhile and is associated with a decreased incidence of macrosomia, fewer emergency cesarean sections, serious perinatal morbidity and improved health-related quality of life.

The Ministry of health and family welfare Govt. of India has also endorsed the DIPSI guideline and recommends the single step testing using 75g oral glucose and measuring plasma glucose 2 hour after ingestion of 75g glucose dissolved in 300 ml water irrespective of whether the woman comes in the fasting or non-fasting state and irrespective of the last meal time. 29 A plasma standardised glucometer should be used to evaluate blood glucose 2hour after the oral glucose load. If vomiting occurs within 30 min of oral glucose intake, the test has to be repeated the next day, if vomiting occurs after 30 minutes, the test is continued. The threshold plasma glucose level of ≥140 mg/dl (more than or equal to 140) is taken as cut off for diagnosis. 33 Laboratory glucose measurement is often not available in less resource settings and testing with a portable glucometer is the only option. 28

The International Federation of...
Gynecology and Obstetrics (FIGO) in its pragmatic and widely accepted International guideline endorsed the DIPSI single step approach and recommended its use in the Indian sub-continent.\(^{19}\)

The FIGO and IDF joint statement and declaration on hyperglycemia in pregnancy states that all pregnant women attending health facilities should be tested for hyperglycemia using a single-step procedure, as advocated by FIGO, IDF and WHO.\(^ {34}\)

**When to test?**

The standard practice is to test women for GDM between 24 and 28 weeks of gestation, however these recommendations are changing. The fact that undiagnosed diabetes in pregnancy has much severe consequences for both the mother and the fetus, it is now recommended that pregnant women without known diabetes should be tested for hyperglycemia at first booking to rule out any preexisting diabetes.\(^ {19}\)

There is also evidence to suggest that women may manifest hyperglycemia early in pregnancy as a consequence of higher insulin resistance and/or reduced capacity to increase insulin secretion resulting in earlier decompensation manifesting as early onset GDM.\(^ {35}\) There are reports that claim that between 40% and 66% of gestational diabetes can be detected in early pregnancy.\(^ {36-38}\) A cross-sectional observational study from India reported that 31.5% and 43.2% of all GDM cases were diagnosed during testing in the first and second trimester respectively.\(^ {39}\) Similar high rates of GDM diagnosis in the first and second trimester have been reported from Sri Lanka. Given this one would recommend testing at booking and if negative testing again in second and third trimester particularly if risk factors such as overweight and obesity, high maternal age, bad obstetric history, excessive weight gain and family history of diabetes particularly maternal diabetes are associated.\(^ {40}\) For this, the glycemic control has to be optimized from the early weeks of pregnancy. Testing for glucose intolerance only between 24 – 28 weeks is not prudent.

**How good should glycemic control be?**

Glycaemic control has to be optimal from early weeks of pregnancy to prevent the development of fetal hyperinsulinemia. As observed by Norbert Freinkel “No single period in human development provides a greater potential (than pregnancy) for long-range ‘pay-off’ via a relatively short-range, period of enlightened metabolic manipulation”. In the Indian setting achieving new born birth weight between 2.5 and 3.5 kg (Figure 2) should be the aim, as both low birth weight babies and large for gestational age babies are prone to develop diabetes in the future.

Hernandez et al.\(^ {41}\) have systematically reviewed and pooled more than 45 years of normal pregnancy glucose data. They showed that normal glucose pattern were very similar across different studies, and glucose level were generally lower than expected, including FBG of 3.9 ± 0.4 mmol/L, one-hour postprandial glucose of 6.0 ± 0.72mmol/L, two-hour postprandial glucose of 5.5 ± 0.55mmol/L, and 24hour mean of 4.9 ± 0.55mmol/L.

Historically, the treatment goal in pregnancies complicated by diabetes has been to mimic pattern of glycaemia in normal pregnancy.\(^ {42}\)

The success of prevention of type 2 DM entirely depends on aiming for target glycemic level, that is, maternal glucose should be maintained similar to non-diabetic pregnant women Figure 3.\(^ {43}\)

It has been documented that occurrence of macrosomia has a continuous relationship to the 2hr plasma glucose above 120 mg/dl (adjusted odds ratio 3.02 [95% CI 1.30 – 7.00], P < 0.05); \(^ {43}\) and to fasting plasma glucose which becomes significant above 90 mg/dl (adjusted odds ratio 2.08 [95% CI 1.24 – 3.48], P = 0.005).\(^ {44}\) FBG < 90 mg/dl prevents macrosomia as well as other adverse outcomes, such as preeclampsia and contrary to belief, neonatal hypoglycemia doesn’t occur in women with GDM.\(^ {45}\) Pregnant women experience less hypoglycemia in response to exogenous insulin in comparison to non-pregnant subjects.\(^ {46}\) Hence, any recommendation to maintain FPG at 95 mg/dl is not equipoise.

**Conclusion**

Preventive measures against Type 2 DM should ideally start even before conception (being conceived by healthy parents is the best gift a child can receive) but certainly during intra uterine period and continue throughout life from early childhood. It is necessary to optimize metabolic control early in pregnancy. This will necessitate pre-
pregnancy planning for women with pre-existing diabetes, as well as for those at increased risk of GDM, and better means to normalize glycemia. It also requires that all women are tested early and appropriately using a single step procedure and receive good care to ensure optimal glucose control is achieved early in pregnancy and is maintained throughout pregnancy.

1. One test with 75g oral glucose in the fasting or non-fasting state.

2. One value to diagnose GDM. 2hr PG ≥140mg/dl.

3. One target for monitoring Mean Plasma Glucose 105 mg/dl

References


Artificial Intelligence and Deep Learning: The Future of Medicine and Medical Practice

Madhusudana Girija Sanal1, Kolin Paul2, Senthil Kumar3, Nirmal Kumar Ganguly4

Abstract
Artificial Intelligence (AI) and access to “Big Data” together with the evolving techniques in biotechnology will change the medical practice a big way. Many diseases such as type II diabetes will no longer be considered as a single disease. Many familiar cancers such as cancer of liver or pancreas will have hundreds of subtypes whose management will be very different. The way we think about diseases will change. It will no longer be possible for clinicians to make a diagnosis, remember the names of diseases, the names of drugs or management protocols without the help of computers. As computer intelligence becomes more important than human intelligence in deciding diagnosis and treatment there will be a paradigm in the role of doctors. Internet, computers and social media will become more important than individuals in decision making. As a result, medicine will go more and more egalitarian (“wiki”) with increasing community participation in health decision making and management. A socialistic pattern will evolve over time globally as an adaptive reaction to the pressures put by artificial intelligence. This is because the individual differences in knowledge or intellect between human beings will become less apparent compared to the super powers of artificial intelligence. Qualities which are unique for humans such as compassion, empathy and emotional care will decide the professional success of future physicians even more than today. Today we are using artificial intelligence in diagnosis and prediction to help clinicians. Clinical algorithms and human experience cannot be replaced by machines. It will take many years to completely merge or replace humans with machines. However, we need to modify our medical education system in order to prepare the medical community and sensitize the society well in advance for a smooth transition.

“I Propose to Consider the Question, ‘Can Machines Think’”: Alan Turing

Artificial Intelligence (AI) as a philosophy and its practical application thereof, relates to a process wherein the operational aspects of the complex functions of the brain (biological neural network) are developed to varying levels of complexity and invested in a non-biological system. The origins of research into AI can be traced to the defence industry in the 1950’s, but since, has been increasingly used in many fields of human endeavour. This includes navigation (ground, sea and air), geosciences, astronomy, education, finance, manufacturing and art. Healthcare is no exception.

Artificial Intelligence, and access to “Big Data”*** together with the evolving techniques in biotechnology will change the medical practice in a big way. We are at the threshold of the era of precision medicine and AI is an integral part of it. AI will affect the various phases of patient care delivery – from risk prediction, to diagnosis, to tailored therapeutics, to monitoring. Although machines empowered by AI will be better, faster, and cheaper and perform without a break, the purpose of AI is not to replace physicians, but to assist them. With this perspective AI may be better expressed as ‘Augmented intelligence’ or Adjunctive intelligence. AI has the potential to become a disruptive innovation which would make many of the current processes and protocols obsolete. Although every conceivable specialty in medicine will eventually be affected and changed by AI, the ones which depend heavily on pattern recognition, such as radiology, pathology, dermatology and neurology will probably benefit the most in the beginning of the AI revolution in medicine.

From White Light comes the Rainbow: With Precision Medicine Diseases will Split into Several Subtypes

As the resolution of the microscope increases we can see two points as separate. Similarly, as our understanding of the diseases at a molecular level and their associations increases, our diagnostic precision increases. Many diseases such as type II diabetes mellitus will no longer be considered as a single disease. Many familiar cancers such as cancer of liver or pancreas will have hundreds of molecular subtypes whose management will be different. It will no longer be possible for clinicians to remember the increasing numbers of diseases, drugs or management protocols. Even today, it is difficult for many of us to remember increasing list of ‘biologicals’ or the HCV drugs! Richard Smith (former Editor BMJ), predicted that there will be a paradigm shift in the role of doctors in future with the evolution of technology.10 As computer intelligence becomes more powerful than human intelligence in deciding diagnosis and treatment...
the difference between ‘doctors’ and common man decreases. This is because the individual differences in knowledge or intellect between human beings will become less apparent compared to the super powers of artificial intelligence. Internet, computers and social media will become more important than individuals in decision making. As a result, medicine will go more and more egalitarian (“wikification”) with increasing community participation in health decision making and management. A socialistic pattern will evolve over time globally as an adaptive reaction to the pressures put by artificial intelligence. Although AI will outperform humans in the volume, velocity and veracity of data processing, the qualities which are unique for humans such as compassion, empathy and emotional care will decide the professional success of future physicians even more today.

“Big-Data” and Sophisticated Sensors will Bring Machines Closer to Man

Last decade witnessed several breakthroughs in the fields of physics, computer science, material science, biotechnology, genomics and proteomics. These silent but disruptive technologies are revolutionizing the practice of medicine in an unprecedented manner. Artificial intelligence equipped with ‘Deep Learning’* algorithms, biotechnological innovations such as precision genome editing, genomics, metabolomics and proteomics and “the Big Data” will change the concept of diseases, their definitions and patient management.1,2 This “Big Data” will make medical practice more “holistic” because the artificial intelligence would be able to consider several variables ranging from your genomics, real time metagenomics (status of one’s gut microbiome) to your social interactions from social media and wearables without breaching your privacy (as long as privacy means our personal data not seen by another human). This is important from the perspective of personalised medicine as well as public health because of its ‘predictive and preventive’ capabilities through extreme modelling and simulation.

Deep Learning is a group of computational methods that allow a program to modify and adapt itself from ‘experience’ by learning from a large set of examples that demonstrate the desired outcome or behaviour.3 Even today we do not completely know how human mind works and the same may be true for “Deep Learning” algorithms because we still do not know the exact protocols which are developed in the “mind” of a Deep Learning machine-it is a “black box of dynamic algorithms and networks”.

Currently, in certain specialties such as radiology, dermatology and pathology “computer-aided detection” is becoming popular. For example in radiology AI algorithms recognise the patterns and highlights suspicious areas, and helps the radiologists not to miss a finding. The software follows certain algorithms and identifies a suspicious lesion. These programs typically do not learn anything from a case. A machine that has “evaluated” a million MRI images or mammographs is no better than one that was exposed to a couple of images. There is nothing called experience. However, the new technology “Deep Learning” algorithms can actually learn and gain ‘experience’-they can teach themselves. At this point a machine which has seen a million images will be several fold better than a machine which has seen a few. Remember that the most experienced radiologists cannot learn from a million images in his life time! Even at this point machines are limited by their senses and inputs. It do not have an idea about the patient’s posture, texture, warm and smell of his skin, gait, facial expression, social and employment history, patient’s family, friends or lifestyle. However, these machines (read networked machines) can come closer to human capabilities if they can receive inputs from sensors (for various frequencies of sound, light (infrared to UV), voltage, pressure, pH, chemicals (dissolved and gaseous)) and “Big-Data” from genomics, proteomic (OMICS) databases as well as from hospital database, social media and personal/wearable devices.

Historically, medical profession is a highly memory dependent profession. Experience of a doctor is often counted and respected. Experience is nothing but seeing more cases. The more one sees the more one learns. Experience means (but not limited to) identifying same thing in different contexts or identifying different things in same context. An eighty year old doctor might have seen 200,000 patients in his entire career.4 On the other hand a modern computer capable of “deep learning” is ‘competent’ to analyse, learn, assimilate and generate new knowledge. An average medical student learns from less than 50,000 cases during his training period but a computer can learn from millions of archived cases. An ‘intelligent machine’ can learn and assimilate the content of 150 years of British periodicals in limited time.5 However, the computer can currently learn only with reference to some specific “features” as machine learning techniques still are very poor at discovering new features.

