Hypertension & CAD
when co-exist can attract complications...

In Hypertensives with symptomatic CAD
Telvas*βeta
Telmisartan & Metoprolol Succinate ER Tablets 25/50 mg

• Helps achieve target BP
• Offers end organ protection
• Helps reducing cardiovascular morbidity and mortality

The Alliance for Assured CV Protection
In Management of Hypertension

ENAM®
Enalapril 2.5 mg / 5 mg / 10 mg tablets

The Trusted Choice in Hypertension

Since 1989

- Only molecule with 24 Years follow-up trial - SOLVD¹
- Proven efficacy to save more lives² & prevent new onset of diabetes³ in patients with CHF


BECELAC® FORTZ
Lactic Acid Bacillus 2000 Lacs, Folic Acid 1.5 mg, Cyanocobalamin 15 mcg, Niacinamide 100 mg & Biotin 100 mcg capsules

Your Trusted Brand Since 25 years

*Data on file * For the use of a Registered Medical Practitioner; Hospital or Laboratory only or as per the description under Form 46 of the Drugs & Cosmetics Act, 1940

Dr. Reddy’s Laboratories Ltd., Global Generics - India, 7-1-27, Ameerpet, Hyderabad - 500 016, India. www.drreddys.com
Bridging the gap between CONTROL & SAFETY

Essential hypertension, Renal parenchymal hypertension, Angina

Rx

EFNOCAR
Efondipine Hydrochloride Ethanolate 20/40 mg Tablets

The Incomparable CCB with Extra Ordinary Care

With Incomparable Properties...

RENAL Protection | CARDIO Protection | SAFETY Profile

Zuventus Lifestyle

Office No. 5119, 5th Floor, D Wing, Oberoi Garden Estates, Chandivali, Andheri (E), Mumbai 400 072.
Contents

EDITORIAL

- Hypertension and Hyperuricemia: A Compelling Correlation
  Mangesh Tiwaskar ............................................................... 11

ORIGINAL ARTICLE

- Hypertension as Determinant of Hyperuricemia: A Case Control Study from the Sub-Himalayan Region in North India
  Sujeet Raina, Vishnu Kumar Agarwal, Dhiraj Kapoor, Kailash Nath Sharma, RS Yadav ........................................... 14

- The Educational Environment of the Indian Undergraduate Medical Students: Is it Good Enough?
  Monica Gupta, Sarabmeet Singh Lehl, Ram Singh .................. 20

- Clinical Profile of Pneumocystis jirovecii Infection – A Comparative Study
  Divya Deadhar, Jency Maria Kashy, Mary John, Aroma Oberoi ................................................................. 28

- A Randomized Controlled Trial Comparing the Efficacy of a Combination of Rifaximin and Lactulose with Lactulose only in the Treatment of Overt Hepatic Encephalopathy
  Shakeb Hasan, Saiak Datta, Sharmistha Bhattacharjee, Smarajit Banik, Sandip Saha, Dipanjan Bandopadhyay .... 32

- SynCOPE: Clinical Study and Outcome of Diagnostic Evaluation
  Ashutosh Chaturvedi, Arun Kumar ........................................ 37

- Study of Central Nervous System Tuberculosis
  Archana Aher, Madhuri Paithankar, Baliram Bhurke ............ 41

- Awareness, Self-Assessment and Help Seeking Behavior for Behavioral Addictions Related to Use of Mobile Technology Among Attendees of a Health Camp
  Yatan Pal Singh Balhara, Neha Dahiya, Mohit Varshney, SuneeLa Garg, Rachna Bhargava ........................................... 45

- Study of Rhythm Disturbances in Acute Myocardial Infarction
  Anjalee Chiwhane, Pradeep ................................................ 54

REVIEW ARTICLE

- Anticoagulation Management in Patients with Valve Replacement
  Devendra Saksena, S Muralidharan, Yogal K Mishra, Vivek Kanhere, Bipin Bihari Mohanty, CP Srivastava, Jagdish Mange, Manish Puranik, Manoj P Nair, Pankaj Goel, Pankaj Srivastava, RM Krishnan, Sathyaki Nambala, Vikrama Raja .................................................. 59

- Treatment of Vitamin D Deficiency and Comorbidities: A Review
  Parminder Singh .................................................................... 75

PICTORIAL CME

- Stars in Abdomen
  Ramesh Kumar, Divendu Bhushan, Mukesh Kumar .......... 83

- Rhabdomyolysis of Unknown Etiology - Initial Suspicion and Detection on 99mTc-MDP Skeletal Scintigraphy
  Nandigam Santosh Kumar, Sandip Saha ............................ 84

CASE OF THE MONTH

- CRAB Manifestations in a Middle-Aged Female: A Diagnostic Dilemma
  Anitha Swamy, Radhakar Gogineni, Animesh Ray, Milind Jha, Smita Manchanda, Sudheer Arava, Rakesh Kumar, Kiran Kumar DVS, Harsh Sahu, Piyush Ranjan, Ranveer S Jodon, Naval K Vikram, Rita Sood ........................................... 86

CASE REPORT

- Two Cases of Early Morning Neuroparalytic Syndrome (EMNS) in the Tropics - Masquerading as Brain Death
  RK Anand, CS Narayanan, V Hande, A Singhal, G Varadaraj ................................................................. 92

- “Three in One” - Polyautoimmunity with Multiple Autoimmune Syndrome
  Arun Agarwal, Amit Sanghi, Manisha Agarwal, Mamta Agarwal ................................................................. 95

- SLE in a Male Patient Presented Initially as Rowell's Syndrome
  Ayan Basu, Yogiraj Roy, Pratik Bhowmik, Mehebubar Rahman, Rama Prosad Goswami .............. 98

- Percutaneous Transcatheter Treatment of Lutembacher Syndrome
  Rohit Mathur, Sanjeev Sanghi, Anil Barapal ........................................ 100

- Adult Onset Still's Disease Masquerading as Sepsis in an Asplenic Patient
  Ramadosh Ramu, Vivek Arya, Rajesh Satyapal Taneja, Mohammad Ali ................................................................. 102

MEDICAL PHILATELY

- Medical Symbols: Part-3
  Jayant P P Dhungat ............................................................. 105

CORRESPONDENCE

- Results of Outcome of Two Pregnancies with Imatinib
  Samrat Shah, Bhise Rohan, B Srinivas, Lunge Snehal ...... 106

- Remitting Serosynovitis with Pitting Edema Associated with Gastric Carcinoma
  Rathindranath Sarkar, Rudrajit Paul, Debaditya Roy, Indranil Thakur, Gautam Lahiri, Tanmay Jyoti Sau, Ratul Ghosh .................................................. 106

ANNOUNCEMENT

- HIV Congress 2018 ............................................................ 18

- First International Vasculitis Symposium ............................ 26

- APICON-2019 - Kochi .......................................................... 36

- Academy of Cardiology (AOC) Fellowship .................... 44

- Referees for JAPI ................................................................. 48
### Association of Physicians of India

#### GOVERNING BODY (2017-2018)

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
<th>Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>President Elect</td>
<td>Pritam Gupta (Delhi) (2018)</td>
<td></td>
</tr>
<tr>
<td>President</td>
<td>BR Bansode (Mumbai) (2018)</td>
<td></td>
</tr>
<tr>
<td>Post President</td>
<td>Gurpreet Singh Wander (Ludhiana) (2018)</td>
<td></td>
</tr>
<tr>
<td>Vice Presidents</td>
<td>Girish Mathur (Kota) (2018)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BB Rewari (New Delhi) (2019)</td>
<td></td>
</tr>
<tr>
<td>Hon. General Secretary</td>
<td>Mangesh Tiwaskar (Mumbai) (2019)</td>
<td></td>
</tr>
<tr>
<td>Jt. Secretary (HQ)</td>
<td>Ashit M Bhagwati (Mumbai) (2019)</td>
<td></td>
</tr>
<tr>
<td>Hon. Treasurer</td>
<td>Charu K Jani (Mumbai) (2020)</td>
<td></td>
</tr>
<tr>
<td>Members</td>
<td>Vijay Viswanathan (Chennai) (2018)</td>
<td>North Zone</td>
</tr>
<tr>
<td></td>
<td>MPS Chawla (New Delhi) (2018)</td>
<td>North West Zone</td>
</tr>
<tr>
<td></td>
<td>Sekhar Chakraborty (Siliguri) (2018)</td>
<td>Central Zone</td>
</tr>
<tr>
<td></td>
<td>DP Singh (Bhagalpur) (2018)</td>
<td>West Zone</td>
</tr>
<tr>
<td></td>
<td>Agam C Vora (Mumbai) (2019)</td>
<td>Mid South Zone</td>
</tr>
<tr>
<td></td>
<td>Shibendu Ghosh (Hooghli) (2019)</td>
<td>South Zone</td>
</tr>
<tr>
<td></td>
<td>JL Punglia (Chittorgarh) (2019)</td>
<td>Mid East Zone</td>
</tr>
<tr>
<td></td>
<td>R Rajasekar (Kurnoolakram) (2019)</td>
<td>East Zone</td>
</tr>
</tbody>
</table>

#### Zonal Members

<table>
<thead>
<tr>
<th>Zone</th>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>North Zone</td>
<td>RM Chhabra (New Delhi) (2020)</td>
</tr>
<tr>
<td>North West Zone</td>
<td>Rajinder K Bansal (Ludhiana) (2020)</td>
</tr>
<tr>
<td>Central Zone</td>
<td>Prabhat Pandey (Durg) (2020)</td>
</tr>
<tr>
<td>West Zone</td>
<td>Narayan Deogaonkar (Nasik) (2020)</td>
</tr>
</tbody>
</table>

#### Invited Member

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pritam Gupta</td>
<td>Editor-in-Chief, API Text Book</td>
</tr>
<tr>
<td>Sandhya Kamath</td>
<td>Chairman, API House Committee</td>
</tr>
<tr>
<td>Siddharth N Shah</td>
<td>Editor-in-Chief, JAPI</td>
</tr>
<tr>
<td>Milind Y Nadkar</td>
<td>Ex-Officio Member</td>
</tr>
</tbody>
</table>

#### Ex-Officio Member

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rohini Handa</td>
<td>Dean, ICP</td>
</tr>
<tr>
<td>YP Munjal</td>
<td>Director, PRF</td>
</tr>
</tbody>
</table>

#### Co-opted Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nihar Mehta</td>
<td>Jt. Secretary (President's place)</td>
</tr>
<tr>
<td>Maj. Gen. (Dr.) A.K. Hooda</td>
<td>Organising Secretary, APICON 2017</td>
</tr>
<tr>
<td>Shashank R Joshi</td>
<td>Organising Secretary, APICON 2018</td>
</tr>
</tbody>
</table>

### Indian College of Physicians

#### FACULTY COUNCIL (2017-2018)

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chairman</td>
<td>BR Bansode (Mumbai) (2018)</td>
<td></td>
</tr>
<tr>
<td>Dean Elect</td>
<td>G Narasimulu (Hyderabad) (2018)</td>
<td></td>
</tr>
<tr>
<td>Vice Deans</td>
<td>RK Goyal (Ajmer) (2018)</td>
<td></td>
</tr>
<tr>
<td>Kamlesh Tewary</td>
<td>Mangesh Tiwaskar (Mumbai) (2019)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A Muruganathan (Tirupur) (2018)</td>
<td></td>
</tr>
<tr>
<td>Jt. Secretary (H.Q.)</td>
<td>Ashit M Bhagwati (Mumbai) (2019)</td>
<td>Jt. Secretary (Dean's place)</td>
</tr>
<tr>
<td>Jt. Secretary (Dean's place)</td>
<td>AP Misra (New Delhi)</td>
<td>Hon. Treasurer</td>
</tr>
<tr>
<td>Elected Members</td>
<td>Rakesh Gupta (New Delhi) (2018)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jayanta Kumar Panda (Cuttack) (2018)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Y Satyanarayana Raiju (Hyderabad) (2018)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shriram V Kulkarni (Khopoli) (2018)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anupam Prakash (New Delhi) (2019)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PS Karmakar (Kolkata) (2019)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sudhir Mehta (jaipur) (2019)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jai Bhagwan (Gurgaon) (2019)</td>
<td></td>
</tr>
</tbody>
</table>

#### Ex-Officio Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Editor-in-Chief, JAPI</td>
<td>Director - PRF</td>
</tr>
</tbody>
</table>

### Physicians Research Foundation

#### BOARD OF DIRECTORS (2017-2018)

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chairman</td>
<td>BR Bansode (Mumbai) (2018)</td>
<td></td>
</tr>
<tr>
<td>Jt. Secretary (Director's Place)</td>
<td>Ghan Shyam Pantey (New Delhi) (2019)</td>
<td></td>
</tr>
<tr>
<td>Hon. Treasurer</td>
<td>Charu K Jani (Mumbai) (2020)</td>
<td></td>
</tr>
<tr>
<td>Hon. General Secretary</td>
<td>Mangesh Tiwaskar (Mumbai) (2019)</td>
<td></td>
</tr>
<tr>
<td>Members</td>
<td>Soumitra Ghosh (Kolkata) (2018)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AK Mukherjee (Kolkata) (2018)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ashok Kumar Das (Puducherry) (2019)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suman Bhandari (New Delhi) (2019)</td>
<td></td>
</tr>
<tr>
<td>Invited Members</td>
<td>Anupam Prakash (Kolkata) (2020)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PS Karmakar (Kolkata) (2020)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sudhir Mehta (jaipur) (2020)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jai Bhagwan (Gurgaon) (2020)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invited Members</td>
<td>YP Munjal (Gurgaon) (2019)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sandhya Kamath (Mumbai)</td>
<td></td>
</tr>
</tbody>
</table>

#### Editor-in-Chief, API Text Book

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milind Y Nadkar</td>
<td></td>
</tr>
<tr>
<td>Rohini Handa</td>
<td></td>
</tr>
<tr>
<td>Sandhya Kamath</td>
<td></td>
</tr>
</tbody>
</table>
Don't let the RBCs shed out their original colour

Retain the Original Colour of RBCs

With DEXORANGE®
Syrup/Capsules/Powderable Syrup
(Feric Ammonium Citrate)
The Masterpiece in Hematinics

- Pregnancy & Lactation
- General Weakness
- Anaemia
- Chemotherapy Induced Anaemia
- High Blood & Iron deficiency
- Loss of Appetite
- Weak Electrolyte Resulted Nerve Loss
- Growth Hormone Deficiency
Better HbA1c control with Tresiba® in real world

- Once-daily, ultra-long duration of action beyond 42 hours
- Significantly lower risk of nocturnal hypoglycaemia
- Flexible day-to-day dosing when needed
...delivered in a once-daily dose

THE POWER OF FULL

42+ HOURS CONTROL

Abbreviated prescribing information: Tresiba® insulin degludec® (Fresenius Kabi) 100 U contains insulin degludec. Tresiba® 100 IU/2 mL = 1 mL of solution contains 100 units insulin degludec (equivalent to 3.6 mg/mL). One pre-filled device contains 300 units of insulin degludec in 3 mL solution. Indications: Treatment of diabetes mellitus in adults. Posology and administration: Tresiba® is a basal insulin for once-daily subcutaneous administration any time of the day, preferably at the same time of day. On occasions when administration of insulin in the same time of day is not possible, Tresiba® allows for flexibility in the timing of its administration. A minimum of 14 hours between injections should be maintained in patients with type 2 diabetes mellitus. Tresiba® may be administered alone or in combination with oral antidiabetic medicinal products. SFDA: receipt agency and only in a spirit of medical ethics, Tresiba® 36 IU can be used with short-acting insulin. Administration by subcutaneous injection should be made in 10-15 minutes. Each 1 mL of concentrated insulin degludec should be mixed in the syringe before use. Mix thoroughly and shake well before injection. When administering Tresiba® to patients with type 2 diabetes mellitus, the recommended dosage is 16 IU to 100 IU/day. Treatment of the dosage regimens should be individualized. The dose of Tresiba® may be increased by increments of 16 IU every 3-4 days. The starting dose need to be determined on an individual basis with a dose reduction considered in all cases doses should be adjusted based on individual prior insulin needs. Further, plasma glucose should be used for estimating glycemic control. In elderly patients and patients with renal impairment, glucose monitoring should be utilized and titrated on an individual basis. Tresiba® dosing is designed to be used with fixed-ratio insulin.

The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment. The information shown in the table below is provided for the use of a reference guide. It should not be used for the sole purpose of treatment.
Hypertension is a public health issue worldwide. A recent analysis of data from 154 countries involving ~87 lakh individuals by Forouzanfar et al\(^1\) estimated that in 2015, 87.4 crore adults had a systolic blood pressure (SBP) of ≥140mmHg. In India, current reports estimate that nearly 3 out of every 10 adults suffer from hypertension with an estimated prevalence of 22.9% in men and 23.6% women by 2025.\(^2\)\(^,\)\(^3\) Reports state that every 20 mmHg and 10 mmHg increase in SBP and diastolic blood pressure (DBP), respectively, results in twice the risk of death from heart disease, stroke or other vascular disease.\(^4\)

According to the 2017 *India: Health of the Nation’s States* report jointly prepared by the Indian Council of Medical Research (ICMR), Public Health Foundation of India (PHFI) and Institute for Health Metrics and Evaluation (IHME), hypertension was the risk factor that caused 8.5% of all disability-adjusted life years (DALYs) with ischemic heart disease and stroke causing 8.7% and 3.5% of all DALYs in 2016.\(^5\) The long-term disease burden of hypertension makes it imperative to assess the risk factors which contribute to its increased prevalence.

**Hypertension and Hyperuricemia**

The association between hyperuricemia and hypertension has been evaluated in several studies. An analysis of the prevalence of hyperuricemia in newly-diagnosed hypertensives could help in enhanced understanding of the disease and its progression. In this issue, Agarwal *et al* have explored this relationship and have conducted an observational case control study in the Department of Medicine, Dr. Rajendra Prasad Government Medical College, Kangra in the sub-Himalayan region of North India on newly-diagnosed adult hypertensive patients along with age and sex-matched normotensive controls. Overall, 40 males and 60 females were included in the study. Patients with conditions or medications which could increase SUA levels such as secondary hypertension, diabetes, gout, alcohol abuse, hypothyroidism, hyperparathyroidism, ischemic heart disease, congestive cardiac failure, chronic kidney disease, any acute illness, pregnancy and steroidal medications were excluded. The normotensive controls were not on any medication. Blood pressure was measured and classified as per the Joint National Committee (JNC) 7 guidelines and SUA was measured by the Uricase method. Fasting blood glucose and lipid levels were also measured. Both the cases and the controls were similar with respect to their family history of hypertension, body mass index (BMI), waist-hip ratio (WHR), fasting blood glucose (FBG) and lipid variables. In the female cases vs controls, there were more smokers and there was a greater prevalence of family history of hypertension.

The overall prevalence of hyperuricemia was significantly higher among the cases (24%) than the controls (6%). Mean SUA levels

---

**Hypertension and Hyperuricemia: A Compelling Correlation**

Mangesh Tiwaskar

**Introduction**

Hypertension is a public health issue worldwide. A recent analysis of data from 154 countries involving ~87 lakh individuals by Forouzanfar *et al*\(^1\) estimated that in 2015, 87.4 crore adults had a systolic blood pressure (SBP) of ≥140mmHg. In India, current reports estimate that nearly 3 out of every 10 adults suffer from hypertension with an estimated prevalence of 22.9% in men and 23.6% women by 2025.\(^2\)\(^,\)\(^3\) Reports state that every 20 mmHg and 10 mmHg increase in SBP and diastolic blood pressure (DBP), respectively, results in twice the risk of death from heart disease, stroke or other vascular disease.\(^4\)

According to the 2017 *India: Health of the Nation’s States* report jointly prepared by the Indian Council of Medical Research (ICMR), Public Health Foundation of India (PHFI) and Institute for Health Metrics and Evaluation (IHME), hypertension was the risk factor that caused 8.5% of all disability-adjusted life years (DALYs) with ischemic heart disease and stroke causing 8.7% and 3.5% of all DALYs in 2016.\(^5\) The long-term disease burden of hypertension makes it imperative to assess the risk factors which contribute to its increased prevalence.

**Hypertension and Uric Acid**

Though several modifiable risk factors for hypertension are well-known, novel risk factors such as hyperuricemia, which is often accompanied by hypertension and other metabolic disorders,\(^6\) are also being evaluated to optimise treatment. Hyperuricemia is defined as serum uric acid (SUA) levels >6.8mg/dl. It is commonly caused by a detrimental lifestyle including a diet with excessive protein, purine nucleotides, carbohydrates and alcohol intake. Moreover, certain drugs such as thiazides and other diuretics also reduce uric acid excretion leading to enhanced SUA levels.\(^7\) The association between hypertension and hyperuricemia was noticed in late 1800s and the theory that uric acid may be a vital component in the development of hypertension was given credence by several large epidemiological studies which showed that hyperuricemia increased the risk of hypertension by 1.2 to 3-fold, even after adjustment for several common risk factors.\(^8\) Moreover, hyperuricemia was associated with incident hypertension in both men and women.\(^9\)
were also significantly higher in cases than in controls. Moreover, the odds ratio for the hyperuricemic hypertensives versus hyperuricemic normotensives was 4.9 indicating a robust positive association between hypertension and hyperuricemia.

Significantly higher hyperuricemia prevalence for newly-diagnosed cases vs controls was also observed by Poudel et al (28.8% vs 13.7%), Shrivastav et al (37.33% vs 14%) and Mishra et al (26% vs 6%). Mean SUA levels (mg/dl) were also significantly higher in newly-diagnosed hypertensive cases vs controls but varied across the studies.

Gender-based differences in hyperuricemia prevalence was also evaluated by Agarwal et al. Overall, the mean SUA level was significantly higher in the male vs female cases. Also, amongst the cases, significantly higher number of males (40%) vs females (13.3%) were hyperuricemic. The prevalence of hyperuricemia in male cases was 4 times that in male controls. Also, mean SUA levels were significantly higher in the male cases vs male controls. On the other hand, mean SUA in female cases was not significantly different from the female controls. However, the authors suggest that this could partly be due to the uricosuric action of oestrogen.

Therapeutic Implications

Though the increase in SUA has been correlated with increased risk for metabolic syndrome in several studies, but in the study done by Agarwal et al there was no significant difference between the cases and control groups with respect to body mass index and fasting lipid profile. Thus hyperuricemia-hypertension risk correlation in this study were irrespective of the presence of metabolic syndrome. Xanthine oxidase inhibitors, which help in reducing uric acid levels, have also been found to reduce blood pressure and may help in the treatment of hyperuricemic hypertensives. The key points brought to light by this study are:

1. There is a strong correlation between hyperuricemia and hypertension in even newly-diagnosed hypertensive patients – Monitor BP in all patients with Hyperuricaemia/Gout, similarly monitor SUA levels in all patients with Hypertension
2. A greater prevalence of hyperuricemia is observed in both male and female hypertensives compared to normotensive individuals and
3. The relationship between hyperuricemia and hypertension exists irrespective of the presence of the metabolic syndrome.

Summary

The long-term effects of hypertension are well-known and India is especially vulnerable to its impact. Since SUA levels are strongly correlated with hypertension, evaluation of SUA levels in patients at risk for hypertension and in those suffering from hypertension should be done as early as possible in the course of the disease. Treatment of hyperuricemia in hypertension with appropriate therapy may thus be a valuable addition to its management.

References

In Hypertension, Zilarbi™
Azilsartan Medoxomil 40/80 mg Tablets

Drop in BP, as it should be...

In Hypertension associated with Angina, IHD, CHF & Post MI,

METPURE-XL®
S(-)Metoprolol PR 12.5/25/50 mg Tablets

Because Heart Matters

Offers high cardioselectivity & Beta-1 blockade over 24 hours1,2

For any medical query, please write to us on emquest@emcure.co.in or call on: 18002004048 (Toll free)

Emcure Pharmaceuticals Ltd.
Survey No 255/2, Phase-1, M.I.D.C., Hirjewadi, Pune-411057 (India)
Tel: +91 20 39821000 Fax: +91 20 39821019 www.emcure.co.in www.chiralemcure.com


For the use of Registered Medical Practitioner or Hospital in a Laboratory only. WHOLLY

THEREOUGHT
Hypertension as Determinant of Hyperuricemia: A Case Control Study from the Sub-Himalayan Region in North India

Sujeet Raina¹*, Vishnu Kumar Agarwal², Dhiraj Kapoor³, Kailash Nath Sharma⁴, RS Yadav⁵

Abstract

Background: Association between hyperuricemia and hypertension has been recognized for many years. Whether hyperuricemia is the cause or the effect is debatable.

Materials and methods: This case control study was conducted to assess serum uric acid (SUA) levels in fifty newly diagnosed essential hypertensive patients and fifty normotensive controls which were matched for age and sex. Detailed anthropometric characteristics including height, weight, body mass index and waist hip ratio were measured. Hypertension was classified according to Joint National Committee (JNC) 7 criteria. Hyperuricemia was defined as SUA level of 6.8mg/dl or more in both men and women. SUA was measured by uricase method. Before collecting the blood samples, patients were advised to proceed on overnight fast of minimum eight hrs. Student's t-test for mean of continuous variables and Chi-square test for proportions were used for statistical significance.

Results: Present study included 50 newly diagnosed cases of essential hypertension and 50 age and sex matched normotensive healthy volunteer. Prevalence of hyperuricemia was 24% among the cases and 6% among the controls (P<0.05). Odds ratio was 4.9 (CI=1.3 to 18.8). The mean SUA was significantly higher in the cases (5.5±1.7 mg/dl) than in the controls (4.9±1.1 mg/dl; P<0.05). Odds ratio in male hyperuricemic hypertensive versus hyperuricemic normotensive was 6(CI=1.0 to 33.2) and 4.46(CI=0.4 to 42.5) among female hyperuricemic hypertensive versus hyperuricemic normotensives.

Conclusion: Strong positive association was observed between hypertension and hyperuricemia in both male and female patients in this study.

Editorial Viewpoint

• Hyperuricemia as a cause or an effect of hypertension is debatable.
• Present study finds hyperuricemia in 24% of hypertensives compared to 6% among controls.

Introduction

Hyperuricemia has been reported in 26% of untreated hypertensive patients having normal blood urea nitrogen levels.¹ Different studies advocate the association between serum uric acid (SUA) level and hypertension. In a large meta-analysis of 18 prospective cohort studies representing data from 55,607 subjects, incident hypertension increased by 13% per 1 mg/dl increase of SUA.² The various mechanism of this association between hypertension and hyperuricemia includes: (a) uric acid induced activation of renin-angiotensin system and action on glomerular apparatus (b) increased insulin resistance and hyperinsulinemia, causing decreased excretion of uric acid, sodium, potassium from renal tubules; and (c) uric acid action in proliferation of vascular smooth muscle, endothelial dysfunction with decreased nitric acid production.³⁻⁸ However, there are numerous confounding factors including metabolic syndrome, diabetes mellitus, obesity, alcohol consumption, salt intake, fluid volume status etc. in the association of hyperuricemia and hypertension. Hyperuricemia is common among adults with pre-hypertension. The observation that hyperuricemia precedes the development of hypertension indicates that it is not simply a result of hypertension per se. Hyperuricemia resulting from

¹Assistant Professor, ²Postgraduate Student, ³Professor, ⁴Associate Professor, ⁵Professor, Dr. Rajendra Prasad Govt. Medical College, Tanda, Kangra, Himachal Pradesh; *Corresponding Author
Received: 09.01.2017; Revised: 14.06.2017; Accepted: 22.06.2017
euglycemic hyperinsulinemia may precede the onset of type 2 diabetes, hypertension, coronary artery disease, and gout in individuals with metabolic syndrome. Though ample amount of literature and studies supporting the causal role of hyperuricemia in hypertension is available in western countries, studies in this regard are scanty in the Indian scenario. In spite of the observational studies to investigate the association between uric acid and hypertension, controversy still remains. The present study was undertaken to generate information and evidence concerning this topic.

Material and Methods

It was an observational case control study conducted in the department of Medicine, Dr. Rajendra Prasad Government Medical College, Kangra at Tanda after getting approval of institutional ethics committee. Fifty newly diagnosed patients with hypertension based on JNC VII and above the age of 18 years were included in this study. Patients with secondary hypertension, diabetes, gout, alcohol abuse, hypothyroidism, hyperparathyroidism, ischemic heart disease, congestive cardiac failure, chronic kidney disease, any acute illness, pregnancy, steroidal medications or any medication likely to increase SUA and patients not willing to participate in the study were excluded. Fifty controls were normotensive healthy volunteer individuals not on any medication among the attendants of the patients or hospital employees fulfilling the exclusion and inclusion criteria. The sample size was calculated using STATCALC from epiinfo software with two sided confidence level of 95%, power of 80%, ratio of case to controls of 1:1, odds ratio of 6.3 and proportion of exposed among cases at 25%. The age and sex between the newly diagnosed hypertension cases and normotensive healthy controls were matched. Detailed anthropometric characteristics including height, weight, body mass index and waist hip ratio were measured. Blood pressure was measured and classified as per the Joint National Committee (JNC) 7 guidelines. Hyperuricemia was defined as SUA level of 6.8 mg/dl or more in both men and women. SUA was measured by uricase method. Fasting blood glucose was done by glucose oxidase-peroxidase method. Total Cholesterol (TC) was measured by CHOD- PAP method, Triglycerides (TG) by GPO-Trinder, high Density Lipoprotein (HDL-C) by Immuno-inhibition and low Density Lipoprotein (LDL-C) by Immuno-inhibition method. Before collecting the blood samples, patients were advised to proceed on overnight fast of minimum eight hrs. The software used for data analysis was Epi Info -7 a free software for statistics developed by CDC - Centers for Disease Control and Prevention. Student’s t-test was used to compare the mean of the continuous variables. Chi-square test was used to compare proportions. No pooled analysis was carried out as pooled analysis in case-control studies is more popular when genetic markers are involved, while pooled analysis in cross-sectional studies is preferred when markers of exposure are explored.