“Change Alone is Eternal, Perpetual and Immortal” - Arthur Schopenhauer

Machines are becoming more and more sensitive at detecting and analysing/ diagnosing the many subtle indications that our bodies are misbehaving and even more importantly they are on the path of excelling humans in systematically investigating and diagnosing diseases. In evaluation of retinal fundus photographs from adults with diabetes, an algorithm based on deep machine learning had high sensitivity and specificity comparable to that of trained ophthalmologists for detecting referable diabetic retinopathy.6 An automated screening based on electronic auscultation at clinic level was successful and could be of great benefit in rural practice where there is an acute shortage of experienced clinicians.7 The sensitivity of a computer aided diagnosis system using artificial intelligence for malignant thyroid nodules was as good as that of the experienced radiologist.8 The performance of convolutional neural networks was not significantly different from the best classical methods and human doctors for classifying mediastinal lymph node metastasis of Non-small cell lung cancer from PET/CT images.9 Machine learning algorithms were comparable to trained clinicians in detecting cancer from mammograms, neural disorders, fractures and other orthopaedic conditions, evaluating echocardiograms, dermatological conditions, and detection of polyps from endoscopic images.10-12 Currently most of the machine learning is
limited to pattern recognition from limited input types (such as images) and therefore inferior to humans who go beyond pattern recognition by analysing inputs from multiple senses. However, ‘pattern recognizing’ machine may have an edge over human doctors who do not use their skills beyond pattern recognition. This is important considering the fact that our defective education system selects “memorizers” over thinkers.

Slowly as the technology improves they can be put to more general use and resulting in decreased medical spending. The evolving technology will enable machines to handle large amounts of patient data from multiple sources and correlating them. Currently, machines may be limited by their inputs but sooner technology will enable them to acquire inputs from multiple levels-genomic data, chemical sensors (Mass Spec, NMR, Raman etc.) which will surpass human chemical senses (such as smell, taste), physical senses (ultrasound, Doppler, elastometry data which will surpass human palpation and auscultation), social context data (input from social media, wearables), and the ‘big data’ from genomics, proteomics, metabolomics. Machines can process this data more effectively than humans leading to decide faster, precision diagnosis and personalised patient management.

Learning algorithms are evolving fast- the speed and quality of learning as well as the creative aspects of machine learning such as conceptualisation, hypothesis generation and even imagination would eventually excel humans. However, the current artificial intelligence systems are nothing more than a tool to help the clinician in improving the diagnosis and prediction. Today, a clinician’s experience cannot be replaced by any computer and it will take many years to completely merge or replace human skills and perceptions with output from machines.

The AI technique which is currently powering social media, self-driving cars, super-human image recognition will soon be saving many lives. It is inevitable that AI will infiltrate most areas of healthcare. The pace at which this happens will only accelerate. It is for the medical community to adapt to and embrace this change.

Footnotes

*Deep Learning: Deep learning (also known as deep structured learning or hierarchical learning) is part of a broader family of machine learning methods based on learning data representations, as opposed to task-specific algorithms. Learning can be supervised, partially supervised or unsupervised (Ref. Bengio, Yoshua; LeCun, Yann; Hinton, Geoffrey (2015), “Deep Learning”. Nature. 521: 436–444.)

**Big Data refers to the use of very large data sets (which are large or complex and beyond the handling capacity of traditional data processing application soft wares) used for predictive analytics, user behaviour analytics, or other advanced data analytics methods.

About

The practice of medicine will be disrupted by artificial Intelligence and its access to Big Data’ from ‘OMICS’; wearable real time monitors, historical patient and genealogical databases, social media and internet databases. The way we think about diseases will change because many diseases such as type II diabetes, non-alcoholic liver disease, hepatocellular carcinoma, pancreatic cancer will no longer be considered as a single disease. They will split into hundreds of subtypes or altogether distinct diseases whose diagnostic criteria, prognosis and treatment would be significantly different. Therefore, it will become, humanly, more and more difficult, to make a diagnosis and remember the management protocols unaided by computers. As computer intelligence gain more importance in medical practice, it will diminish the importance of human intellect and the current role of doctors will change. Medicine will go more and more egalitarian with increasing community participation (“wikification”) in health decision making and management. Medical education and training should be adapted to accommodate this foreseeable future. For future medical practitioners, human qualities such as compassion, empathy and emotional care will be increasingly more vital determinants of professional success.

References

A Young Adult with Tracheal Bronchus and Congenital Cystic Adenomatoid Malformation

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24-yr-old male presented to the Department of Pulmonary Medicine, Government Medical College and Hospital, Chandigarh with history of recurrent sore throat, hemoptysis and generalized weakness since 3 months and fever since 20 days. There was no past history suggestive of tuberculosis or repeated infections. Chest radiograph revealed left sided bullous lesions, one with an air fluid level (Figure 1). Sputum for AFB and gram stain were negative and pyogenic culture and sensitivity was sterile. Complete haemogram showed raised total leukocyte count. Spirometry was normal. Patient was managed with antibiotics. After resolution of fever, bullectomy was planned. As a part of routine work-up as per surgical advice, Fibre-optic bronchoscopy (FOB) was done and Contrast enhanced computed tomography (CECT) of the chest was planned. FOB revealed an aberrant bronchus (tracheal bronchus) arising from lateral tracheal wall superior to carina (Figure 2). Negotiation of tracheal bronchus with bronchoscope revealed two openings (Figure 3). Rest of the bronchial tree was normal except that separate right upper lobe bronchus was not seen arising from the right main bronchus.

Our patient was an immunocompetent young adult who presented to the hospital for the first time with infected bullous lesions but otherwise normal intervening lungs. There was no significant past history suggestive of long standing respiratory illness. Hence literature was searched for the associations of the incidental tracheal bronchus with parenchymal involvements, if any.¹,² Since it was found that tracheal bronchus may coexist with other congenital conditions,² a CECT chest was specifically ordered, to find out any such anomaly.

CECT showed lobulated thin walled bullous lesions in the left lower lobe with minimal adjacent fibrosis and the rest of the lung parenchyma was normal. There was no evidence of emphysema or any other sequelae to infective etiology. The bullous lesion was not having any systemic blood supply, so the radiological diagnosis of congenital cystic adenomatoid malformation (CCAM) was made. Thus, it supported the clinical suspicion of associated congenital anomaly post bronchoscopy. CT reconstruction also...
confirmed the findings of a displaced tracheal bronchus supplying the right upper lobe. The displaced tracheal bronchus showed two divisions, one supplying the apical segment, and the other one further dividing and supplying the anterior and posterior segments (Figures 4 and 5).

The patient was taken up for surgery, and the histopathology of the resected bullous lesion confirmed it to be a CCAM. Thus, in our patient, it was found that CCAM mimicked a bulla on initial presentation.

Tracheal bronchus is defined as a bronchus originating from the lateral tracheal wall. It is usually found within 2-6 cms of the carina.1,2 It may coexist with other congenital anomalies, CCAM being one of them.3 CCAM is characterized by a multicystic mass of pulmonary tissue with abnormal proliferation of bronchial structures.3 Most of the congenital abnormalities of the respiratory system are diagnosed in early life. However, some may be diagnosed only in adulthood.3 CCAM is also one of them, as it usually presents in neonatal period or by the first 2 years of life, rarely can it present in adult life.

Detailed assessment of tracheobronchial tree, keeping in mind the presence of aberrant bronchi/segments, and correlating them with the associated congenital malformations, if any, is of great clinical relevance. Firstly, since the congenital abnormalities are usually present in early age groups, they have to be kept in mind and specifically looked for, in adult populations. Secondly, these entities should be known to the chest physicians and surgeons, as they may pose difficulties in diagnosis due to their mimicry with malignancy or sequestration. Recurrent pneumonias and pneumothorax have also been reported in them.4 Thirdly, some patients may need surgery to avoid life threatening complications associated with these congenital malformations.5 And on intubation of such patients during surgery, if the displaced tracheal bronchus is overlooked and an endotracheal tube is placed too distally, gross one lung ventilation may occur, causing further complications and endangering life.6

References


Hematoma of Sternocleidomastoid: Aspirin can be a Cause

Priyanka Verma1, Sanjay Fotydar2, VK Katyal3

A 82 year old female patient presented with chief complaints of diffuse bulge over right side of neck since 5 days (Figure 1). Patient is known case of ischemic heart disease on tablet aspirin 75 mg and tablet atorvastatin 20 mg. No history of trauma/any other drug intake.

On examination hematoma over right sternocleidomastoid muscle is noted, of size approx. 7 cm x 5 cm. color is purple to brownish, warm and non-tender. No thyroid swelling felt. Not associated with difficulty in breathing or swallowing. All baseline investigation came out to be normal regarding hematoma formation.

Pt. was managed conservatively i.e., aspirin was stopped. Hematoma started to regress in size spontaneously in 12 to 15 days and completely disappear in 25-28 days (Figure 2) and on further follow up visit there were no such swelling at that site.

Antiplatelet therapy reduces the rates of re-infarctions and stent thrombosis after intervention in Acute Coronary Syndrome. Antiplatelet therapy is associated with hemorrhagic events, may involve almost all organ systems of body G.I. haemorrhage and IC bleed are the most feared one which may require transfusion of platelets.1

Decreased blood coagulation, increased B.P., liver disease, thrombocytopenia, insufficient thrombin generation, increased INR, insufficient platelet function (as in our case) may all foster the hematoma growth. Complete evaluation must be done to find out the cause in hematoma formation and its progressive enlargement.2

Early recognition, discontinuation of medicine and appropriate management resulted in resolution of hematoma and good clinical outcome.

Hematoma of sternocleidomastoid muscle is a rare complication of aspirin as it has not been reported in literature till now.

References


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B Cell ALL with Pyrexia of Unknown Origin, Masquerading as Inflammatory Arthritis

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Abstract

We present a young male, with long standing fever, weight loss, bone pains, hepatosplenomegalaly, cytopenias and severe joint pains. With normal peripheral smear and predominant joints involvement, he was started on corticosteroids. The partial response prompted the physician to continue the steroids. After some time, however, joints and bony pains worsened.

After referral to us, he was found to have multiple bony lytic lesions and peripheral smear suggested B cell ALL. So, presentation predominantly with musculoskeletal symptoms, a normal peripheral smear and a partial therapeutic response to steroids as treatment of Systemic Juvenile Idiopathic Arthritis, delayed the diagnosis significantly leading to complications.

So through our report we would like to stress that suspecting and diagnosing leukemia early is important to prevent complications and resistance to treatment. An early bone marrow examination should also be instituted as a standard of care in peripheral smear negative patients.

Table 1: Investigations relevant to evaluation of fever. (Abbreviations: mg – milligram, g – gram, ng – nanogram, mm – millimeter, U – Units, dl – deciliter, L – Liter, RF- Rheumatoid factor, ANA- Anti nuclear antibody )

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>4 g/dl</td>
</tr>
<tr>
<td>TLC</td>
<td>2500 /dl</td>
</tr>
<tr>
<td>Platelet</td>
<td>102000 /dl</td>
</tr>
<tr>
<td>ESR</td>
<td>60 mm in the first hour</td>
</tr>
<tr>
<td>CRP</td>
<td>172.8 mg/L</td>
</tr>
<tr>
<td>LDH</td>
<td>2664 U/L</td>
</tr>
<tr>
<td>Ferritin</td>
<td>2095 ng/ml</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>670 mg/dl</td>
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<tr>
<td>Triglycerides</td>
<td>232 mg/dl</td>
</tr>
<tr>
<td>rK 39</td>
<td>Negative</td>
</tr>
<tr>
<td>RF</td>
<td>16</td>
</tr>
<tr>
<td>ANA</td>
<td>1380</td>
</tr>
</tbody>
</table>

Case Summary

A 17 year old male patient resident of Bihar presented to us with high grade continuous fever, joint pains and weight loss since 1½ years. Joint pains involved large joints of all the limbs, migratory type, asymmetrical with night time exacerbations without any associated redness or swelling. With these complaints he was diagnosed outside as a case of Juvenile Idiopathic Arthritis (JRA). Erythrocyte sedimentation rate (ESR) and C Reactive protein (CRP) were elevated but RF and ANA were negative. He has been receiving Disease modifying anti rheumatic drugs (DMARDS) and steroids with intermittent improvement in fever but the joint pains persisted.

After investigations like Computed tomography scans, Ultrasonography etc, he was started on empirical ATT for Pyrexia of unknown origin (PUO) based on prevalence of Tuberculosis in our country and as the most common cause of PUO. Peripheral smear during all this time was normal except for pancytopenia.

On examination, he had severe pallor, hepatosplenomegaly and tender joints with no generalized lymphadenopathy. With these findings we kept the differentials of Adult onset still disease (AOSD), Lymphoma/Leukaemia, Kala Azar, Secondary Macrophage activation Syndrome and TB. Important investigations are mentioned in Table 1.

Peripheral smear showed pancytopenia. With these lab investigations we also thought it to be a case of Adult Onset Stills Disease (AOSD) with Macrophage activation syndrome (MAS) and treated with DMARDS. But since the case was not completely fitting into AOSD criteria (Patient had leucopenia in contrast to expected leukocytosis) and previously treated on similar lines with no improvement and severe weight loss, anorexia, symptoms of joint pains out of proportion to signs with severe pancytopenia, organomegaly and elevated LDH, our suspicion for haematological malignancy was still high, so we did not start the patient on steroids.

We did a CECT chest and abdomen which revealed hepatosplenomegalaly with hypodense cortical lesions bilateral kidney. Multiple lytic/sclerotic lesions were present in pelvic bones, bilateral femur and multiple ribs. This radiological finding strengthened our suspicion for haematological malignancy. Bone marrow touch smear showed near total replacement by blasts which were MPO negative, Peripheral smear showed 70% blast (Figure 1).

Flow cytometry analysis of the bone marrow aspirate revealed CD 45 dim blasts which were CD 34 +, CD 19+, cCD 79a dim +, CD 81+, CD 58+, HLA DR +, CD 10 +, CD 123+, CD 38+, and negative for cMPO, sCD 3, cCD 3, CD 7, CD 20, CD 22, and CD 117 (Table 2). Thus diagnosed as B cell ALL. He was put on standard B ALL chemotherapy protocol. The patient has completed the induction phase of treatment with oral Prednisolone (60 mg/m2), intravenous Vincristine (1.5 mg/m2), L-Asparginase 10000 IU/m2 and is doing well. He is planned to be shifted on to consolidation and maintenance phase.

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Discussion

The usual clinical features suggesting ALL are a young patient presenting with fever, weight loss, night sweats with pancytopenia, lymphadenopathy and hepatosplenomegaly.\(^1,2\) This patient had symptoms of fever, joint pains and weight loss with joint pains as predominant manifestation. Common clinical differentials of such patients include haematological malignancy, Tuberculosis, Leishmaniasis, Hemophagocytic lymphohistiocytosis (HLH), Systemic Juvenile Rheumatoid arthritis and adult onset stills disease.

Arthralgia or even signs of arthritis is a frequent finding in ALL ranging from (18.5%-20%).\(^3,4\) Malignancies are to be suspected when pain is disproportionately severe compared to the physical examination findings, and when pancytopenia, and an elevated LDH level are present. Joint pain being the predominant complaint in our patient diverted the attention to a rheumatological diagnosis. Few studies have shown that osteoarthritis ranges from 8.4 to 35 %\(^5,6\) in pediatric acute leukaemias. Osteoarthritis in leukemic patients tends to be migratory, asymmetric, mono- or oligoarthralgia and poor inflammatory findings for their severe pain\(^7\) but often indistinguishable from early stage of JIA. Unlike JRA, pain from leukemia may, but not always, be point tenderness over the diaphysis rather than diffusely over the joint(s). Our patient also had diffuse pain. Such presentation can occur in 15% to 30% of ALL cases at disease onset, when peripheral blood changes are subtle or even absent.

Infact we also initially thought it could be a case of AOSD as he was partially fitting in the Yamaguchi criteria.\(^5\) He did not have the typical rash or leukocytosis. In the background of pancytopenia, we suspected Macrophage activation syndrome (MAS) secondary to AOSD. Although our working diagnosis was AOSD with MAS, we did not initiate steroids because to make a diagnosis of AOSD we hadn’t excluded infection or malignancy which is an important prerequisite in this diagnosis. Also, since we had suspicion of haematological malignancy which would partially respond to steroids and mask the diagnosis. Earlier too, probably the diagnosis of Systemic Juvenile Rheumatoid arthritis was rushed into without adequately ruling out malignancy.

There was clearly a delay in the diagnosis – 1.5 yrs in our case. The mean Symptom Presentation Interval(SPI) in a study by Marwaha et al was 91 days (range: 30- 365 days) while the mean presentation diagnosis interval was 7.6 days (range : 2- 18 days).\(^6\) Thus, even after admission there was an average diagnostic delay of about a week underscoring the importance of appropriate investigations to rule out ALL in patients with atypical features of JIA. Other investigators have also reported a mean SDI of 3–5 months with a range of up to 18 months. Why this delay occurs is probably due to the close mimic of symptoms, the negative peripheral smear in early cases, partial response to steroids.

Study by Jones et al has shown that 75% of children with ALL did not have blasts in the peripheral blood at the time of evaluation by pediatric rheumatologists.\(^8\) Thus underscoring the importance of bone marrow examination in such patients. Our case also had repeated peripheral smears negative for blasts leading to a possible delay in the diagnosis.

The 3 most important factors that predicted a diagnosis of ALL in the study by Jones et al were low white blood cell count (< 4 x 10(9)/L), low-normal platelet count (150-250 x 10(9)/L), and history of night time pain, which were all present in our patient. In the presence of all 3, the sensitivity and specificity for a diagnosis of ALL were 100% and 85%, respectively. Rheumatologists usually anticipate increased, not decreased, WBC and platelet counts when considering a diagnosis of systemic JRA, and increased platelet counts are not unusual for any type of JRA.

ANA as a test is not a good test to rule in a diagnosis of a rheumatological condition as it can be positive in ALL as well. A twofold or above increase of LDH is almost exclusively seen among children with ALL.\(^9\) Although the frequency of finding an abnormal radiograph was similar between ALL and JRA, presence of radiolucent bands, lytic lesions, and sclerotic lesions should alert the physician to consider malignancy until proven otherwise. Our patient too had an elevated LDH and bony lytic lesions.

There were multiple observations which were made as to where the
diagnosis was missed. If we look at his clinical presentation it is important to note that it was not just joint pains but he had bone pains with nocturnal exacerbations which was missed and the significant weight loss was never explained. His pancytopenia was not worked up, although a peripheral smear was always normal. The probable hypothesis for this could be a partial response of ALL to steroids. Before labelling the patient as AOSD or JIA and starting on steroids, malignancy was not excluded despite persistent pancytopenia. Thus bone marrow examination is important in every patient presenting with atypical features of JIA and a normal peripheral smear to rule out an underlying haematological malignancy.

Conclusion

We presented here a case of B cell ALL which was for more than a year treated AOSD with steroids. So we would like to conclude by emphasising that before labelling a patient as AOSD, a bone marrow examination is important in every patient presenting with atypical features of JIA and a normal peripheral smear to rule out an underlying haematological malignancy. Because the treatment of the condition with steroids might mask the diagnosis of an underlying haematological malignancy further delaying the diagnosis and later the malignancy may become steroid resistant.

References

Abstract
Rupture sinus of Valsalva aneurysm (SVA) is an uncommonly encountered condition. It can present with a wide range of manifestations from an asymptomatic murmur to cardiogenic shock. The case discussed in this report had a rare combination of ruptured SVA with subaortic membrane. Corrective cardiac surgery was advised, but due to financial constraints, the patient was not willing for surgery.

Introduction
Sinus of Valsalva aneurysm is a rare cardiac anomaly with a prevalence of 1.09% of all congenital heart diseases in the Oriental population and 0.2% in the Western population. Subaortic membrane is a fibrous membrane below the aortic valve with a prevalence of 6.5% among acyanotic congenital heart disease patients. Ruptured SVA and subaortic membrane individually being very rare, their combined presence is extremely rare. We present a rare case of a 27-year-old female with ruptured right SVA into right ventricular outflow tract (RVOT) with left to right shunt and subaortic membrane causing severe left ventricular outflow tract obstruction.

Case Report
A 27-year-old female patient was admitted with complaints of shortness of breath, palpitations and retrosternal non-radiating chest pain for seven days. She also had swelling both feet and paroxysmal nocturnal dyspnea. She did not have any significant past medical history. On examination she had respiratory rate of 22/min, regular bounding pulse of rate 112/min, blood pressure 140/50 mm of Hg, prominent carotid pulsation, elevated jugular venous pressure, apical impulse in left 6th intercostal space (ICS), lateral to mid clavicular line and continuous thrill over left 3rd and 4th ICS. On auscultation there was a normal S1, normally split S2 with loud P2, and loud continuous murmur heard along upper left sternal border. Laboratory findings revealed WBC count 12500/µL with 70% neutrophils and 28% lymphocytes, hemoglobin 9.5 gm%, total bilirubin of 1.96 mg/dl, direct bilirubin of 0.64 mg/dl, AST 78 U/L, ALT 69 U/L, normal renal function and electrolytes. Electrocardiogram revealed left ventricular hypertrophy and X-ray chest showed cardiomegaly with left ventricular configuration. Transthoracic echocardiogram revealed 14 mm ruptured right SVA into RVOT causing left to right shunt. There was presence of subaortic membrane causing severe left ventricular outflow tract obstruction with peak pressure gradient of 117 mm of Hg, concentric left ventricular hypertrophy, minimal pericardial effusion, normal left ventricular systolic function, normal right atrial and right ventricular size (Figures 1 and 2). Patient was managed conservatively with diuretics, ACE inhibitors and digoxin as she refused for surgery due to financial constraints and was discharged in stable condition on medications.

Discussion
Sinus of Valsalva aneurysms are rare but well described clinical entity. It is more common in Asians in whom it typically presents in adolescence and young adulthood. It is usually congenital in origin, most often caused by weakness at the junction...
of the aortic media and the annulus fibrosus. Unruptured SVA usually remain asymptomatic and are found incidentally during diagnostic studies. As the aneurysms are frequently clinically silent, their exact prevalence is unknown; however an autopsy study of 8,138 individuals suggests a prevalence of 0.09% in the general population. Approximately 65–85% of SVA originate from the right sinus of Valsalva, while SVA originating from non-coronary (10–30%) and left sinuses (<5%) are less common. SVA are usually diagnosed in the setting of clinical sequelae of a rupture. Majority of SVA arising from right coronary sinus rupture into right ventricle (RV) and less commonly to right atrium (RA), left ventricle (LV) or left atrium (LA). Those arising from non-coronary sinus rupture mostly into RA and less commonly in RV. Left aortic sinus aneurysms commonly rupture into LV or LA. Most ruptures develop well after puberty, between 20 and 40 years of age. The consequences of rupture depend on the size, the rapidity of the process and the chamber into which rupture occurs.

Sinus of Valsalva aneurysms may be associated with other cardiac anomalies which include ventricular septal defect (30–60%), aortic insufficiency (25–45%), bicuspid aortic valve (10%), pulmonary stenosis, coarctation of the aorta, atrial septal defect, and subvalvular aneurysms. Discrete subaortic membrane is a rare cardiac anomaly and its combined presence with SVA is extremely rare. There is no data on prevalence of subaortic membrane in SVA patients. Jain et al. described a case of subaortic membrane with rupture of SVA presenting with infective endocarditis and its thromboembolic complications. Among 234 SVA patients who underwent surgical repair between January 1999 and December 2009, Guo et al. from China described discrete subaortic membrane in seven (2.99%) patients. The resultant effects of subaortic membrane are essentially the same as valvular aortic stenosis: left ventricular hypertrophy from the pressure overload, myocardial ischemia, heart failure, and sudden death. In addition, a subaortic membrane may cause aortic insufficiency and permanent structural damage to the aortic valve due to alteration of left ventricular outflow dynamics. Hence surgical management with resection of the subaortic membrane and repair of SVA is recommended. The rare combination of rupture of right SVA and subaortic membrane was found in our case. Our patient refused for surgery and was discharged on conservative management.

References

Movement Disorder - A Rare Presentation of Diabetic Ketoacidosis

Sneha Garg1, Priyansh Jain1, Vinod Kumar Sharma1, Sanjiv Maheshwari2

Abstract

Diabetic ketoacidosis is a common acute complication of Diabetes Mellitus. Diabetic ketoacidosis is known to cause impaired consciousness due to the osmolar and acid base imbalance which in turn cause central nervous system involvement. Here we report a rare presentation of Diabetic ketoacidosis with movement disorder in form of hemichorea and facial tics. The movement disorder improved with treatment of ketosis.

Introduction

Diabetic ketoacidosis is an acute complication of Diabetes Mellitus. It is associated with volume depletion, electrolyte and acid-base abnormalities. Common presenting symptoms are nausea, vomiting, excessive thirst, polyuria, abdominal pain, shortness of breath, etc.

Here we are presenting rare case of diabetic ketoacidosis as movement disorder in form of hemichorea and facial tics in a previously undiagnosed young female of Diabetes mellitus. Nonketotic hyperglycemia is an established cause of chorea and many cases have been reported. On the other hand, Diabetic ketoacidosis has rarely been reported as a cause of chorea.

Case Report

An 18 year old female, married, one parity, presented to us in casualty medicine unit in altered sensorium. As per history given by the mother and brother she had complains of irrelevant talking, abnormal movements of right arm and right side of face since one day. The onsets of these symptoms were described as gradual and then she was in altered sensorium when brought to hospital. She also had complaint of generalized abdominal pain, moderate in intensity, dull in character and without any precipitating/relieving factor since 10 days. She had no history of vomiting or aspiration. She had no significant past medical/surgical history, no history of seizure disorder, and no psychiatric illness and no significant family history.

On examination, the patient was fairly built and nourished, was not fully conscious and oriented, her Glasgow Come scale was E2M4V2.

Her vitals were: pulse rate – 138/min; BP 140/70 mmHg; RR- 34/min; afebrile; oxygen saturation- 98% on room air. Pupils were round, regular and reactive.