Results

Fifty newly diagnosed hypertension cases and 50 normotensive controls matched for age and sex were included. The clinical and laboratory characteristics of the study population are shown in Table 1. Prevalence of hyperuricemia was significantly higher among the cases (24%) than controls (6%) (P<0.05). Hyperuricemia was found in 40% male cases and in 13.3% female cases. Hyperuricemia was significantly more in male cases than female cases (p<0.05). Mean serum UA level in male patients was 6.5±1.5 mg/dl. In female patients mean SUA levels was 4.9±1.6 mg/dl and the difference is statistically significant (p<0.05). In our study the mean SUA levels were higher in cases (5.5±1.7) than in controls 4.9±1.1 and the difference is statistically significant. (p<0.05). The mean SUA levels were significantly higher in male hypertensive patients (p<0.05). Mean SUA was significantly higher in the male cases (6.5±1.5 mg/dl) than in the male controls (5.4±1.0 mg/dl; P<0.05), and the prevalence of hyperuricemia was 40% among the cases and 10% among the controls (P<0.05). In our study mean SUA was not significantly different in the female cases (4.9±1.6 mg/dl) than in the female controls (4.6±1.0 mg/dl; P=0.46). But prevalence of hyperuricemia was significantly higher in female cases (13.3%) than among the controls (p<0.05). The odds ratio for the hyperuricemia among cases and controls is shown in Table 2. The anthropometric, clinical and laboratory characteristics of hypertensive patients with and without hyperuricemia are compared with controls in Table 3. We found that hyperuricemia was present in 6% normal healthy controls and was more frequent in males (10%) than females (3%).

Discussion

The prevalence of hypertension, a major risk factor for noncommunicable diseases is increasing in developing countries. By the year 2020, deaths due to non-communicable diseases will overtake communicable diseases by almost four times in developing countries. The identification of individual risk factors of hypertension and taking effective preventive measures will control the rising burden. Elevated uric acid levels are often associated with established traditional cardiovascular risk factors; it is not quite sure whether uric acid is the cause or consequence of
**Table 1: Clinical, anthropometry and laboratory characteristics of the study patients and controls and comparison between male and female subjects**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n=50)</th>
<th>Controls (n=50)</th>
<th>p-value</th>
<th>Male (n=20)</th>
<th>Controls (n=20)</th>
<th>P-value</th>
<th>Female (n=30)</th>
<th>Controls (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>12 (24%)</td>
<td>8 (16%)</td>
<td>0.31</td>
<td>10 (50%)</td>
<td>8 (40%)</td>
<td>0.52</td>
<td>2 (6.7%)</td>
<td>0</td>
<td>0.15</td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td>12 (24%)</td>
<td>14 (28%)</td>
<td>0.25</td>
<td>3 (15%)</td>
<td>8 (40%)</td>
<td>0.13</td>
<td>9 (30%)</td>
<td>6 (20%)</td>
<td>0.30</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>24.9±2.8</td>
<td>25.5±3.7</td>
<td>0.35</td>
<td>24.8±2.4</td>
<td>25.0±3.3</td>
<td>0.81</td>
<td>25.0±3.1</td>
<td>25.8±4.0</td>
<td>0.34</td>
</tr>
<tr>
<td>WHR</td>
<td>0.94±0.03</td>
<td>0.89±0.04</td>
<td>&lt;0.05</td>
<td>0.93±0.05</td>
<td>0.87±0.02</td>
<td>&lt;0.05</td>
<td>0.95±0.02</td>
<td>0.89±0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>96.4±12.7</td>
<td>87.6±18.9</td>
<td>&lt;0.05</td>
<td>89.7±12.5</td>
<td>92.7±22.5</td>
<td>0.60</td>
<td>100.9±10.9</td>
<td>84.2±15.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SUA (mg/dl)</td>
<td>5.5±1.7</td>
<td>4.9±1.1</td>
<td>&lt;0.05</td>
<td>6.5±1.5</td>
<td>5.4±1.0</td>
<td>0.01</td>
<td>4.9±1.6</td>
<td>4.6±1.0</td>
<td>0.46</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>12 (24%)</td>
<td>3 (6%)</td>
<td>&lt;0.05</td>
<td>8 (40%)</td>
<td>2 (10%)</td>
<td>0.01</td>
<td>4 (13.3%)</td>
<td>1 (3.3%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Table 2: Odds ratio for hyperuricemia and hypertension among study subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=50)</th>
<th>Controls (n=50)</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperuricemia</td>
<td>12 (24%)</td>
<td>3 (6%)</td>
<td>4.9 (CI=1.3 to 18.8)</td>
</tr>
<tr>
<td>Males</td>
<td>8 (40%)</td>
<td>2 (10%)</td>
<td>6 (CI=1.0 to 33.2)</td>
</tr>
<tr>
<td>Females</td>
<td>4 (13.3%)</td>
<td>1 (3.3%)</td>
<td>4.46 (CI=0.4 to 42.5)</td>
</tr>
</tbody>
</table>

**Table 3: Distribution of study subjects according to hyperuricemia and association with clinical, anthropometry and laboratory characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=50)</th>
<th>Normal SUA (n=38)</th>
<th>P-value</th>
<th>Elevated SUA (n=12)</th>
<th>Controls (n=47)</th>
<th>Normal SUA (n=3)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>4 (33.3%)</td>
<td>8 (21.1%)</td>
<td>0.38</td>
<td>2 (66%)</td>
<td>12 (25.5%)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td>3 (25%)</td>
<td>9 (23.6%)</td>
<td>0.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>25.7±4</td>
<td>24.6±2.4</td>
<td>0.26</td>
<td>20.7±3.2</td>
<td>25.8±3.5</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td>0.95±0.03</td>
<td>0.94±0.04</td>
<td>0.26</td>
<td>0.85±0.04</td>
<td>0.89±0.04</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>163.6±10.6</td>
<td>169.2±16.3</td>
<td>0.27</td>
<td>108.6±2.3</td>
<td>114±13.0</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>102.6±7.3</td>
<td>102.8±10.4</td>
<td>0.94</td>
<td>64±4</td>
<td>71.9±1</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>92.7±10.7</td>
<td>97.6±13.2</td>
<td>0.25</td>
<td>81.3±22</td>
<td>88±18.9</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>214±54.5</td>
<td>202.8±50.6</td>
<td>0.51</td>
<td>203.6±37.4</td>
<td>199.3±48.9</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>204.3±88</td>
<td>188.9±83.7</td>
<td>0.58</td>
<td>150.6±19.2</td>
<td>198.7±118.8</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>54.9±9.2</td>
<td>53.2±11</td>
<td>0.73</td>
<td>46.3±3.5</td>
<td>51.8±11.6</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>118.6±42.4</td>
<td>113.8±41.3</td>
<td>0.72</td>
<td>128.0±9.5</td>
<td>107.3±41.4</td>
<td>0.39</td>
<td></td>
</tr>
</tbody>
</table>

n-number; BMI= body mass index; WHR= waist hip ratio; FBS= fasting blood sugar; SUA= serum uric acid; TC= total cholesterol; TG= triglycerides; HDL= high density lipoprotein; LDL= low density lipoprotein.

Hyperuricemia is fairly common with the prevalence between 2.6% and 47.2% in various populations. A significant association between SUA and blood pressure has been observed in age group less than 59 years. A study from another northern part of India found hyperuricemia in 37% of hypertensive cases and 17% of controls. Other studies have reported prevalence of hyperuricemia in newly diagnosed hypertensive from 25.4% to 31.8% which are closer to our study. In present study odds ratio in hyperuricemic hypertensive versus hyperuricemic normotensive was 4.9 (CI=1.3 to 18.8) and it is suggestive of a strong positive association between hypertension and hyperuricemia. Hyperuricemia was significantly more in male cases than female cases in present study. The statement is an outcome of difference in proportion of hyperuricemia in male and female although may lack generalisation because of sample chosen, points to an important issue which can be taken up on a larger sample. Other studies found that hyperuricemia was almost equal in both males and females. Bibek et al observed higher prevalence of hyperuricemia in female hypertensives (29.2%) than male hypertensives (28.4%).

The mean SUA in hypertensives observed in this study was 5.5±1.7 and is close to mean SUA levels found in study conducted by Neki et al, Perlstein et al and Strasak et al. They found mean uric acid level 5.8 ± 1.3 mg/dl, 5.8 ± 0.9 mg/dl and 5.7 ± 1.2 mg/dl respectively. Similar results observed in a study conducted in Bangladesh by Kashem et al in which mean SUA was 5.8±1.5 mg/dl. However, higher mean SUA levels were observed by Feig et al, where they found mean uric acid was 6.9 mg/dl in their study patients. Mean SUA levels is lower in our study.
in comparison to 6.0 ± 1.2 mg/dl found in a study conducted at a higher altitude of 4300 m and 6.1 ± 1.6 mg/dl as found in other study conducted at an altitude of more than 3500 m. However, it is higher in comparison to 4.7±1.0 mg/dl found in a study conducted at a tertiary care hospital in the Northern hilly state of Himachal Pradesh, India. Bibek et al. Mean SUA level is also higher in comparison to 4.8±1.4 mg/dl found in the study conducted by Bibek et al. Kashem et al. found that mean SUA in males was 6.0 ± 1.4 mg/dl and in female patients mean SUA 5.5 ± 1.3 mg/dl. They found that mean serum acid levels in female hypertensives (4.4±1.3 mg/dl) than normotensives (3.7±1.4 mg/dl). Prevalence of hyperuricemia was also significantly higher in female cases (29.2%) than female controls (12.9%). In another study conducted by Bibek et al. in Nepal also observed higher mean SUA level in males 5.23±1.48mg/dl in comparison to females 4.4±1.3mg/dl.

It has been observed that mean SUA level was significantly higher in male cases (5.2±1.4 mg/dl) than male normotensives (4.4±1.7 mg/dl) in the study conducted by Bibek et al. Prevalence of hyperuricemia was also higher in hypertensives (28.4%) than normotensives (14.3%) in this study. Kashem et al. also observed that mean serum acid levels in male hypertensives (6.0±1.4 mg/dl) was significantly higher than normotensives (4.8±1.4 mg/dl) and prevalence of hyperuricemia was also significantly higher in male cases (25%) than male controls (8%). Odds ratio in female hyperuricemic hypertensive versus hyperuricemic normotensive was 4.46 (CI=0.4 to 42.5) and it shows a strong association between hyperuricemia and hypertension in females.

In this study we found that hyperuricemia was present in 6% normal healthy controls and was more frequent in male (10%) than females (3%). While studying the select nomad tribal population of Rajasthan, India the prevalence of hyperuricemia was found to be 13.5%. Hyperuricemia was more frequent in men (14.4%) than women (12.8%). In the study conducted by Kashem et al hyperuricemia was found in 9.8% controls and prevalence of hyperuricemia was higher in normotensives males (11.5%) than normotensive females (8%). Bibek et al. found high prevalence of hyperuricemia (13.7%) in normal healthy controls and prevalence was higher in males (14.3%) than females (12.9%).

In our study statistically significant difference was observed when SUA, fasting blood sugar, waist hip ratio of the hypertensives was compared with the normotensive healthy controls. And these are the components of metabolic syndrome, so indirectly hypertensive patients with hyperuricemia also have other components of metabolic syndrome. There was no statistically significant difference in body mass index and fasting lipid profile of hypertensives and normotensives. In a meta-analysis of 17 studies while studying the prognostic values of hyperuricemia on the development of complications in hypertensive patients, it was observed that hyperuricemia could slightly increase the risk of cardiovascular diseases and diabetes in patients with hypertension. In different studies on effects of xanthine oxidase inhibitors on renal function and blood pressure in hypertensive patients with hyperuricemia it was observed that these drugs may delay the progression of renal dysfunction and decrease blood pressure.

It can be concluded that hyperuricemia is significantly associated with hypertension and hyperuricemia-hypertension risk relationship is present in patients irrespective of metabolic syndrome. Large randomized trials are required to study the effect of urate-lowering therapy on the prevention or treatment of hypertension.

References

Celebrate Allergy Free Season

In Allergic Rhinitis and Allergic Asthma

RX MONLEVO Tablets
(Montelukast Sodium 10 mg + Levocetrizine Hydrochloride 5 mg)

RX MONADINE Tablets
(Montelukast Sodium 10 mg + Fexofenadine Hydrochloride 120 mg)
The Educational Environment of the Indian Undergraduate Medical Students: Is it Good Enough?

Monica Gupta1*, Sarabmeet Singh Lehl1, Ram Singh1

Abstract

Background: The educational environment (EE) is a crucial determinant of successful outcomes in an undergraduate (UG) medical education programme. The present study utilized the Dundee Ready Education Environment Measure (DREEM) which is a validated tool for this assessment in medical schools.

Aims and Objectives:

a. To explore the perceptions of undergraduate medical students of their learning environment
b. To identify both strengths and weaknesses in students’ educational environment
c. To suggest remedial measures to overcome the deficiencies

Methodology: The present cross-sectional, questionnaire-based study was conducted in the Academic year 2015. A printed form of the validated inventory DREEM, was distributed among undergraduate students of second, fourth, sixth and eighth semester, maintaining anonymity of the respondents. The mean item scores, domain scores and global scores were calculated and the results were analyzed using SPSS Version 15 and one-way ANOVA.

Results: The composite overall perception of EE i.e. DREEM score for the Medical College was 118.4±16.9, indicating that the perception was positive. The fourth and sixth semester rating were lower at 115.90±3.76 and 106.10± 3.46, respectively while the second and eight semester students rated it higher at 123.13±5.03 and 127.05± 3.95, respectively. This difference was statistically significant. The highest rated items were knowledgeable teachers, having good friends, and a pleasant accommodation. The most problematic items were a poor support system for stressed students, inability to memorize everything, and over-emphasis on factual learning. Students also perceived the teachers to be authoritarian. They observed that the teaching was teacher-centric, burdensome and boring.

Conclusions: This study helped us to introspect and identify remediable areas in the EE of our medical college with special emphasis on a student-centered curriculum focusing on the national needs as well as student interest. Teachers need to change their approach to teaching-learning environment by introducing changes in their teaching methodology, assessment methods and interaction with students.

Editorial Viewpoint

- This study is introspection of education environment of undergraduate medical students based on feedback received from them.
- Case based learning is desired by students.
- Feedback should also be obtained from teachers before implementing change in medical education system.

Introduction

One of the main goals of medical graduate education is to produce a workforce of competent doctors who are able to deliver preventive, promotive and curative services to all strata of society in a cost-effective manner. The first step in this process is creating an enriched learning environment through a stimulating medical curriculum. Identifying various factors that influence a medical student’s progress and the relationship between them is complex. Learning is influenced by motivation (intrinsic and extrinsic) and an actively engaging

1Professor, Department of General Medicine, Government Medical College and Hospital, Chandigarh; Corresponding Author
Received: 07.06.2016; Revised: 22.07.17; Accepted:03-08-2017
environment for the learner. Adult learning theory indicates a major role for the contextual nature of learning and the learning climate, over the delivery of information or knowledge. Therefore, the ‘educational environment’ which encompasses everything that happens within the classroom, department, faculty or university is a crucial element in determining the success of an undergraduate medical education programme.

The accomplishment and contentment of students depends upon their learning environment. Educational environment (EE) research assesses the medical college environment and the information from this paves the way for changing the curriculum to enhance students' satisfaction and achievement. In the existing medical teaching structure there is no provision of need-assessment of students’ EE. There is a high probability that this need has not been addressed suitably, and this deficit may contribute to poor motivation and lower capacity building of a large number of medical graduates. In the long term, it culminates in doctors with less than optimal capability in handling the need-based problems of the population they serve.

Students’ perception of their EE influences their behavior, academic progress and sense of well-being. There are areas of concern of a majority of students that might, unintentionally be neglected by educators. It is imperative to discover these areas by an anonymous feedback system and address them. Our medical college follows the traditional discipline based MBBS course as per Medical Council of India (MCI) guidelines. The curriculum and its delivery are periodically monitored; however, the ‘educational environment’ which is crucial to the success of undergraduate medical education is not regularly assessed. Thus, the present study aimed to assess the students’ perception of the educational environment using the Dundee Ready Education Environment Measure (DREEM) questionnaire.

Aim and Objectives

a. To explore the perceptions of undergraduate medical students of their learning environment
b. To identify both strengths and weaknesses in students’ educational environment
c. To suggest remedial measures to overcome the deficiencies

Material and Methods

The present cross-sectional study utilized the pre-validated DREEM inventory. The study was undertaken after approval of project proposal from the Institutional Research and Ethics committees of the Government Medical College and Hospital, Chandigarh.

Study setting and participants: The Medical College conducts the Bachelor of Medicine and Bachelor of Surgery (MBBS) Undergraduate course in accordance with guidelines and framework of the MCI. The students from second, fourth, sixth and eighth semester were enrolled in the study. All the students who attended the schedule of questionnaire administration were enrolled. Over 75% students completed the proforma in each batch.

Methodology: After a brief explanation of the aims and objectives, written informed consent was obtained from the participants. Anonymity was ensured in the questionnaire format in which the participant could not be identified. The self-administered questionnaire in a printed format was distributed during a face-to-face session. The days were fixed as per convenience to ensure maximum participation. The students were informed that completion of the questionnaire was voluntary and assured that non-participation would not have any adverse repercussions in their medical course. The respondents were asked to read each item carefully, understand and to respond on a five-point Likert scale ranging from Strongly agree, Agree, Unsure, Disagree, Strongly disagree. Simultaneously, another semi-structured questionnaire was administered focusing on student's demographic information, study and extracurricular habits and usage of learning resources.

Study Instrument and Data collection: Students’ perception of EE was assessed by DREEM inventory, a universally available, validated ‘cultural-free’ tool for gathering information about the EE in medical colleges. It contains 50 statements relating to a range of topics directly relevant to the education climate. A guide to interpreting the subscales is shown below.

Students’ Perception of Learning

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
<td>Very Poor</td>
</tr>
<tr>
<td>13-24</td>
<td>Teaching is viewed negatively</td>
</tr>
<tr>
<td>25-36</td>
<td>A more positive perception</td>
</tr>
<tr>
<td>37-48</td>
<td>Teaching highly thought of</td>
</tr>
</tbody>
</table>

Students’ Perception of teachers

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-11</td>
<td>Terrible</td>
</tr>
<tr>
<td>1-22</td>
<td>In need of some retraining</td>
</tr>
<tr>
<td>1-33</td>
<td>Moving in the right direction</td>
</tr>
<tr>
<td>1-44</td>
<td>Model teachers</td>
</tr>
</tbody>
</table>

Students’ Academic Self Perceptions

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-8</td>
<td>Feelings of total failure</td>
</tr>
<tr>
<td>1-16</td>
<td>Many negative aspects</td>
</tr>
<tr>
<td>1-24</td>
<td>Feeling more on the positive side</td>
</tr>
<tr>
<td>1-32</td>
<td>Confident</td>
</tr>
</tbody>
</table>

Students’ Perception of Atmosphere

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>A terrible environment</td>
</tr>
<tr>
<td>1-24</td>
<td>There are many issues which need changing</td>
</tr>
<tr>
<td>1-36</td>
<td>A more positive attitude</td>
</tr>
<tr>
<td>1-48</td>
<td>A good feeling overall</td>
</tr>
</tbody>
</table>

Students’ Social Self Perceptions

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>Miserable</td>
</tr>
<tr>
<td>1-14</td>
<td>Not a nice place</td>
</tr>
<tr>
<td>1-21</td>
<td>Not too bad</td>
</tr>
<tr>
<td>1-28</td>
<td>Very good socially</td>
</tr>
</tbody>
</table>

Overall score of Educational Environment

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-50</td>
<td>Very Poor</td>
</tr>
<tr>
<td>51-100</td>
<td>Plenty of Problems</td>
</tr>
<tr>
<td>101-150</td>
<td>More Positive than Negative</td>
</tr>
<tr>
<td>151-200</td>
<td>Excellent</td>
</tr>
</tbody>
</table>
Data tabulation and Statistical analysis: The data collected from the questionnaires was entered in MS office excel software. Mean and standard deviation was calculated for all the items. Total scores for each domain and overall score was calculated for all the semesters, individually and combined. The overall DREEM score (out of 200) was also calculated. To identify lacunae within the learning environment, items with a mean score below 2 were taken as problem areas needing remediable action and items with a mean score of 3 and above were considered as positive. Items with a mean score between 2 and 3 were considered as those that could possibly be addressed. The statistical significance of difference in the mean scores of each domain was evaluated using one-way analysis of variance (ANOVA), by the statistical package for the social sciences (SPSS) software package for Microsoft Windows. \( P < 0.05 \) at 95% confidence interval was considered as significant.

Focused group discussion: Once the questionnaires were received further explored using focused group discussion in small voluntary student groups.

### Results

Only those questionnaires that were complete in all respects were included in the analysis. Scoring the DREEM: Items were scored as: 4 for Strongly Agree (SA), 3 for Agree (A), 2 for Uncertain (U), 1 for Disagree (D) and 0 for Strongly Disagree (SD). However, 9 of the 50 items (numbers 4, 8, 9, 17, 25, 35, 39, 48 and 50) being negative statements were scored in the reverse manner i.e. 0 for SA, 1 for A, 2 for U, 3 for D and 4 for SD. The 50-item DREEM has a maximum score of 200 indicating the ideal EE as perceived by the student.

A total of 250 students were administered the DREEM questionnaire, of which 13 forms had to be rejected since they were incomplete. Thus 237 (94.8%) participant’s forms were analyzed. These included 77 out of 100, 78 out of 100, 42 out of 50 and 40 out of 50 second, fourth, sixth and eighth semester students, respectively.

1. **Students’ Perception of Learning (SPOL):** 68.4% students had a positive perception, while 25.7% viewed teaching negatively. The major contributors to this negative perception were students of fourth (30.8%) and sixth (52.4%) semester. The problem areas were an over-emphasis on factual and teacher-centered learning.

2. **Students’ Perception of Teachers (SPOT):** 79.8% students observed that the teachers were “moving in the right direction”, while 16% perceived a “need for some retraining of teachers”. 90% of the final year students viewed their teachers favorably and 5% even perceived the teachers to be ideal models. The major problem areas identified in this domain were authoritarian teachers and teachers getting angry in class, while others observed that students irritate the teachers. The heartening feature was that a majority of students perceived their teachers to be knowledgeable.

3. **Students’ Academic Self
Table 2: Mean scores of individual questions of the DREEM questionnaire

<table>
<thead>
<tr>
<th>Item</th>
<th>Scores (max score 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Students’ Perception of Learning (SPoL)</strong></td>
<td></td>
</tr>
<tr>
<td>Q1. I am encouraged to participate during teaching sessions</td>
<td>2.65 2.54 1.90 2.88 2.49 0.36</td>
</tr>
<tr>
<td>Q7. The teaching is often stimulating</td>
<td>2.68 2.23 2.10 2.65 2.41 0.25</td>
</tr>
<tr>
<td>Q13. The teaching is student-centered</td>
<td>2.64 2.23 1.81 2.80 2.37 0.38</td>
</tr>
<tr>
<td>Q16. The teaching helps to develop my competence</td>
<td>2.68 2.69 2.43 2.83 2.66 0.14</td>
</tr>
<tr>
<td>Q20. The teaching is well-focused</td>
<td>3.00 2.56 1.98 3.40 2.74 0.53</td>
</tr>
<tr>
<td>Q22. The teaching helps to develop my confidence</td>
<td>2.57 2.23 2.12 2.65 2.39 0.22</td>
</tr>
<tr>
<td>Q24. The teaching time is put to good use</td>
<td>2.51 2.35 2.26 2.83 2.48 0.22</td>
</tr>
<tr>
<td>Q25. The teaching over-emphasizes factual learning*</td>
<td>1.31 1.46 1.43 1.38 1.39 0.06</td>
</tr>
<tr>
<td>Q38. I’m clear about the learning objectives of the course</td>
<td>2.77 2.73 2.26 2.83 2.65 0.22</td>
</tr>
<tr>
<td>Q44. The teaching encourages me to be an active learner</td>
<td>2.44 2.35 1.64 2.70 2.28 0.39</td>
</tr>
<tr>
<td>Q47. Long-term learning is emphasized over short-term learning</td>
<td>3.00 2.12 2.48 3.30 2.72 0.46</td>
</tr>
<tr>
<td>Q48. The teaching is too teacher-centered*</td>
<td>1.91 1.73 1.67 2.13 1.86 0.18</td>
</tr>
<tr>
<td><strong>Students’ Perception of Teachers (SPoT)</strong></td>
<td></td>
</tr>
<tr>
<td>Q2. The teachers are knowledgeable</td>
<td>3.43 3.15 3.29 3.55 3.35 0.15</td>
</tr>
<tr>
<td>Q6. The teachers adopt a patient-centered approach to consulting</td>
<td>2.51 2.58 2.21 2.98 2.57 0.27</td>
</tr>
<tr>
<td>Q8. The teachers ridicule the students*</td>
<td>2.43 2.23 1.95 2.13 2.18 0.17</td>
</tr>
<tr>
<td>Q9. The teachers are authoritarian*</td>
<td>1.78 1.73 1.45 1.68 1.66 0.13</td>
</tr>
<tr>
<td>Q18. The teachers have good communication skills with patients</td>
<td>2.56 2.88 2.90 3.38 2.93 0.29</td>
</tr>
<tr>
<td>Q29. The teachers are good at providing feedback to students</td>
<td>2.62 2.19 1.95 2.53 2.32 0.27</td>
</tr>
<tr>
<td>Q32. The teachers provide constructive criticism here</td>
<td>2.47 2.50 2.07 2.50 2.38 0.18</td>
</tr>
<tr>
<td>Q37. The teachers give clear examples</td>
<td>2.77 2.69 2.24 2.80 2.62 0.23</td>
</tr>
<tr>
<td>Q39. The teachers get angry in teaching*</td>
<td>1.74 1.81 2.07 1.60 1.80 0.17</td>
</tr>
<tr>
<td>Q40. The teachers are well-prepared for their teaching sessions</td>
<td>3.05 2.92 2.50 2.98 2.86 0.21</td>
</tr>
<tr>
<td>Q50. The students irritate the teachers*</td>
<td>1.18 1.38 1.98 1.98 1.63 0.35</td>
</tr>
<tr>
<td><strong>Students’ Academic Self-Perception (SASP)</strong></td>
<td></td>
</tr>
<tr>
<td>Q5. Learning strategies that worked for me before continue to work for me now</td>
<td>2.38 2.54 2.14 2.50 2.39 0.15</td>
</tr>
<tr>
<td>Q10. I am confident about my passing this year</td>
<td>2.83 3.19 3.14 2.55 2.93 0.26</td>
</tr>
<tr>
<td>Q21. I feel I am being well prepared for my profession</td>
<td>2.49 2.19 1.98 2.63 2.32 0.25</td>
</tr>
<tr>
<td>Q26. Last year’s work has been a good preparation for this year’s work</td>
<td>2.27 2.46 2.24 2.20 2.29 0.10</td>
</tr>
<tr>
<td>Q27. I am able to memorize all I need</td>
<td>2.03 1.85 1.45 1.65 1.74 0.21</td>
</tr>
<tr>
<td>Q31. I have learnt a lot about empathy in my profession</td>
<td>2.58 2.69 2.76 3.13 2.79 0.20</td>
</tr>
<tr>
<td>Q41. My problem-solving skills are being well developed here</td>
<td>2.45 2.27 1.81 2.43 2.24 0.26</td>
</tr>
<tr>
<td>Q45. Much of what I have to learn seems relevant to a career in healthcare</td>
<td>2.62 2.77 2.69 2.95 2.76 0.12</td>
</tr>
<tr>
<td><strong>Students’ Perception of Atmosphere (SPoA)</strong></td>
<td></td>
</tr>
<tr>
<td>Q11. The atmosphere is relaxed during ward teaching</td>
<td>2.39 2.19 1.71 2.08 2.09 0.25</td>
</tr>
<tr>
<td>Q12. This school is well time-tabled</td>
<td>2.30 2.38 1.48 2.73 2.22 0.46</td>
</tr>
<tr>
<td>Q17. Cheating is a problem in this school*</td>
<td>2.14 1.62 1.74 1.70 1.80 0.20</td>
</tr>
<tr>
<td>Q23. The atmosphere is relaxed during lectures</td>
<td>2.45 2.42 2.71 2.88 2.62 0.19</td>
</tr>
<tr>
<td>Q30. There are opportunities for me to develop my interpersonal skills</td>
<td>2.65 2.23 2.36 2.30 2.38 0.16</td>
</tr>
<tr>
<td>Q33. I feel comfortable in class socially</td>
<td>2.77 2.69 2.83 2.93 2.80 0.09</td>
</tr>
<tr>
<td>Q34. The atmosphere is relaxed during class/seminars/tutorials</td>
<td>2.53 2.38 1.98 2.88 2.44 0.32</td>
</tr>
<tr>
<td>Q35. I find the experience disappointing*</td>
<td>2.40 2.50 2.17 2.73 2.45 0.20</td>
</tr>
<tr>
<td>Q36. I am able to concentrate well</td>
<td>2.53 2.00 1.74 2.03 2.07 0.29</td>
</tr>
<tr>
<td>Q42. The enjoyment outweighs the stress of the course</td>
<td>2.38 1.96 1.81 2.25 2.10 0.23</td>
</tr>
<tr>
<td>Q43. The atmosphere motivates me as a learner</td>
<td>2.55 2.19 1.76 2.45 2.24 0.30</td>
</tr>
<tr>
<td>Q49. I feel able to ask the questions I want</td>
<td>2.57 2.19 1.50 2.18 2.11 0.39</td>
</tr>
<tr>
<td><strong>Students’ Social Self-Perception (SSSP)</strong></td>
<td></td>
</tr>
<tr>
<td>Q3. There is a good support system for students who get stressed</td>
<td>1.91 1.58 1.29 1.95 1.68 0.27</td>
</tr>
<tr>
<td>Q4. I am too tired to enjoy the course*</td>
<td>2.10 1.73 1.55 1.78 1.79 0.20</td>
</tr>
<tr>
<td>Q14. I am rarely bored in this course</td>
<td>1.77 1.46 1.14 2.08 1.61 0.35</td>
</tr>
<tr>
<td>Q15. I have good friends in this course</td>
<td>3.30 3.35 3.12 3.13 3.22 0.10</td>
</tr>
<tr>
<td>Q19. My social life is good</td>
<td>3.01 2.62 2.67 2.88 2.79 0.16</td>
</tr>
<tr>
<td>Q28. I seldom feel lonely</td>
<td>2.18 2.19 2.29 2.55 2.30 0.15</td>
</tr>
<tr>
<td>Q46. My accommodation is pleasant</td>
<td>2.86 2.92 3.40 3.15 3.08 0.21</td>
</tr>
</tbody>
</table>

*Negative questions

Items with a mean score below 2 were taken as problem areas needing remediable action (Red colour)
Items with a mean score of 3 and above were considered as positives (Green colour)
Items with a mean score between 2 and 3 were considered as aspects that could be possibly enhanced (Black colour)
5. Students’ Social Self Perceptions (SASP): 65% students had positive feelings about their academic achievements while 27.8% perceived negative aspects. The most prominent was the problem of cheating among students.

6. Students’ Perception of Atmosphere (SPOA): 66.2% students felt a more positive attitude towards the learning atmosphere of the college; nonetheless 27% believed that there were many issues that needed a change and this aspect was observed primarily by the sixth semester students. The biggest problem seemed to be an inability to memorize all that was needed.