Her nervous system examination revealed GCS- 6, no signs of meningeal irritation, generalized increase in tone in all four limbs, with normal deep tendon reflexes and superficial reflexes. Planter reflexes were bilateral mute. She was having choreiform movements on right side of the body along with facial tics on same side.

At the time of admission her random blood sugar was 452 mg% and urine ketones were large. Complete blood count, peripheral blood smear, renal function tests, liver function tests, serum electrolytes, ECG, chest skiagram, and USG abdomen, all were within normal limits.

On the basis of the above evaluation the patient was shifted into ICU and treatment of diabetic ketoacidosis was started. After 2 days when the ketones were nil in the urine, the patient was taken on the basal-bolus insulin regime.

Even after regaining full consciousness, her choreiform movements involving the right arm and tics on right side of face persisted which could not be suppressed with voluntary effort, although marked reduced during sleep.

For further neurological evaluation detail fundoscopy by expert ophthalmologist and EEG were performed and found unremarkable.

MRI brain showed significant subcortical T2 and FLAIR hyper intensity seen predominantly in the left parieto-occipital lobe and part of left temporal lobe with subtle hyperintensity in the overlying cortex, which includes possibilities of either hyperglycemic injury or subacute hypoxic insult (Figures 1, 2, 3).

The frequency and the amplitude of choreiform movements decreased as the serum glucose approached normal levels. She was discharged on insulin basal bolus regimen.

On follow up after one month she was alert and oriented with disappearance of choreiform movements. Only the facial tics persisted which were milder in intensity as compared to when she was admitted

Discussion

Movement disorders e.g. chorea or ballismus have been reported in different states of diabetes mellitus. Despite the large number of cases of chorea being reported in nonketotic hyperglycemia, after excluding other causes diabetic ketoacidosis has been reported rarely as sole trigger for movement disorder, as seen in our case. This was confirmed by the temporal relationship between diabetic ketoacidosis and the abnormal movements.

The pathophysiology of movement disorders in Diabetic ketoacidosis remains speculative. It is probably multifactorial and hyperglycemia is undoubtedly one of the factors.

One hypothesis is related to the lowered threshold for seizure or dysfunction of the basal ganglia due to a deficiency of the inhibitory neurotransmitter gamma amino butyric acid (GABA). During hyperglycemic crisis the activity of tircarboxylic acid cycle (Krebs cycle) and glucose...
Figs. 1(a, b, c) MRI brain images showing significant subcortical T2 and FLAIR hyperintensity seen predominantly in the left parieto-occipital lobe and part of left temporal lobe with subtle hyperintensity in the overlying cortex

utilization are depressed in the brain, so the cerebral metabolism shifts to alternative pathways.\(^1\)

Another hypothesis involves transient focal cerebral ischemia caused by hyperglycemia. Cerebral hypoperfusion may result from an increase in cerebrovascular resistance due to the higher brain water content during hyperglycemia or to a loss of flow regulation caused by impaired metabolism.\(^1\)

In patients with Diabetic Ketoacidosis, cerebral oxygen utilization is impaired, and there is hyper viscosity of the blood. A substantial part of the brain’s energy source is derived from ketones, which themselves can depress sensorium. Extracellular hyper osmolality is present, which may also contribute to the genesis of coma. In addition, most ketoacidotic patients have associated medical conditions, which may further impair consciousness. Biochemical changes in the brains of animals with DKA include impairment of both phosphofructokinase activity and pyruvate oxidation and accumulation of citrate. The net effect upon sensorium in ketoacidotic patients probably represents the interaction of most of the above factors and differs markedly among individuals.\(^2\)

The hyper intensity on MRI histologically corresponds to selective neuronal death and gliosis with preservation of the macroscopic structure of the brain that appear after brief ischemia. These microscopic lesions may offer an explanation why movement disorder sometimes outlast the period of hyperglycemia, as seen in our patient. The focal neurological deficits are more easily explainable in the cases of non ketotic hyperglycemia.\(^1\)

Patients with non ketotic hyperglycemia manifest not only depression of sensorium, but also focal motor seizures, hemiparesis, and other neurologic changes, such as aphasia, hyperreflexia, sensory defects, autonomic changes, and brainstem dysfunction. Most of the aforementioned changes revert to normal after correction of hyper osmolality.\(^2\)

We suggest that multiple mechanisms are involved in pathogenesis of movement disorder in diabetic ketoacidosis. Diabetic vasculopathy with a consequent cerebrovascular insufficiency is another hypothesized mechanism but this may not hold true in our case as she is a case of new onset diabetes.\(^3\)

Neuromuscular irritability in diabetic ketoacidosis is also ascribed to electrolyte imbalance especially hyperkalemia, hyponatremia and hypocalcemia. These may lead to localized involuntary movements at different places. Subtle basal ganglia injury can also occur in context of ketosis and is reported in literature as a complication of ketogenic diet.\(^4\)

**Conclusion**

The case presenting as the choreiform movements and facial tics as the initial presentation of Diabetic ketoacidosis is a rare entity. The possible hypothesis have been cited. The treatment proven effective was the adequate management of hyperglycemia with adequate insulin regime and dietary advice.

Therefore although DKA has been rarely reported as a trigger for chorea, it should be in the differential diagnosis of a patient presenting with an acute chorea. Given the reversible nature of this disease, early recognition and treatment are imperative.

**References**

1. Focal Neurological Symptoms as the Presenting Manifestations of Nonketotic Hyperglycemia Report of Two Cases-Sheng-Feng Sung et al–Division of Neurology, 1 Division of Endocrinology and Metabolism, Chia-Yi Christian Hospital, Chia-Yi, Taiwan 2007.
Acute Bilateral Cataract in Patient with Type 1 Diabetes Mellitus and Celiac Disease

Ashish Kumar Bhagat1, Harnoor Bhardwaj2, Bachan Lal Bhardwaj3, Sanjay Goyal1, Salil Jaura4, Pallav Jain4

Introduction

Cataract represents one of the most frequent eye complications in type 1 DM and type 2 DM patients; contrarily, acute cataract in young diabetic patients occurs very rarely. Only few cases with acute bilateral cataract - all relatively shortly after the diagnosis of type 1 DM have been reported. It can affect visual acuity from slight visual impairment to complete blindness. Although usually associated with chronic hyperglycaemia, it may also occur on rapid restoration of euglycaemia. Early detection of diabetes and adequate glycaemic control, particularly in female adolescents, may prevent this debilitating complication of diabetes.

Case Report

A 21-year-old female was diagnosed as type 1 DM/Celiac disease 3 yrs back when she presented with complaints of polyuria, polydipsia, weight loss and put on insulin therapy.3 months back patient developed sudden blurring of vision in both eyes which progressed over a duration of 7 days. On ophthalmologic examination visual acuity was found to be restricted to hand movements in both eyes. There was no history of previous eye problems and visual acuity was normal in both eyes at the start of treatment. Slit-lamp biomicroscopy revealed dense cortical cataracts bilaterally. No fundus details were visible in either eye. The patient was treated with bilateral phaco emulsification once sugar levels fell within normal limits.

Discussion

Young patients with diabetes mellitus can present with eye problems during the early course of the disease and treatment. The exact mechanism of diabetic cataract is not known although it is thought to be related to poor glycaemic control and abnormalities in the polyol pathway. Reduction of glucose to sorbitol by aldose reductase (AR) leads to accumulation of sorbitol, which produces osmotic stress. It also produces oxidative stress by depleting cofactor NADPH that is an important cofactor for regeneration of reduced glutathione (GSH). Some authors also mention the probable importance of genetic factors in their case studies but the mechanism is still poorly understood. Some other researchers have suggested that rapid glyemic improvement on institution of insulin therapy leads to a hypoxic phenomenon which may also affect the activities of the protective enzymes in the lens, resulting in increased oxidative stress and subsequently to acute cataract formation. The factors associated with cataract in young persons with diabetes include high HbA1c levels, adolescence and female gender. A female preponderance has been suggested in various case series on acute catartas and newly diagnosed cases of type 1 diabetes.

Conclusion

In conclusion, acute-onset visual loss from cataracts is an unusual manifestation of type 1 diabetes. These cataracts once developed can be irreversible in spite of good metabolic control and require surgical intervention. Clinicians should stress on adequate and gradual control of hyperglycaemia in newly diagnosed type 1 diabetes adolescents while at the same time balancing the risk of rapid glycaemic control in these patients.

Abbreviations

DM: Diabetes mellitus; NV: Normal value; FPG: Fasting plasma glucose; NADPH: Nicotinamide adenine dinucleotide phosphate.

References

Sweet’s Syndrome in a Case of Ulcerative Colitis—Case Report and Review of Literature

Mukesh Nasa¹, Zubin Dev Sharma², Lipika Lipi³, Randhir Sud⁴

Abstract
Sweet syndrome, also known as acute febrile neutrophilic dermatosis, is one of the rare cutaneous association of ulcerative colitis. Only few cases of Sweet syndrome associated with ulcerative colitis have been reported in literature. We herein describe a case of young female with acute exacerbation of ulcerative colitis associated with erythematous, papular skin lesions which on biopsy were consistent with Sweet syndrome. Treatment with intravenous steroids resulted in improvement of ulcerative colitis and disappearance of cutaneous lesions. Cutaneous lesions of Sweet syndrome in ulcerative colitis parallel the bowel disease activity in majority of the cases but sometimes may precede the intestinal symptoms and rarely may appear after proctocolectomy for acute severe ulcerative colitis.

Introduction
Inflammatory bowel disease, that comprises ulcerative colitis and Crohn’s disease, is associated with variety of extra-intestinal manifestations involving different organ systems including the skin. Extra-intestinal manifestations are more frequent in ulcerative colitis. Overall prevalence of these manifestations is 21% and more than one extra-intestinal manifestation occurs in about 25% of patients. Extra-intestinal involvement occurs involving kidneys, eyes, joints, lungs and skin.

Cutaneous involvement occurs in 5% of the patients of ulcerative colitis. Skin involvement may occur during the acute exacerbation of bowel disease activity or sometimes it may precede the bowel involvement. Among the different cutaneous manifestations, the most common is erythema nodosum.

Sweet syndrome is one of the rare associations of ulcerative colitis. It is also known as acute febrile neutrophilic dermatosis. Its first description was given in 1964 by Robert Douglas Sweet. Its association with ulcerative colitis was first reported in 1988. It is characterized by acute onset fever accompanied by leucocytosis and histology reveals neutrophilic infiltration of the upper dermis.

There have been only few cases of Sweet syndrome associated with ulcerative colitis reported in literature. We therefore report this rare association of ulcerative colitis.

What’s known
1. Sweet syndrome, acute febrile neutrophilic dermatosis, is characterized by acute onset fever accompanied by leucocytosis and skin rash and histology of skin lesions histology reveals neutrophilic infiltration of the upper dermis.
2. It is one of the rare associations of ulcerative colitis.

Case Report

Our patient was 23 years old female, known case of ulcerative colitis, who was in remission on treatment with oral mesalamine and azathioprine. Presented with 3 days history of acute onset high grade fever, skin eruptions in the form of tender, well demarcated red colored lesions (Figure 1). These lesions were non-pruritic. She gave history of increased frequency of stools, 5-6 times, watery in consistency with blood and mucus. There was no abdominal pain, cough, chest pain, headache or joint pains. In the past, the clinical course of ulcerative colitis has been waxing and waning with few flares in last couple of years managed with oral steroids. Prior to current admission, her disease was in remission.

On examination, she was febrile, there were ulcers on the uvula, the skin lesions were tender, well demarcated papules with few showing pustular transformation. There were spread throughout the body including face, trunk and limbs. There were no genital ulcers. Abdominal examination was unremarkable.

She was admitted under gastroenterology unit. Complete blood counts showed leucocytosis. Her tests for malaria, dengue, leptospiroa, Weil Felix, Cytomegalovirus (CMV IgM) and Ebstein Barr Virus (EBV IgM) were all negative. Her Anti-nuclear antibody by immunofluorescence was negative.
The findings were suggestive of Acute Negative. All the above staining for immunohistochemistry, IgA was negative. There was no evidence of granulomas or dysplasias. On histological examination, there were cell infiltrates composed of lymphocytes and neutrophils. There was no evidence of spontaneous remission of Sweet syndrome. Her colonoscopy showed loss of vascular pattern of mucosa, with mild ulcerations. There was no spontaneous oozing or friability. Colonic biopsy showed disorganization of crypt architecture, dilated and branched crypts, crypt destruction with cryptitis and crypt abscess. The lamina propria showed dense acute and chronic inflammatory infiltrate. All the findings were suggestive of moderate activity in a case of ulcerative colitis.

Skin biopsy (Figures 2 and 3) was taken from one of the lesions which showed inflammatory exudate covering the epithelium. There were neutrophilic abscesses in epithelium as well as sub epithelium, mainly concentrated around vessels and adnexal tissues. There were perivascular inflammatory cell infiltrates composed of lymphocytes and neutrophils. There was no evidence of granulomas or dysplasias. On immunohistochemistry, IgA was negative. All the above staining were suggestive of Acute Neutrophilic Dermatoses.

She was started on intravenous hydrocortisone (100 mg thrice daily). Her clinical symptoms including skin lesions, responded well by day 5 of treatment. She was subsequently discharged on tapering dose of oral steroids.

**Discussion**

Sweet syndrome, also known as acute febrile neutrophilic dermatoses is one of the rare cutaneous manifestation of ulcerative colitis. Other conditions reported to be associated with Sweet syndrome are- Sarcoidosis, rheumatoid arthritis, subacute thyroiditis, Behcet’s disease, ankylosing spondylitis, Sjogren’s syndrome, and malignancies specially the haematological malignancies like lymphoma. It has also been reported in association with some medications like trimethoprim, nitrofurantoin, sulfamethoxazole, diclofenac and ofloxacin.

In majority of the cases, Sweet syndrome occurs during the periods of acute exacerbation of the intestinal disease but it may precede the bowel disease activity and sometimes it may occur even after procto-colectomy. In a retrospective analysis of 29 cases of Sweet syndrome, underlying disease could be identified only in four cases (lymphoma, polycythemia, sarcoidosis and ulcerative colitis), while another study of 16 cases of Sweet syndrome by Ginarte, M. et al, one had ulcerative colitis and another two had underlying malignancy. Neutrophils infiltration occurs in upper dermis in Sweet syndrome but the factors that stimulate the neutrophil migration into skin have not been elucidated. Sweet syndrome was reported in patients with T cell immunodeficiency and in patients receiving G-CSF treatment. Endogenous G-CSF might play role in mediating neutrophil migration to the dermis. In patients of inflammatory bowel disease, Sweet syndrome is more frequently seen with colonic disease and it is more common in females. Idiopathic Sweet Syndrome can present as photo-dermatoses.

Treatment of Sweet syndrome is the immunosuppression mainly with systemic steroids. Other drugs that have been tried like Cyclosporin, indomethacin, dapsone, colchicine and clofazimine also been reported for successful treatment. There have been few case reports of spontaneous remission of Sweet syndrome.

**What’s new**

Sweet syndrome is one of the rare cutaneous association of ulcerative colitis. Skin lesions mostly appear during the periods of acute exacerbation of the disease and respond to steroid treatment.

**References**

Mahendra Lal Sircar - Science Visionary

Jayant Pai-Dhungat

Mahendra Lal Sircar (1833-1904) was born in 1833 in a poor family at Kolkata. He lost both parents early in life and was brought up by his maternal uncle. He learned Bengali and English from home tutors, and secured admission to Hare School as a free student, in 1840. At the school David Hare, a great educationist made a lasting impression on him. Later he left for Calcutta Medical College, as he was bent upon studying medicine. Sircar obtained his IMS in 1861 and MD degree in 1863. (Second MD of the then Calcutta University).

Although educated in modern system of medicine, he was attracted by Homoeopathy after reading William Morgan’s book. Convinced with the alternative medicine, he soon read a paper “the supposed uncertainty of medical science” at the British Medical Association meeting (1867), and advocated support for homeopathy. BMA disapproved his stand and dismissed him from the Association. Although ostracized for his interest in homoeopathy, his practice in modern medicine rose steadily. Soon Mahendra found himself at the top of his profession with an unchallenged supremacy and also went on to be a leading homeopath practitioner of India.

Amidst the demands of his time, he initiated the historic science movement in August 1869, by starting it as a science class at his residence, every Sunday. His pamphlets brought enthusiastic response from students and several newspapers. Over Rs/-8,000 were received as donations. With these funds the Indian Association for the Cultivation of Science (IACS) came into being on 29th July 1876, with Mahendra Lal as the Secretary. The foundation stone was laid by Lt. Governor Sir Richard Temple, while Viceroy agreed to become the Patron. The visionary in Sircar relentlessly carried the flame of Indian science with zeal and optimism. Within few decades, Sir C. V. Raman brought in vindication of the pioneer’s vision. It is at the laboratory of IACS, that the legendary Raman discovered Noble Prize winning Raman Effect in 1928. Raman paid a rich tribute to Sircar during a Civic reception in Calcutta when he received Nobel Prize in physics (1931). Raman found that light scattered by the molecules in a solution was altered in wavelength. From the nature of alteration, deduction could be made about the structure of the molecule. The principle of molecules altering wavelengths of the light (Raman spectrum) indirectly became the bases for CT Scans, nuclear magnetic resonance or MRI imaging.

Mahendra Lal became Hon. Magistrate and Sheriff of Calcutta (1883), and was made a C. I. E. (1887). In 1898, he was honored with a Doctor of Law degree by Calcutta University.

In the course of his career, he treated several notable people, like noted author Bankimchandra, Maharaja of Tripura and the great ascetic Ramakrishna Paramhansa. Sircar visited the spiritual giant several times between October 1885 and August 1886. He diagnosed his disease as cancer of the throat and made a plea to him to stop his extensive discourses, singing, and dancing. However, Ramakrishna did not heed his advice.

In 1898 Sir J.N.Tata (1839-1904) bequeathed a part of his property, worth Rs/-30 Lakhs toward establishment of a new institute of science, which took shape as IIS at Bangalore. Mahendra Lal was disillusioned with his countrymen, particularly rich Bengalis; He felt that Bengal had rejected its own 30 yrs old IACS. At one of the meetings, he concluded his speech with a couplet:

“Now my weary lips I close
Leave me, leave me to repose”
Better performers have Volibo®

for GI therapy
An Expert Review and Recommendations on the Rational Use of Proton Pump Inhibitors: Indian Perspective

Shobna Bhatia1, Akash Shukla2, David Johnson3, Urmila Thatte4, Parimal Lawate5, Sethu Babu6, Pravin Rathi7, Sudeep Khanna8, MS Sandeep9, Vijay Raj10, Nikhil Parchure11, Vinod Agrawal12

Abstract

Background: Proton pump inhibitors (PPIs) are the mainstay of treatment for acid peptic diseases (APDs), but are often irrationally prescribed in clinical practice. Appropriate prescription of PPIs is needed to optimize outcomes, and minimize risks and cost burden on the healthcare system.

Objective: To review available literature on efficacy and safety of proton pump inhibitors (PPIs) and give recommendations for rational use of PPIs from an Indian perspective.

Methods: Twelve healthcare professionals (9 gastroenterologists, 1 cardiologist, 1 orthopedist, 1 clinical pharmacologist) comprised the expert group; members disclosed conflicts of interest. The creation of the expert review was through a process that included meetings (in-person, online, telephone) where each professional contributed their experiences with regards to efficacy and safety of PPIs. Articles published between the years 2000 and 2017 were reviewed for evaluation of safety and efficacy of PPIs in treatment of various APDs.

Conclusion: This expert review provides key recommendations for decision making in order to minimize the irrational use of PPIs. Some significant recommendations include: patients with GERD and acid-related complications should take a PPI for minimum 12 weeks for healing of esophagitis, and for maximum up to 48 weeks for symptom control. Patients with Barrett’s esophagus should take long-term PPI. Patients at high risk for ulcer-related bleeding from NSAIDs including aspirin should take a PPI if they continue to take NSAIDs. Best practice recommendations are meant to merely assist with decision making in conjunction with patients’ clinical history, and are not intended to dictate mandatory rules.

Introduction

Acid peptic diseases (APDs) are prevalent worldwide; changing lifestyles and dietary habits may be attributable to the rising disease burden. A systematic review of 28 studies indicated ethnic and geographical variations in prevalence of gastroesophageal reflux disease (GERD) [18.1–27.8 % in North America, 8.8–25.9 % in Europe, and 2.5–7.8 % in East Asia]. A survey of 1000 clinicians from India showed a high prevalence of GERD (39.2%), peptic ulcer disease (PUD, 37.1%) and non-ulcer dyspepsia (25.2%) with nearly 50% of patients requiring prompt endoscopy. Specific symptoms need to be identified accurately in order to avoid under-diagnosis or over-treating APDs.

Medications available for treating these acid related diseases are proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RA), antacids, sucralfate and prostaglandin analogues. The PPIs available in the Indian market for clinical use are dexlansoprazole, dexcelabeprazole, esomeprazole, ilaprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole. Their CDSCO (Central Drugs Standard Control Organization) approved indications are presented in Table 1.

Irrational prescription has been rampant with PPIs being prescribed to patients not presenting with valid indications warranting PPI use. A study by Churi et al. (2014) showed intravenous (IV) PPIs being inappropriately prescribed to 89.2% of internal medicine ward patients and 34.04% of surgery ward patients. Parenteral PPIs, being relatively expensive compared to oral PPIs and H2RAs, can significantly increase the cost for patients in hospitals. In another study at a tertiary care teaching hospital in Raichur, Karnataka, 50% of PPIs were orally prescribed to patients. Improper utilization of PPIs can lead to adverse effects, which in turn may result in an economic burden on patients seeking treatment. Quality variability across formulations manufactured by different companies may be an issue peculiar to India. In view of these concerns, the current expert recommendations have been developed to assist physicians in the rational use of PPIs.

Methods

The expert review team (ERT) comprised of 12 experts- 9 gastroenterologists, an orthopedist, a cardiologist and a clinical pharmacologist. All ERT members had
Table 1: Approved PPIs and their Indications in India as per the CDSCO

<table>
<thead>
<tr>
<th>Indications</th>
<th>Esomeprazole (10, 20, 40 mg)</th>
<th>Omeprazole (20, 40 mg)</th>
<th>Lansoprazole (30 mg)</th>
<th>Pantoprazole (10, 20, 40 mg)</th>
<th>Rabeprazole (10, 20 mg)</th>
<th>Deslansoprazole (30, 60 mg)</th>
<th>Dexrabeprazole (5, 10, 30 mg)</th>
<th>Ilaprazole (5, 10 mg)</th>
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<tbody>
<tr>
<td>Route</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Injection</td>
<td>Oral</td>
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<tr>
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<td>✓</td>
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<td>✓</td>
<td>Injection</td>
<td>✓</td>
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<td>Erosive esophagitis</td>
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<td>Reflux esophagitis</td>
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<td>Peptic Ulcer Disorder</td>
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<td>Gastric Ulcer</td>
<td>✓</td>
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<td>Duodenal Ulcer</td>
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<td>✓</td>
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<tr>
<td>Prophylaxis of NSAID induced ulcer</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td>Zollinger-Ellison syndrome</td>
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<td>Eradication of H. pylori</td>
<td>✓</td>
<td>✓</td>
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</tbody>
</table>