7. Students’ Social Self Perceptions (SSSP): 75.5% students felt “not too bad” while 20.7% felt it was “not a nice place”. Many of the negative perceptions centered on the lack of support for stressed students and the course being burdensome, tiring and boring. The good feelings were about having excellent friends and a pleasant accommodation.

83.55% of the students rated the educational environment as more positive than negative while 14.4% observed that there were plenty of problems that needed attention. Only 2.1% thought that the EE was excellent. The most satisfied were the eighth semester and the least were the sixth semester students. The global and semester-wise scores for EE and its various domains are shown in the Table 1.

The mean scores for each individual statement are shown in Table 2 along with the items which scored positive and negative. As is discernible from the table, the mean scores for most of the items are lowest for the sixth semester students although the values are quite variable across all the semesters. The noticeable aspect is that most of the problematic or favorable points are quite consistent across all the semesters.

The composite overall perception of the EE and all its domains semester-wise is reflected in the Table 3. As compared to the overall medical college score of 118.41±16.9, the fourth and sixth semester rated it lesser at 115.90±3.76 and 106.10±3.46 respectively whereas the second and eighth semester students rated it higher at 123.13±5.03 and 127.05±3.95 respectively.

Table 4 shows the statistical significance of the data between semesters (using one-way ANOVA) in the scores of each of the five domains and the total EE. A comparison of the mean scores across these aspects showed that the difference among the groups of students was highly statistically significant, except for the parameter of Academic Self-Perception, which showed no statistical difference.

Salient Points that Emerged from Focused Group Discussions with Students

5 students’ volunteers from each semester were selected for this purpose. They were asked to reflect upon the identified problem areas and to give suggestions for improvement. Students wanted the teaching to be case based, integrated, interactive and enjoyable, and they be given more opportunities to ask questions, as well as a more relaxed ward teaching atmosphere. They wanted teachers to shed authoritarianism, be more approachable and friendly, as well as teach items that were less factual and more relevant. They also impressed upon better time management in the teaching schedule. They preferred blackboard teaching to powerpoint presentations in order to make the process interactive and provide more opportunities to clarify concepts.

Discussion

Students’ perception of their EE has a significant impact on their academic performance. The quality of EE is indicative of the effectiveness of an educational programme or curriculum.
Information on educational milieu can also be a basis for implementing modification and optimizing EE.[7] A medical student’s academic performance influences many stakeholders including the community which they serve, faculty, medical college selection committees and curriculum planners. EE research can guide medical teachers to introspect, devise and incorporate the best teaching strategy for the betterment of the EE. A positive educational environment and positive learning outcomes go hand in hand.[8]

The perceptions of quality of the EE may assist in developing a student-centered curriculum and to overcome problems faced by students by redesigning the induction course at entry level, having more orientation programs for fresh entrants with sessions on study skills, mind mapping, time and stress-management. Remedial programs can be organized for slow learners by incorporating causal analysis, counseling, enrichment classes, assignments, small group discussions and formative assessments. The students may be asked to focus on their weaknesses by a trained process of reflection, development of critical thinking skills, identification of deficiencies in knowledge, skills and enhance their self-directed learning capabilities. The students also, through the process of reflection, develop critical thinking skill, identify deficiencies in knowledge or skills, and try to create an action plan for enhanced self-directed learning.[9]

Students’ perceptions of their EE has been evaluated by several methods, but only the Dundee Ready Education Environment Measure (DREEM) inventory is specific to the unique environment that relates to medical education.[10,11] It was developed by an international Delphi panel in Dundee, Scotland, UK. It is a universal, validated instrument which provides medical education researchers with a diagnostic aid to measure the overall state of affairs in the learning environment of medical colleges. It focuses on identifying the gap between students’ idealized expectations and actual experiences. One of important outcomes of this form of evaluation is by providing a standardized way for international comparisons between medical schools as well as enabling them to benchmark the unique educational climate of the institution.[12]

Our DREEM score of 118/200 is quite similar to that reported by other Indian authors, but differs considerably from studies outside India. The DREEM scores for medical schools in Iran, Sri Lanka, United Kingdom, were variably reported as 99.6/200, 108/200, 139/200 respectively.[7,13,14] The mean DREEM score for a medical school in India (Abraham et al) was reported as 117/200 while in another study (Kiran et al) it was 120/200.[15,16] In addition, the present study has reported a highly statistically significant difference between the student experiences of EE at different stages of their medical education. Recently, a study by Pales et al has reported similar differences in educational climate perception by preclinical and clinical medical students in five Spanish medical schools.[17]

Based on the results of the present study, it is obvious that there is a need to create a congenial environment where teaching-learning process becomes an enlightening rather than stressful experience for both students and teachers. It is essential to create good support systems for handling crisis situations, and to provide an encouraging and nurturing environment. The process of teaching should aim at developing the problem solving and critical thinking abilities of students through emphasis on case based teaching. The basic and para-clinical departments could incorporate appropriate integration of clinical material to empower the students for a confident future in clinical practice settings.

The study identifies gaps in the teaching–learning environment from the students’ perspective. This information provides suggestions and emergence of recommendations for the curricular reforms. Student’s participation gives them an active participatory role as responsible stakeholders empowered in formation of the curriculum. Reflection by medical graduates will enable lifelong learning skills. Faculty and Medical Education Units will understand the students’ perspective and improvise better curricula and assessment and evaluation methods for developing competent medical graduates.

Limitations

Despite the good sample size and uniform representation across all semesters of MBBS we observe certain limitations of this study. The opinions provided by students may not be completely honest due to cross discussions. While DREEM is a reliable instrument, some statements may not be
applicable or appropriate for a particular student (e.g. For preclinical students “The teachers adopt a patient-centered approach to consulting” may be tricky). Some questions also lack clarity. DREEM in its current format may not be completely appropriate for clinical and bedside teaching as it appears to concentrate more on classroom teaching.

**Conclusions**

The present study has highlighted that the students’ perception of the EE was positive. However, some improvement is required across all domains of the EE at our institution. The study helped faculty to identify remediable areas in the educational environment of our medical college. A modification of the curriculum based on the inputs from the DREEM questionnaire analysis indicates that an environment that nurtures integrated, case-based learning in a stress-free environment will go a long way in developing competent graduate medical students who have the right attitudes and problem solving skills as well as temperament to manage myriad problems which are a part of the medical landscape.

**Acknowledgements**

I gratefully acknowledge the support of the faculty at CMC, Ludhiana, my departmental colleagues and MBBS students who have participated in this study.

**References**

Clinical Profile of *Pneumocystis jirovecii* Infection – A Comparative Study

Divya Deodhar¹*, Jency Maria Koshy², Mary John³, Aroma Oberoi⁴

Abstract

**Objectives:** Pneumocystis *jirovecii* pneumonia (PCP) can differ in HIV and non-HIV population due to degree of immunity. This study was undertaken with an aim to highlight the differences between the two groups.

**Methods:** It was an observational study conducted in the department of Medicine of a tertiary care institution in North India. All cases tested positive for Pneumocystis *jirovecii* from January 2009 to December 2014 were included in the study. Demographic profile, clinical presentation, risk factors, treatment and course in hospital were noted and analyzed.

**Results:** Among the 42 patients who had PCP, 13 (30.9%) patients were HIV positive and 29 (69%) were HIV negative. Cough was seen maximum in 10(79.3%) patients in HIV group compared to non HIV whereas fever and breathlessness predominated in the non HIV group.

The outcome was better in the non HIV group compared to the HIV group which was 16 (55.2%) versus 6 (46.1%) patients respectively.

**Conclusion:** Clinical presentation differed slightly in both these groups. Difference in the outcome was also noted, however, larger numbers may be required to show the difference. It may form the basis of further research. The study successfully compared the presentation and outcome of PCP in the two groups.

Introduction

*Pneumocystis jirovecii* pneumonia (PCP) is a potentially life-threatening condition occurring commonly in immunocompromised individuals.¹ It remains the most important AIDS defining illness in HIV infected patients and also occurs particularly in those who are deficient in cell mediated immunity. PCP is also seen in non-HIV infected persons who receive immunosuppression for organ transplant, connective tissue disorders and malignancy. However, in immunocompetent individual it may occur as asymptomatic lung colonization.²

This infection is considered to result from de novo acquisition of the fungus rather than latent forms of *P. jirovecii* present in the lungs.³ Due to its host specificity, PCP in humans is considered to be an anthroponosis and can have a large spectrum of clinical presentation ranging from mild infection like pulmonary colonization to severe infection presenting as ARDS and shock.⁴

Defective T cell immunity is the primary risk factor and signs and symptoms in HIV infection reflect the degree of CD4 count depletion.⁵

Due to varied risk factors depending on the degree of immunity, the presenting features may vary. A careful questioning may reveal a slowly progressive disease in non HIV compared to the rapid progression of PCP in HIV patients.⁶ Clinical examination may be non-specific with presence of rales and rhonchi. Spontaneous pneumothorax is the presenting feature in 2-6% of the cases.⁷

In the presence of risk factors, with minimum symptoms of cough, fever and dyspnoea having an unremarkable chest radiograph with low oxygen saturation (partial pressure of Oxygen < 75 mm of Hg) should raise a high suspicion of PCP. Elevated serum LDH levels although not specific may correlate to the severity of the illness.⁸

The diagnosis of Pneumocystis

---

¹Associate Professor, Dept. of Medicine, Christian Medical College and Hospital, Ludhiana, Punjab; ²Associate Professor, Department of Medicine, Believers’ Church Medical College, Thiruvalla, Kerala; ³Professor and Head, Dept. of Medicine, ⁴Professor and Head, Department of Microbiology, Christian Medical College, Ludhiana, Punjab; ⁵Corresponding Author

Received: 21.01.2017; Accepted: 03.06.2017
Table 1: Baseline characteristics of the study subjects

<table>
<thead>
<tr>
<th>Presenting complaint</th>
<th>HIV positive (n=13)</th>
<th>HIV negative (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>7 (53.8)</td>
<td>18 (62)</td>
</tr>
<tr>
<td>Cough</td>
<td>10 (76.3)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>7 (53.8)</td>
<td>18 (62)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2 (15.4)</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td><strong>Clinical findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachypnoea</td>
<td>11 (84.6)</td>
<td>24 (82.8)</td>
</tr>
<tr>
<td>Crepitations</td>
<td>12 (92.3)</td>
<td>22 (75.9)</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>1 (7.7)</td>
<td>8 (27.3)</td>
</tr>
<tr>
<td>Decreased breath</td>
<td>1 (7.7)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>sounds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial breath</td>
<td>0</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>sounds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2 (15.3)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>12 (92.3)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>(Hb &lt; 10 gm/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytosis</td>
<td>3 (23.1)</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>(TLC &gt; 11000/cumm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (30.8)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>(&lt; 1 lac)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxia (PaO2 &lt; 60)</td>
<td>10 (76.9)</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td><strong>Chest X-ray findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrates</td>
<td>8 (61.5)</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>Consolidation</td>
<td>4 (30.8)</td>
<td>8 (27.6)</td>
</tr>
<tr>
<td>Nodules</td>
<td>1 (7.7)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Cavitation</td>
<td>0</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Effusion</td>
<td>0</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td><strong>Specimen used for diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induced sputum</td>
<td>10 (76.9)</td>
<td>15 (51.7)</td>
</tr>
<tr>
<td>Endotracheal</td>
<td>3 (23.1)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>secretions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini BAL</td>
<td>0</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Bronchoscopy and</td>
<td>0</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>BAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen by mask</td>
<td>3 (23.1)</td>
<td>13 (44.9)</td>
</tr>
<tr>
<td>Noninvasive</td>
<td>6 (46.1)</td>
<td>2 (6.8)</td>
</tr>
<tr>
<td>ventilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>4 (30.8)</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>13 (100)</td>
<td>24 (82.8)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>13 (100)</td>
<td>24 (82.8)</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged</td>
<td>6 (46.1)</td>
<td>16 (55.2)</td>
</tr>
<tr>
<td>Expired</td>
<td>6 (46.1)</td>
<td>10 (34.5)</td>
</tr>
<tr>
<td>Disch. on request</td>
<td>1 (7.7)</td>
<td>3 (10.3)</td>
</tr>
</tbody>
</table>

% in parenthesis

jirovecii pneumonia is achieved by microscopy with staining of the isolated respiratory specimens. Most commonly used specimens are induced sputum and bronchoalveolar lavage. With staining of induced sputum, the diagnostic yield is 50 to 90 percent in HIV infection but is lower in non HIV patients due to the lower burden of the organism. Similar results are seen even with bronchoalveolar lavage. The use of polymerase chain reaction in induced sputum or bronchoalveolar lavage may be useful in diagnosis among the non HIV population compared to the HIV infected individuals and increases the diagnostic yield compared to the conventional staining.

The initial choice of treatment is trimethoprim-sulphamethoxazole (TMP-SMX) which can be used as intravenous and oral therapy. Prior to initiating treatment oxygen saturation should be taken to assess the need of adjunct corticosteroid therapy. Alternative therapy can be given with Clindamycin plus primaquine, TMP- dapsone and Pentamidine.

Primary prophylaxis with TMP-SMX in HIV infected patients reduces the PCP nine-fold when the CD4 count is less than 200 cells/ microl. Alternatives to TMP-SMX for prophylaxis are Dapsone 100mg daily and Atovaquone suspension 1500 mg daily.

There appears to be some differences in the clinical characteristics and treatment outcome of PCP amongst HIV infected and non HIV infected population and hence this study was undertaken with an aim to highlight the differences between the two groups.

Material and Methods

This was an observational study conducted at Christian Medical College and Hospital, Ludhiana, a tertiary care hospital in Northern part of India. All cases that tested positive using silver methenamine stain demonstrating the cell wall of the cyst, from January 2009 to December 2014 were included in the study. Their details regarding presenting complaints, examination findings, and investigations and other clinical details including the treatment received and outcome were recorded from the inpatient charts obtained from the Medical records of the hospital. The data collected was entered in proforma and analyzed using appropriate statistical methods. The descriptive analysis were expressed as mean and categorical variables as percentages. All statistical analysis was performed using SPSS, version 21.0 Armonk.

Results

There were a total of 42 patients confirmed with pneumocystis jirovecii infection, of which 13 (30.9%) patients were found to be positive for retroviral infection whereas 29 (69%) patients were HIV negative. The average age of the patients was 42.5 years with M: F ratio of 2.4:1. Majority of the patients i.e. 40 out of 42 (95.2%) were from Punjab. There was one patient each from Himachal Pradesh and Qatar respectively. The patient from Qatar had been on holiday in North India when he became symptomatic.

The study cohort was divided into two groups, HIV infected and the non HIV group whose baseline characteristics were as mentioned in Table 1. The most common presenting complaints found in our study were fever, cough and breathlessness. Amongst the HIV population, cough was the most common presentation seen in 10 (79.3%) patients followed by fever and breathlessness which were seen in 7 (53.8%) patients in each category. Amongst the non HIV group, most common presentation was fever and breathlessness which was seen in 18 (62%) patients whereas cough was seen in 5 (17.2%) of the patients.

HIV infection was one of the most common risk factors amongst all our subjects, seen in 13 (30.9%) patients. Other risk factors noted were malignancy, found in 8 (19%)
patients followed by diabetes mellitus and chronic lung disease in 7 (16.7%) patients each. Chronic kidney disease and connective tissue disorder were the risk factor in 5 (11.9%) patients each and chronic liver disease was present in three (7.14%) patients (Figure 1). Four (14.8%) patients had multiple risk factors.

Majority of the patients were tachypneic (84.6% in the HIV group compared to 82.8% in the non HIV group). On respiratory system examination, crepitations and rhonchi were the most prominent clinical findings. The presence of crepitations was 92.3% in the HIV group compared to 75.9% in the non HIV group. Rhonchi were predominantly seen in 27.5% patients amongst the non HIV group. Other findings were decreased breath sounds and presence of bronchial breath sounds.

On investigating these patients, 12 (92.3%) of them were anemic in the HIV group compared to 6 (20.7%) in the non HIV group. High total leucocyte counts were seen in 14 (48.4%) patients in the non HIV group whereas only 3 (23.1%) of them had leukocytosis amongst the non HIV group.

Ten (76.9%) patients were hypoxic in the HIV group compared to 12 (41.4%) patients in the non HIV group. Chest X-ray findings seen in our study were infiltrates, non-homogenous opacification, nodules, cavitation and effusion. The most common finding was the presence of infiltrates on the chest X-ray which was seen in 8 (61.5%) patients in the HIV group compared to 14 (48.3%) patients in the non HIV cohort.

High resolution CT scan was done in 12 patients on the study group which revealed cavitation in 4 (33.3%) patients, nodules in 2 (16.7%) and ground glassing in 6 (50%) patient.

The diagnosis of PCP was made by induced sputum examination in majority of the patients, 10 (76.9%) amongst the HIV group and 15 (51.7%) in the non HIV group. Endotracheal secretion testing was the other mode of diagnosing PCP which was seen in 3 (23.1%) patients in the HIV group compared to 2 (17.2%) in the non HIV group. The other modalities of diagnosis were Minibal in 5 (17.2%) patients and bronchosopic lavage in 4 (13.8%) patients in the non HIV group.

Amongst all the patients diagnosed with PCP, 13 (100%) of them were treated using Cotrimoxazole and steroids in the HIV group as compared to 24 (82.8%) patients in the non HIV group. In the non HIV group, one patient was treated with Clindamycin and Primaquine due to hypersensitivity to cotrimoxazole. However, 3 (10.3%) patients in the non HIV group expired before treatment could be initiated.

The supportive treatment included oxygen by face mask in 3 (23.1%) patients in the HIV group compared to 13 (44.9%) in the non HIV group; endotracheal intubation and ventilation was required in 4 (30.8%) patients in the HIV group compared to 14 (48.3%) in the non HIV group; noninvasive ventilation in 6 (46.1%) and 2 (6.8%) amongst the HIV and the non HIV patients respectively.

The outcome was better in the non HIV group where 16 (55.2%) patients were discharged after completing the treatment compared to 6 (46.1%) patients in the HIV group. There were more deaths in HIV patients i.e. 6 (46.1%) patients as compared to 10 (34.5%) patients without HIV. Four patients were discharged before completing treatment and their outcomes are unknown.

Discussion

The appearance of PCP in healthy gay was the initial sign of emergence of AIDS and it was one of the AIDS defining illnesses in 60 percent of the cases. In our study, HIV infection was seen in 30 percent of the patients. Early diagnosis of HIV and effective prophylaxis has contributed to 70 percent decline in PCP. Similar to the study done by Stansell JD et al, HIV infection remained the most important risk factor for PCP, others being hematological and solid organ malignancies present in about a third of the total population in our study. Prior to the routine use of prophylaxis, PCP was seen as high as 66 percent amongst the patients with hematological malignancies majority of which would be leukemia and lymphoma.

The other risk factors in our study were diabetes mellitus and chronic lung disease which was seen in 16 percent of the patients in comparison to the study conducted in116 patients in Mayo Clinic in whom glucocorticoid therapy was an important risk factor 95 percent of the patients in non HIV population. In India due to rampant use of indigenous medications for chronic Lung disease which
contain corticosteroids, there may be an increased risk of PCP as it leads to depressed cell mediated immunity. Some individuals appear to have colonization of lungs with this organism and may be the cause of infection in the other immunocompromised individuals. Patients who have CLD may show a higher degree of colonization and further depressing the immunity may lead to increased infection in these individuals.2

Clinical presentation seen in our study was cough, dyspnea and fever. Amongst the HIV infected patients cough was the most important presenting complaint seen in two third of the patients compared to non HIV group in whom fever and breathlessness predominated and was seen in fifty percent of the patients. Several studies 22 have documented a fulminant respiratory failure in non HIV patients compared to HIV infected patients who have an indolent presentation. Laboratory investigations and treatment were comparable in both the groups. Most of the patients received TMP-SMX along with corticosteroids.

Outcome seen in our study was better among the non HIV group, 55 percent compared to 46 percent in the HIV group who were discharged after completion of treatment. This can be compared to the observations made by Kovacs et al23 and Mansharamani et al 24 where mortality was seen in 50 percent in the HIV infected group compared to the 26 percent in the non HIV patients.

Conclusion

Hence our study was successful in comparing and contrasting the differences in the clinical features and the outcomes of PCP seen amongst the HIV infected and the non HIV population. HIV infection is the most common risk factor to acquire PCP but chronic lung diseases may also be considered as one of them especially in developing countries where steroids are easily available and are being misused for chronic respiratory diseases. Clinical presentation and the course of illness and outcome may vary in these two groups of patients. Smaller number of patients is the limitation of our study and studies with larger number may form a future prospective.

References

A Randomized Controlled Trial Comparing the Efficacy of a Combination of Rifaximin and Lactulose with Lactulose only in the Treatment of Overt Hepatic Encephalopathy

Shakeb Hasan¹, Saikat Datta²*, Sharmistha Bhattacharjee³, Smarajit Banik⁴, Sandip Saha⁴, Dipanjan Bandyopadhyay⁵

Abstract

Background: Hepatic encephalopathy (HE), or portosystemic encephalopathy, represents a reversible decrease in neurologic function caused by liver disease, and treatment has traditionally been with non-absorbable disaccharides along with antibiotics and supportive measures. The present study was undertaken to evaluate if their combination therapy were superior to the established therapy in management of HE.

Methods: Ninety six (96) patients of hepatic encephalopathy were randomly assigned to receive either lactulose and rifaximin in standard dosage or lactulose only and their response to therapy was monitored using standard assessment tools. The statistical analysis was done using Kaplan–Meier methods to estimate the percentage of patients maintaining survival over time.

Results: The patients who were on lactulose and placebo revealed to have lower mortality than those on lactulose and rifaximin. Also, improvement in neurological status was of Grade 1 or more was more in patients on lactulose and placebo when compared to those on lactulose and rifaximin. Although survival analysis revealed no statistical difference between two groups, the mean survival in the placebo group was higher.

Conclusion: The present study reveals that improvement in neurological status of the group treated with lactulose only was that of a higher percentage than that of the group being treated with lactulose and rifaximin, which reiterates the recommendation that lactulose be used as a first line therapy in overt hepatic encephalopathy (OHE). Also the outcome was better in patients who had a lower grade of encephalopathy on admission.

Introduction

Hepatic encephalopathy is a neuropsychiatric syndrome caused by hepatic insufficiency associated with acute or chronic liver disease. The cause is considered to be the body’s inability to remove ammonia from the blood stream, and the resultant accumulation of neurotoxins in the blood affecting brain function. It has been reported that approximately 70% of cirrhotic patients present with subclinical or mild hepatic encephalopathy and 23-40% progress to a more severe form of the disease. One and three year survival rates after experiencing an episode of hepatic encephalopathy have been reported to be 42% and 23% respectively.¹

The diagnosis of overt hepatic encephalopathy (OHE) is basically a clinical diagnosis utilising clinical scales to analyse its severity. Specific quantitative tests are only needed in study settings. The gold standard is the West Haven criteria (Conn score).²

¹Senior Registrar, General Medicine, AMRI, Dhakuria, Kolkata, West Bengal; ²Associate Professor, Department of Medicine; ³Assistant Professor, Department of Community Medicine; ⁴Assistant Professor; ⁵Professor and Head of the Department, Department of Medicine, North Bengal Medical College, Darjeeling, West Bengal; *Corresponding Author

Received: 08.02.2017; Revised: 04.05.2017; Accepted: 04.10.2017
Treatment of HE has evolved slowly over the last 50 years, with several breakthroughs.\(^8\) Options include Lactulose (b-galactosidofructose) and lactitol (b-galactosidosorbitol) as initial treatment. Once in the colon, lactulose is fermented by anaerobic bacteria yielding important weak acids and gases which leads to the acidification of ammonia into ammonium resulting in its poor absorption. Additionally, antibiotics are used to eliminate the ammonia producing gut bacteria, thus reducing the total ammonia load. Neomycin was one of the first antibiotics used in HE. Subsequently, various other antibiotics have been tried with varied results.

Rifaximin is a minimally absorbed oral antimicrobial agent that is concentrated in the gastrointestinal tract, has broad-spectrum in vitro activity against gram-positive and gram-negative aerobic and anaerobic enteric bacteria, and has a low risk of inducing bacterial resistance.\(^8\) Rifaximin has been used for the therapy of HE in a number of trials comparing it with placebo, other antibiotics, nonabsorbable disaccharides, and in dose-ranging studies. These trials have revealed that the effect of rifaximin was equivalent or superior to the compared agents with good tolerability.\(^10\)

Rifaximin has been found to significantly reduce the risk of an episode of hepatic encephalopathy, in comparison to placebo, over a 6-month period. A breakthrough episode of hepatic encephalopathy occurred in 22.1% of patients in the rifaximin group, as compared with 45.9% of patients in the placebo group.\(^11\)

In a systematic review, rifaximin has been found to be at least equally effective or superior to non-absorbable disaccharides and antimicrobials in relieving signs or symptoms observed in patients with mild-to-moderately severe HE.\(^12\) In another meta-analysis, no serious adverse events were reported following either rifaximin or disaccharides therapy.\(^13\)

In this context, the current study was undertaken to compare a combination therapy against monotherapy with the hypothesis that response of treatment with lactulose and rifaximin is non-inferior when compared to standard therapy with lactulose only.

**Methodology**

**Study design**

A non-inferiority type of randomized controlled trial was conducted among the indoor patients of the General Medicine ward of North Bengal Medical College and Hospital.

**Study population**

Adult patients with diagnosed chronic liver disease having encephalopathy (grade I to IV), after exclusion of metabolic/infective causes, were included in the study.

**Exclusion criteria**

- Age <18yrs
- Presence of any diagnosed neuropsychiatric illness and/or current use of antipsychotic/antidepressant medications
- Presence of any intestinal obstruction or inflammatory bowel disease
- Diagnosed hypersensitivity to Rifamycin or disaccharides
- Serum creatinine > 1.5 mg/dl
- Electrolyte abnormality (sodium <125 or >150 mEq/l)
- Minimal hepatic encephalopathy [Conn grade 0]\(^2\)
- Hypoglycaemia (capillary blood glucose < 70 mg/dl)
- Consent not given

A caregiver was present with the patient at all times to monitor any changes in the patient’s health or HE status and to ensure that the patient takes the study medications as scheduled.

**Sampling**

According to previous studies, anticipated percentage of study patients with chronic liver disease and encephalopathy was 50%. The sample size was estimated to be 120 patients, assuming a 10% dropout rate. According to the literature, 19% dropouts are expected in the control group and 12% in the intervention group.

**Methodology**

**Study design**

A non-inferiority type of randomized controlled trial was conducted among the indoor patients of the General Medicine ward of North Bengal Medical College and Hospital.

**Study population**

Adult patients with diagnosed chronic liver disease having encephalopathy (grade I to IV), after exclusion of metabolic/infective causes, were included in the study.

**Exclusion criteria**

- Age <18yrs
- Presence of any diagnosed neuropsychiatric illness and/or current use of antipsychotic/antidepressant medications
- Presence of any intestinal obstruction or inflammatory bowel disease
- Diagnosed hypersensitivity to Rifamycin or disaccharides
- Serum creatinine > 1.5 mg/dl
- Electrolyte abnormality (sodium <125 or >150 mEq/l)
- Minimal hepatic encephalopathy [Conn grade 0]\(^2\)
- Hypoglycaemia (capillary blood glucose < 70 mg/dl)
- Consent not given

A caregiver was present with the patient at all times to monitor any changes in the patient’s health or HE status and to ensure that the patient takes the study medications as scheduled.

**Sampling**

According to previous studies, anticipated percentage of study patients with chronic liver disease and encephalopathy was 50%. The sample size was estimated to be 120 patients, assuming a 10% dropout rate. According to the literature, 19% dropouts are expected in the control group and 12% in the intervention group.

**Methodology**

**Study design**

A non-inferiority type of randomized controlled trial was conducted among the indoor patients of the General Medicine ward of North Bengal Medical College and Hospital.

**Study population**

Adult patients with diagnosed chronic liver disease having encephalopathy (grade I to IV), after exclusion of metabolic/infective causes, were included in the study.

**Exclusion criteria**

- Age <18yrs
- Presence of any diagnosed neuropsychiatric illness and/or current use of antipsychotic/antidepressant medications
- Presence of any intestinal obstruction or inflammatory bowel disease
- Diagnosed hypersensitivity to Rifamycin or disaccharides
- Serum creatinine > 1.5 mg/dl
- Electrolyte abnormality (sodium <125 or >150 mEq/l)
- Minimal hepatic encephalopathy [Conn grade 0]\(^2\)
- Hypoglycaemia (capillary blood glucose < 70 mg/dl)
- Consent not given

A caregiver was present with the patient at all times to monitor any changes in the patient’s health or HE status and to ensure that the patient takes the study medications as scheduled.

**Sampling**

According to previous studies, anticipated percentage of study patients with chronic liver disease and encephalopathy was 50%. The sample size was estimated to be 120 patients, assuming a 10% dropout rate. According to the literature, 19% dropouts are expected in the control group and 12% in the intervention group.
population in the Rifaximin and Lactulose combination group that responds to treatment would be 76% and in Lactulose group 50%. Assuming dropout rate to be 10%, 95% confidence interval and 80% power, the sample size was calculated as 46 each in test and control group. Randomization to each treatment group and control group was calculated as 46 each in test and 80% power, the sample size be 10%, 95% confidence interval mortality.