Data extracted from CDSCO.4

Table 2: Review of clinical studies of efficacy of various PPIs in GERD (ERD and NERD)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Study Drugs and Sample Size</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. 2017</td>
<td>PRISMA- compliant network meta-analysis</td>
<td>Esomeprazole (60 mg), Omeprazole (40 mg), Pantoprazole (40 mg), Lansoprazole (30 mg), Rabeprazole (20 mg), Omeprazole (20 mg)_N=25,088</td>
<td>• Esomeprazole 40 mg showed significantly higher healing rate at 4 weeks [versus omeprazole 20mg, lansoprazole 30 mg, rabeprazole 20 mg, pantoprazole 40 mg] and at 8 weeks [versus omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg]</td>
</tr>
<tr>
<td>Zheng et al. 2009</td>
<td>RCT</td>
<td>Omeprazole (20 mg; n=68), Lansoprazole (30 mg; n=69), Pantoprazole (40 mg; n=69), Esomeprazole (40 mg; n=68), Esomeprazole (40 mg)</td>
<td>• Heartburn relief was significantly better with esomeprazole 40 mg compared to omeprazole 20 mg and lansoprazole 30 mg</td>
</tr>
<tr>
<td>Edwards et al. 2006</td>
<td>Systematic review and meta-analysis</td>
<td>Lansoprazole (30 mg), Omeprazole (20 mg), Pantoprazole (40 mg), Rabeprazole (20 mg)_N=14,800</td>
<td>• D Lansoprazole 60 mg exhibited the significantly increased withdrawal rates compared with omeprazole 20 mg, pantoprazole 40 mg, lansoprazole 30 mg, and rabeprazole 20 mg</td>
</tr>
<tr>
<td>Gralnek et al. 2006</td>
<td>Meta-analysis of RCTs</td>
<td>Esomeprazole (40 mg), Omeprazole (20 mg), Lansoprazole (40 mg), Esomeprazole (40 mg)</td>
<td>• Complete resolution of heartburn in reflux esophagitis patients treated with esomeprazole for 5 days compared with omeprazole, lansoprazole and pantoprazole</td>
</tr>
<tr>
<td>Nagahara et al. 2014</td>
<td>RCT</td>
<td>Omeprazole (20 mg QD; n=106), Rabeprazole (10 mg QD; n=103)</td>
<td>• Healing rates of reflux esophagitis showed a significant benefit in favor of esomeprazole at 4 weeks (RR 0.92; 95% CI: 0.90, 0.94; P &lt; 0.00001) and at 8 weeks (RR 0.95; 95% CI: 0.94, 0.97; P &lt; 0.00001)</td>
</tr>
<tr>
<td>Delchier et al. 2009</td>
<td>RCT</td>
<td>Rabeprazole (20 mg QD; 104), Rabeprazole (10 mg BID; 103), Omeprazole (20 mg QD; 103)</td>
<td>• No significant differences were seen between the groups in the rate of endoscopic healing of reflux esophagitis at week 8</td>
</tr>
<tr>
<td>Liu et al. 2017</td>
<td>Meta-analysis</td>
<td>Lansoprazole (15 mg, 30 mg, 60 mg), Omeprazole (10 mg, 20 mg, 40 mg)_N=8752</td>
<td>• Esomeprazole conferred an 8% (RR, 1.08; 95% CI, 1.05–1.11) relative increase in the probability of GERD symptom relief at 4 weeks</td>
</tr>
<tr>
<td>Srikanth et al. 2014</td>
<td>Prospective RCT</td>
<td>Pantoprazole (40 mg; n=55), Esomeprazole (40 mg; n=55)</td>
<td>• At both 4 and 8 weeks, a 10% (RR, 1.10; 95% CI, 1.05–1.15) and 5% (RR, 1.05; 95% CI, 1.02–1.08) relative increase in the probability of healing with esomeprazole versus alternative PPIs observed</td>
</tr>
<tr>
<td>Moraes-Filho et al. 2014</td>
<td>RCT</td>
<td>Pantoprazole-Mg (40 mg; n=290), Esomeprazole (40 mg; n=288)</td>
<td>• Mucosal healing rates were high and not significantly different in both treatment groups</td>
</tr>
<tr>
<td>Vedamanickam et al. 2017</td>
<td>Open, comparative Rabeprazole (20 mg; n=70) clinical trial</td>
<td>Esomeprazole (40 mg; n=70)</td>
<td>• At the end of 8th week, 90% relief from GERD-symptoms was noted with esomeprazole and 92% relief was noted in rabeprazole group</td>
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Contd...
Expertise in the clinical management of patients taking PPIs. PubMed database was used to ensure studies of safety and efficacy of PPIs published between the years 2000 and 2017 were captured. The search was made using the following Medical Subject Headings (MeSH) terms: Anti-inflammatory Agents- Non-Steroidal, Drug Interactions, Dyspepsia, Deprescriptions, Histamine Antagonists, Drug-related Side Effects and Adverse Reactions, Acute Kidney Injury, Proton Pump Inhibitors, Helicobacter pylori, Gastrointestinal Motility, Benznamides/metabolism, Amidine Antagonists, Parasympathomimetics, Cardiovascular Diseases/complications, dexlansoprazole, dexrabeprazole, esomeprazole, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole. The ERT reviewed published as well as unpublished literature on PPI safety and efficacy in Indian population and gave recommendations on the rational use of PPIs in alignment with those provided by the American Gastroenterological Association (AGA) 2017.

The expert review is presented here under efficacy of PPIs in various indications, safety of PPIs including drug interactions, selecting appropriate PPIs, deprescribing PPIs and Indian recommendations for rational use of PPIs. Recommendations were articulated by the ERT.

### Efficacy of PPIs

#### Gastro-esophageal Reflux Disease (GERD)

The most effective treatment choice for frequent GERD symptoms are PPIs, which provide effective symptomatic relief in about 56-76% patients,9 and esophageal lesion healing rate of 80-85% at 8 weeks.10 The standard doses of PPIs once daily (QD) should be best taken 30-60 minutes before breakfast. Despite the well-recognized efficacy, approximately 30% of GERD patients remain symptomatic on this dose with a possibly increased risk of other complications such as Barrett's esophagus.11 Although PPIs are an effective option in gastric acid control, a subgroup of patients such as those with non-erosive reflux disease (NERD) may remain refractory to standard PPI treatment.12 Table 2 summarizes a review of clinical studies of the efficacy of various PPIs in GERD.

#### Peptic Ulcer Disease (PUD)

Defects in the gastrointestinal (GI) mucosa that may also extend through the muscularis mucosa can be attributed to peptic ulcers (gastric and duodenal).13 PPI therapy for ulcer bleeding in the Asian population has been more efficacious than in Western countries.14 With endoscopy being a treatment most utilized for bleeding peptic ulcers, PPI therapy can significantly reduce re-bleeding in patients after endoscopy.15 The link between the pathogenesis of upper GI diseases and the presence of H. pylori infection has been investigated to understand the relation of its eradication with peptic ulcer healing. It is crucial to diagnose whether patients suffering from PUD have an H. pylori infection to aid in a treatment strategy.

PPIs decrease acid secretion by inhibiting the H+K+-ATPase. However, a correlation between higher or lower doses affecting healing of NSAID-induced ulcers is unclear. The local and systemic action of NSAIDs on the gastric mucosa combined with the failure of mucosal protective defense is the pathogenic process for development of NSAID-related gastroduodenal ulcers. As these risks are dose- and time-dependent, high-dose and long-term NSAID users may have a higher risk of developing peptic injury.16 Furthermore, reduction in ulcer re-bleeding, surgery and mortality has been observed in patient with ulcer bleeding and on PPI therapy.17,18 Table 3 summarizes a review of clinical studies of the efficacy of various PPIs in PUD.

#### Functional Dyspepsia (FD)

With a global prevalence of 11-29.2% for functional dyspepsia (no organic cause to explain symptoms),19 dyspeptic symptoms have been reported in the Indian community ranging from 7.6-
Table 3: Review of clinical studies of efficacy of various PPIs in PUD, eradication of *H. pylori* and prophylaxis of NSAID-induced ulcers

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Study Drugs and Sample Size</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peptic Ulcer Disease</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hu et al. 2017</td>
<td>Pairwise and network meta-analysis of RCTs</td>
<td>Lansoprazole (15 mg; 30 mg), Rabeprazole (20 mg), Pantoprazole (40 mg), Ilaprazole (10 mg), N=6,188</td>
<td>No significant difference in the healing rate for duodenal ulcer treated with different PPIs in different doses except Pantoprazole 40 mg versus Lansoprazole 15 mg (RR = 3.57; 95% CI= 1.36–10.31) and Lansoprazole 30 mg versus Lansoprazole 15 mg (RR = 2.45; 95% CI = 1.01-6.14)</td>
</tr>
<tr>
<td>Zeng et al. 2015</td>
<td>Meta-analysis</td>
<td>Lansoprazole, Omeprazole, N=774</td>
<td>No significant differences between patients treated with lansoprazole combinations and omeprazole combinations in terms of healing rate (RR = 1.04, 95% CI = 0.99-1.09, P = 0.93)</td>
</tr>
<tr>
<td>Wang et al. 2006</td>
<td>Meta-analysis</td>
<td>Omeprazole (20 mg), Lansoprazole (30 mg), Omeprazole (20 mg), N=5,998</td>
<td>No significant difference for the rate of adverse effects between different PPIs in different doses</td>
</tr>
<tr>
<td>McNicholl et al. 2012</td>
<td>Meta-analysis</td>
<td>Esomeprazole (40 mg; 20 mg, 10 mg), Lansoprazole (80 mg), Omeprazole (20 mg), N=5,998</td>
<td>Higher eradication rates for esomeprazole than for first-generation PPIs: 82.3% vs. 77.6%; OR = 1.32 (1.01–1.73); NNT = 21</td>
</tr>
<tr>
<td>Gisbert et al. 2004</td>
<td>Meta-analysis</td>
<td>Esomeprazole (20 mg), Omeprazole (20 mg), Metronidazole (250 mg), Amoxicillin (1 g)</td>
<td>Mean H. pylori eradication rates (intention-to-treat) with esomeprazole plus antibiotics was 85% and 82% when omeprazole was used (OR 1.19; 95% CI: 0.81–1.74)</td>
</tr>
<tr>
<td>Hawkey et al. 2003</td>
<td>RCT (n=87), OCA (n=96), RCM (n=87), OCM (n=97), R, rabeprazole 20 mg, O, omeprazole 20 mg, C, clarithromycin 500 mg, A, amoxicillin 1000 mg, M, metronidazole 400 mg</td>
<td>R, rabeprazole 20 mg, O, omeprazole 20 mg, C, clarithromycin 500 mg, A, amoxicillin 1000 mg, M, metronidazole 400 mg</td>
<td>No statistically significant difference in eradication rates between esomeprazole-based and other PPI-based regimens (OR 1.17, 95% CI: 0.89, 1.54, p&lt;0.25)</td>
</tr>
<tr>
<td>Gisbert et al. 2003</td>
<td>RCT (n=87), OCA (n=96), RCM (n=87), OCM (n=97), R, rabeprazole 20 mg, O, omeprazole 20 mg, C, clarithromycin 500 mg, A, amoxicillin 1000 mg, M, metronidazole 400 mg</td>
<td>R, rabeprazole 20 mg, O, omeprazole 20 mg, C, clarithromycin 500 mg, A, amoxicillin 1000 mg, M, metronidazole 400 mg</td>
<td>Analyses of low-dose (20 mg BID) esomeprazole and high-dose (40 mg BID) esomeprazole showed no significant differences in <em>H. pylori</em> eradication rates between esomeprazole-based and other PPI-based regimens (OR 1.20, 95% CI: 0.92, 1.56, p=0.17 and OR 3.21, 95% CI: 0.31, 32.93, respectively)</td>
</tr>
<tr>
<td>Scheiman et al. 2011</td>
<td>RCT (OBERON)</td>
<td>Low-dose acetylsalicylic acid (75-325 mg), Esomeprazole (40 mg, n=817,20 mg, n=804), Placebo (n=805)</td>
<td>After 26 weeks, esomeprazole (40 mg and 20 mg) significantly reduced the cumulative proportion of patients developing peptic ulcers</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>The 1.5% of esomeprazole 40 mg and 1.1% of esomeprazole 20 mg recipients, compared with 7.4% of placebo recipients, developed peptic ulcers (both p&lt;0.0001 vs placebo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acid-suppressive treatment with once-daily esomeprazole 40 mg or 20 mg reduces the occurrence of peptic ulcers in patients at risk for ulcer development who are taking low-dose ASA</td>
</tr>
</tbody>
</table>

*Contd...*
95% CI, 1.8%–34.3%). Furthermore, a reduction [RRR] of 10.3%; 95% CI, 2.7%–8.6% was observed in the efficacy for patients with ulcer-like FD symptoms in patients (Relative Risk Difference [RRD], 10.3%; 95% CI, 2.7%–8.6%).

Wang et al. (P<0.001).25 The ENTER trial showed a significant difference at 8 weeks (P=0.009).24 Furthermore, a systematic review of 23 RCTs to study PPIs with respect to global symptoms of dyspepsia revealed similar efficacy rates of low-dose as well as standard-dose PPIs.22

The major PPIs that have been explored for the treatment of dyspepsia are omeprazole, esomeprazole and lansoprazole. Results from the BOND (n=642) and OPERA (n=606) randomized clinical trials revealed complete relief of symptoms achieved in 38.2% of the 20 mg omeprazole group (p=0.002) and in 36.0% of the 10 mg omeprazole group (p=0.02) compared with 28.2% in the placebo group of patients with dyspepsia.23 The ENTER trial showed a significant efficacy of 4-week esomeprazole (40 mg) for symptom relief compared to placebo, but no statistically significant difference at 8 weeks (P=0.009).24 Peura et al. (2004) showed significantly greater symptomatic relief at 8 weeks in FD patients with lansoprazole (15 mg or 30 mg OD) compared with placebo (P<0.001).25

Safety of PPIs

Adverse events (AEs) with PPI Use

Proton pump inhibitors are well tolerated in patients with the frequency of adverse effects being <5%; the most common being headache, diarrhea, abdominal pain and nausea.26 The American Gastroenterological Association (AGA) has outlined an evidence of potential adverse events based on the GRADE methodology. Some of the reported potential PPI-associated adverse effects identified in observational studies are kidney disease, bone fracture, myocardial infarction, C. difficile infection, pneumonia, micronutrient deficiencies, dementia, GI malignancies.27 However, the quality of evidence is low to very low which most likely is attributed to a stratification bias which predisposes to these conditions, independent of PPI exposure. Retrospective database analyses cannot correct for this type of potential bias unless the database was constructed from the onset.27 Table 4 highlights some of the most commonly observed adverse effects with PPI use.

There are many published articles highlighting the long-term safety concerns of PPIs. However, the US FDA has issued PPI class warnings only for three conditions viz. Clostridium difficile-associated diarrhea (released in the year 2012), low magnesium levels (year 2011), and possible increased risk of fractures of the hip, wrist, and spine (year 2011). However, these associations of harm have not been accepted as valid in more recent expert consensus reports.27

The alleged safety concerns highlighted with the long-term use of PPIs are class effects and not specific to any PPI molecule. The choice of PPI and duration of its use should be based on clinical condition of the patient under treatment and associated comorbid conditions.45

Drug Interactions with PPIs

The concomitant prescription of PPIs with other drugs may pose a risk to patients due to PPI metabolic interactions. The safety profiles of various PPIs need to be thoroughly understood with respect to a patient’s medical history in order to avoid unwanted outcomes. Pharmacokinetic mechanisms by which PPIs exhibit drug-drug interactions are by altering drug absorption, modifying hepatic metabolism via either enzyme inhibition or induction, and affecting renal elimination of concomitant drugs.46 PPIs have also been observed to reduce the oral bioavailability of antiretroviral drugs such as atazanavir, darunavir and fosamprenavir by about 50%; thereby requiring their concomitant use with PPIs to be restricted.46 Some prominent drugs and their pharmacokinetic effects with concomitant PPI use have been highlighted in Table 5.

Selection of Appropriate PPIs

In order to appropriately prescribe a drug to a patient, factors such as the efficacy, safety, suitability and cost need to be taken into account by the prescriber. The WHO recommends that when two drugs appear to be similar, factors such as thorough clinical investigations, pharmacokinetic profile and reliability of local manufacturing facilities need to be taken into account for selection.48 While efficacy is a critical decider for many prescribers, unnecessary prescription of a stronger or more sophisticated PPI to treat a large number of patients, and taking side effects into secondary consideration, may provide minimal benefit. Moreover, kinetic characteristics that could be irrelevant to the drug profile, but stressed to promote an expensive drug often lead to cheaper alternatives.
Table 4: Summary of studies that report adverse events with adjusted odds ratio or hazard ratio

<table>
<thead>
<tr>
<th>Author, Year and Country</th>
<th>Results</th>
<th>Adjusted OR/HR and 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiu et al., 2010, Taiwan (28)</td>
<td>Risk of hip fracture for ≥28 defined daily doses* of PPI</td>
<td>OR 1.04 (0.73–1.49)</td>
</tr>
<tr>
<td></td>
<td>Risk of hip fracture for ≥97 defined daily doses* of PPI</td>
<td>OR 1.67 (1.11–2.51)</td>
</tr>
<tr>
<td></td>
<td>Risk of hip fracture for ≥70 defined daily doses* of PPI</td>
<td>OR 2.51 (1.77–3.55) (p value for trend &lt;0.0001)</td>
</tr>
<tr>
<td>Ding et al., 2014, USA (29)</td>
<td>Risk of any fracture with use of PPI</td>
<td>HR 1.27 (1.12–1.43; p=0.0002)</td>
</tr>
<tr>
<td></td>
<td>Risk of major osteoporotic fractures with use of PPI</td>
<td>HR 1.28 (1.09–1.51; p=0.003)</td>
</tr>
<tr>
<td></td>
<td>Risk of hip fracture with use of PPI</td>
<td>HR 1.32 (1.01–1.71; p=0.04)</td>
</tr>
<tr>
<td></td>
<td>Risk of vertebral fracture with use of PPI</td>
<td>HR 1.69 (1.26–2.27; p=0.0005)</td>
</tr>
<tr>
<td>Lee et al., 2013, Korea (30)</td>
<td>Risk of hip fracture with PPI use</td>
<td>OR 1.34 (1.24–1.44)</td>
</tr>
<tr>
<td></td>
<td>Risk of hip fracture with PPI use not on bisphosphonate treatment</td>
<td>OR 1.30 (1.19–1.42)</td>
</tr>
<tr>
<td></td>
<td>Risk of hip fracture with PPI use on bisphosphonate treatment</td>
<td>OR 1.71 (1.31–2.23)</td>
</tr>
<tr>
<td>Clostridium difficile infection</td>
<td>Risk of C. difficile infection with use of PPI</td>
<td>OR 1.51 (1.26–1.83)</td>
</tr>
<tr>
<td>Gomm et al., 2012, USA (31)</td>
<td>Risk of vitamin B12 deficiency with ≥2-year supply of PPI</td>
<td>OR 1.65 (1.58–1.73)</td>
</tr>
<tr>
<td></td>
<td>Risk of vitamin B12 deficiency with ≥2-year supply of H2RA</td>
<td>OR 1.25 (1.17–1.34)</td>
</tr>
<tr>
<td>Jung et al., 2015, USA (34)</td>
<td>Risk of vitamin B12 deficiency with ≤10 months of PPI/H2RA</td>
<td>HR 1.83 (1.36–2.46; p value 0.00)</td>
</tr>
<tr>
<td>Kidney Diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leonard et al., 2012, UK (35)</td>
<td>Risk of acute interstitial nephritis with use of PPI</td>
<td>OR 3.20 (0.80–12.79)</td>
</tr>
<tr>
<td>Xie et al., 2016, USA (36)</td>
<td>PPI group had an increased risk of incident eGFR &lt;60 ml/min/1.73 m²</td>
<td>HR 1.22 (1.18–1.26)</td>
</tr>
<tr>
<td></td>
<td>Risk of incident CKD</td>
<td>HR 1.28 (1.23–1.34)</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gomm et al., 2016, Germany (37)</td>
<td>Risk of incident dementia with use of PPI</td>
<td>HR 1.44 (1.36–1.52; p&lt;0.001)</td>
</tr>
<tr>
<td>Community-Acquired Pneumonia (CAP)</td>
<td>Risk of CAP with current use of PPI</td>
<td>OR 1.5 (1.3–1.7)</td>
</tr>
<tr>
<td></td>
<td>Risk of CAP with past use of PPI</td>
<td>OR 1.2 (0.9–1.6)</td>
</tr>
<tr>
<td></td>
<td>Risk of CAP with recent initiation of PPI</td>
<td>OR 5.0 (2.1–11.7)</td>
</tr>
<tr>
<td>Johnstone et al., 2010, Canada and Europe (39)</td>
<td>Risk of CAP with use of PPI</td>
<td>OR 1.36 (1.12–1.65; p=0.001)</td>
</tr>
<tr>
<td>Meijvis et al., 2011, Netherlands (40)</td>
<td>Risk of CAP with past PPI exposure</td>
<td>OR 1.2 (0.72–2.1; p=0.46)</td>
</tr>
<tr>
<td></td>
<td>Risk of CAP with current PPI exposure</td>
<td>OR 1.6 (1.2–2.2; p=0.01)</td>
</tr>
<tr>
<td></td>
<td>Risk of CAP with initiation of PPI in last 30 days</td>
<td>OR 3.1 (1.4–7.1; p=0.01)</td>
</tr>
<tr>
<td>Lambert et al., 2015, USA, Canada, Asia, Europe (41)</td>
<td>Risk of CAP with ambulatory PPI therapy</td>
<td>Pooled OR 1.49 (1.16–1.92; p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Risk of hospitalization for CAP with PPI therapy</td>
<td>Pooled OR 1.61 (1.12–2.31)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danziger et al., 2013, USA (42)</td>
<td>Risk of hypomagnesemia with use of PPI</td>
<td>OR 1.54 (1.22–1.95; p=0.001)</td>
</tr>
<tr>
<td>Cheungpasitporn et al., 2015, USA (43)</td>
<td>Risk of hypomagnesemia with use of PPI</td>
<td>Pooled RR 1.43 (1.08–1.88)</td>
</tr>
</tbody>
</table>

Notes: *Defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults. The studies mentioned above include case-control, prospective/retrospective cohort, meta-analyses and systematic review studies. Abbreviations: OR, odds ratio; HR, hazard ratio; RR, relative risk; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonists; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CAP, community-acquired pneumonia

being underutilized.44

Special populations such as elderly, children, pregnant women and those with kidney or liver disease need to be closely followed-up when initiating treatment with PPIs.

The cost of a drug needs to be taken into account based on the clinical setting as patients in resource limited countries. In India, most patients have inadequate access to health insurance and medical reimbursement schemes thereby limiting their affordability for more expensive medications because most of the healthcare expenditure is out of pocket.45 Although the safety and efficacy across PPIs are relatively similar, differences in their cost can play a major role in governing their utilization across clinical settings in India.

Certain PPIs, particularly branded drugs, may be expensive as compared to generics, therefore, the social status of the patient, length of the treatment, the total cost of the treatment apart from efficacy and safety, need to be taken into account when initiating a drug therapy for a patient. Long-term PPI therapy may be required in underprivileged sections of the society, and prescribing drugs purely based on efficacy, safety and tolerability may diminish patient adherence due to unaffordable healthcare costs. This in turn would increase the burden of unwanted complications that would lead to increased economic burden on a hospital, and ultimately, the country.

De-prescribing PPIs

Although PPIs have a number of benefits and are viewed as safe, inappropriate prescription or prolonged usage with limited or no benefit can potentially cause adverse reactions. Deprescribing refers to stopping, stepping down or reducing the doses of PPIs by discontinuing tapering, abruptly stopping/tapering, the doses of PPIs by discontinuing/stopping, stepping down or reducing long-term drug therapy for a patient. Long-term PPI therapy may be required in underprivileged sections of the society, and prescribing drugs purely based on efficacy, safety and tolerability may diminish patient adherence due to unaffordable healthcare costs. This in turn would increase the burden of unwanted complications that would lead to increased economic burden on a hospital, and ultimately, the country.

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adults with Barrett’s esophagus, severe esophagitis (GRADE C or D) and documented history of bleeding GI ulcers, de-prescription should be based on patient’s history and medical judgement.

The American College of Gastroenterology (ACG) 2013 guideline for treatment of GERD, recommends an initial therapy of PPIs for 8 weeks, followed by discontinuation with a need for maintenance therapy to be assessed. Reducing the PPI to the lowest effective dose before discontinuation, while exploring a symptom management strategy that could include on-demand PPIs, could improve the stepping-down approach for clinicians and decrease potential long-term adverse effects in patients. Long term continuation of PPIs is appropriate for risk reduction of nonsteroidal anti-inflammatory (NSAID) prophylaxis in appropriate patients. 

### Fixed Dose Combinations of PPIs with Prokinetic Drugs

In India, the combination of PPI and prokinetic agent is being increasingly used by medical practitioners in patients with severe and resistant GERD. Although PPIs lower acid production, have high healing rates, and rates of resolution of reflux symptoms at 4 weeks, the downside is their inability to improve underlying disturbance in gut motility or improve tone of cardiac sphincter; causing relapse in most cases. The ACG 2013 guideline recommends that therapy for GERD other than acid suppression, including prokinetic therapy and/or baclofen, should not be used in GERD patients without diagnostic evaluation (conditional recommendation, moderate level of evidence). Prokinetic therapy with metoclopramide in addition to PPI therapy is another option often considered for patients with incomplete response to PPI therapy. For the small number of patients who may
benefit from a prokinetic, another option is domperidone, a peripherally acting dopamine agonist. The ACG 2017 guideline recommends that dyspepsia patients under the age of 60 not responding to PPI or H. pylori eradication therapy should be offered prokinetic therapy (very low quality evidence). The combination of prokinetic and PPI therapy regimen versus PPI monotherapy has been investigated to understand safety and efficacy profiles. Ren et al. (2014) analyzed 12 RCTs where participants were treated with 5-HT agonists, GABA-B receptor agonists, dopamine-receptor antagonists, each with PPI therapy. A reduction in the number of reflux episodes in GERD (95% CI: -5.96 to 1.78, P = 0.0003) with the combined therapy was observed, however, the effect on acid exposure time was insignificant (95% CI: -0.37 to 0.60, P = 0.65). A double blind randomized clinical trial conducted by Ndraha et al. (2011) among sixty dyspeptic patients having heartburn and/or regurgitation revealed a statistically significant improvement with a combination of omeprazole and domperidone in GERD patients with high frequency scale of symptoms for GERD (FSSG) score, compared to omeprazole monotherapy (P = 0.02). The use of prokinetics have had variable success in patients with functional dyspepsia however, they fail to promote healing of esophagitis leaving them inadequate for GERD treatment. Despite a positive outcome, further studies with different PPI and prokinetic combinations need to be conducted to understand the utility of the FSSG score for the addition of a prokinetic to PPI therapy in different populations. Adverse drug reactions such as headache, lethargy, giddiness, diarrhea, xenostomia and QT prolongation have been found in studies involving metoclopramide and levosulpiride, and the former four AEs have also been found in domperidone. A prospective, randomized study by Jain et al. (2017) revealed superiority of levosulpiride (25 mg TID) over domperidone (10 mg TID) in patients with FD (n=182), but reported more adverse effects than the latter. Further, the impact of prokinetic therapy on clinical outcomes such as pneumonia, mortality and ICU length stay in critically ill patients remains unclear.

A safe and effective prokinetic agent, over PPI therapy, may be an appropriate empiric choice when heartburn occurs with symptoms of impaired gastric emptying. In clinical practice, although agents such as PPIs are effective in acute treatment and are preferred for maintenance therapy, a ‘step-down’ approach may allow them to be replaced with either a prokinetic agent or H2RA.

### Expert Panel Recommendations

The Clinical Practice Updates Committee of the American Gastroenterological Association (AGA) in 2017 formulated 10 best practice recommendations based on expert opinions and related publications for the treatment of GERD, Barrett’s esophagus and NSAID bleeding prophylaxis. The expert panel has adapted AGA recommendations with Indian context as shown in the Table 6.
References


Conclusion

This expert review provides key recommendations for decision-making in order to minimize the irrational use of PPIs. Best practice recommendations are meant to merely assist with decision-making in conjunction with patients’ clinical history, and are not intended to dictate mandatory rules.
Prevalence and Determinants of Tobacco Product Use Among the Tribal Community of West Bengal: A Cross-sectional Survey

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Sir,

Tobacco addiction is a global problem. Studies from South Asia have shown high rates of smoking (30-55%) among adult males. In females, the rate is generally lower, except in some areas. While smoking is important, there are various smokeless forms of tobacco which are equally prevalent.