Table 2: Outcome in both the groups (N=91)

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin Group</th>
<th>Placebo group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unchanged/worsened</td>
<td>12</td>
<td>8</td>
<td>0.646</td>
</tr>
<tr>
<td>(27.9%)</td>
<td>(20.0%)</td>
<td>(0.232, 1.794)</td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>31</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>(72.1%)</td>
<td>(80.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>32</td>
<td>32</td>
<td>0.727</td>
</tr>
<tr>
<td>(74.4%)</td>
<td>(80.0%)</td>
<td>(0.259, 2.046)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>(25.6%)</td>
<td>(20.0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Sociodemographic characteristics and presenting features of patients in two groups. (N=91)

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin group</th>
<th>Placebo group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD)</td>
<td>44.73 ± 10.59</td>
<td>44.98 ± 10.12</td>
<td>0.910</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (80.0%)</td>
<td>38 (82.6%)</td>
<td>0.793</td>
</tr>
<tr>
<td>Female</td>
<td>9 (20.0%)</td>
<td>8 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol addiction</td>
<td>42 (93.3%)</td>
<td>39 (84.8%)</td>
<td>0.315</td>
</tr>
<tr>
<td>Presenting signs and symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>22 (48.9%)</td>
<td>28 (60.9%)</td>
<td>0.174</td>
</tr>
<tr>
<td>Haematemesis</td>
<td>9 (20.0%)</td>
<td>5 (10.9%)</td>
<td>0.180</td>
</tr>
<tr>
<td>Melaena</td>
<td>12 (26.7%)</td>
<td>11 (23.9%)</td>
<td>0.813</td>
</tr>
<tr>
<td>Jaundice</td>
<td>34 (75.6%)</td>
<td>36 (78.3%)</td>
<td>0.807</td>
</tr>
<tr>
<td>Ascites</td>
<td>43 (95.6%)</td>
<td>42 (91.3%)</td>
<td>0.677</td>
</tr>
<tr>
<td>Initial Sensorium level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0.0%)</td>
<td>2 (4.3%)</td>
<td>0.477</td>
</tr>
<tr>
<td>2</td>
<td>13 (28.9%)</td>
<td>10 (21.7%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17 (37.8%)</td>
<td>19 (41.3%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15 (33.3%)</td>
<td>15 (32.6%)</td>
<td></td>
</tr>
<tr>
<td>SBP (Mean ± SD)</td>
<td>117.38 ± 22.02</td>
<td>115.87 ± 18.06</td>
<td>0.721</td>
</tr>
<tr>
<td>DBP (Mean ± SD)</td>
<td>71.96 ± 13.54</td>
<td>72.02 ± 12.47</td>
<td>0.981</td>
</tr>
</tbody>
</table>

After enrolling, the patients were randomly divided into two groups—one receiving Lactulose 15ml three to four times a day titrated so as to produce 3-4 loose stools per day along with Rifaximin 400 mg thrice daily, and the other group receiving Placebo with Lactulose. Both groups received supportive measures as indicated (including but not limited to IV antibiotics, enema, inotropic support, blood and blood products) (Figure 1). Follow up

The patients were followed up till recovery of Hepatic Encephalopathy or a maximum of ten days. Endpoint of the study

Any reduction in grade of encephalopathy according to Conn scale was considered as improved, and any increase in encephalopathy grade was considered as worsened.

Statistical analysis

Data were entered in Microsoft Excel datasheet and demographical and baseline disease characteristics were summarised using descriptive statistics. Kaplan–Meier methods were used to estimate the percentage of patients maintaining survival over time. A log rank test was run to determine if there were differences in the survival distribution for the two groups. Results and Analysis

Of a total of 120 patients screened for the study, 96 were enrolled. Finally, a total of 91 patients were randomised to receive rifaximin (n = 45) or placebo (n = 46) in the trial. The mean age of the study population was 44.97 ± 10.448 years. 87.3% population was male in the present study. The majority of the study population was from the rural areas (63.3%). 91.1% of the study population had history of regular alcohol intake. 53.2% of the study population had history of constipation on admission.

11 patients (13.9%) of the population had a history of upper GI bleed in the form of haematemesis. 24.1% of the population under study had a history of melaena. The differences were statistically not significant. 89.9% of the total population had ascites at the time of admission. The demographical and baseline disease characteristics were similar in both the groups (Table 1).

The overall mortality was 25.4%. The rifaximin group had a mortality
of 28.9% as compared to 21.2% in the placebo group. 70.3% of the total population had improvement in the neurological status. 68.4% of the patients in the rifaximin and lactulose whereas 72.2% of patients on lactulose and placebo showed improved neurological status by 1 or more grade (Table 2).

100% of the cases having initial sensorium level of Grade 1 improved, 89.5% presenting with Grade 2, 65.5% with initial Grade 3 and 58.3% with Grade 4 improved post admission.

Survival analysis by Kaplan Meier method revealed no difference in the overall survival distributions between the groups. The mean survival in the placebo group was higher (Figure 2).

**Discussion**

The study populations in the two groups were similar with respect to age. 38% of the study population was in the age group 40-49 years, 27.9% in 50-59 year age group and 16.5% in the age group of 30-39 years. Patil et al reports that age wise, prevalence of liver cirrhosis is higher in age group of 31-40 years i.e. 30 cases (30%) and next highest in the age group 41-50 years i.e. 28 cases (28%).

63% of the total study population were from rural area. It has been reported that prevalence rate is high in the illiterate patients as compared to literate patients. In rural and urban area wise, higher number of cases have been seen in rural area patients i.e., 62% as compared to urban area patients i.e. 38%.

Incidence of HE in the present study was higher in males (87.3 % of the total study population). The sex wise distribution of prevalence of liver cirrhosis cases has been reported to be higher in males (74%), as compared to females, in whom the prevalence rate was 26%.

91% of the population in the present study was alcoholic. Sundaram et al have also found that the leading cause of cirrhosis in India is alcohol consumption. 15

14% and 24 % population in this study had history of hematemesis and melaena, respectively. It has been reported that 30 to 40% of patients with compensated cirrhosis of the liver and 60% of patients with ascites present with esophageal varices and associated increased chance of upper GI bleed. 16

92.4% of the patients had history of abdominal swelling, and 89.9% were having ascites on admission. This can be correlated with a study where overt hepatic encephalopathy has been reported in subjects without cirrhosis with extensive portal systemic shunting. 17

The rifaximin group had a mortality of 28.9% as compared to the placebo group where the mortality was found to be 21.2%. This is in contrast to the study by Sharma et al where a mortality of 23.8% in rifaximin and lactulose group against 49.1% mortality in lactulose and placebo group was reported, with a p value of < 0.05. 12

According to Bustamante et al it was 42% at 1 year of follow up and 23% at 3 years. 18 Mortality of 15% has been reported in developed countries of the world. 19

68.4% of the patients in the rifaximin and lactulose group of this study had improvement in neurological status whereas 72.2% of patients on lactulose and placebo showed improved neurological status by 1 or more grades, as assessed by Conn score (West Haven criteria). 2

Sharma et al reported the respective improvement to be 76% and 50.8%. 13 Mas et al had reported equal effectiveness of rifaximin and lactitol, however most of the patients were in grade 1 or 2 HE. 20

**Conclusion**

The present study reveals that improvement in neurological status of the group treated with lactulose was that of a higher percentage than that of the group being treated with lactulose and rifaximin.

Although the p value is > 0.05, however the study reiterates the recent recommendation that lactulose be used as the first line therapy in OHE. 21

Also the outcome was better in patients who had a lower grade of encephalopathy on admission.

Mortality rate is still an important concern, with this study projecting an overall mortality of 25.4% of which 61% were in the group receiving combination therapy.

The statistically higher mortality rate and the worsening of neurological status could be attributed to a small sample size, a co-existing sepsis or a worse grade of encephalopathy on presentation, or even to a preceding history of HE in the past, all of which do worsen the prognosis as has been seen on reviewing the available literature.

**Limitations**

1. Monitoring of all patients in closed environment, i.e. intensive care facility, might have affected some outcomes
2. Etiological investigation would be another avenue to pursue for relative prognosis and expected response

**References**


We extend a hearty welcome to Kochi, the God’s own country for APICON 2019.

Date & venue: 07/10 February 2019 in Hotel Grand Hyatt, Bolgatty, Kochi, one of the largest convention center equipped with the latest infrastructure and facilities.

The Pre-launch of APICON 2019, Kochi will be done on 22nd Feb 2018 at Bengaluru. The Website will be launched at the venue of APICON 2018. For the first time in the history of APICON a feature filled mobile APP will also be launched. Come prepared for the early bird registration in Bengaluru for an unbeaten offer. Assured gifts for all early bird registrants. Kochi is getting ready for you. We look forward to receiving you in Kochi for APICON 2019.

Dr Sujit Vasudevan, Chairman, APICON 2019
website: www.apiconkochi2019.com

dr.sreenivasakamath@gmail.com
Organising Secretary, APICON 2019
Syncope: Clinical Study and Outcome of Diagnostic Evaluation

Ashutosh Chaturvedi1*, Arun Kumar2

Abstract

Background: Syncope is a common clinical presentation in emergency department. The diagnostic workup for syncope causes significant man-hour loss and expensive investigations. Most often the battery of investigations does not lead to any conclusive diagnosis.

Materials and Methods: This was a descriptive study in which included 50 consecutive patients with the diagnosis of syncope. These patients were admitted to a tertiary care hospital between Sep 2009 to Aug 2011. Patients of both sexes above 12 years of age were included in the study. The patients were evaluated on the basis of history, clinical examination, ECG, TMT (for exertional syncope), 2DECHO, HUTT, Holter monitoring and EEG.

Results: Mean age of males were 46.11 yrs and that of females were 41.33 years (confidence interval 95%). Out of 50 patients, 38 were males and 12 were females. The percentages of co morbidities in our sample population were CAD- 6.90%, CVA- 1.72%, Hypertension- 17.24%, APD-1.72%, Dyslipidemia- 3.45%, Hypothyroidism- 3.45%, RHD with Mitral Stenosis- 1.72%, Type 2 Diabetes Mellitus- 5.17% and no co morbidities in 55.17%. Out of 50 patients 30% had some or the other diagnosis rest 70% patients had no definitive diagnosis. 90% of the patients had cardiogenic syncope and rest 10% had non-cardiogenic syncope. None of the patients in our sample population had orthostatic hypotension. In our study 15 (30%) patients had history of recurrent syncope. On evaluation with ECG, 4 patients had Bundle Branch Block rest 46 had normal ECG. In 96% of the patients 2DECHO was normal. Holter monitoring revealed Supraventricular tachycardia only in 2 patients. Out of 15 patients of explained syncope 10 had positive HUTT (66.7%) whereas 5 had negative HUTT (33.3%); compared to 35 patients with unexplained syncope HUTT was inconclusive. Neurological evaluation revealed no abnormal EEG though it was our exclusion criteria.

Conclusion: While evaluating syncope most often the battery of investigations does not lead to any conclusive diagnosis. There was male predominance in presentation. Out of 50 patients 10% had cardiogenic, 20% had neurocardiogenic and in 70% diagnosis was not established. Only 20% had HUTT positive. Echocardiography is the investigation of choice in patients of valvular heart disease. A thorough clinical evaluation is must, investigations are of limited value.

Editorial Viewpoint

• The findings of our study were well correlated with other studies.
• In recurrent syncope Holter monitoring has got definite added advantage.
• The predictive value of HUTT is not 100%.

Introduction

Syncope is a transient loss of consciousness and postural tone with spontaneous recovery and no neurological sequelae.1 Syncope is a common clinical problem that affects up to 3.5% of the general population. In 40% of cases presented with syncope the exact cause remains elusive. Approximately 30% of affected patients experience recurrent episodes.2

Syncope is caused by a decrease in perfusion to the reticular activating system in the brainstem which supports consciousness. Most often it occurs while standing. In the standing position blood pressure and blood flow to the brain are critically dependent on a normally functioning cardiovascular system. Abnormalities in cardiac output or in autonomic reflexes controlling blood pressure may cause syncope. Further complicating the appropriate diagnosis, some patients may present with pre-syncope, an often ill-defined
transient episode of altered consciousness accompanied with features of autonomic abnormality. Syncope causes significant loss of man-hours and costly investigations.

The aims and objectives of the study were-

- To evaluate and determine the cause in 50 consecutive patients who presented with syncope and admitted to a tertiary care hospital.
- To describe the various epidemiological variants e.g. age and sex distribution and various co-morbid conditions among patients presenting with syncope.
- Role and outcome of HUTT (Head Up Tilt Test) in determining the cause of syncope.

Material and Methods

This study was undertaken in 50 consecutive patients admitted in a tertiary care hospital with history of syncope between Sep 2009 to Aug 2011. The aim was to study the clinical profile and evaluate the outcome of various diagnostic tools e.g. ECG, 2DECHO, HUTT, TMT, Holter and EEG.

1. Place of study: The study was carried out at a tertiary care hospital in India.
2. Study Population: This was a descriptive study. The sample study included 50 consecutive patients with the diagnosis of “SYNCOPE” reported to a tertiary hospital between Sep 2009 to Aug 2011 (02 Years). The study population comprised of patients of both sexes above 12 years of age. These patients were evaluated on the basis of history, clinical examination, ECG, TMT, 2DECHO, HUTT, Holter monitoring and EEG.
4. Target Population: Employees and their dependents or cases referred to this hospital from various service hospitals.
5. Sample Population: A total of 50 patients were drawn from target population.
6. Performa Variables

i. Baseline Characteristic:-
   - Age,
   - Sex,
   - History of smoking,
   - Anemia,
   - Malnutrition,
   - Hypertension,
   - Diabetes Mellitus

ii. Investigations:-
   - ECG
   - Echocardiography
   - TMT
   - HUTT
   - Holter monitoring
   - EEG
7. Inclusion Criteria
   The patients above 12 years of age with history of syncope were included in the study.
8. Exclusion Criteria
   - Known seizure disorder
   - Seizure recurrence
   - Pre-syncope
   - Dizziness without clear loss of consciousness

Results

In an effort to evaluate the patients admitted with history of syncope, a total of 50 patients were evaluated, out of which 12 (24%) were females and 38 (76%) were males. The mean age of males were 46.11 years and that of females were 41.33 (confidence interval 95%).

The P value was 0.432 (>0.05) i.e. this difference was not significant (Table 1).

Some patients had single and others had multiple co-morbidities with 3.45% functional (Depression) disability. The percentages of other co-morbidities (Table 2) in our sample population were Coronary Artery Disease- 6.90%, CVA- 1.72%, Hypertension-17.24%, Acid Peptic disease- 1.72%, Dyslipidemia- 3.45%, Hypothyroidism- 3.45%, Rheumatic Heart Disease with Mitral Stenosis 1.72%, Type 2 Diabetes Mellitus- 5.17% and no co-morbidities in 55.17%. Out of 50 patients 30% had some or the other diagnosis rest 70% had no definite diagnosis. 90% of the patients had cardiogenic syncope and 10% had non cardiogenic syncope. None of the patients had orthostatic hypotension.

15 patients of the study population had history of recurrent syncope. Out of these 15 patients who had history of recurrent syncope, 11(73.3%) were less than 60 years of age while 4 (26.7%) were more than 60 years of age compare to 35 patients with no history of recurrent syncope, 27 (77.1%) were less than 60 years of age and 8 (22.9%) were more than 60 years of age.

On routine evaluation 12 (24%), patients had haemoglobin less than 10 g/dl. On CVS evaluation none of the patients had carotid bruit. On evaluation with ECG, 4 patients had Bundle Branch Block and rest 46 patients had normal
Table 3: Association between diagnosis and HUTT cross tabulation

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explained</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>10</td>
<td>5</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Percent</td>
<td>66.7%</td>
<td></td>
<td>33.3%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Unexplained</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>0</td>
<td>35</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Percent</td>
<td>0.0%</td>
<td></td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>40</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Percent</td>
<td>20.0%</td>
<td></td>
<td>80.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Chi-Square tests

<table>
<thead>
<tr>
<th>Value</th>
<th>P value</th>
<th>Association is</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.167</td>
<td>0.0001</td>
<td>Significant</td>
</tr>
<tr>
<td>2.92E-07</td>
<td>&lt;0.001</td>
<td>Significant</td>
</tr>
</tbody>
</table>

ECG. 4 patients had CAD and one had Brugada syndrome (Right Bundle Branch Block pattern with ST elevation in leads V1 to V3).

Echocardiography of the patients revealed normal ECHO in 48 (96%), 1 (2%) patient had RWMA (Regional Wall Motion Abnormality) and 1 (2%) patient was suffering from Severe Mitral stenosis. Out of the study population 2 patients had exertional syncope in which stress test was negative. On Holter monitoring 2 patients had SVT (Supraventricular Tachycardia).

Out of 15 patients of explained syncope 10 had HUTT positive (66.7%) (Table 3) whereas 5 had negative HUTT (33.3%) compared to 35 patients with unexplained syncope HUTT was inconclusive. 15 patients with history of recurrent syncope 4 (26.7%) were HUTT positive while 11 (73.3%) were HUTT negative. Out of 35 patients with no history of recurrent syncope 6 (17.1%) were HUTT positive while 29 (82.9%) had negative HUTT.

Neurological evaluation revealed no abnormal EEG though it was our exclusion criteria.

Discussion

Syncope is a common clinical presentation of varied aetiology. In our study population mean age of males were 46.11 years and that of females were 41.33 years (confidence interval 95%). The P value was 0.432 (>0.05) i.e. this difference was not significant. There was no correlation between age of the patient and history of recurrent syncope (P value 0.773). In contravention to our study, the findings of Olde Nordkamp et al.³ (Am J Emerg Med 2009; 27, Soteriades ES et al: NEJM 2002; 347, Moya A and Sutton R et al:⁴ Eur Heart J 2009; 30) women are more likely than men to report such an episode. The reason in our case could be young patients with prolong standing while at work.

Most of the patients in our study had no co-morbidities. Some had single and others had multiple co-morbidities with 3.45% had functional (Depression) problem. In our study none of the patients had orthostatic hypotension. In our study population only 15 (30%) had definitive diagnosis, rest 35 (70%) had unexplained syncope. No definitive diagnosis was established in 54.4% of the patients in OESIL 2 (Osservatorio Epidemiologico della Sincupe nel Lazio) study⁵. This variation in statistics is due to our study population (serving soldiers) admitted with history of syncope. In the study population 10% of our patients had Cardiogenic syncope whereas in Framingham Heart Study conducted from 1971 to 1998, the most frequently identified causes were vasovagal (21.2 percent), cardiac (9.5 percent), and orthostatic (9.4 percent). In 36.6 percent of the cases the cause was unknown.

In our series three or more episodes of syncope were considered as recurrent syncope. Out of 50 patients 15 had history of recurrent syncope, 11 (73.3%) were less than 60 years of age while 4 (26.7%) were more than 60 years of age compare to 35 patients with no history of recurrent syncope, 27 (77.1%) were less than 60 years of age and 8 (22.9%) were more than 60 years of age. Syncope may be the presenting symptom in elderly with acute MI. It rarely occurs with Coronary artery spasm and Aortic dissection. In our study 12 patients (24%) had anemia (haemoglobin less than 10 mg/dl), which could be the precipitating factor associated with valvular heart disease or congestive cardiac failure to cause syncope.

The carotid impulse may reveal evidence for aortic stenosis but a carotid bruit does not provide a direct cause of syncope. In our study none of the patients had carotid bruit.

On evaluation through ECG, 4 patients had bundle branch block and rest had normal ECG. 4 patients had CAD. Although the diagnostic yield of ECG was very low (5%), it is recommended in all patients of syncope since the test is risk free and relatively inexpensive. The evaluation of haematological and biochemical parameters are not of much help in discerning the cause. The random blood sugar level may indicate hypoglycaemia as cause.

2D echocardiography is an important tool to reveal valvular pathology (stenotic or regurgitant lesions). In our study most of the patients (96%) had normal echocardiography, one had RWMA with severe Left ventricular dysfunction (02%) and another had severe Mitral stenosis.

In our series Logistic Regression for cardiogenic syncope as dependent variable and ECG, 2DECHO, and past history of cardiovascular co-morbidities revealed no significant association between these tests and cardiogenic syncope. Valvular heart Disease constituted only 1.72%. The cause of syncope was severe Mitral Stenosis. Two patients had exertional syncope
in which stress test was negative and in two patients it was not done because of contraindication (one had severe LV dysfunction and another had severe Mitral stenosis). It might precipitate complications like pulmonary oedema. Stress test (TMT) is indicated in patients who had history of Angina and had exertional syncope. TMT indicates ischemic event even though it is highly unlikely that it will induce syncope. Holter monitoring is a continuous ECG recording. Holter is indicated in patients in whom Ventricular Tachycardia or other rhythm disturbance is suspected. As per the study of Mark Linzer et al the Holter monitoring is non diagnostic in over 90% of cases.\(^8\) In our study out of 50 patients only 2 patients had supraventricular tachycardia rest 48 (96%) patients had normal Holter.

The main indication of HUTT is to investigate the vasovagal syncope. In our study the tilt angle was kept 70 degrees with duration of 50 minutes. Fitzpatrick et al have suggested tilt duration of 45 minutes.\(^9\) Keeping with this result, tilt duration of 50 minutes would seem appropriate since it would encompass mean ± 2 SD. Blood pressure was measured at 5-minute intervals by an automated non-invasive blood pressure monitor. Blood pressure was also taken whenever patients reported symptoms. Passive head up tilt produces a significant reduction in central blood volume and this is known to trigger the vasovagal reaction.\(^9\)

In our study, out of 50 patients, 10 (20%) had HUTT positive while rest 40 (80%) had HUTT negative. Out of 15 patients of explained syncope 10 had HUTT positive (66.7%) whereas 5 had negative HUTT (33.3%) compare to 35 patients with unexplained syncope HUTT was inconclusive (0%). Orthostatic intolerance in this condition has been associated with decreased peripheral vasoconstriction during orthostatic stress. All 35 patients had HUTT negative. 15 patients with history of recurrent syncope 4 (26.7%) were HUTT positive while 11(73.3%) had HUTT negative. Out of 35 patients with no history of recurrent syncope 6 (17.1%) had HUTT positive while 29 (82.9%) had HUTT negative. The association between history of recurrent syncope and HUTT positivity was not significant (P value >0.05). The fact that nearly 50% of patients with unexplained syncope had a positive tilt table test suggests that a neural mechanism is involved in its aetiology since prolonged upright tilt is known to trigger the vasovagal reaction.\(^9\) The incidence of positive tests was higher in patients with recurrent syncope further supports a neural pathogenetic mechanism.

Neurological causes should be considered in patients with syncope, although syncope is an unusual manifestation of neurological diseases. In our study none of the patients had abnormal EEG, though it was our exclusion criterion (Patients with history of seizures were excluded from the study). Several studies\(^11\)\(^\text{14}\) concluded that EEG monitoring was of little use in unselected patients with syncope. In the absence of a history of seizure activity, electroencephalography has provided few diagnoses in more than 500 patients reported in the literature. Electroencephalography is not recommended for patients with routine syncope evaluation and may only be beneficial in patients with a history of seizures.

**Conclusion**

Syncope is a common clinical presentation in emergency department. In most of the patients the cause of syncope could not be established. HUTT is an important diagnostic tool in vasovagal syncope though the predictive value of HUTT is not 100%.

**Echocardiography** is the investigation of choice in valvular pathology. Dysautonomia and polypharmacy are much more common in elderly patients. It is therefore concluded that proper history taking and clinical examination are the most important steps in establishing the cause. Investigations are of limited value.

**Abbreviations**

CAD—Coronary Artery Disease; ECG—Electrocardiography; ZECHO-2 Dimensional Echocardiography; TMT—Treadmill Test; HUTT—Head Up Tilt Test; EEG—Electroencephalography; APD—Acid Peptic Disease; RHD—Rheumatic Heart Disease; CVA—Cerebro Vascular Accident; HTN—Hypertension.

**References**

Study of Central Nervous System Tuberculosis

Archana Aher¹*, Madhuri Paithankar², Baliram Bhurke³

Abstract
Aims and Objective: To assess the clinical features, complications and outcome in patients with central nervous system tuberculosis (CNS TB) and to correlate the clinical, laboratory and radiological findings of CNS TB.

Material and Methods: In a cross sectional study, total 50 diagnosed cases of CNS TB (either TB meningitis or tuberculoma) were studied. The data on demographic factors, clinical features, complications and laboratory findings, details of treatment and outcome were recorded and analyzed. Follow up was done during hospital stay and at the end of six months after completion of chemotherapy.

Results: Out of 50, 42 patients had TBM (tuberculous meningitis) and 8 patients had tuberculoma. Mean age of patients was 33.5 yrs with male preponderance (M: F = 6.2:1), 66% patients had duration of symptoms more than 4 weeks. Common symptoms were fever (100%), headache (70%) and vomiting (64%). CSF staining for AFB was positive in 8% patients, mean CSF protein was 157 mg%, 32 patients had CSF lymphocytosis, (count >90%), CSF PCR was positive in 92.85%, CSF ADA levels were high (> 10 U/L) in 90.47%. On neuroimaging, 62 % patients had meningeal enhancement and 8 patients had tuberculomas. 10 patients were in stage I of disease, 24 in stage II and 16 in stage III. 30% mortality was observed, more in HIV positive patients with stage III disease. On followed up after 6 months of discharged patients (n=35), 10 patients had full recovery and 17 had recovery with neurological deficit, however 8 patients lost follow up.

Conclusion: Diagnosis of CNS TB should be based on clinical features and 3 or more supportive criteria rather than CSF positivity on staining or culture. Rapid and early diagnosis by positive CSF PCR and CT/MRI findings should replace CSF AFB staining and culture in further for the diagnosis of CNS TB.

Introduction
Central nervous system (CNS) tuberculosis (TB) is a devastating infection with high rates of morbidity and mortality worldwide and may manifest as meningitis, intracranial tuberculoma, spinal arachnoiditis and rarely tuberculous encephalopathy. In the order of frequency pathological changes are seen in meninges, ependyma, choroid plexus, blood vessels and brain parenchyma.¹,² Tuberculous meningitis (TBM) presents as acute meningitic syndrome, as insidious subacute demyelinating process or tuberculous encephalopathy. Risk factors for the development of TBM are extremes of age, alcoholism, diabetes, malignancy, recent corticosteroid use and HIV infection.³ The early and exact diagnosis of TBM is important but difficult due to time definitive microbiological procedure.⁴

Diagnosis on pure clinical ground is impossible necessitating the importance of CSF studies and neuroimaging. CSF studies being the principle diagnostic tool in TBM. CSF shows pleocytosis with lymphocytes, elevated protein ranging from 60 mg% to 400 mg% or even higher, sugar between 20 mg%-40 mg%. It is sterile on routine bacterial culture. Demonstration of tubercle bacilli by AFB staining or culture remains the most important step of CSF study but its yield is much low.⁵

Though WHO has included CNS TB in category 1, CNS TB requires long term treatment and follow up, as high mortality, squeal, and complications are often seen in these patients if not diagnosed early and treated properly. As there is still paucity of Indian studies on

¹Associate Professor, ¸Ex. Professor, ¸Ex. Resident, Department of Medicine, Government Medical College, Nagpur, Maharashtra; ¹Corresponding Author
Received: 23.11.2016; Revised: 23.10.2017; Accepted: 25.10.2017
CNS TB, we undertook this two year study to know the clinical profile of CNS TB and to study the clinical, laboratory and radiological correlation of CNS tuberculosis.

Material and Methods

After obtaining Institutional Ethical Committee approval and written informed consent from patients or relatives, this hospital based cross sectional study was carried on 50 adult (>12 years) patients, hospitalized at Government medical College and Hospital, Nagpur over a period of two years. The patients were evaluated in detail and were grouped in three stages according to severity of illness at presentation as per the criteria of modified British Medical Research Council as stage I – Nonspecific symptoms, few or no clinical signs of meningitis, stage II – Signs of meningitis, drowsy, cranial nerve palsies and stage III – Stupor or coma, systemic toxicity, paralysis.

Diagnosis of CNS TB was done on the basis of clinical features like fever >2 wks, headache, vomiting, convulsions, signs of meningeal irritation with or without neurological deficit and positive CSF studies (staining or culture) or clinical features and supportive criteria (3 or more criteria) such as I - CSF examination suggestive of TB i.e. proteins >60 mg%, sugar <40 mg%, cells >50 cumm, lymphocytosis > 60 %, II – CSF PCR positive for TB and CSF ADA >10u/L, III – CT/MRI findings (one or more) – meningeal enhancement, infarcts, basal exudates, obstructive hydrocephalus, tuberculomas, IV – evidence of additional culture positive or histopathologically proved and radiological evidence of extrapolumary TB or milliary TB and V – Response to treatment

All patients were thoroughly investigated with routine tests as well as specific tests for TB like ESR, Montoux test, sputum and aspirate from lymph node for ziehl neelsen stain and CSF analysis for microscopy and biochemistry, ADA, CSF and serum ELISA for IgM antibody using A60 antigen and a CAT scan of brain. All patients received antituberculous therapy as per RNTCP guidelines. Steroids were given to stage 2 and 3 patients for 4 to 6 weeks with tapering of doses as recommended. Follow up was done for 6 months after completion of chemotherapy. Statistical evaluation was done using chi square test and p value calculated using student’s t test.

Results

Total 50 cases were diagnosed with CNS TB based on clinical, laboratory and radiological features and were studied, among them 42 patients had TB (tuberculous meningitis) and 8 patients had tuberculosis. Mean age of patients was 33.5 yrs with male preponderance (M: F = 6.2:1). Symptoms and signs of the patients are shown in Table 1. Common symptoms were fever (100%), headache (70%) and vomiting (64%). 66% patients had duration of symptoms more than 4 weeks. Out of 50-18 patients were HIV positive.

CSF examination was done in all patients of TBM. The abnormal results of CSF examination are shown in Table 2. CSF staining was positive in 8% patients, mean CSF protein was 157 mg%, 32 patients had CSF lymphocytosis, (count >90%), CSF PCR was positive in 92.85% patients, CSF ADA levels were high (> 10 U/L) in 90.47%.

CT/MRI findings are depicted in Table 3. 62 % patients had meningeal enhancement and 8 patients had tuberculomas.

In our study 10 patients were in stage I of disease, 24 in stage II and 16 in stage III. Total 30% mortality was observed, more in HIV positive patients with stage III disease. Discharged patients (n=35) were...
followed up after 6 months and it was observed that 10 patients had full recovery and 17 patients had recovery with neurological deficit, however 8 patients lost follow up.

**Discussion**

In present study TBM affected all age groups, with mean age 33.7 years. We observed that the disease was common in adults as compared to elderly people, as also mentioned in study of Karstaedt et al. Males outnumbered females with Male: Female = 6.2:1; this discrepancy could be due to more number of males being admitted as compared to females during the study period.

The triad of symptoms observed in most cases was fever, headache, vomiting, and fever being the commonest symptom present in all patients. The duration of symptoms was more than 4 weeks in 33 patients and 2–4 weeks in 17 patients. As mentioned by various studies in our study also, signs of raised intracranial tension were present in the form of altered consciousness (56%), vomiting (64%), headache (70%), convulsions (22%) and coma (16%). Among the signs of meningeal irritation neck stiffness was present in maximum number of patients of TBM (84%), Kernig’s sign and Brudzinski’s sign were present in 76% and 72% of patients respectively. The incidence of hemiplegia, quadriplegia and cranial nerve palsies mentioned in various studies varies from 20–30%. In our study 24% patients had hemiplegia, 8% patients had quadriplegia and 16% patients had cranial nerve palsies. These 16% patients with cranial nerve palsies had tuberculoma. Most commonly 3rd, 6th and 7th cranial nerves were involved. 26% patients had cough with expectoration, 8% patients had lymphadenopathy. We could get extrameningeal foci of TB in 30 patients, 22 patients had pulmonary (10 – milliary, 10 – parenchymal and 2 – pleuroparenchymal) and 4 patients had tuberculous lymphadenopathy.