A study from Kerala, India has shown that the indigenous tribal population have a much higher rate of tobacco use compared to the general population. Studies concentrating on tobacco use of specific population groups like indigenous tribal and ethnic minorities are scarce from Eastern India. In this study, we aimed to conduct a survey on the patterns of tobacco use among the adults of a tribal population in West Bengal.

Patients and Methods

This was a hospital-based, cross-sectional, questionnaire based survey. The study was conducted simultaneously in a tertiary care medical college of West Bengal and a peripheral rural hospital. Full ethics committee permission was taken.

The survey was conducted using a pre-tested and validated structured questionnaire. The survey was conducted over a period of three months. Subjects were randomly chosen from the patients attending the outwards of the two hospitals.

Calculation of sample size

In a recent survey from Eastern India, tobacco use prevalence in the rural population has been found to be 31.9%. Taking this as a reference, the sample size was calculated to be 334 (for a precision of 0.05). The data was entered from the patient data sheet in to SPSS (Ver. 19) worksheet. Appropriate statistical tests were done.

Results

We had 345 subjects in our study with male: female ratio of 231: 114. Mean age of the study subjects was 43.1±8.7 years. Out of the study subjects, 175 (50.7%; 95% C.I.: 45.3—56.1%) had knowledge about the harmful effects of tobacco. In the female subset, 82 (71.9%) had the knowledge while in the male subset, only 93 (40.3%) were aware (p=0.0001).

Overall, 218 subjects (63.2%; 95% C.I.: 57.9-68.3%) used one or more tobacco products. 74.5% of the male subjects used tobacco products (one or more) while only 40.4% of the female subjects used tobacco. In this study, 82% used only one or more tobacco products. 74.5% of the male subjects used tobacco products (one or more) while only 40.4% of the female subjects used tobacco. In this study, 82% used only one or more tobacco products. 74.5% of the male subjects used tobacco products (one or more) while only 40.4% of the female subjects used tobacco.

Of the study subjects who used tobacco (n=218), 35 (16%) used only the smoking form (biri or cigarette). The rest used either only the smokeless form or a combination of both. Of the tobacco products used in our study subjects, khaini was the most popular (n=95; 43.6%; 95% C.I.: 36.9—50.4%). The next most used products were gutkha (n=78), Biri (n=72) and Zarda (n=71). In the male subset, 80 (46.5%) preferred khaini. Tobacco use through smoking was done by 93 (40.3%) male subjects. But in the female subset, the most popular form of tobacco used was gutkha (n=26; 22.8%) followed by guraku (n=19; 16.7%). Only 6 female subjects (5.3%) reported smoking.

Among the study subjects, khaini-gutkha combination was the most popular (n=20), followed by gutkah-zarda (n=18). Out of the female subjects who were labourers (n=27), rate of tobacco use was 77.8% (n=21).

The average age of initiation of tobacco use was 23.6±4 years. Regarding the influence behind initiation of tobacco use, peer pressure was overall the most common factor (n=80; 36.7%; 95% C.I.: 30.3-43.5%). As Figure 2 shows, in females, family member influence was a more important factor in initiating tobacco use (34.8%) than male (26.7%).

Discussion

In a study from Kerala, India it was found that the prevalence of tobacco use among tribal population was 73.8%. Of them, 82% used only smokeless forms of tobacco while only 8% were pure smokers. The average age of onset was 16.4 years for smoking and 17.5 years for smokeless forms. In our study, the average age of initiation was 23.6 years, considering all forms together. In the Kerala study, 40% of the subjects cited family influence and 23% cited peer pressure as factors in tobacco initiation.

Another similar study was conducted among Tribal adolescents in Maharashtra. It was found that 50% of them used smokeless forms while 23% were smokers. In this study, chewing tobacco with betel quid was the most popular form of smokeless tobacco, followed by pan masala. But in our survey, khaini was the most popular form, followed by gutkha.

A study from Madhya Pradesh
found that the prevalence of tobacco use among tribal population was 43.4%. Khaini was the predominant form used and only 5% smoked biri or cigarette. In this study, 39.5% of the female subjects reported tobacco use, which is similar to our data.

Trends from national sample survey of India between 2000 and 2012 have found that while overall tobacco use may have decreased slightly by a few percentage points among the tribal population, the use of smokeless tobacco has actually increased. The trend in the use of multiple tobacco products has also increased in this time period.

However, although India is the world’s largest market for smokeless tobacco, effective prevention strategies have often lagged behind the tobacco industry’s aggressive marketing. Instead of using the term “Smoking is injurious to health”, a better approach could be “Tobacco is injurious to health.”

Conclusion

Tobacco use is significantly high among the tribal population of West Bengal. The use of smokeless tobacco is much higher compared to smoking. There is a gender difference in the preference for particular tobacco products.

Acknowledgement

BMOH, Salboni Rural Hospital.

References


Juvenile Idiopathic Arthritis and Role of Anti-CCP Antibody

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Sir,

Juvenile Idiopathic Arthritis (JIA) is a WHO/ILAR endorsed; internationally accepted umbrella term that has replaced all previously used nomenclatures including Juvenile Rheumatoid Arthritis (JRA) and Juvenile Chronic Arthritis (JCA). The chief clinical feature of JIA is persistent joint swelling in the absence of any defined cause, which begins before the age of 16 years. The term JIA covers at least seven clinical subtypes of arthritis.1,2 Although classification of diseases without knowing the exact cause is difficult and somehow preliminary it is particularly important to recognise that 95% of arthritis affecting children and adolescents is clinically and immune-genetically distinct from rheumatoid arthritis (RA) in adults.3 In contrast to other juvenile auto immune connective tissue diseases the true RA is difficult to define.

I would like to discuss two cases of chronic inflammatory arthritis of juvenile onset, which were presented to physician in their adulthood. Both had different duration of diseases and both were classified as JIA. Case One: A 18-year-old girl was presented with history of bilaterally symmetrical joint pain involving metacarpophalangeal (MCP), proximal interphalangeal (PIP), wrist, elbow, knee, ankle and metatarsophalangeal (MTP) joints with early morning stiffness of more than 1 hour for 3½ years. General and systemic examination was normal. Musculoskeletal examination showed evidence of synovitis at all MCP, MTP and wrist joints bilaterally. Case Two: A 27-year-old female was presented with complain of cough, breathlessness and vomiting for three days. She had history of bilaterally symmetrical joint pain involving MCP, wrist, elbow and knee joints with early morning stiffness of more than 1 hour for 14 years. She was on herbal medicine and over the counter treatment for pain since last few years. Patient was having tachycardia and tachypnoea on admission and BP was 190/130 mm of Hg. She had pallor and mild pedal oedema. On systemic examination mild inspiratory craps were present bilaterally in infra axillary regions. Musculoskeletal examination showed evidence of synovitis at both wrist joints and deformity at right elbow joint. Investigations done in both cases are summarised in Table 1.

Both cases had certain similarity such as age at onset near 16 year, female gender, polyarticular onset, high titre anti CCP antibody, homogenous ANA pattern at low titre and negative ENA profile. The second case experienced erosive disease and systemic complications after few years of onset. However it is difficult to compare future course of individual patient on the bases of two cases, one can still observe that may be high titre of anti CCP antibody predicts poor outcome in these small group of patients with JIA just like in adult with RA especially related to erosive diseases.

RF positive JIA is subtype that resembles adult RF positive RA. However, the ILAR classification criteria do not capture all children with childhood onset RA due to specific exclusion criteria while the ACR/ EULAR criteria used for diagnosing adult RA do not have these exclusions, and they include the highly specific anti-CCP antibodies. Surprisingly Anti CCP antibody, one of the more specific

Table 1: Investigation results for cases

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Case one</th>
<th>Case two</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine protein</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>10.2 gm%</td>
<td>7.1 gm%</td>
</tr>
<tr>
<td>TC/PC</td>
<td>Within normal limits</td>
<td>Within normal limits</td>
</tr>
<tr>
<td>ESR</td>
<td>14 mm/hour</td>
<td>40 mm/hour</td>
</tr>
<tr>
<td>CRP</td>
<td>90 Mg/L</td>
<td>17.2 Mg/L</td>
</tr>
<tr>
<td>S.Creatinine</td>
<td>0.7 mg/dl</td>
<td>1.9 mg/dl</td>
</tr>
<tr>
<td>SGPT</td>
<td>18 IU/L</td>
<td>65 IU/L</td>
</tr>
<tr>
<td>RF</td>
<td>1:16 by latex</td>
<td>12.06 IU/ML by turbido-metric</td>
</tr>
<tr>
<td>ANA</td>
<td>+2 Homogenous</td>
<td>+1 Homogenous</td>
</tr>
<tr>
<td>Ena Profile</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti CCP antibody</td>
<td>&gt;200 U/ml by ELISA</td>
<td>48.34 U/ml by ELISA</td>
</tr>
<tr>
<td>X-rays</td>
<td>Chest-normal</td>
<td>Chest-normal</td>
</tr>
<tr>
<td></td>
<td>Both hands with wrist and feet</td>
<td>Both hands with wrist- AP shows erosion on right 2&lt;sup&gt;nd&lt;/sup&gt; MCP and X-ray right elbow shows deformed joint at right elbow</td>
</tr>
</tbody>
</table>

Others | - | USG abdominal-medical renal disorders |

Position Change followed by Early Ambulation after Coronary Angiography via Femoral Approach: A Randomized Controlled Trial

Parishra Rai1, Manju Dhandapani2, Shiv Bagga3, L Gopichandran4, Yash Paul Sharma5

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Coronary angiography is the gold standard test for detecting coronary artery disease. Femoral route is usually preferred but due to risk of vascular complications, bed rest is recommended. The aim of present study was to assess effect of position change followed by early ambulation after coronary angiography via femoral approach on comfort, fatigue and vascular complications of the patients.

A randomized controlled trial was conducted on 80 adult conscious patients (40 each in control and experimental group) undergoing coronary angiography in a tertiary care medical and research institution in North India. Ethical approval was obtained from the Institute Ethics Committee and CTRI registration was done under Indian Council of Medical Research. After taking informed written consent, the patients were randomly allocated to experimental and control group using computer generated random table. Patients in control group were placed in supine position and ambulated after 6 hours. Patients in experimental group were kept in supine position for 2 hours after angiography, followed by right lateral position (1 hour), supine position (1 hour) and ambulated after 4 hours. Comfort (Kolcaba’s General Comfort Questionnaire), back pain (Numerical rating scale) & fatigue (Fatigue Visual Numeric Scale) were assessed at 2, 4, 6 & 24 hours after angiography. Incidence of vascular complications was documented at 24th hour.

Demographical and clinical profile of patients in both the group were comparable. More than three-fourth of the patients in the control group and more than half of the patients in the experimental group were diagnosed with coronary artery disease. It was observed that back pain was significantly lower in experimental group as compared to the control group at 6th hour and 24th hour after angiography. At 4th and 6th hour after angiography, fatigue experienced by experimental group was significantly lower than control group. There was no significant difference between the two groups in vascular complications.

Results of the present study showed that position change followed by early ambulation at four hours after coronary angiography reduced back pain, enhanced comfort and decreased fatigue, without increasing the risk of the vascular complications.

To avoid vascular complications, patients are usually instructed to rest in bed in a supine position with the affected leg in a straight position for 6-8 hours after coronary angiography. Due to this enforced supine bed rest, immobilization and restricted positioning, patients frequently experience back pain discomfort and fatigue. Lying on the back for a long time imposes pressure, and causes cellular ischemia, muscle spasm, fatigue and pain in the lumbar muscles. Inner-muscle pressure in lumbar muscles has a direct relation with the patients’ position and the imposed load on the muscles. Therefore, patients intend to change their position so as to reduce the pain and discomfort. Moreover early ambulation allows the patient to sit comfortably and eat without difficulty. Leg numbness and urinary discomfort are also decreased.

Similar to present study findings, it is reported in the literature that ambulating patients four hours after coronary angiography via the femoral route is safe and do not increase the vascular complications. While few studies have focused on only the effect of early ambulation after coronary angiography on back pain, comfort and vascular complications, others have only demonstrated the effect of various modified positions of the patients after coronary angiography via femoral route. Present study has combined the effect of modified positioning with early ambulation.

In the light of the findings of the present study, it can be suggested that the position of the patients can be safely changed followed by an early ambulation of four hours after coronary angiography via the femoral route.

References

3. Chari SV. Early mobilisation after transfemoral catheterisation is not associated with increased vascular incidents, and reduces back pain. Evidence Based Nursing 2014; 18:20.
3 LAWS OF MOTION

- **Inertia**
- **F = MA**
- **F = F2**

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