CSF staining was positive in 4 patients and as CSF culture facility was not available, CSF culture was not done. However from the literature review we found that positivity of CSF culture varies greatly from 0% to 57%. Therefore, although CSF culture and staining are described as gold standard for diagnosis of CNS TB, they are being replaced by other supportive CSF studies like CSF biochemical and microscopic examination, CSF PCR and CSF ADA. In our study CSF was straw coloured in 16% cases, cobweb was present in 47.61% cases. All patients of meningitis had CSF sugar < 40 mg%, proteins > 60 mg% and lymphocytosis; mean CSF sugar being 38 mg%, mean CSF protein was 157 mg% and the mean CSF lymphocyte count was 179.5/cumm. Similar findings were described by various authors.

We did CSF PCR and ADA examination in all (42) patients of TBM out of which CSF PCR was positive in 39 cases (92.85%) this was compared with study of Dil Afroz et al and Fiju chacko and Prabhakar et al. In our study CSF ADA level > 10 U/L was present in 38 out of 42 patients of TBM. Mean CSF ADA level was 18 U/L, this result was correlated with previous studies. Thus as CSF examination for PCR and ADA is rapid, early and special tests available for TB, it can be taken as important supportive criteria for diagnosis of CNS TB.

On CT or MRI examination out of 50 patients of neurotuberculosis 8 patients had tuberculomas. Remaining 42 patients showed various signs suggestive of meningitis. Maximum number of patients had meningeal enhancement (62%), 16 patients had infarcts, 4 patients had basal exudates and 4 patients had hydrocephalus. Our findings were in accordance with other case studies. Thus neuroimaging studies make the diagnosis of CNS TB within hours. Diagnosis of meningitis is favoured by the presence of meningeal enhancement which is better seen on MRI. Arteritis and infarctions are critical consequences of tuberculosis. (1. c 38 patients had anaemia, raised ESR (>60 mm at the end of 1 hr) was present in 43 patients and only 20 patients had positive montoux test.

There were 18 HIV patients in our study, 16 patients had TBM and 2 patients had tuberculomas. 2 patients had CD4 count <50, 8 patients had count between 51–100, 6 patients had counts 101 – 150 and 2 patients had counts 151 – 200. Out of 50 cases, 10 patients were in stage I of disease, 24 in stage II and 16 in stage III. Demonstration of culture positive, histologically proved, radiological positive TB as extra meningeal foci also remains an important supportive criteria to diagnose CNS TB. In our study 30 patients had evidence of TB at site other than CNS; 22 patients had pulmonary TB and 8 patients had tubercular lymphadenitis. Response to treatment was also taken as supportive criteria in Venugopal et al study. However it holds true for cases of tuberculosis and in cases of TBM, for stage 1 disease only.

Our patients were treated by 2 (HRZE) 3 + 4 (HR) 3 for 6 months as per RNTCP guidelines, along with other conservative management. Ventriculoperitoneal shunt was done in two patients. 18 HIV positive patients were treated by antiretroviral therapies as per advice of our ART physician. Steroids were added as par indication along with other supportive management. (where H – Isoniazide 600 mg, R – Rifampicin, Z – Pyrazinamide 1500 mg, E – Ethambutol 1200 mg). Drug toxicity was negligible. Regarding duration of treatment controversy still exists. It is the treating physician’s clinical judgement which decides whether to continue AKT for 9 or 12 or 18 months and so on. However the principle of therapy is that the therapy should be initiated as soon
as disease is suspected. Hence there is need of the tests confirming the disease as early as possible. For HIV patients CNS TB Bis 09 draft for consultation (2009) recommends the antituberculous regimen should be the same as that recommended for HIV negative individuals. Adjunctive corticosteroid therapy should also be given to these patients.

During hospital stay 15 patients died (30 % mortality). There were 10 patients in stage I disease and was no mortality in this group. 24 patients had stage II disease, with 29 % mortality, and 16 patients had stage III disease with 50 % mortality. Thus although mortality increased with staging, it was not statistically significant. There were 18 HIV positive patients in our study, out of them 8 patients had stage II disease, amongst these, 2 patients died (mortality 25 %) and 10 HIV patients had stage III disease among these 8 patients died (80 %), this was statistically significant. We tried to correlate various factors e.g. the duration of illness, age of patients, presence of coma, raised CSF proteins, CSF lymphocytosis, obstructive hydrocephalus, staging of disease and HIV status to the mortality. We tried to find the predictors of mortality in these patients and it was observed that except stage III disease with HIV positive status no other factors were found to be significant in our study.

Discharged 35 patients were followed up for 6 months after completion of chemotherapy. 8 patients lost follow up and 27 patients were followed up at the end of 6 months. Out of 27, 10 patients (TBM – in 6 patients, tuberculoma – 4 patients) had full recovery and 17 patients had recovery with neurological deficit (TBM – 15, tuberculoma – 2 patients).

Conclusion

Diagnosis of CNS TB should be based on clinical features and 3 or more supportive criteria rather than CSF positivity on staining or culture which may be negative many times, takes more time to get the report. Hence supportive criteria like CSF examination (raised proteins, lymphocytosis, low sugar) along with positive CSF PCR, raised CSF ADA levels >10 IU/L, positive CT / MRI findings, evidence of culture positive, histologically proved or radiological tuberculosis anywhere in the body and response to treatment should be considered for the diagnosis of CNS TB. Rapid and early diagnosis by positive CSF PCR and CT/MRI findings should replace CSF AFB staining and culture in further for the diagnosis of CNS TB. After completion of cat 1 regime of treatment (RNTCP) for 6 months duration of treatment should be decided by treating physician, neurophysician.

References


Academy of Cardiology (AOC) Fellowship

AOC invites applications for one national and one international fellowship during each financial year. The aim is to promote growth of advanced electrophysiology, paediatric, interventional and preventive cardiology in India.

The criteria are as follows:

1. DM / DNB cardiology below 40 years of age.
2. The candidates should get a placement from the institution where he/she proposes to work.
3. The objective of the training should be approved by the guide/ supervisor/ consultant in the host institution. The period of training should preferably be 6 months.

The academy will provide a lump sum amount to the eligible candidate.

(Apply to Academy of Cardiology at Mumbai, Kirti Manor, S.V. Road, Santacruz (West), Mumbai 400054)
Awareness, Self-Assessment and Help Seeking Behavior for Behavioral Addictions Related to Use of Mobile Technology Among Attendees of a Health Camp

Yatan Pal Singh Balhara¹*, Neha Dahiya², Mohit Varshney³, Suneela Garg⁴, Rachna Bhargava⁵

Abstract

Introduction: Behavioral addictions are increasingly being recognized as a major public health problem. While this issue continues to hog the limelight in the media, there is limited scientific research on this theme from India.

Objectives: We aimed at presenting the findings on assessment of the awareness, self-assessment and help seeking behavior for behavioral addictions related to use of mobile technology among attendees of a trade promotion event.

Methods: We report findings from a health camp organized as part of a large trade promotion event in the northern part of India. The trade promotion event was open to the general public. As part of the screening services offered at the health camp, the visitors were offered to screen themselves on the theme of behavioral addictions related to use of mobile technology using a self-administered questionnaire. We carried out a chart review of the data gathered at the health camp.

Results: We assessed records of a total of 817 respondents who completed the screening using the self-administered questionnaire. The mean age of the respondents was 32.35 years (SD ± 13.62). Approximately 56% of the respondents rated themselves to be having at least one of the nine features of behavioral addictions. Around 15% of the respondents endorsed five or more features. Around 41% of the respondents mentioned that they shall agree to the professional help in case they are having behavioral addiction related to use of mobile technology. Fifteen percent of the respondents agreed to have sought some help in the past. The logistic regression analysis revealed that the odds of help seeking increased significantly with every single increase in the number of self-assessed feature of behavioral addiction.

Editorial Viewpoint

- Behavioral addictions for use of mobile is increasing.
- This survey from health camp reports that 56% of respondents had at least 1 feature of behavioral addiction.

Introduction

Behavioral addictions are increasingly being recognized as a major public health problem. Penetration of mobile technology has grown steadily over the last decade and an increasing proportion of Indian population has access to the smartphones and internet enabled hand held devices.

Behavioral addictions related to use of mobile technology is a major area of concern.¹ In spite of this growing concern, most of the discourse on this theme continues to be outside the scientific domain. While this issue continues to hog the limelight in the media,²⁻⁴ there is limited scientific research on this theme from India. Majority of the existing research has focused on

¹Associate Professor of Psychiatry, Behavioral Addictions Clinic (BAC), Department of Psychiatry and National Drug Dependence Treatment Center, All India Institute of Medical Sciences (AIIMS), New Delhi; ²Senior Resident Doctor, Department of Community Medicine, Maulana Azad Medical College, New Delhi; ³DM (Addiction Psychiatry) Resident, National Drug Dependence Treatment Center, All India Institute of Medical Sciences (AIIMS), New Delhi; ⁴Director Professor, Department of Community Medicine, Maulana Azad Medical College, New Delhi; ⁵Associate Professor, Department of Psychiatry and National Drug Dependence Treatment Center, All India Institute of Medical Sciences (AIIMS), New Delhi; *Corresponding Author

Received: 21.08.2017; Accepted: 31.10.2017
Table 1: Socio-demographic variables and behavioral addiction related features and awareness among the respondents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educational qualification</td>
<td>Upto 5th standard</td>
<td>1.22</td>
</tr>
<tr>
<td></td>
<td>Upto 10th standard</td>
<td>6.91</td>
</tr>
<tr>
<td></td>
<td>Upto 12th standard</td>
<td>18.42</td>
</tr>
<tr>
<td></td>
<td>Graduates</td>
<td>49.73</td>
</tr>
<tr>
<td></td>
<td>Post-graduates</td>
<td>23.72</td>
</tr>
<tr>
<td>Occupation</td>
<td>Unemployed and student</td>
<td>39.13</td>
</tr>
<tr>
<td></td>
<td>Self employed</td>
<td>24.21</td>
</tr>
<tr>
<td></td>
<td>Homemaker</td>
<td>5.12</td>
</tr>
<tr>
<td></td>
<td>Unskilled worker</td>
<td>2.91</td>
</tr>
<tr>
<td></td>
<td>Skilled worker</td>
<td>24.13</td>
</tr>
<tr>
<td>Self rated awareness on behavioral addictions related to use of mobile technology</td>
<td>Very good</td>
<td>32.61</td>
</tr>
<tr>
<td></td>
<td>Relatively good</td>
<td>28.42</td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>4.20</td>
</tr>
<tr>
<td></td>
<td>Limited</td>
<td>31.13</td>
</tr>
<tr>
<td></td>
<td>Unaware</td>
<td>3.74</td>
</tr>
<tr>
<td>Self assessed features of behavioral addictions related to use of mobile technology</td>
<td>I have preoccupation or obsession with it</td>
<td>21.4</td>
</tr>
<tr>
<td></td>
<td>I experience withdrawal symptoms when not doing it</td>
<td>24.8</td>
</tr>
<tr>
<td></td>
<td>More time needs to be spent doing it as I have become tolerant to it</td>
<td>19.6</td>
</tr>
<tr>
<td></td>
<td>I have tried to stop or curb it, but has failed to do so</td>
<td>19.4</td>
</tr>
<tr>
<td></td>
<td>I have had a loss of interest in other life activities, such as hobbies</td>
<td>19.7</td>
</tr>
<tr>
<td></td>
<td>I have continued overuse of it even with the knowledge of how much it impacts my life</td>
<td>19.7</td>
</tr>
<tr>
<td></td>
<td>I have lied to others about my behaviour related to it</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td>I use it to relieve anxiety or guilt—it’s a way to escape</td>
<td>16.0</td>
</tr>
<tr>
<td></td>
<td>I have lost or put at risk and opportunity or relationship because of it</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Specific population groups. Even the media reports are based on a few case studies and fail to present the bigger picture.

Perception and awareness of general public about a health condition is an important determinant of help seeking behavior, demand for health care services, and acceptance of prevention program. Such findings are likely to help while formulating the blue print to address the behavioral addictions in the country.

We aimed at presenting the findings on assessment of the awareness, self-assessment and help seeking behavior for behavioral addictions related to use of mobile technology among attendees of a trade promotion event. The trade promotion event offered access to general public and a unique opportunity to screen the attendees for the behavioral addictions related to use of mobile technology. Also, it offered an opportunity to understand their level of awareness and help seeking behavior.

**Subjects and Methods**

We report findings from a health camp organized as part of a large trade promotion event in the northern part of India. The trade promotion event was open to the general public. The health camp was organized with an aim to offer screening services for various medical conditions. Also, it was aimed at promoting the awareness on various health conditions among the general public. The visitors of the trade promotion event could avail the facilities at the health camp voluntarily and at no additional cost.

As part of the screening services offered at the health camp, the visitors were offered to screen themselves for their level of awareness on behavioral addictions related to use of mobile technology using a self-administered questionnaire. The term ‘behavioral addiction’ referred to various non-chemical (psychoactive substance) addictions. The behaviors related to use of mobile technology such as gaming, internet use, social media, etc. were assessed as part of this screening.

Study questionnaire comprised of a total of nine items that explored socio-demographic details (age, educational qualification, occupation) and awareness on behavioral addictions related to mobile technology. The responders self assessed themselves for behavioral addictions related to mobile technology using the items from the DSM 5 criteria for internet gaming disorder (total nine items) that were adapted for behavioral addictions related to mobile technology. Also, the respondents were enquired about the help seeking behavior for the behavioral addictions related to use of mobile technology. The study questionnaire was kept brief in view of the high workload at the health camp and to ensure high completion rate.

The current article reports the findings from this screening. We carried out a chart review of the data gathered at the health camp. The data were analyzed using the SPSS ver 21 (IBM Inc, New York). Descriptive statics included the frequency distribution of responses and chi square test. Logistic regression was carried out to assess the relationship of severity of self-assessed behavioral addiction and socio-demographic variables with help seeking behavior. The level of statistical significance was kept at p< .05 for all the tests.

**Results**

We assessed records of a total of 817 respondents who completed the screening using the self-
Table 2: Findings from logistic regression for help seeking behavior

<table>
<thead>
<tr>
<th>Covariates for 'ever sought help' (n- 808)</th>
<th>Age</th>
<th>Educational qualification (in years)</th>
<th>Self rated symptoms present</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exp (B) / Odds ratio</strong></td>
<td>0.99</td>
<td>1.15</td>
<td>1.16</td>
</tr>
<tr>
<td><strong>95% Confidence interval</strong></td>
<td>0.98 – 1.01</td>
<td>0.89 – 1.48</td>
<td>1.06 – 1.26</td>
</tr>
<tr>
<td><strong>SE</strong></td>
<td>0.01</td>
<td>0.13</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>0.48</td>
<td>0.28</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Covariates for 'acceptability of help' (n- 808)</th>
<th>Age</th>
<th>Educational qualification (in years)</th>
<th>Self rated symptoms present</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exp (B) / Odds ratio</strong></td>
<td>0.98</td>
<td>1.00</td>
<td>1.25</td>
</tr>
<tr>
<td><strong>95% Confidence interval</strong></td>
<td>0.97 – 0.99</td>
<td>0.99 – 1.00</td>
<td>1.16 – 1.34</td>
</tr>
<tr>
<td><strong>SE</strong></td>
<td>0.01</td>
<td>0.00</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>&lt;.01</td>
<td>0.64</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

^95% Confidence interval close to 1

administered questionnaire. The mean age of the respondents was 32.35 years (SD ± 13.62). More than two-thirds of the participants were graduate or postgraduates. More than half of the participants were gainfully employed. Students and those unemployed constituted 39.13% of the respondents (Table 1).

Approximately 56% of the respondents rated themselves to be having at least one of the nine features of behavioral addictions (Table 1). Of these 35.41% endorsed 1-2 features; 14.23% endorsed 3-6 features; and 5.52% endorsed 7-9 features of behavioral addiction. Around 15% of the respondents endorsed five or more features. Close to one third (34.87%) of the participants reported limited or poor awareness of behavioral addictions related to use of mobile technology.

Around 41% of the respondents mentioned that they shall agree to the professional help in case they are having behavioral addiction related to use of mobile technology. Within this sub-group, 97 respondents endorsed five or more self-assessed features of behavioral addiction and 363 endorsed less than five features. A significantly greater (Chi square-23.8, df- 1, p< .01) proportion of respondents who endorsed five or more features (63.2%) agreed to idea of professional help as compared to those who endorsed less than five features (38.4%). However, the two groups did not differ significantly with regards to actual help been sought in the past (19.6% v/s 14.2%; chi square- 2.5, df- 1, p= 0.12).

Fifteen percent of the respondents agreed to have sought some help in the past. Twenty eight percent of those who agreed to idea of being offered help had already sought some help in the past.

The logistic regression analysis revealed that the odds of help seeking increased significantly with every single increase in the number of self-assessed feature of behavioral addiction. Age and education level did not significantly predict the odds of help seeking (Table 2).

**Discussion**

The existing information on the perception and awareness of the general public on behavioral addictions related to use of mobile technology is largely based on media reports. The limited scientific literature on behavioral addictions in the country has focused on specific population groups. Consequently, the treatment needs and help seeking behavior of the general public on behavioral addictions remain mostly speculative.

The findings of the current study offer insights into the presence of self-assessed clinical features of behavioral addictions related to use of mobile technology. It also offers insights into the help seeking behavior of the general public for behavioral addictions related to use of mobile technology. The self-assessed features were adapted from the DSM-5 criteria for internet gaming disorders.

In our study having five or more self-assessed features was found to be a significant predictor of acceptance of help seeking. This type of correlation has not been reported previously from India. It is difficult to draw comparison of the current work with the previous published research on this theme from the country, as there are no published reports that have been carried out among such population and used similar methodology. A previously published report of a household survey in certain urban localities of Bengaluru reported a prevalence of 5.4% for 'internet addiction' and 'cell phone addiction'.

Close to half of the respondents in the current study reported that they believed to be having at least one of the nine features of behavioral addictions with around 15% of the respondents endorsing five or more features. The DSM 5 criteria for internet gaming disorder recommends presence of at least five of the nine criteria to consider the diagnosis. However, less than half of the respondents mentioned that they shall agree to the professional help in case they are having behavioral addiction related to use of mobile technology. Also, around one-third of the participants reported limited or poor awareness of behavioral addictions related to use of mobile technology.

There is a need to formulate a comprehensive blue print to address behavioral addictions in the country. The focus of the clinical services has to be on various aspects related to screening, diagnosis, management and prevention. The urgent requirement to spread awareness and establishment of specialized clinics countrywide has been identified. Also, there is a need to have a comprehensive
policy that addresses behavioral addictions. While behavioral addictions share many commonalities with the addictions to psychoactive substances, there are certain differences as well. Internet is a modern day necessity for many. With the increasing penetration of internet and availability of affordable and more powerful hand held mobile devices an increasing proportion of Indian population is likely to get exposed to the agent- ‘the internet’ and ‘the mobile device’. There is a need to focus on ‘the host’ as well as ‘the environment’ (along with ‘the agent’) to have realistic action plan to address this issue.

Further research is needed to identify the barriers that impact help seeking in individuals suffering from behavioral addictions. The development of health screens and formal diagnostic instruments to assess the full range of behavioral addictions may help with early identification and intervention.

There are certain limitations of the current study. It was based on review of records of a pre-concluded screening. The screening questionnaire was self-administered and was deliberately kept brief to ensure high completion rate. The prevalence of behavioral addictions among the respondents can be ascertained following assessment by qualified mental health professionals. Also, since the screening was based on self-assessment, there is a possibility of recall bias.

Conclusion

A significant proportion of individuals attending the health camp reported to have at least one feature of behavioral addiction related to use of mobile technology, with close to 15% endorsing five or more features. Less than half of the respondents were agreeable to the idea of seeking help in case they were screened positive for behavioral addiction. The awareness on behavioral addictions was limited among a third of the respondents. There is a need to formulate a comprehensive blue print to address the behavioral addictions in the country.

Author contribution

YPSB was involved in conceptualization, writing and review of manuscript. ND was involved in conceptualization, data collection and writing of manuscript. MV was involved in data analysis and writing the manuscript. SG was involved in conceptualization of the manuscript. RB was involved in the conceptualization and review of manuscript.

References


Referees for JAPI

API Members with minimum ten years experience of clinical practice and who are interested to contribute for JAPI as Referee may please send your details as listed below.

Name, Years of experience, Current designation and Affiliations, Area of interest, List of publications, e-mail id and Mobile number.

Kindly send above information at the earliest to: onlinejapi@gmail.com

Prof. Milind Y. Nadkar
Editor-in-Chief, JAPI
TRIPLE POWER
for enhanced glycemic control

GLYCYPHAGE-RVG
Metformin SR 500 mg + Voglibose 0.2 mg + Glimepiride 1 mg / 2 mg Tablets
Powers HbA1c Control
In Type 2 Diabetes,

**Start with**

**Glycomet®-GP 1**
Metformin Hydrochloride 850 mg SR + Gilimepride 1 mg

**Glycomet®-GP 1/850**
Metformin Hydrochloride 850 mg SR + Gilimepride 1 mg

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

**Glycomet®-GP 2**
Metformin Hydrochloride 850 mg SR + Gilimepride 2 mg

**Glycomet®-GP 2/850**
Metformin Hydrochloride 850 mg SR + Gilimepride 2 mg

**Glycomet®-GP FORTE**
Metformin Hydrochloride 1000 mg SR + Gilimepride 2 mg

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

**Glycomet®-GP FORTE**
Metformin Hydrochloride 1000 mg SR + Gilimepride 3 mg

**Glycomet®-GP 4/850**
Metformin Hydrochloride 850 mg SR + Gilimepride 4 mg

**Glycomet®-GP 0.5**
Metformin Hydrochloride 500 mg SR + Gilimepride 0.5 mg

**Glycomet®-GP 0.5 FORTE**
Metformin Hydrochloride 1000 mg SR + Gilimepride 0.5 mg

**Purity outshines...100% commitment.**
In Type 2 Diabetes with High PPHG

Choose the No. 1 brand

Start Early

Glycomet® Trio 1mg
Metformin HCl 500 mg SR + Glimperide 1 mg + Voglibose 0.2 mg

Glycomet® Trio 2mg
Metformin HCl 500 mg SR + Glimperide 2 mg + Voglibose 0.2 mg

Uptitrate to

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

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

In Obese Type 2 Diabetes with HbA1c > 9%

Start Early

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

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

Ref.: # - MAT AIOCD : Dev 2016
The most Economical & widely Available statin combination

In Management of CAD

Active 4 for Active HEART

Ecosprin® AV 75
(Enteric Coated Aspirin 75 mg + Atorvastatin 10 mg)

Ecosprin® AV 75/20
(Enteric Coated Aspirin 75 mg + Atorvastatin 20 mg)

Ecosprin® AV 150
(Enteric Coated Aspirin 150 mg + Atorvastatin 10 mg)

Ecosprin® AV 150/20
(Enteric Coated Aspirin 150 mg + Atorvastatin 20 mg)
Chellaram Diabetes Institute

2nd International Diabetes Summit - 2018
Pune
9th - 11th March, 2018 (Friday - Sunday)

With Faculty From
Karolinska Institute, Sweden ● University of Gothenburg, Sweden ● Mayo Clinic, USA
University of Florida, USA ● University of Turin, Italy ● University of London, UK
University of Manchester, UK

Highlights -
1st International Diabetes Summit - 2017
• 50 National and 12 international speakers from USA and Europe
• 1500 attendees, Oral/Poster presentations by 35 young researchers.
• The Maharashtra Medical Council awarded 7 Credit Points to the program.
• Visit www.cddiabetesummit.org for details.

REGISTRATION FORM

First Name __________________________ Surname __________________________ Gender M / F
MMC / Other Council No. __________________________
Hospital / Institution __________________________
Qualification __________________________ Speciality __________________________
Address for Communication __________________________
City __________________________ Pincode __________________________ State / Country __________________________
Mobile Number / Contact No (with area code) __________________________ Email Id __________________________

PAYMENT DETAILS

<table>
<thead>
<tr>
<th>Category</th>
<th>Up to 1st Jan 2018</th>
<th>Up to 8th March 2018</th>
<th>Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Delegate</td>
<td>Rs. 7,000/-</td>
<td>Rs. 7,500/-</td>
<td>Rs. 9,500/-</td>
</tr>
<tr>
<td>PG Student*</td>
<td>Rs. 4,000/-</td>
<td>Rs. 4,500/-</td>
<td>Rs. 5,500/-</td>
</tr>
<tr>
<td>HCPs</td>
<td>Rs. 7,000/-</td>
<td>Rs. 7,500/-</td>
<td>Rs. 9,500/-</td>
</tr>
<tr>
<td>International Delegate</td>
<td>USD 200/-</td>
<td>USD 250/-</td>
<td>USD 300/-</td>
</tr>
</tbody>
</table>

*This includes PHFI candidates
Medvents Conferences & Events Pvt Ltd
E-mail: reachmedvents@hotmail.com
Supriya Tak: +91 7767834459

Chellaram Foundation Diabetes Research Award 2018 for best abstract. Contact : ids@cdi.org.in

Please send the cheque/DD in favour of “Chellaram Foundation” to:
The Secretariat Address: 2nd International Diabetes Summit 2018
Chellaram Diabetes Institute, Lalani Quantum, Pune-Bangalore-Nh4
Bavdhan (Budruk) Pune -411021 | E-mail : ids@cdi.org.in
Contact Ms. Shraddha U. Mahajan : 020 - 66839722 / 8329037854
Study of Rhythm Disturbances in Acute Myocardial Infarction

Anjalee Chiwhane¹*, Pradeep¹

Abstract

Introduction: Cardiac rhythm disturbances are common presentation in acute coronary syndromes and are cause of frequent serious complications in acute myocardial infarction (AMI). However due to availability of early reperfusion therapy and primary angioplasty, arrhythmias have cause a reduction in mortality. Arrhythmias are key events before, during or after the occurrence of acute MI. There are few clinical studies describing the types of arrhythmias, their correlation with the clinical profile of acute MI and effect on outcomes. In rural tertiary care centre, patients of acute MI receive reperfusion therapy. The Indian population from central India is mostly a farming community from rural areas with limited medical aid resources. A tertiary care centre can only provide early reperfusion therapy in acute MI. There is very little data on rhythm disturbances in acute myocardial infarction from this geographic region.

Objectives: To study rhythm disturbances in acute myocardial infarction(AMI) and its effect on outcome.

Methods: All cases of acute ST elevation and non ST elevation MI having rhythm disturbances during reperfusion or ICU stay admitted between April 2012 to 2014.

Results: Rhythm disturbances were seen in 40-69 years of age. Chest pain (97%) and palpitation (63%) were commonest complaints. Hypertension was commonest risk factor. Sinus tachycardia (86%), ventricular ectopics (17%) and ventricular tachycardia (16%) were commonest tachyarrhythmias and sinus bradycardia (68%), right (23%) and left (18%) bundle branch blocks commonest bradyarrhythmias. Mortality was higher in tachyarrhythmias.

Conclusion: Compared to studies elsewhere it was observed that sinus tachycardia and bradycardia were commonest arrhythmias in AMI. That atrial fibrillation as observed in most studies elsewhere was not a common arrhythmia in this study. Mortality was statistically significant in tachyarrhythmias in both AWMI(55.71%) and IWMI(17.14%) as compared to bradyarrhythmias with p<0.0001.

Background

Cardiovascular diseases(CVD) are leading cause of mortality in India. An estimated 23.6 million cases of CVD will be reported in patients younger than 40 yrs in 2015. Coronary artery disease is progressively increasing in Indian population and will be the commonest cause of mortality in patients younger than 50 years. Various studies from India have shown high prevalence of the disease, approaching approximately 11% in the urban population and 7% in the rural population across India.¹ Cardiac rhythm disturbances are common presentation in acute coronary syndromes and are cause of frequent serious complications in acute myocardial infarction (AMI). There are few related studies on arrhythmias and their effect on outcomes. Some studies observed that due to availability of early reperfusion therapy and primary angioplasty there is reduction in mortality due to arrhythmias.² In few studies, such as the Cardiac Arrhythmia Suppression Trial (CAST)³⁴ and the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico study (GISSI-2),⁵ investigators assessed the frequency of premature ventricular complexes (PVCs). Also researchers documented tachyarrhythmias like ventricular tachycardia and fibrillation as common events in acute MI.⁶,⁷ Arrhythmias are key events before, during or after the occurrence of acute MI. There are few clinical

¹Professor, JNMC, Sawangi Wardha, Maharashtra; ∗Corresponding Author
Received: 15.05.2016; Revised: 12.10.2017; Accepted: 25.10.2017
studies describing the types of arrhythmias, their correlation with the clinical profile of acute MI and their outcomes. In resource poor hospitals or rural tertiary care centre, patients of acute MI receive reperfusion therapy preferably over primary PCI. The Indian population from central India is mostly a farming community from rural areas. This tertiary care centre provides limited healthcare services to rural population. There is very little data on rhythm disturbances in admitted cases of acute myocardial infarction from this geographic region. We sought to study the clinical profile of arrhythmias in our tertiary care center.

Objective
1. To study the arrhythmias that occur in patients hospitalised for acute myocardial infarction (AMI).
2. To study effect of rhythm disturbances on outcome in AMI

Material and Methods

Study setting
Medical intensive care unit of rural tertiary care hospital of central India.

All patients admitted between April 2012 till April 2014 were included in the study. Data on 116 cases was collected and reported. Cases of both acute ST elevation and non ST elevation AMI were admitted to ICU. According to the Third Universal Definition of myocardial infarction (MI) expert consensus document published in October 2012 by the global Myocardial Infarction Task Force, acute myocardial infarction was defined as increased cardiac biomarkers during 1) symptoms of myocardial ischemia 2) new significant ST-T wave changes or left bundle branch block 3) development of pathological q waves on ECG 4) new loss of viable myocardium or regional wall motion abnormality on imaging 5) intracoronary thrombus on angiography or autopsy.

Inclusion criteria
1. All adult cases of acute myocardial infarction (STEMI or NSTEMI) as per the above definition; 2. Who developed arrhythmias detected during either reperfusion therapy or hospital stay.

Exclusion criteria
1. Any history of rheumatic heart disease
2. Infective endocarditis
3. Cardiomyopathy
4. Dyselectrolytemia
5. Old MI

Detailed clinical examination, laboratory reports and electrocardiogram (ECG) were sought. Multipara ECG monitor and print ECG records were observed during patient’s hospital stay. ECG was recorded on admission, just before starting thrombolytic therapy, mid thrombolysis and after thrombolysis. Those who were not thrombolysed, ECG was recorded on occurrence of an event on the monitor. Patient’s detailed history, clinical examination and cardiac biomarkers like CKMB were done and recorded in the data collection form. Co-investigators took ECG and recorded in the data collection form. Co-investigators took ECG records at timely intervals and whenever the event was noticed and then reported. The patients on multipara monitors had storage of data records in central monitor which was later on reassessed for any missed events. The date and the time of event was noted down in the data collection form. The reports were reviewed by co investigators. We analysed arrhythmias in a 12 lead ECG taken over length of monitoring period in those on reperfusion therapy as well as those not thrombolysed. In those thrombolysed, the time from admission to reperfusion and post thrombolysis, ECG was done to document arrhythmias.

Results
In our study more number of cases both males and females were in the age group of 40-69 years. Average age of females was 63 years as compared to 58 years in males and the difference in age in relation to gender carried a statistically significant p value=0.04, Z -value 2.07.

Precordial chest pain (97.41%) followed by palpitation (62.93%), sweating (43.10%) and breathlessness (37.07%) were the most significant complaints.

Hypertension was the commonest risk factor.

There were more cases with one risk factors (44.82%) and least number of cases had three or more risk factors (8.62%). However presence of more than one risk factor carried no statistically significant correlation with mortality.

Cardiac biomarkers, CKMB above 25 IU/L was considered elevated and observed in 84.48%. ECG showed ST elevation in the anterior leads (86.25%). Pathological q waves were recorded in 32.50% of AWMI and 27.78% of IWMI. There was no statistical significant differences in ECG evidence in both types of MI.

Thrombolysis was given to 64.29% cases of AWMI and 35.71% cases of IWMI. These patients received intravenous streptokinase infusion. None of these patients underwent PCI. 12 cases presented with chest pain of a duration between 6.1 to 24 hours. Out of these 4 received thrombolysis. Statistical analysis revealed p value of <0.0001 which was significant. Odd’s ratio showed strong correlation when applied.

Thrombolysis was given to 70 out of 116 cases. While thrombolysis was given in 64.29% of AWMI, and 36% of IWMI, in comparison to 76% of AWMI and 24% of IWMI who did not receive thrombolysis, this difference was statistically significant (p<0.005).
Tachyarrhythmias (83%) were common in AMI and bradyarrhythmias (86.11%) were common in IWI, these observations were statistically significant (Table 1).

Both types of rhythm disturbances were analysed in terms of distribution of age. However, between 50 to 69 years the occurrence of both tachyarrhythmias (27.59%) and bradyarrhythmias (23.28%) was highest. But this analysis carried no statistical significance. The correlation of types of rhythm disturbances and the gender showed both types of arrhythmias were common in the male cases. An attempt to see the correlation of tachyarrhythmias or bradyarrhythmias in particular age group and gender, it was observed as 117 events in the 72 tachycardia (16.09%) (Table 2).

Commonest tachyarrhythmia observed was sinus tachycardia (86.21%), followed by ventricular ectopics (17.24%) and ventricular tachycardia (16.09%) (Table 2).

Bradyarrhythmias were observed as 117 events in the 72 cases. Commonest event observed was sinus bradycardia (68.06%) followed by right and left bundle branch block (Table 3).

Out of the 116 cases of acute myocardial infarction admitted, 70 cases received thrombolysis. Rhythm disturbances recorded in the post thrombolysis period showed tachyarrhythmias in 72.86% cases and bradyarrhythmias in 58.57% cases. All these were reperfusion arrhythmias, the differences in occurrence of the rhythm disturbances in thrombolysed and in non thrombolysed cases carried statistical significance p=0.000 and Chi square 73.21.

Both non q MI and q wave MI was commonly seen in AMI as compared to IWI and this difference was statistically significant (p<0.005).

Tachyarrhythmias caused high mortality in both AMI and IWI as compared to bradyarrhythmias and this was statistically significant (Table 4).

Overall mortality was 12.50% in AMI and 19.44% in IWI. Mortality was comparatively higher in IWI.

Discussion

This cross sectional study of 116 cases of acute myocardial infarction admitted in the rural tertiary care hospital was conducted to find out occurrence of rhythm disorders and the outcome in cases of AMI during hospital stay. There were 82 (70.69%) males and 34 (29.31%) females. In both the gender rhythm disturbances were observed in the age group of 60-69 years. Mean age of males was 57 years and females was 63 years.
had a favourable outcome as seen by statistically significant p value.

Both q wave MI and non q MI were common in AWMI as compared to IWMI and this difference was statistically highly significant.

Cardiac monitoring revealed arrhythmias in 105 cases (90.52%) during the hospital stay. Of the 80 cases of anterior wall MI, there were 66 (82.50%) tachyarrhythmic events and 41 (51.25%) bradyarrhythmic events. In 36 cases of inferior wall MI, 21 (58.33%) had tachyarrhythmias and 31 (86.11%) had bradyarrhythmias. Tachyarrhythmias were commonly observed in anterior wall MI (82.50%) and bradyarrhythmias in inferior wall MI (51.25%). This difference was statistically significant. Both these events occurred in similar proportions across all age groups. Around 12% cases had no arrhythmic events. However, both types of arrhythmias were more frequent in males as compared to females and this difference was statistically significant.

Commonest arrhythmias observed were sinus tachycardia followed by ventricular ectopics, supraventricular ectopics and ventricular tachycardia. In most other studies atrial fibrillation was reported in between 4 to 26%, in study the event occurred merely in 1 case. Also there was 100% mortality reported in cases of AMI with atrial fibrillation. Ventricular tachycardia was also a common event (67%) in other studies, in our study it was reported in only 16% cases. In our study sinus tachycardia was the commonest documented event (86%), but in all other studies it was documented between 30-40%. Ventricular fibrillation was a rare event (1.15%) in this study compared to other studies (2 to 4%).

The bradyarrhythmias commonly recorded was sinus bradycardia (69%) and observed to be transient in AMI, however mortality in these cases was 20%. Contrary to other study, it was not a common event (14-20%). The other common rhythm disturbance was bundle branch blocks (41.67%). Few studies recorded a very low incidence of bundle branch blocks, (3%) cases. This study observed a mortality of only 23.52% in RBBB and 15.38% in LBBB, other studies reported a mortality of as high as 30-60%.

The difference in distribution of cases receiving thrombolysis and site of infarction showed statistical significance. There were 51 tachyarrhythmic (72.86%) and 45 bradyarrhythmic (58.57%) reperfusion events. Whereas 36 tachyarrhythmic and 31 bradyarrhythmic events in those not receiving thrombolysis. This difference in the types of rhythm disturbances was statistically significant (p=0.000, S<0.05).

70 cases underwent thrombolysis and out of these 45 (64.29%) cases had AWMI, and 25 (35.71%) cases had IWMI, this difference in the distribution of patients thrombolysed in relation to site of infarction was statistically significant.

In this study 62 out of 70 cases thrombolysed had reperfusion arrhythmias, the commonest being sinus tachycardia and sinus bradycardia, followed closely by ventricular ectopy, RBBB and LBBB.

Mortality in AWMI was 12.5% and in IWMI was 19.44%. However, this difference carried no statistical significance. Of the 70 cases who received thrombolysis both tachyarrhythmias and bradyarrhythmias caused similar mortality which was 12.86%. In non thrombolysed cases mortality with tachyarrhythmia was 15.22% and with bradyarrhythmia 17.39%. This carried no statistical significance.

The occurrence of reperfusion arrhythmias in relation to the site of infarction revealed that tachyarrhythmias (55.71%) were commonest in AWMI and statistically significant as compared to bradyarrhythmias (17.14%). However bradyarrhythmias had equal frequency (40-45%) in both types of MI.

Conclusion

The clinical profile of arrhythmias in acute MI may vary from one centre to the other. It is imperative to document the events and understand their course and outcome. This study observed that compared to global trend the profile of arrhythmias was different from that observed elsewhere.

Limitations

The study had time constraints therefore long term post discharge followup was not possible. Hence annual mortality could not be calculated. Sequential CK MB measurements were done in few cases only. Inability to evaluate modifiable risk factors. Technical and economy constraints did not allow coronary angiography and 2D Echo in most cases. Holter monitoring again could not be done in all these cases, rather by multipara monitors, again due to resource limitation.

References


Anticoagulation Management in Patients with Valve Replacement

Devendra Saksena1, S Muralidharan2, Yugal K Mishra3, Vivek Kanhere4, Bipin Bihari Mohanty5, CP Srivastava6, Jagdish Mange7, Manish Puranik8, Manoj P Nair9, Pankaj Goel10, Pankaj Srivastava11, RM Krishnan12, Sathyaki Nambala13, Vikrama Raja14

Abstract

Background: Prosthetic valve implantation requires postoperative prophylactic anticoagulation to preclude thrombotic events. The aim of this review is to assess the role of anticoagulation therapy in the management of valve replacement patients.

Methodology: Literature from PubMed, Embase, Medline and Google Scholar were searched using the terms “valvular heart disease”, “anticoagulant”, “mechanical heart valve”, “bioprosthesis”, “bridging”, “Vitamin K antagonist (VKA)”, and “acenocoumarol”. A committee comprising leading cardiothoracic surgeons from India was convened to review the literature and suggest key practice points.

Results: Prosthetic valve implantation requires postoperative prophylactic anticoagulation to preclude thrombotic events. A paramount risk of thromboembolic events is observed during the first three months after surgery for both mechanical and bioprosthetic devices. The VKA therapy with individualized target international normalized ratio (INR) is recommended in patients after prosthetic valve replacement. Therapies for the management of prosthetic valve complications should be based on the type of complications. Special care is mandated in distinguished individuals and those with various co-morbidities.

Conclusion: In patients with prosthetic valve replacement, anticoagulant therapy with VKA seems to be an effective option. The role for non-VKA oral anticoagulants in the setting of prosthetic valve replacement has yet to be established. Furthermore, whether the novel oral anticoagulants are safe and efficacious in patients after placement of a bioprosthetic valve remains unanswered.

Introduction

Valvular heart disease (VHD) is one of the common causes of cardiac morbidity and mortality. The burden of VHD is growing worldwide due to the high incidence of rheumatic heart disease (RHD), especially in developing countries and the increase in degenerative etiologies in industrialized nations. In industrialized countries, the prevalence of VHD is estimated at 2.5% (2). Data on the burden of RHD in India comes from hospital data (20-50%), population based studies (2.2-1.6%) and school surveys (0.67-4.54%). The pattern of valve involvement is mitral (54.4%), aortic (11.1%), mitral and aortic (18.0%), tricuspid (10.7%) or pulmonary (0.04%). Overall, RHD contributed 63.4% to the prevalence of VHD. This pattern of VHD in India is in contrast to the developed countries, where the most frequently involved valve type is aortic with degenerative etiology. Surgical repair using either a mechanical or bioprosthetic valve is a common solution practiced globally. The worldwide annual rate of valve replacement is projected around 275,000 to 370,000; of which 55% are mechanical heart valves (MHVs) and 45% are bioprostheses heart valves. In India this number is estimated to be in excess of 10000. Globally, the prosthetic valve implantations are increasing at a rate of 5-7% per year. An ideal prosthetic valve with excellent...
hemodynamic performance and long-term durability without enhanced thromboembolic risk or the requirement for long-term anticoagulation therapy does not exist. Choice of operation and the prosthesis used for those patients undergoing valve replacement is important for each individual patient and ideally should be made together by the patient, cardiologist, and surgeon.

Prosthetic valve implantation requires postoperative prophylactic anticoagulation to preclude thrombotic events; which are the common cause of morbidity and mortality after surgery for VHD. A paramount risk of thromboembolic events is observed during the first three months after surgery for both mechanical and bioprosthetic devices. Nevertheless, mechanical valves exhibit life time thrombotic risk. Atrial fibrillation (AF), which is a common arrhythmia in VHD, necessitates lifelong anticoagulation in the majority of patients; especially if it involves mitral valve. Therefore, patients on anticoagulants are at risk of thrombosis and bleeding, if the target INR levels are not maintained. Restrictions on certain physical activities are advised subsequently after surgery to reduce chances of bleeding accidents and these compromises the lifestyle of the young patients. These considerations emphasize the importance of addressing proper anticoagulation techniques to minimize postoperative thrombotic complications, while maintaining acceptable levels of risk related to bleeding.

**Anticoagulation in Prosthesis**

**Anticoagulants in mechanical prosthesis**

Apart from the thrombogenicity of the intravascular prosthetic material, mechanical valves cause abnormal flow conditions with flow zones within their components and areas of high shear stress. This could stimulate platelet activation leading to valve thrombosis and embolic events. A line of evidence shows marked benefits with vitamin K antagonist (VKA) therapy after mechanical valve placement. A meta-analysis including 13,088 patients for 53,647 patient-years compared no antithrombotic therapy with VKA therapy after mechanical valve replacement. The patients with mechanical aortic valve were randomized to Coumadin vs aspirin/clopidogrel in this trial. The trial was stopped after valve thrombosis events reported in 22 patients in the APA group. Succeeding studies have shown that the addition of aspirin to VKA therapy in patients with mechanical valves leads to reduction in risk of thromboembolism and mortality when compared to VKA therapy alone (65% observed risk reduction in major systemic embolism or death in the aspirin plus VKA group). The addition of at least 50 to 75 mg/day of aspirin is, therefore, recommended in the current ACC/AHA and ACCP guidelines in all patients with mechanical valves, though care must be taken to an individual patient’s bleeding risk.

**Anticoagulants in bioprosthesis**

Thromboembolic events with

---

**Table 1: The target INR values for prosthetic valve patients on VKA**

<table>
<thead>
<tr>
<th>Type of valve</th>
<th>Aortic position</th>
<th>Mitral position</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uncomplicated/ without risk factors</td>
<td>With risk factors</td>
</tr>
<tr>
<td>Mechanical Valve*</td>
<td>2.0-3.0</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>Bileaflet</td>
<td>2.0-3.0</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>Tilting disc</td>
<td>2.5-3.5</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>Caged ball</td>
<td>2.5-3.5</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>Caged disc valve</td>
<td>2.0-3.0</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Bioprosthetic**</td>
<td>2.0-3.0</td>
<td>2.0-3.0</td>
</tr>
</tbody>
</table>

AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions; VKA plus aspirin, class I indication by ACC (75-100 mg o.d.), ACCP (50-100mg o.d.) recommends aspirin only in high risk patients; VKA for 3 months in all except uncomplicated aortic valve replacement where ACCP recommends aspirin over VKA and it should be continued if there is no other indication of anticoagulation. Postoperative aspirin (80-100mg o.d.) is recommended for all by ACC, while ACCP recommend aspirin 3 months after replacement.
Bioprosthetic valves have been reported to range from 0.2% to 3.3% per year. The risk is higher in the mitral position compared to valves in the aortic position. Studies have demonstrated that bioprosthetic devices have an increased risk for thromboembolic events during the first three months after the procedure but less than that associated with mechanical valves.

Several large cohort studies have addressed the need of VKA anticoagulation with and without APA after bioprosthetic valve replacement. Numerous Indian studies have demonstrated the benefits of adding APA to anticoagulants. The optimal antithrombotic regimen and its duration after placement of a bioprosthetic device are less clear across these studies. The optimal antithrombotic regimen and its duration after placement of a bioprosthetic device are less clear across these studies.

The variation in an optimal antithrombotic regimen and its duration after valve replacement in the literature have made the recommendations given by guidelines for bioprostheses to be dissimilar compared with the mechanical prosthesis. The ACCP currently recommends VKA therapy with target INR 2.5 (range 2.0 to 3.0) for the first three months after bioprosthetic mitral valve replacement. For aortic valve replacement with a bioprosthetic device, the ACCP recommends aspirin (50 to 100 mg/day) over VKA therapy for the first three months after bioprosthetic valve replacement. For aortic valve replacement with a bioprosthetic device, the ACCP recommends aspirin (50 to 100 mg/day) over VKA therapy for the first three months after bioprosthetic mitral valve replacement. For aortic valve replacement with a bioprosthetic device, the ACCP recommends aspirin (50 to 100 mg/day) over VKA therapy for the first three months after bioprosthetic mitral valve replacement. For aortic valve replacement with a bioprosthetic device, the ACCP recommends aspirin (50 to 100 mg/day) over VKA therapy for the first three months after bioprosthetic mitral valve replacement.

Recommendations from the ACC/AHA largely leave the choice of the antithrombotic regimen in the setting of bioprosthetic valve replacement up to individual clinicians. Several factors that may influence a clinician’s decision include institutionally-specific outcomes, the likelihood for patient adherence to medication regimen, prior personal experience, regional convention, and personal preference. The duration and intensity of treatment with aspirin are also left up to the individual clinician’s discretion. These recommendations have been summarized in Table 1.

**Anticoagulants in TAVR**

Transcatheter aortic valve replacement (TAVR) has become established as a treatment option for patients with symptomatic aortic stenosis. In comparison with surgical aortic valve replacement, TAVR offers superior quality of life with similar mortality rates among patients at very high surgical risk. However, thromboembolic complications from TAVR are significant, and stroke, in particular is a concern. While the immediate procedural risk relates to valvular debris embolization, 50% of strokes develop after the first day and may relate to non-procedural events. The incidence of cerebrovascular events after TAVR remains raised for ≤60 days. This implies that the prothrombotic environment of the bioprosthesis...
itself may be implicated in distal thromboembolism, and therefore antiplatelet or antithrombotic treatment should play an important role in stroke prevention.\textsuperscript{39}

Various combinations of antithrombotic regimens (single-antiplatelet, dual-antiplatelet, or VKAs) have been used, but evidence-based guidance remains lacking. A number of randomized and non-randomized studies evaluated the risk of embolization, optimal antithrombotic regimen and duration thereof after TAVI.\textsuperscript{36-41} The evidence on anticoagulation after TAVI from India is limited to only few case reports.\textsuperscript{42-43} Antithrombotic recommendations for TAVI from various guidelines are illustrated in Figure 1.

### Key points

**Anticoagulants in mechanical prosthesis**

- VKA therapy with a target INR range of 2.0 to 3.0 is recommended in patients with mechanical aortic valve replacement without risk factors.
- VKA therapy with a target INR range of 2.5 to 3.5 is recommended in patients with mechanical aortic valve replacement with risk factors- AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions.
- In mechanical mitral valve replacement, VKA therapy with a target INR range of 2.5 to 3.5 is recommended in patients with and without additional thromboembolic risk factors.
- With mechanical valves in both the aortic and mitral position, a target INR range of 2.5 to 3.5 is recommended.
- VKA therapy in combination with antiplatelet therapy (aspirin 75-100mg) is recommended for long-term management over no antiplatelet therapy with mechanical valve prosthesis.

**Anticoagulants in bioprosthesis**

- VKA therapy is recommended in bioprosthetic aortic valve and mitral valve replacement, with a target INR range of 2.0 to 3.0 over no VKA therapy for 3 months.
- In patients with dual valve replacement (aortic, mitral) VKA therapy is recommended with a target INR range of 2.5 to 3.5.
- After bioprosthetic aortic or mitral valve replacement, antiplatelet therapy at a dose of 75 to 100 mg/day is recommended.

### Bridging Anticoagulation

The perioperative management of patients who are receiving VKAs or antiplatelet drugs and require a surgical or invasive procedure presents a dilemma for practicing clinicians. Several factors such as type, location and number of heart valve prosthesis and type of procedure and risk factors should be taken into account while managing patients with mechanical heart valves in whom interruption of anticoagulation therapy is needed for diagnostic or surgical procedures. To minimize the delay in achieving therapeutic anticoagulation, a “bridging” anticoagulant is prescribed. The “bridge” is administered parenterally (short acting anticoagulant as UFH or LMWH), thereby providing an immediate anticoagulant effect. However, the use of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) as perioperative bridging is an off-label use because their use is not approved by regulatory authorities or drug manufacturers in this clinical setting as a bridging agent. There is a relative paucity of well-designed clinical trials to enlighten best practices. There are a disproportionately large number of methodologically weak observational studies.

Large number of studies have evaluated, and proposed an interval of 1-3 days preoperatively and 7 days postoperatively for VKA interruption.\textsuperscript{44} However, VKA interruption may not be required in minor procedures like dental procedures,\textsuperscript{45-50} minor dermatological procedures,\textsuperscript{51-53} and cataract surgery.\textsuperscript{54} Furthermore, no well standardized studies were performed regarding the use of LMWH and UFH. However, a study showed no significant difference in thromboembolic and major bleeding between patients bridged with LMWH and those bridged with UFH.\textsuperscript{55} Most studies assessing the use of LMWH as bridging anticoagulation have used therapeutic dose regimens; for detailed information refer Douketis et al.\textsuperscript{56} Two studies have used low dose LMWH (including patients with mitral valve prosthesis).\textsuperscript{57,58} However, whether the dose utilized is sufficient is not known clearly as it can be argued that higher doses of LMWH are needed for the prevention of arterial thrombosis. The latter, however, is also not established.

On account of the current evidence, ACC and ACCP recommend uninterrupted VKA with local hemostasis optimizing agents in procedures with minimal bleeding, such as surgeries on the skin (excision of basal and squamous cell skin cancers, actinic keratosis, and premalignant or cancerous skin nevi), cataracts, glaucoma and dental cleaning or simple treatment for dental caries. For tooth extractions and endodontic procedures, ACCP recommend uninterrupted VKA with co-administration of an oral prohemostatic agent or stopping VKAs for 2 to 3 days (partial reversal). However, both guidelines recommend interruption of VKA with bridging anticoagulation in patients with any mitral valve prosthesis, caged-ball, tilting disc aortic valve prosthesis, bileaflet AVR with additional risk factors such as the recent (within 6 months) stroke or transient ischemic attack, prior thromboembolism during the temporary interruption of VKAs. In such cases when the interruption is required, ACC recommends stopping for 2-4 days while ACCP recommends not less than 5 days before the procedure. Both recommend restarting approximately 12 to 24 h after surgery when there is adequate hemostasis instead of later resumption of VKAs. Moreover, the reversal of VKA required during emergency surgery or invasive procedures can be achieved by administration of fresh frozen plasma (FFP) or intravenous prothrombin complex concentrate (PCC).
Key points

- It is not recommended to interrupt VKA therapy during minor dental procedures (cleaning), dermatological procedures and cataract surgery due to minimal bleeding.
- In patients with low thrombotic risk (bileaflet AVR without any risk factors) it is recommended to interrupt VKA without bridging.
- Bridging anticoagulation is recommended in patients with any mitral valve prosthesis, any caged-ball or tilting disc aortic valve prosthesis, bileaflet AVR with additional risk factors, patients with recent (within 6 months) stroke or transient ischemic attack, patients with prior thromboembolism during temporary interruption of VKAs.
- When interruption of VKA therapy is required, it is recommended to stop 2-4 or not more than 5 days before the procedure. The VKA should be restarted after 12-24 hours after surgery.
- The reversal of VKA therapy during emergency surgeries can be achieved by administration of FFP or PCC. Low dose vitamin K may be administrated with caution to sustain effects with FFP as rebound is known with vitamin K.
- Interruption of VKA therapy with bridging anticoagulants is recommended for not more than 2 days in case of major surgeries.

Point of Care INR Testing

The subtherapeutic target INR increases the risk of thromboembolic events, on the other side, above the therapeutic INR presents the patient to bleeding risk. Apart from the assistance in deciding the appropriate dosage regimen, monitoring helps in avoiding over coagulation. Routine monitoring can help detect dangerous situations well in time, allowing dose adjustment, as well as actions can be taken to prevent recurrence of such situations. The prothrombin time (PT) test is the most common test used to monitor anticoagulation therapy that is expressed as the INR. Further, the time in therapeutic range (TTR) is a good overall measure of the quality of antithrombotic treatment with VKAs in patients with valvular heart disease.

The gold standard for monitoring INR is the lab testing of blood obtained by venipuncture, in the hospital. The point of care (POC) INR systems can be an alternative to older laboratory testing of INR. POC testing involves putting a single drop of blood from a finger stick, onto a test strip. POC is aimed at convenience for the patient, faster test results to a healthcare provider, faster decision making, improved clinical outcome and reduced healthcare resources. However, these devices are economical as they reduce the cost of visiting the healthcare facility. This is of great importance in India, as most of INR facilities are available far from the urban or semi urban area. These POC devices have shown to be cost-effective for patients on long term anticoagulants. Studies have found a statistically significant advantage of self-management methods for achieving better INR control in patients with mechanical valves. Nevertheless, ACC/AHA recommends the practice of self-management of patients over outdoor INR monitoring for VKA anticoagulation, in patients who are motivated, and can demonstrate competency in self-management strategies.

Key points

- Practice of self-management is recommended in patients who are living in urban and semi-urban areas, who are competent of doing the same.
- Use of POC devices can be alternated with the conventional laboratory testing to reduce hospital visits and the cost of the treatment.

Management of Prosthetic Valve Complications

Thromboembolic events

The annual risk of thromboembolic events in patients with a mechanical heart valve is 1% to 2% versus 0.7% with a bioprosthetic valve, even with appropriate antithrombotic therapy. Transesophageal echocardiogram (TEE) is the first step in the evaluation of suspected prosthetic valve thromboembolism to evaluate valve hemodynamics. However, transesophageal echocardiography (TEE) is needed often, particularly for mitral prosthetic valves. However, if the echocardiography findings are unchanged the prosthetic valve should be considered the source of thromboembolism in suspected cases.

The patients with the thromboembolic event should be evaluated for the adequacy of anticoagulation and any issues related to compliance with medical therapy. Screening questions about symptoms that may be related to embolic events are especially important if anticoagulation has been suboptimal. Measures to improve patient compliance and more frequent monitoring should be instituted. Patients’ education about symptoms related to embolic events and instructing them to promptly report to a healthcare provider immediately after onset of an event should be in routine.

Thrombosis of prosthetic valves

The prevalence of mechanical valve thrombosis is 0.3-1.3% per patient-year in developed countries and 6.1% per patient-year in developing countries. Type of valve and location also affect the risk of thrombosis. Thrombosis is 20 times more likely to occur in the tricuspid position; mitral prosthetic valve thrombosis is 2-3 times more common than aortic prosthetic thrombosis.

It is suggested to perform TTE in suspected cases of thrombosis. This will allow evaluation of valve hemodynamics and detection of valve stenosis or regurgitation, measurement of left ventricular (LV) size and systolic function, left atrial size, right heart function, and an estimation of pulmonary pressures. The TEE allows direct imaging of mechanical valve thrombosis particularly for thrombi on the left atrial side of the mitral valve. In addition to TTE and TEE, fluoroscopy can be used to assess annular or valvular calcification, as it enables calcification to be distinguished from fibrosis with a higher specificity than echocardiography. It is also useful to assess the kinetics of the mobile part of a mechanical prostheses. However, ACC recommends TTE in patients with suspected prosthetic valve
thrombosis to assess hemodynamic severity and resolution of valve dysfunction, and if the thrombus is detected, TEE to assess thrombus size and valve motion. The left sided prosthetic heart valve thrombosis can be treated either with fibrinolytics or surgical intervention. When treating left-sided PVT, the risks associated with re-operative surgery must be weighed against the risks of embolic complications and bleeding associated with the use of fibrinolytic therapy. Factors that identify patients at risk for adverse outcomes of fibrinolytic therapy include active internal bleeding, history of hemorrhagic stroke, recent cranial trauma or neoplasm, diabetic hemorrhagic retinopathy, large thrombi, mobile thrombi, systemic hypertension (>200 mm Hg/120 mm Hg), hypotension or shock, and New York Heart Association (NYHA) class III to IV symptoms. The degree of risk is directly related to thrombus size. Thrombus area (2D TEE) >0.8 cm² and thrombus diameter 1.0 cm is associated with increased embolic risk. Rate of complications increases 2.4-fold, per 1.0 cm² increase in size, which makes surgery better option. In patients with recent hemorrhagic stroke, surgery is a better choice because of the bleeding risks associated with fibrinolysis. Although RCTs have not been performed, the weight of the evidence favors surgical intervention for left-sided prosthetic valve thrombosis unless the patient is asymptomatic and the thrombus burden is small. However, fibrinolysis of right-sided valve thrombosis appears better option with the resulting small pulmonary emboli seem to be well tolerated and systemic emboli are uncommon. ACC and ACCP recommend fibrinolytics or surgical intervention for management of PVT; the clinical judgment should be based on the position of the valve (left or right) and thrombus burden as assessed by echocardiography.

### Bleeding complications

The incidence of major bleeding complications in patients with a mechanical valve and taking oral anticoagulants varies from 0.34% to 1.32% per patient-year. The prominent feature of anticoagulant overdose is bleeding, which may be manifested as nasal bleeds, haematemesis, haemoptysis, gastrointestinal bleeding, vaginal bleeding, haematuria, cutaneous haemorrhages, gingival bleeding, haematomata, and bleeding into joints or menorrhagia. Numerous risk scores have been developed to help predict bleeding events, considering the other comorbidities such as previous gastrointestinal bleeding, chronic kidney disease, previous stroke or myocardial infarction, and anemia (Table 2). Furthermore, excessive anticoagulation (INR ≥ 5) greatly increases the risk of hemorrhage. Discontinuation of anticoagulation for 1-2 weeks had a low probability of thromboembolic events in patients with high embolic risk.

### Key points

**Thromboembolic events**
- TTE is recommended for diagnosis of thromboembolic events.
- Treatment with tPA and heparin is recommended to patients with stroke; other vascular occlusions should be managed by surgery.
- Daily aspirin (75-80 mg) is recommended in patients with thromboembolic events.
- In patients with bioprosthetic valve, who are already on aspirin, addition of VKA can be considered.
- Measures to increase patient compliance (patient education) are recommended in all patients with thromboembolic events.

**Thrombosis of prosthetic valves**
- It is recommended to address adequacy of anticoagulation (low INR), and exclusion of other causes of high gradients like anemia, tachycardia, fever.
- TTE is recommended in patients with suspected prosthetic valve thrombosis to assess hemodynamic severity and resolution of valve dysfunction.
Factors Affecting VKA Therapy

Pharmacogenetics
Growing evidence indicates that up to 60% of the individual pharmacological response to warfarin might be due to genetic variables and affected by polymorphisms in the genes mainly, vitamin K epoxide reductase complex subunit 1 (VKORC1), the target enzyme of warfarin and cytochrome P450 2C9 (CYP2C9), the main enzyme involved in warfarin metabolism. Recently, FDA has recommended pharmacogenetics testing before initiating warfarin. However, ACCP remains against the routine use of pharmacogenetics testing for guiding doses of VKA in patients initiating VKA therapy.

Anticoagulant interactions

Drug-drug interaction
As VKAs are metabolized mainly by cytochrome P-450 (CYP) 2C9, the inhibition of CYP 2C9 results in a decreased catabolism of VKAs and a stronger anticoagulant effect, whereas its induction enhances their catabolism and leads to a lower anticoagulant effect. Drugs such as amiodarone, flunoxazalone, fluva statin, fluvoxamine, izoniazid, lovastatin, miconazole, metronidazole, trimethoprim-sulfamethoxazole, phenylbutazone are known inhibitors of CYP 2C9, thus potentiating VKAs effect.

Antibiotics, which cause decreased production of vitamin K by the intestinal microbiota result in an increased sensitivity to VKAs. Barbiturates (carbamazepine, rifampicin) are inducers of CYP 2C9. Over the counter medications, i.e. paracetamol and other nonsteroidal anti-inflammatory drugs (NSAIDS) were shown to enhance the anticoagulant effect of warfarin, thus patients receiving warfarin must monitor their INR more frequently when taking these medications especially, paracetamol at doses exceeding 2g/day. However, acenocoumarol compared to warfarin may elicit lower drug interactions due to less sensitive to metabolic enzymes (CYP2C9) and easy clearance from the body.

Drug-Herb interaction
The interaction of VKAs with herbs is well reported in literature. These includes the interaction with Panax ginseng, Hypericum perforatum, Salvia miltiorriza, Gingko biloba, Serenoa repens, Angelica sinensis, Vaccinium species, Allium sativum, Zingiber officinale, Tanacetum parthenium, Lucium barbaram, Matricaria chamomilla, Boswellia serrata and Camellia sinensis have been estimated.

Drug-food interaction
Indians with their different dietary habits compared to their western counterparts are more prone for VKAs-food interactions. An average Indian consumes more of dietary green leafy vegetables, which would prevent the achievement of target INR in patients with warfarin/acenocoumarol and cause variabililty in INR values. The interaction between the dietary vitamin K and VKAs is well known. Evidence has demonstrated that anti-coagulated patients should maintain a steady intake of vitamin K once INR stability has been achieved. Patients should be educated not to avoid Vitamin K rich foods; however, they should be advised to maintain the vitamin K content of diet constant. The best way to achieve this is by avoiding changes to normal eating patterns. ACCP suggests against routine use of vitamin K supplementation for patients on VKA.

Key points

Drug-drug interaction
- It is recommended to avoid drugs metabolized by cytochrome P450 enhancing or inhibiting VKAs effect during the therapy.
- It is recommended to educate patients on drug interaction with over the counter drugs and antibiotics; and need for frequent monitoring INR when they are used.

Drug-food interaction
- Patients are advised to maintain constant Vit K composition in the diet to avoid fluctuation of VKA therapy.
- Food inhibiting (Cabbage, spinach, brussels, sprouts) and potentiating (Mango, grapefruit, cranberry) the efficacy of VKAs should be taken in moderation while maintaining regularity

Anticoagulation in Special Patient Populations

Pregnancy
Pregnancy is a hypercoagulable state, due to increase in fibrinogen,
factors VII, VIII and X, von Willebrand factor, and a relative decrease in protein S activity, stasis, and venous hypertension. The increase in total blood volume affects the distribution of anticoagulants during pregnancy contributing to unpredictable changes in the amount of medication required. This state of hypercoagulability extends into the postpartum period too, and requires a persistently higher maintenance dose of warfarin.

Thus, optimal anticoagulation therapy is considered essential, but the appropriate choice of agent among the options available (VKAs, heparin or LMWH) is highly debatable.

The low molecular weight of warfarin enables it to cross the placental barrier and cause embryopathy. The embryopathy actions are dose dependent; reduced adverse events are seen with dose <5mg. However, warfarin can be replaced with LMWH since they do not cross the placenta. The use of heparin is associated with reported incidence of 12-24% of the increased risk of maternal thromboembolic events. Henceforth, women of childbearing age should be warned about the teratogenic and harmful effects of VKAs, especially in early pregnancy. They should be advised to use secure methods of contraception while on VKAs. If pregnancy is suspected, early pregnancy test 5 weeks from last menstrual period must be offered. Hence, if patients are not prior educated about the teratogenic effects, the risk of embryopathy increases with continuous use of VKAs in the 1st trimester.

The current ACC, ACCP guidelines recommend warfarin in first trimester if dose required for target INR is <5mg (or equivalent acenocoumarol dose). VKAs should be replaced with heparin at 36th week of gestation before delivery. The recommendations from ACC, ACCP and ESC have been summarized in Table 3.

Elderly population

Management of anticoagulation in elderly patients represents a particularly challenging issue. Indeed, this patient population is at high thromboembolic and hemorrhagic risk. Assessment of the benefit-risk balance of anticoagulation is the key point when decisions are made about introducing and/or continuing such treatments in the individual elderly patient. In order to maximize the safety of anticoagulation in the elderly, factors like comorbidities and co-medication, pharmacokinetic and pharmacodynamics alteration due to the renal and hepatic function associated with aging, consequences due to insufficient education, need to be considered, The European society of cardiology-working group on thrombosis recommend considering all of the above factors for antithrombotic therapy in elderly.

Renal impairment

As VKAs are metabolized in the liver, no dosage adjustments are required in patients with chronic renal impairment. Pharmacokinetic studies have shown that anti-Xa activity is prolonged in patients with severe renal impairment (creatinine clearance <30 mL/min) and, to a lesser extent, in patients with moderate dysfunction (30-50 mL/minute). The prevalence of AF is reported to be higher in patients with renal impairment. Also, the risk of AF development increases with worsening of renal function. Heparin derivatives depend largely on renal excretion; dosage adjustment is necessary in order to avoid accumulation and hence over-anticoagulation. Dosage adjustment for factor Xa inhibitors in patients with renal insufficiency is recommended by ACCP.

Concomitant Cardiac Disease

Heart failure

Prosthetic valve patients are at high risk of congestive cardiac failure due to significant cardiac compromise. Cardiac medicines like angiotensin converting enzyme inhibitors, diuretics, and digoxin should be given as per the standard heart failure management guidelines.

CAD

The concurrent use of dual antiplatelet agents with VKAs has been a major issue in percutaneous coronary intervention (PCI) patients in an era of widespread use of drug-eluting stents (DES).
Oral (VKA) • Can be used throughout pregnancy (class IIa) with substitution by UFH/LMWH during weeks 6-12 of gestation if
- preferred by the patient
- dose of warfarin required to achieve target INR >5mg (class IIa)
- just before planned delivery has to be replaced by UFH or LMWH (class I)
- Strongly recommended in MPV in 2nd and 3rd trimesters

Heparin derivatives

• Recommendations on 1) s.c use of LMWH and UFH throughout pregnancy2) s.c UFH in the 1st trimester completely removed in current 2014 guidelines.
• The patients who prefer: **LMWH administered twice daily and the dose should be adjusted to attain peak anti-factor Xa levels: 0.8–1.2 U/mL approx. 4–6 hours after the injection.
• Alternatively, continuous IV UFH (with aPTT at least twice that of the control) during the 1st trimester is permissible if the dose of warfarin >is 5 mg/day
• IV UFH in the first trimester is difficult from a practical standpoint, as a three-month hospital admission is required.

All of the above guidelines agree that LMWH should be given twice daily and that it is harmful to administer LMWH without regularly monitoring the patient’s anti-factor Xa levels

Aspirin

• Low dose (75-100mg/day) given in second and third trimesters (Class I)

Target INR

• 3 for all prosthetic valve patients

After 36 gestational weeks

• The ACC/AHA guidelines suggest stopping warfarin at 36 weeks and starting continuous IV UFH with aPTT monitoring, which should be continued until approximately 2–3 weeks before the planned delivery.
• Additionally, they recommend that UFH be discontinued 4–6 hours before the planned delivery and restarted 4–6 hours after delivery.
• In the absence of significant bleeding, oral warfarin should then be initiated 24 hours after the birth.

• ESC guidelines suggest stopping warfarin at 36 weeks and starting dose-adjusted IV UFH or LMWH.
• This treatment should continue until 36 hours before delivery, when LMWH should be replaced by IV UFH

Approximately 5% of patients requiring PCI also present with an indication for oral anticoagulation therapy. In such cases, the type of stent selected; the use of oral anticoagulants, antiplatelet, or their combinations; the target INR; and the duration of treatment is essential considerations in relation to the risk of thrombosis/thromboembolic events and bleeding risk. Whenever possible, shorter durations of triple therapy are favored in preference to longer durations of triple therapy. The WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial is the first published study to address the question of optimal antiplatelet therapy in patients taking oral anticoagulant medication. Patients randomized to single antiplatelet treatment with clopidogrel had significantly fewer bleeding complications and no increase in thrombotic events compared with those randomized to DAPT with aspirin and clopidogrel.

The ACC/AHA recommends in patients with non ST segment elevation acute coronary syndrome (NSTE-ACS) who require oral anticoagulation for AF, mechanical heart valve, deep venous thrombosis, or other conditions, a bare-metal stent may offer the advantages of lower bleeding risk over a DES because of the potentially shorter duration of triple antithrombotic therapy. However, these recommendations do not specify the optimal treatment.
according to the various indications for anticoagulation or the duration of treatment, nor do they take into account the estimated thrombosis and bleeding risks.

### Atrial Fibrillation

Overall, it is estimated that the incidence of post-operative atrial fibrillation is approximately 30% after pure coronary artery bypass grafting (CABG) surgery, 40% following valve replacements or repair, and increases to approximately 50% after combined CABG / valvular procedures.\(^{126,127}\) In a large prospective trial, the Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair (PAPABEAR), amiodarone was compared with placebo. Oral amiodarone prophylaxis of atrial tachyarrhythmia after cardiac surgery was effective and safe.\(^ {128}\) Furthermore, a meta-analysis of 19 trials comparing amiodarone with placebo has demonstrated a significant reduction in AF (reduced by 50% in the amiodarone group), ventricular tachyarrhythmia, strokes, and hospital stay. Prophylactic amiodarone should be implemented as a routine therapy for high-risk patients undergoing cardiac surgery.\(^ {129}\) The addition of beta-blockers can also help in reducing sympathetic triggers of AF post-operatively.\(^ {130}\) The European Society of Cardiothoracic Surgery recommends the perioperative use of beta blockers as the first choice in all patients undergoing cardiac surgery, unless otherwise contraindicated.\(^ {131}\)

### Cardiac catheterization in patients with prosthetic valves

**BRUISE CONTROL trial, COMPARE trial and some similar trials** evaluated warfarin in patients undergoing implantation of a pacemaker or implantable cardioverter-defibrillator. As compared to heparin or discontinuation of warfarin with bridging, a strategy of continued warfarin treatment markedly reduced the incidence of clinically significant device-pocket hematoma, risk of the stroke and bleeding, and reduction of in-hospital stay.\(^ {132,133}\)

The European Heart Rhythm Association (EHRA) position document on anti-thrombotic management in patients undergoing electrophysiological procedures, recommends un-interrupted VKA in patients undergoing ablation procedures like pulmonary vein isolation ablation (PVI).\(^ {134}\) Patients on VKS requiring implantation of cardiac implantable electronic devices should be operated on VKA unless they are at very low risk for a thromboembolic event. In this particular case, it recommends interrupting VKA without bridging with heparin. The ACC recommends only slight modification in VKA dosing for procedures with a low bleeding risk, such as coronary angiography from the radial approach. With interventional procedures at higher risk, stopping VKA anticoagulation and using bridging therapy as is done for other surgical procedures has been recommended.\(^ {21}\)

### Follow up cardiac evaluation

Doppler echocardiography at baseline (before discharge) serves as a reference for subsequent examinations. The measurements should include regional and global left and right ventricular systolic function and size, diastolic LV function (not assessable with mitral valve prosthesis), atrial size, function of the native valves, estimates of pulmonary artery pressure, pressure gradient across the newly implanted prosthesis, effective valvar orifice area, presence of paravalvular leaks.\(^ {135}\) The first postoperative workup should include echocardiography along with all other physical and blood tests.\(^ {135,136}\) Ideally, all patients who have undergone valve surgery should continue to be followed-up at a cardiac center in order to detect deterioration in prosthetic function, recurrence of regurgitation following valve repair, or progression of disease at another valve site at an early stage.\(^ {136}\) The frequency of future follow-up should be determined by the patient’s progress and availability of local facilities. The frequency of echocardiography during follow-up should be determined by the results of previous echocardiography, symptomatic status, the type of surgery, and the existence of other pathology. However, ESC recommends the first post-operative visit to a hospital or a cardiac specialist within 6 weeks of discharge if there has been no period of inpatient rehabilitation or within 12 weeks if a rehabilitation program has been completed. The current 2014 ACC VHD guideline recommends annual follow up for cardiac history and physical examination in an asymptomatic uncomplicated patient. It also recommends an echocardiographic examination at 6 weeks to 3 months after valve implantation, while AS-Echo guideline recommends a baseline TTE at discharge or 2-4 weeks after hospital discharge; as an essential component of the first post-operative visit. Both guidelines recommend further follow up by TTE and/or TEE if clinical symptoms or signs suggestive of prosthetic valve dysfunction or other cardiac pathology persist; with preference to TTE for initial examination. ACC and As-Echo recommend no further echocardiographic testing after the initial postoperative evaluation in stable mechanical valve patients and who have no symptoms or clinical evidence of prosthetic valve or ventricular dysfunction or dysfunction of other heart valves. ACC recommend TTE after the first 10 years, while AS-Echo recommends annual echocardiography after the first 5 years in bioprosthetic valve patients; even in the absence of a change in clinical status.\(^ {21,67}\)

### CT and MRI scan—Post valve implantation

Prosthetic cardiac valves are generally made up of metals, polymers, and carbons. However, there is a hypothetical probability of electromagnetic interaction with metal in valves that may cause interruption of opening and closing of valves (referred to as the Lenz effect). Nevertheless, no such cases have been reported in clinical practice.\(^ {137}\) Consequently, these patients are unlikely to be at risk for valve dehiscence and the
heating due to MR was reported to be minor.138-141 Consequently, prosthetic heart valves, as well as metal sternal sutures and mediastinal clips, should not be considered as contraindications for an MRI at 3 T or less any time after implantation.142,143

According to AHA scientific statement, the presence of a prosthetic heart valve or annuloplasty ring that has been formerly evaluated for MR safety should not be considered a contraindication for an MR examination at 3 T or less (and possibly even 4.7 T in some cases) any time after implantation. MR examination of patients with sternal wires is generally considered to be safe and patients with endocarditis and risk of valve dehiscence cannot undergo MRI.144

**Prosthetic Valve - Endocarditis**

Prosthetic Valve Endocarditis (PVE) is a serious complication of cardiac valve replacement and is an important cause of morbidity and mortality. Echocardiography should be performed in all cases in which there is a medium or high clinical suspicion or when the patient is severely ill, after excluding other common causes of fever.145 The diagnostic strategy proposed by Durack and colleagues (the Duke criteria) combines echocardiographic findings with clinical and microbiological data. Three echocardiographic findings were considered to be major criteria for the diagnosis of endocarditis: (1) presence of vegetation defined as mobile echo dense masses implanted in a valve or mural endocardium in the trajectory of a regurgitant jet or implanted in prosthetic material with no alternative anatomical explanation; (2) presence of abscesses; or (3) presence of a new dehiscence of a valvular prosthesis.146

The reported sensitivity and specificity for the diagnosis of perivalvular abscesses with TTE are 28% and 98%, respectively, and with TEE, 87% and 95%, respectively.147-150 Bioprosthesis valve leaflets may become infected with secondary destruction of leaflet tissue. The distinction between wear-and-tear degeneration of tissue valves and endocarditis is often difficult. TEE also led to an improved diagnostic accuracy in the diagnosis of endocarditis on bioprosthetic valves.151 TEE is therefore necessary in cases in which infective endocarditis is strongly suspected, even when no significant findings are seen on TTE.152 Further, multiple TEE planes combined with TTE views must be exploited to minimize the risk of missing a significant finding when images are technically difficult to obtain. When both TEE and TTE studies are negative, there is a 95% negative predictive value.153,154

Antimicrobial therapy remains the mainstay of therapy; however, most patients require surgical removal and replacement of infected prosthesis. The delay in embolization prevention is associated with stroke within 3 days of diagnosis.155 The risk of embolism is related to the size, and mobility of vegetation, the risk is increased in large (>10 mm) vegetation and particularly high with very mobile and large (>15 mm) vegetation. The risk of new embolism is highest during the first days following initiation of antibiotic therapy and decreases after 2 weeks.156

In a case-control study, Agarwal et al identified the risk factors for prosthetic valve endocarditis in Indian population.156 These risk factors were functional class III or IV (New York Heart Association), alcohol consumption, prior history of endocarditis, fever in the intensive care unit, and gastrointestinal bleeding. Functional class III or IV and complications of the surgical wound were independent predictors of early infective endocarditis, whereas fever in the intensive care unit and gastrointestinal bleeding were predictors of prosthetic valve endocarditis late after the operation.156 However, there are no randomized studies assessing the impact of antithrombotic therapy on PVE. The results of observational studies suggest that the risk of continuing anticoagulation outweighs the benefits.155,157-160

In patients on VKA for a prosthetic valve who develop IE, ACCP suggest VKA be discontinued at the time of initial presentation until it is clear that invasive procedures will not be required and the patient has stabilized without signs of CNS involvement. When the patient is deemed stable without contraindications or neurologic complications, reinstitution of VKA therapy is recommended.19

**Key points**

- Concomitant heart failure should be managed as per standard heart failure management guidelines.
- In patients with non ST segment elevation acute coronary syndrome (NSTE-ACS) who are on anticoagulation, bare metal stent is preferred over drug eluting stent that offers the advantages of lower bleeding risk because of the potentially shorter duration of triple antithrombotic therapy.
- Beta blockers should be used for management of perioperative atrial fibrillation, unless otherwise contraindicated.
- Un-interrupted VKA can be offered in patients undergoing ablative procedures like PVI.
- Interruption of VKA should not be performed during implantation of cardiac implantable electronic devices unless patients are at very low risk of thromboembolic events. However, if required can be interrupted without bridging.
- Low bleeding risk procedures like coronary angiography by radial approach can be performed with slight modification in VKA dose. However, interventional procedures with high risk of bleeding should be performed with interruption of VKA and bridging as with other surgeries.

**Follow up cardiac evaluation**

- The first postoperative workup should include echocardiography along with all other physical and blood tests.
- The frequency of future follow-up should be determined by the patient’s progress and availability of local facilities.

**CT and MRI scan - Post valve implantation**

- Patients with prosthetic valve which is formerly evaluated for MR safety can undergo MR examination at 3T or less any time after implantation. However, patients at risk of valve dehiscence should not undergo MR examination

**Prosthetic Valve - Endocarditis**

**Diagnosis**

- TTE in recommended in suspected IE, in case of negative TTE in suspected PVE, TEE is recommended. If initial examinations are negative, repetition of TTE/TEE is recommended within 7-10
Future Anticoagulants

In the current era of expanding strategies for anticoagulation, investigators have yet to establish the role for non-VKA oral anticoagulants in the setting of prosthetic valve replacement. To date, there are no large randomized clinical trials enrolling to answer this question. New anticoagulants that are direct thrombin inhibitors or factor Xa inhibitors (dabigatran, apixaban, and rivaroxaban) have been approved by U.S. Food and Drug Administration for anticoagulant prophylaxis in patients with AF not caused by VHD.261 There was no evidence of a differential effect of apixaban over VKAs in reducing stroke or systemic embolism, causing less over VKAs in reducing stroke or a differential effect of apixaban in patients with AF not caused by anticoagulant prophylaxis in the capacity of employee of Abbott Healthcare Pvt Ltd., Dr. Vikrama Raja, Medical Affairs has authored this publication in the future.

Disclaimer

This publication was funded by Abbott Healthcare Pvt Ltd. Dr. Vikrama Raja, Medical Affairs has authored this publication in the capacity of employee of Abbott Healthcare Pvt Ltd., Dr. Devendra Saksena, Dr. S. Muralidharan, Dr. Bipin Bihari Mohanty, Dr. C.P. Srivastava, Dr. Jagdish Mange, Dr. Manish Puranik, Dr. Manoj P Nair, Dr. Pankaj Goel, Dr. Pankaj Srivastava, Dr. RM Krishnan, Dr. Sathyaki Nambala, Dr. Vivek Kanhere, Dr.Yugal K Mishra have co-authored this publication. The authors have declared and confirmed that there is no conflict of interest with respect to this authored publication.

References


134. Tolosana JM, Berne P, Mont L, et al. Preparation for pacemaker or implantable


Treatment of Vitamin D Deficiency and Comorbidities: A Review

Parminder Singh

Abstract
Vitamin D is essential for the maintenance of calcium and phosphorus homeostasis, skeletal growth and various other metabolic processes. The prevalence of vitamin D deficiency in India is 50-90% in various studies. Factors such as low sunlight exposure, age-related decrease in cutaneous synthesis, and low dietary intake of vitamin D contribute to the high prevalence of vitamin D inadequacy which has emerged as a highly pervasive condition. Bone diseases such as rickets in children, osteomalacia and osteoporosis in adults are related with vitamin D insufficiency. Literature evidences show that low vitamin D levels are also related with increased risk of falls, fractures, muscle pain, muscle weakness, cardiovascular risk, diabetes mellitus, polycystic ovary syndrome (PCOS), infections, and autoimmune disorders also. Adequate intake of vitamin D is necessary for all individuals of any age group. Sunlight exposure, food fortification and routine supplementation can only fulfill the deficiency of vitamin D.

This review article emphasizes on the prevalence of vitamin D deficiency, potential implications, and effect of supplementation on cardiovascular disease, diabetes mellitus, polycystic ovary syndrome (PCOS), autoimmune disorders, sleep disturbance and pain. In addition, the present review discusses the screening, treatment, and prevention strategies for vitamin D deficiency.

Introduction
Vitamin D has an established role in skeletal health, apart from this it also causes, inhibition of cellular proliferation, angiogenesis and renin production, stimulating insulin production, and macrophage cathelicidin production etc. As per the Endocrine Society Clinical Practice Guideline, infants require at least 400 IU/d, children who are ≥1 year require at least 600 IU/d, adults between 19–70 years require at least 600 IU/d, and elders ≥70 years of age require at least 800 IU/d of vitamin D to maximize bone health and muscle function. Vitamin D status is measured through assay of 25-hydroxy vitamin D [25(OH)D], its major circulating form. Its deficiency occurs when 25(OH) D level falls below 20 ng/mL (50 nmol/L) in serum. On the other hand, vitamin D insufficiency is defined as 25(OH)D level of 21–29 ng/mL.

Vitamin D deficiency is one of the most common nutritional deficiencies worldwide. Globally, an estimated one billion individuals had vitamin D deficiency/insufficiency across all ethnicities and age groups as estimated in 2007. Approximately, 50-90% population in India is vitamin D deficient. According to a report released by the International Osteoporosis Foundation in 2009, 96% of neonates, 91% of healthy school girls, 78% of healthy hospital staff, and 84% of pregnant women in North India were diagnosed with hypovitaminosis D. Causes of vitamin D deficiency include inadequate exposure to sunlight, obesity, fat malabsorption syndrome, nephrotic syndrome, and autoimmune disorders also. Individuals with vitamin D deficiency experience bone diseases, such as rickets in children and osteomalacia and osteoporosis in adults. Additionally, it results in skeletal mineralization defects, bone deformities, short stature leading to increased risk of falls and fractures, muscle pain, muscle weakness, increased cardiovascular risk, diabetes mellitus, polycystic ovary syndrome (PCOS), infections, autoimmune disorders, sleep disturbance, and pain.

According to a meta-analysis conducted by the Endocrine Society, vitamin D supplementation was associated with a statistically significant (p=0.01) reduction in risk of falls (odds ratio [OR] for the risk
of experiencing at least one fall: 0.86; 95% confidence interval [CI] 0.77–0.96; 26 trials). Similarly Ceglia et al, in a randomized, double-blind, placebo-controlled study including 21 elderly, mobility-limited, vitamin D-insufficient women (aged ≥65 years) demonstrated that vitamin D₃ supplementation increased intramyonuclear vitamin D receptor concentration by 30% and muscle fiber size by 10%.

To highlight the importance of vitamin D and associated comorbidities, the present review article discusses vitamin D deficiency and its comorbidities in detail. The review further discusses treatment and prevention strategies for vitamin D deficiency.

**Vitamin D Deficiency and Cardiovascular Risk**

Vitamin D deficiency may be associated with an increased prevalence of cardiovascular disease. A cross-sectional case control study done in north India which included 201 adults reported that 90.2% patients with essential hypertension had deficient or insufficient levels of vitamin D. Hypertension occurs due to an imbalance between vasoconstriction and vasodilation, which is controlled by the interaction of genetic and epigenetic factors. Vitamin D deficiency may disturb these epigenetic factors. One of the mechanism is the disturbance of renin-angiotensin-aldosterone system (RAAS). Low vitamin D levels are also associated with secondary elevation of parathyroid hormone, increased arterial resistance, and endothelial dysfunction leading to hypertension as shown in Figure 1. It is also believed to increase the risk of cardiovascular diseases as it promotes vascular stiffness and calcification.

Another studies demonstrated that vitamin D is a potent endocrine inhibitor of renin synthesis which is one of the regulator of Renin Angiotensin Aldosterone system. An interventional study included 33 patients with essential hypertension and hypovitaminosis D. All the patients treated with cholecalciferol 50 000 IU/week orally for a period of eight weeks in the study demonstrated normalized plasma 25(OH)D values with reduction in levels of plasma renin activity (1.17 ± 0.3 vs. 1.51 ± 0.4 ng/ml/h, p=0.02), renin (13.4 ± 1.7 vs. 19.2 ± 2.9 pg/ml, p < 0.001), angiotensin II (11.6 ± 1.6 vs. 15.8 ± 2.7 pg/ml, p=0.02) at the end of the study.

Although global studies evaluating the prevalence of cardiovascular disorders in patients with vitamin D deficiency are scarce, multiple studies have been conducted across different parts of the world to evaluate this prevalence. A prospective case-control study which included 100 chronic stable angina patients and 100 matched controls showed a high prevalence of vitamin D deficiency in 75 angina patients (75%) as compared to 10 (10%) in controls. Further, among 100 Indian patients undergoing coronary angiography, 80% of the patients were having vitamin D deficiency and had significantly higher prevalence of double- or triple-vessel coronary artery disease (53% vs. 38%), diffuse coronary artery disease (56% vs. 34%), and impaired flow-mediated dilation (FMD) (50.6% vs. 7%).

**Fig. 1: Effect of vitamin D deficiency on parathyroid hormone and renin-angiotensin-aldosterone system**

- Sun (UV B Light) → 7 dehydro cholesterol → Vitamin D3
- Vitamin D Deficiency (Low serum calcium) → 25(OH) D Liver (25 hydroxylase) → 1, 25 (OH) 2D kidney
- Increase Parathyroid Hormone → Mobilize Calcium (Increase Serum calcium and Phosphate)
- Renin → Angiotensin II
- Aldosterone (Salt and Water retention) → Vasoconstriction (Increased Blood Pressure)
Supplementation with vitamin D might play an important role in improving the condition of the patients with cardiovascular disorders. However, there are very few studies supporting this hypothesis. An interventional study in obese individuals with hypertension and vitamin D insufficiency showed that vitamin D₃ therapy for a period of one month (15,000 IU/d) increased 25(OH)D levels (18 to 52 ng/mL) and basal renal plasma flow (+5%), and lowered supine mean arterial pressure (-3%) (p<0.01 each). Similarly Larsen T et al investigated the effect of 75 μg (3,000 IU) cholecalciferol per day in a randomized, placebo-controlled, double-blind study in 130 hypertensive patients. Supplementation with cholecalciferol effectively increased vitamin D levels resulting in decreased central systolic blood pressure to a significant extent (7/2 mm Hg, p=0.007/0.15) as compared with placebo. In addition Rahimi-Ardabili et al investigated the effect of cholecalciferol (3 oral capsules of 50,000 IU vitamin D₃ every 20 days for 2 months) on cardiovascular disease risk factors in PCOS women with vitamin D deficiency and concluded that vitamin D₃ therapy increased serum vitamin D (7.00 ± 2.80 to 22.9 ± 6.14 ng/mL), and led to significant decrease (p<0.05) in cardiovascular risk factors like serum total cholesterol (196.6±32.8 to 179.1±34.1 mg/dL), triglycerides (156.8±73.0 to 130.5±56.5 mg/dL), and very low density lipoprotein (31.4±14.6 to 26.1±11.3 mg/dL).

However, a meta-analysis of 46 trials with 4541 participants showed no effect of vitamin D supplementation on systolic blood pressure (p=0.97) or diastolic blood pressure (p=0.84). On the other hand, no significant relationship was found between vitamin D levels and endothelial dependent vasodilation (EDV, β±SE: 0.70±1.0; p=0.48), flow mediated vasodilaion (FMD, β±SE, 0.12±0.33; p=0.70), and refractive Index (RI, β±SE, -0.02±0.05; p=0.57) in older individuals but a positive association was found in women between vitamin D and endothelium independent vasodilation (EDV, β±SE: 1.41±0.54; p=0.001). Also, no improvement was observed in endothelial dependent vasodilation (6.3±3.6% at baseline to 6.1±4.6% at 8 weeks; p=0.78) after repletion of vitamin D in non-hypertensive, non-diabetic overweight, or obese individuals with vitamin D deficiency.

**Vitamin D Deficiency and Diabetes Mellitus**

Vitamin D may improve pancreatic β-cell function, decrease insulin resistance, and improve systemic inflammation. It directly acts on pancreatic β-cells by binding β-cell vitamin D receptor to produce insulin and on the muscle and fat cells to improve insulin action by reducing insulin resistance. Further, it indirectly improves insulin production and its action by increasing the level of calcium inside the cells, which is essential for insulin-mediated intracellular processes in insulin-responsive tissues such as skeletal muscles and adipose tissues.

Vitamin D also increases insulin sensitivity and β-cell survival by modulating the generation and effects of cytokines which play an important role in β-cell dysfunction by triggering β-cell apoptosis.

Evidences from clinical studies also show a correlation between vitamin D deficiency and diabetes mellitus. A retrospective study (n=4628) in South India showed 3304 (71.4%) of the diabetic patients to be vitamin D deficient and 694 (15%) patients to be vitamin D insufficient, suggesting that vitamin D deficiency is highly prevalent among diabetic patients.

In another study which was conducted to establish a correlation between vitamin D deficiency and diabetes reported that of the 100 diabetic patients included in the study, 68% of the patients were vitamin D deficient. Further, a prospective case control study in North India showed that 91.1% of the patients with youth-onset diabetes were vitamin D deficient as compared to 58.5% of the healthy controls, suggesting vitamin D deficiency is common in individuals with youth onset diabetes.

Another study showed an inverse association between serum 25(OH) D levels and A1C levels (r = -0.116, p=0.003) in 715 patients with type 2 diabetes mellitus (T2DM). A study evaluating the incidence of T2DM in children (n=50) between the age of 6 to 12 years showed that 29 (58%) of the children with T2DM were also vitamin D deficient as compare to control. (20.02 ± 10.63 ng/mL vs. 26.16 ± 12.28 ng/mL, p=0.009). Further, a meta-analysis of 20 observational studies including 9209 pregnant women showed a consistent association between vitamin D deficiency and an increased risk of gestational diabetes mellitus (odds ratio [OR] = 1.53; 95% CI: 1.33-1.75).

Zhou et al, demonstrated that oral vitamin D supplementation (oral calcitriol 0.5 μg/d) in patients with T2DM led to significant improvement in body mass index (-0.7±1.7 kg/m² and 0.4±1.4 kg/m², p<0.05), fasting plasma glucose (-1.2± 2.3 mmol/L and -0.6±2.8 mmol/L, p<0.05), fasting insulin (-1.6±2.2 μU/mL and -0.32±1.49 μU/mL, p<0.05), and hemoglobin A1c (-0.1±0.6% and -0.03±0.94%, p<0.05). An Indian study showed that vitamin-D supplementation (60,000 U) was associated with significant reduction in the progression of diabetes (6/55 vs. 13/49; p=0.04), higher reversal to normoglycemia (23/55 vs. 10/49; p=0.02).

**Vitamin D Deficiency and Polycystic Ovary Syndrome**

Vitamin D deficiency is commonly found in women with
PCOS as approximately 67-85% of PCOS women are having serum concentrations of 25-hydroxy vitamin D less than 20 ng/mL. Low vitamin D levels are believed to be associated with increase in para thyroid hormone and sex hormone binding globulin (SHBG) which may cause metabolic disturbances in PCOS, including ovulation, menstrual irregularities, infertility, hyperandrogenism, increased testosterone, obesity, insulin resistance, and increased risk of cardiovascular diseases.

The role of vitamin D deficiency in the pathology of PCOS is illustrated in Figure 2.

In a case-control study, 100 infertile PCOS women were evaluated to assess the efficacy of calcium and vitamin D supplementation (calcium 1000 mg/day and vitamin D 100000 IU/month for 6 months). While 83% of women showed vitamin D deficiency, 35% were severely deficient. Calcium and vitamin D supplementation regulate follicle maturation (28% vs. 22%, p=0.698), menstrual abnormalities (70% vs. 58%, p=0.211), and hyperandrogenism (18% vs. 12%, p=0.401) to a considerable but not significant extent among infertile women with PCOS. However, another study showed that administration of vitamin D improved endometrial proliferation in PCOS women during Intra Uterine Insemination (IUI) cycle as compared to the placebo group (p=0.003). In an Indian study, vitamin D levels were significantly lower in PCOS cases (p<0.05) as compared to healthy controls (15.31±2.11 ng/mL vs. 28.3±3.5 ng/mL, n=44) and was related to metabolic and hormonal disorders in PCOS.

Vitamin D Deficiency and Other Comorbidities

Autoimmune Disorders

Vitamin D binds to vitamin D receptors on various cells which participate in immune responses, and modulate both activation and deactivation of the innate and adaptive responses. Vitamin D may induce innate tolerance by promoting tolerogenic dendritic cells as well as induce a robust macrophage response to infections.

A cohort study in patients with rheumatoid arthritis (n=44), showed that the level of vitamin D was significantly low (15.26±1.07 ng/mL) as compared with the healthy control group (25.8±1.6 ng/mL, p<0.001), and suggested that vitamin D supplementation might be needed in patients with rheumatoid arthritis. Further, 102 newly diagnosed autoimmune thyroid disorder patients were evaluated for the effect of cholecalciferol 60,000 IU weekly and calcium 500 mg/day for 8 weeks. Vitamin D supplementation showed a positive impact on autoimmunity by significantly reducing the fall in thyroid peroxidase antibody (p=0.028). Vitamin D supplementation is also believed to modulate T-cell function in human immunodeficiency virus (HIV)-infected patients, and may represent a useful adjunct to highly active antiretroviral therapy.

Infectious Disorders

Several studies conducted previously have indicated an association of low levels of vitamin D levels with increased susceptibility of sepsis. A meta-analysis of 10 observational studies has shown a pooled OR of sepsis to be 1.78 (95% CI: 1.55-2.03, p<0.01) in patients with vitamin D deficiency. Another meta-analysis evaluated the association between 25-hydroxyvitamin D and sustained virological response (SVR) in hepatitis C virus (HCV) infected patients and showed that 71% of HCV infected patients had low vitamin D levels (n=1575). Further, it was suggested that vitamin D supplementation improved SVR in HCV infected individuals (OR = 4.59; 95% CI: 1.67-12.63). Another study indicated that vitamin D supplementation 50,000 IU twice weekly for 5 weeks, then 8000 IU twice weekly to 63 vitamin D insufficient HIV+ adults for 24 weeks improved cluster of differentiation 4 (CD4) recovery (r = 0.44, p = 0.01) and 83% vitamin D repletion (95% CI: 71–90%) showing improvement on immunologic recovery during HIV treatment.

Respiratory Diseases

Vitamin D deficiency may be associated with chronic lung diseases such as asthma, cystic fibrosis, chronic obstructive lung disease and interstitial pneumonia as it may influence various cytokines, cellular elements, oxidative stress and protease/antiprotease levels and affect
A meta-analysis of 10 studies showed high prevalence of vitamin D deficiency among asthmatic patients as compared to control (relative risk [RR]=1.59, 95% CI: 1.07-2.36; prevalence 60% vs. 32%). Further, a meta-analysis of five studies which included 48 participants suggested a reduction (RR 0.41, CI: 0.27-0.63) in asthma exacerbation with vitamin D therapy (2000 IU/day). Manousaki et al, a Mendelian randomized study including 33,996 individuals showed no association of genetic study including 33,996 individuals, a Mendelian randomized

Vitamin D status Vitamin D levels
Deficiency <20 ng/ml
Insufficiency 21-29 ng/ml
Sufficiency >30 ng/ml
Toxicity >150 ng/ml
lunge fibroproliferation and its functions. A meta-analysis of 10 studies showed high prevalence of vitamin D deficiency among asthmatic patients as compared to control (relative risk [RR]=1.59, 95% CI: 1.07-2.36; prevalence 60% vs. 32%). Further, a meta-analysis of five studies which included 48 participants suggested a reduction (RR 0.41, CI: 0.27-0.63) in asthma exacerbation with vitamin D therapy (2000 IU/day). Manousaki et al, a Mendelian randomized study including 33,996 individuals showed no association of genetic 2(OH)D alleles with asthma (OR: 1.03; 95% CI: 0.90-1.19, p=0.63), childhood-onset asthma (OR: 0.95; 95% CI: 0.69-1.31, p=0.76), and atopic dermatitis (OR: 1.12; 95% CI: 0.92-1.37, p=0.27). Cancer

The biologically active form of vitamin D hormone, 1α,25(OH)2D3, can modulate gene expression, inhibit the cellular proliferation, induction of differentiation, and apoptosis ultimately inhibiting the cell growth of cancer. When prostate, colon, breast, lung and melanoma cancer cell lines are exposed to vitamin D3, growth inhibition takes place. An increased incidence of vitamin D insufficiency (80.4%) was observed in children of less than 18 years suffering from cancer (leukemia/lymphoma or solid tumors) as compared to the control (50.1%). In another study, vitamin D supplementations (400-833 IU/day) reduced total cancer mortality (RR=0.88, 95% CI=0.78-0.98). In a cohort study of 492 patients, the association of pre-transplant Vitamin D deficiency with higher relapse rate was observed to a significant extent (HR, 2.55; p=0.014) in myeloid patients. Pre-transplant vitamin D deficiency was associated with a higher risk of relapse in patients allografted for myeloid malignancies.

Vitamin D Deficiency, Sleep and Pain

In sleep and pain. A case series of 28 veterans with multiple areas of chronic pain showed that supplementation with 1200 IU/day cholecalciferol in an insufficient serum 25(OH)D and 50,000 IU/week in deficient serum 25(OH)D significantly improved the pain score (p<0.001), sleep latency (p=0.019), sleep duration (p=0.012), body pain (p=0.014), and general health (p=0.006).

Prevention and Treatment Strategies

Screening

As per the Endocrine Society, screening of vitamin D deficiency is recommended in individuals with rickets, osteomalacia, osteoporosis, chronic kidney disease, hepatic failure, malabsorption syndromes, cystic fibrosis, inflammatory bowel disease, Crohn’s disease, bariatric surgery, radiation enteritis, and hyperparathyroidism. Further, it is recommended for African-American and Hispanic children and adults, pregnant and lactating women, older adults with history of falls, older adults with history of non-traumatic fractures, obese children and adults, and people who are suffering from granuloma. Recommendations of the Endocrine Society of India are in line with the international guidelines. Universal screening is not recommended by the Endocrine Society of India and target screening in at-risk population is advised. Competitive protein binding, immunoassay, high-performance liquid chromatography, combined high-performance liquid chromatography, and mass spectrometry are currently available screening methods used in routine testing of 25 hydroxy vitamin D in clinical laboratories. Different levels of vitamin D deficiency in blood are shown in Table 1 as per the US Endocrine Society classification.

Recommended Dietary Allowance and Treatment of Vitamin D Deficiency

Indian Council of Medical research (ICMR) committee had recommended outdoor physical activity to achieve adequate vitamin D as the young growing children and adults in India mainly in the urban areas are physically less active and are not being exposed outdoors which reduces the chances of vitamin D formation. The committee has not made any specific suggestions on the intake of vitamin D in different groups of people. A daily supplement of 400 IU (10 μg) is specifically recommended in case of minimal exposure to sunlight. According to Institute of Medicine (IOM), adults of age 19 to 70 need a daily supplement of at least 400 IU of vitamin D, and recommended dietary allowance of at least 600 IU as shown in Table 2. Obese adults need at least two to three times more vitamin D to treat and prevent vitamin D deficiency.

The vitamin D deficiency often remains undiagnosed or is undertreated due lack of recommended age-dependent adequate intake and the dearth of vitamin D toxicity. Endocrine Society of India recommends vitamin D supplementation to combat high prevalence of vitamin D deficiency. The guideline recommendations for the treatment of vitamin D deficiency as per the Endocrine Society Clinical Practice Guidelines recommend treatment of vitamin D deficiency with varying daily/weekly vitamin D2 or vitamin D3 for a period of six weeks.
for different age groups. Keeping the international clinical practice guidelines in consideration, Balasubramanyam et al, reviewed the current guidelines available for the treatment of vitamin D deficiency. The article reported that varying daily/weekly doses of vitamin D3 or vitamin D2 for a period of 8-12 weeks for different age groups are required for the treatment of vitamin D deficiency. Indian physicians often prescribe 60,000 IU (1500 μg) cholecalciferol per week for 8 weeks for vitamin D deficiency. In a meta-analysis which included randomized controlled trials (RCTs, n=1016), the effectiveness of vitamin D2 (cholecalciferol) was significant (p=0.0002) in increasing serum 25-hydroxyvitamin D concentration as compared to vitamin D2 (ergocalciferol) (p=0.001). We have also shown that, regardless of whether supplementation with vitamin D was in small daily doses or in larger and more infrequent bolus dosages, the favoring toward cholecalciferol was still evident. Reason for this would be the metabolism of different forms of vitamin D as suggested by evidence. Once the 2-step 25-hydroxylation process has been completed and 1,25-dihydroxyvitamin D has been formed, an additional step occurs that involves 24-hydroxylation at the kidney to form 24,25(OH)2D3 [1,2,24-trihydroxyvitamin D; 25(OH)D2 can also be converted to 24,25-dihydroxyvitamin D at this point] It is this 24-hydroxylation step that truly demarcates the impact of ergocalciferol compared with that of cholecalciferol. This differentiation between ergocalciferol and cholecalciferol is due to the fact that once 1,24,25(OH)3D2 has been formed, ergocalciferol has been deactivated and, therefore, is irretrievable. In contrast, cholecalciferol (now 1,24,25(OH)3D3) retains its capacity to bind to the VDR and still requires an additional side-chain oxidation to become deactivated. Thus, this additional step gives a vast advantage and potential for cholecalciferol to remain biologically active and, thus, maintain vitamin D status, which only strengthens the hypothesis that cholecalciferol is the preferred substrate compared with ergocalciferol. The detailed treatment strategies are presented in Table 3.

### Table 3: Treatment regimens for the vitamin D deficiency

<table>
<thead>
<tr>
<th>Age group</th>
<th>Holick et al (Therapy duration: 6 weeks)</th>
<th>Balasubramaniam et al (Therapy duration: 8-12 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 mo</td>
<td>2000</td>
<td>50,000</td>
</tr>
<tr>
<td>1-12 mo</td>
<td>2000</td>
<td>50,000</td>
</tr>
<tr>
<td>1-18 yr</td>
<td>5000</td>
<td>50,000</td>
</tr>
<tr>
<td>&gt;18 yr</td>
<td>6000</td>
<td>50,000</td>
</tr>
<tr>
<td>Special Cases*</td>
<td>6000-10000</td>
<td>3000-6000</td>
</tr>
</tbody>
</table>

*Obese patients, patients with malabsorption syndromes, patients on medications which affect vitamin metabolism.
D status. This suggests that 25(OH)D concentrations during childhood might be more relevant for bone outcomes than 25(OH)D concentrations during fetal life. In another randomized, double-blind, placebo-controlled clinical trial including 51 pregnant women, supplementation with 4400 IU of vitamin D₃ enhanced broad-spectrum proinflammatory cytokine response of cord blood mononuclear cells to a significant extent (p=0.0009). Study concluded by saying vitamin D exposure during fetal development influences the immune system of the neonate, which can contribute to protection from asthma-related, including infectious, outcomes in early life.

**Conclusion**

In conclusion, the role of vitamin D has been established in several interventional, case control, retrospective, and observational studies. Inadequate vitamin D levels may be responsible for the progression of cardiovascular disorders, diabetes mellitus, PCOS, autoimmune disorders, sleep disturbance and pain to a considerable extent. Therefore, more awareness is needed to combat the increasing prevalence of vitamin D inadequacy throughout all age groups. Aggressive screening and treatment strategies are required for vitamin D inadequacy. Adequate intake of vitamin D through supplementation can only be achieved when one is educated appropriately regarding vitamin D deficiency and its impact on various comorbidities adequately.

**Acknowledgements**

The authors acknowledge Turacoz Healthcare Solutions (www.Turacoz.com), Gurugram, India for their writing and editing support.

**References**

Stars in Abdomen

Ramesh Kumar¹, Divendu Bhushan², Mukesh Kumar²

A 24-year-old male who presented to our emergency department with the history of having ingested mercury due to accidental breakage of the tip of mercury thermometer. He had 3 bouts of vomiting following ingestion; however, mercury beads were not seen in the vomitus. On admission, the patient was clinically stable, and his physical and systemic examinations were unremarkable. His routine investigations which included complete blood count, liver function test, kidney function tests, coagulation profiles, blood glucose, and electrocardiogram were normal. A chest x-ray revealed no evidence of inhaled mercury in the respiratory tract. His plain abdominal x-ray revealed scattered beads of mercury throughout the small intestine (Figure 1a). A repeat x-ray on day-2 revealed confinement of most of the mercury beads in the region of right hemicolon (Figure 1b), while x-ray on day 4 revealed near complete disappearance of mercury beads (Figure 1c). Following hospitalization, patient did not show any untoward symptoms or complications, and he remained well till discharge.

Mercury is the only metal that is liquid at room temperature. The likelihood of mercury intoxication varies according to the type of mercury, type of exposure, and individual sensitivity. Simple elemental mercury in liquid form is not poisonous.¹,² Because it is not absorbable through mucus membrane, most of ingested liquid mercury is expected to be excreted right away from gastrointestinal tract. In our case, the ingested mercury beads traversed through stomach and small bowel rapidly and were retained in the colon during most of time before being excreted out. In a similar case of mercury ingestion by a broken thermometer, no signs of intoxication were seen.³ Elemental mercury is only hazardous in vapour form.⁴ Around 80% of the inhaled mercury vapor is absorbed through alveolar membrane. It may cause harmful effects to the nervous, digestive, respiratory, renal, and immune systems.¹ Though ingestion of liquid mercury does not cause direct harm, the mercury once released into the environment can remain for a longer period, and can cause both acute and chronic toxicity. Mercury, when metabolized into methyl mercury becomes highly toxic.⁴ Healthcare activities are believed to contribute the substantial part of the mercury found in the environment. The World Health Organization has issued guidelines for all health care sectors to become mercury free. Several types of non-mercury thermometers are now available which use non-toxic and biodegradable liquid. Some of them have additional safety feature such as teflon coating which help to prevent contamination in case of accidental breakage.

References


¹Department of gastroenterology, Institute of Gastrosciences, ²Department of Medicine, Paras Hai Medical Research Institute, Patna, Bihar
Received: 07.09.2016; Accepted: 02.02.2017
Rhabdomyolysis of Unknown Etiology - Initial Suspicion and Detection on $^{99m}$Tc-MDP Skeletal Scintigraphy

Nandigam Santosh Kumar¹, Sandip Basu²

The classical bone scan findings of Rhabdomyolysis is presented in this illustration. A 60 year old female patient with complaints of low backache and bilateral lower limbs weakness over 1 year was referred for whole body skeletal status evaluation. Whole body skeletal scintigraphy undertaken 3 hrs after I.V injection of 15 mci of $^{99m}$Tc-MDP revealed bilaterally symmetrical diffuse skeletal muscle tracer activity in deltoid, lattisimus dorsi, diaphragm, paraspinal muscles, gluteus muscles and muscles of thigh. On biochemical investigations for evaluation of skeletal muscle uptake revealed elevated serum creatinine, LDH, serum potassium. The ultrasonography of kidney revealed grade I renal parenchymal changes. ECG showed normal findings.

Rhabdomyolysis manifests with muscle pains, restricting muscle activity and may present with low backache. Etiology of Rhabdomyolysis is nonspecific and can occur due to many causes (usage of drugs such as antipsychotics, statins, alcohol, toxemia, infections, malignant hyperthermia, heat stroke, crush injury etc). In our case no inciting cause of Rhabdomyolysis could be elicited. CT scan can reveal calcification of muscles with nonspecific hypo-attenuating areas in the involved muscles. Bone scan has the advantage of evaluating the whole body in a single examination.

References


¹Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Hospital Annex, Mumbai, Maharashtra; ²Department of Medicine, Vijaya Diagnostic Centre, Visakhapatnam, Andhra Pradesh

Received: 13.09.2016; Accepted: 08.02.2017
In frequent urination, delay of urination, weak stream & terminal dribbling associated with BPH

Veltam®
Tablets
Tamsulosin MR 0.2 mg & 0.4 mg

The first tablet formulation of Tamsulosin in India

In patients with fast progression of LUTS in BPH

Veltam® Plus
Tamsulosin MR 0.4 mg + Dutasteride 0.5 mg Tablets

The smallest size tablet to combat BPH

In patients with slow progression of LUTS in BPH

Veltam® F
Tamsulosin MR 0.4 mg + Finasteride 5 mg Tablets

Trust your experience

For any further details, write us: medical@intaspharma.com

INTAS PHARMACEUTICALS LTD.
Chinshali Centre, Off. Nehru Bridge, Ashram Road, Ahmedabad : 380 009, INDIA
CRAB Manifestations in a Middle-Aged Female: A Diagnostic Dilemma

Anitha Swamy, Ratnakar Gogineni, Animesh Ray, Milind Jha, Smita Manchanda, Sudheer Arava, Rakesh Kumar, Kiran Kumar DVS, Harsh Sahu, Piyush Ranjan, Ranveer S Jadon, Naval K Vikram, Rita Sood

Abstract
A 56 year old lady, presented to our institute with six months history of low grade fever, generalized weakness, decreased food intake and fluctuating sensorium. Initial investigations revealed hypercalcemia, renal dysfunction and anemia. Initial working diagnosis of likely underlying hematological malignancy such as lymphoma or multiple myeloma (MM) was kept after hyperparathyroidism was ruled out. Her skeletal survey revealed lytic lesions in the skull, bone marrow aspirate showed 12% plasma cells and beta-two microglobulin level was markedly elevated. However, the criterion for MM was not fully satisfied. In view of persistent altered sensorium, MRI brain was done which suggested the diagnosis of disseminated tuberculosis and was further confirmed through MR spectroscopy, bone marrow biopsy (showing granulomas) and whole body PET. She was started on anti-tubercular therapy along with steroids with marked response within a week. We describe the details of this interesting case through a systematic approach to the various features.

Introduction
Multiple myeloma is a disorder characterized by malignant proliferation of plasma cells. It accounts for 1% of all cancers. The diagnosis is suspected in light of certain clinical features such as hypercalcemia, renal dysfunction, unexplained anemia and bone lytic lesions on skeletal survey (CRAB). Malignancy and hyperparathyroidism account for most of the cases of hypercalcemia. However, chronic granulomatous diseases such as tuberculosis are also a rare cause. Also, there are very few cases of tuberculosis presenting with lytic lesions in the skull. Our case highlights the importance of systematic and thorough work up in order to avoid early and erroneous labelling of a particular diagnosis.

Case Description
A 56 year old female, presented to our hospital with one month history of mild to moderate grade fever associated with generalized weakness and decreased food intake. She was bedridden and unable to perform her routine daily activities for the past 20 days and had altered sensorium for the past 7 days. She had a history of multiple hospitalizations in the past six months at a private hospital with complaints of generalized weakness, fluctuating sensorium and decreased appetite. She was diagnosed as a case of chronic kidney disease (CKD) two months back on the basis of persistent deranged renal parameters. She was on oral hypoglycaemic agents and anti hypertensives in view of diabetes mellitus and hypertension respectively, for the past two years which well controlled. She had undergone two sessions of haemodialysis and also received two units of packed red blood cell (PRBC) transfusion two months back. She had no other significant past history. On examination, the patient was drowsy with a Glasgow Coma Score (GCS) of E3V3M6. Her vitals were stable. There was no peripheral lymphadenopathy or any organomegaly. Rest of the systemic and general physical examinations were unremarkable.

Our patient was in a state of altered consciousness with no focal neurological signs on testing. This can be caused by many complex medical conditions including primary neurological disorders,
systemic conditions as well as extrinsic factors.\(^1\) In this patient, hypercalcemia was the evident cause. A wide range of disorders can produce hypercalcemia as mentioned in Table 1. Primary hyperparathyroidism and malignancy account for 80-90% of the cases. The normal range of serum calcium lies between 8.5 and 10.5 mg/dL (2.1-2.5 mmol/L). About 40-45% of the serum calcium is bound to albumin. When there is increased binding, elevation in the total calcium level can occur without an increase in the ionized calcium. Thus, during evaluation of hypercalcemia, elevation in the physiologically active unbound or ionized calcium needs to be confirmed first. Hypercalcemia can be classified as mild (Serum calcium < 12 mg/dL), moderate (12-14 mg/dL) or severe (> 14 mg/dL). The clinical manifestations of hypercalcemia are varied and depend upon the severity and rapidity of development.\(^2\)

Our patient had anemia and renal dysfunction along with severe hypercalcemia [Serum calcium at presentation (15.7 mg/dL)] and constitutional symptoms for past six months. Evaluation of anemia revealed normocytic normochromic morphology of the RBCs with a decreased corrected reticulocyte count and no features of hemolysis. There was no pathology evident on chest x-ray (Figure 1) and the parathyroid hormone level was within the normal range. The kidney size was normal on ultrasound and the urine output was well preserved. The initial non contrast computed tomography (NCCT) head was unremarkable. The total leukocyte count and the serum procalcitonin were also not suggestive of an infectious etiology. Thus, hematological malignancies such as lymphoma or multiple myeloma (MM) were considered a strong possibility and she was worked up for the same. She was started on saline diuresis and calcitonin in view of hypercalcemia. Further
dehiscence (PCD) was performed which was grossly normal. The diagnosis of multiple myeloma (MM) requires the presence of ≥ 10% clonal plasma cells in the bone marrow or biopsy-proven plasmacytoma along with evidence of end-organ damage. The definition of MM has recently been expanded by the international myeloma working group (IMWG) to include any one of the myeloma defining biomarkers even in the absence of end-organ damage (Table 2). The clonality of the plasma cells needs to be established by demonstration of kappa/lambda (k/\(\lambda\)) light-chain restriction by immunofluorescence, or by demonstration of phenotypic clonality by flow cytometry, or by immunoglobulin gene rearrangement studies.\(^3\)

Our patient’s skeletal survey showed two lytic lesions in the skull (Figure 2). There are a wide range of abnormalities which can result in calvarial lytic lesions as listed in Table 3.\(^{4,5}\) In light of the occurrence of the lytic lesions, along with the findings of hypercalcemia, renal dysfunction and anemia; the possibility of diagnosis of MM was further strengthened and we went ahead with the bone marrow examination. The bone marrow aspirate revealed 12% plasma cells (Figure 3). However,
Table 2: International Myeloma Working Group (IMWG) diagnostic criteria for multiple myeloma

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following CRAB features and myeloma-defining events (MDE):</td>
<td>Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:</td>
</tr>
<tr>
<td>HyperCalcemia</td>
<td>Serum calcium &gt;0.25 mmol/L (&gt;1mg/dL) higher than the upper limit of normal or &gt;2.75 mmol/L (&gt;11mg/dL)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Creatinine clearance &lt;40 mL per minute or serum creatinine &gt;177 μmol/L (&gt;2mg/dL)</td>
</tr>
<tr>
<td>Anemia</td>
<td>Hemoglobin value of &gt;20g/L below the lowest limit of normal, or a hemoglobin value &lt;100g/L</td>
</tr>
<tr>
<td>Bone lesions</td>
<td>One or more osteolytic lesion on skeletal radiography, CT, or PET/CT. (If bone marrow has &lt;10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.)</td>
</tr>
<tr>
<td>Any one or more of the following biomarkers of malignancy (MDEs):</td>
<td>60% or greater clonal plasma cells on bone marrow examination</td>
</tr>
<tr>
<td></td>
<td>Serum involved / uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100mg/L</td>
</tr>
<tr>
<td></td>
<td>More than one focal lesion on MRI that is at least 5 mm or greater in size.</td>
</tr>
</tbody>
</table>

Table 3: Differential diagnosis of calvarial lytic lesions

<table>
<thead>
<tr>
<th>Category</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal variant</td>
<td>Arachnoid granulations</td>
</tr>
<tr>
<td></td>
<td>Transcalvarial venous channels and venous lakes</td>
</tr>
<tr>
<td>Congenital</td>
<td>Encephalocele</td>
</tr>
<tr>
<td></td>
<td>Sinus pericranii</td>
</tr>
<tr>
<td></td>
<td>Dermo/epidermic cysts</td>
</tr>
<tr>
<td></td>
<td>Meningiocele</td>
</tr>
<tr>
<td>Traumatic</td>
<td>Posttraumatic defect</td>
</tr>
<tr>
<td></td>
<td>Leptomeningeal cyst</td>
</tr>
<tr>
<td>Inflammatory/Infection</td>
<td>Eosinophilic granuloma/</td>
</tr>
<tr>
<td></td>
<td>Langerhans cell</td>
</tr>
<tr>
<td></td>
<td>Histiocytosis</td>
</tr>
<tr>
<td></td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Metabolic/developmental</td>
<td>Paget disease of bone</td>
</tr>
<tr>
<td></td>
<td>Fibrous dysplasia</td>
</tr>
<tr>
<td></td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Osteoma</td>
</tr>
<tr>
<td></td>
<td>Hemangioma</td>
</tr>
<tr>
<td></td>
<td>Hemangiopericytoma</td>
</tr>
<tr>
<td></td>
<td>Aneurismal bone cyst</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td></td>
<td>Leukemia, lymphoma</td>
</tr>
<tr>
<td></td>
<td>Metastasis</td>
</tr>
</tbody>
</table>

Table 4: Differential diagnosis of multiple ring enhancing lesions in the brain in an adult

<table>
<thead>
<tr>
<th>Category</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Neurocysticercosis</td>
</tr>
<tr>
<td></td>
<td>Tubercular granulomas</td>
</tr>
<tr>
<td></td>
<td>Abscess</td>
</tr>
<tr>
<td></td>
<td>Bacterial, fungal, tubercular</td>
</tr>
<tr>
<td></td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td></td>
<td>Fungal infections</td>
</tr>
<tr>
<td></td>
<td>Histoplasmosis, Cryptococcosis</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Glioblastoma multiforme</td>
</tr>
<tr>
<td></td>
<td>Primary CNS lymphoma</td>
</tr>
<tr>
<td></td>
<td>Metastasis</td>
</tr>
<tr>
<td>Vascular</td>
<td>Resolving hematomas</td>
</tr>
<tr>
<td>Lesions</td>
<td>Thrombosed aneurysm</td>
</tr>
<tr>
<td>Infarct</td>
<td>Tomography (PET-CT) scan was also done to rule out malignancy as a source of hypercalcemia. It showed metabolically active granulomas in the brain and extensive miliary lesions in the lungs along with retroperitoneal nodes and involvement of vertebrae and para spinal soft tissues and cold abscess along the ribs (Figure 6). The bone marrow biopsy report was available by then, which also revealed granulomas (Figure 7). The fundus examination also revealed choroid tubercles bilaterally. With these, the diagnosis of disseminated tuberculosis was established and the patient was started on antituberculous therapy. Cerebrospinal fluid (CSF) examination was normal. However, the patient was started...</td>
</tr>
</tbody>
</table>
Fig. 4: Axial T1WI (A), T2WI (B), and post gadolinium T1WI (C and D) sections of MRI Brain reveal multiple, small ring enhancing lesions in bilateral cerebral (white arrows) and cerebellar hemispheres (arrowhead) and pons (black arrow). Lesions show T1 and T2 peripheral hyperintensity and central hypointensity.

Fig. 5: Multivoxel MR spectroscopy shows lipid peak (arrow) and Cho/Cr ratio of 1.13. MRI and MRS findings are suggestive of Tuberculomas.

on corticosteroids (Dexamethasone 8mg TDS) in view of meningeal enhancement on MRI.

The differential diagnosis of multiple ring enhancing lesions is listed in Table 4.7 Neoncocysticercosis followed by tuberculosis are the most common etiology of multiple ring enhancing lesions in our country.8 Magnetic Resonance Spectroscopy (MRS) is a superior technique to MRI and is useful in characterization of lesions, especially those inaccessible for biopsy. The specific metabolites in the microenvironment of the lesions produce certain changes which is detected by MRS. The type of microorganism can then be assumed based on the expected products for a particular microorganism as reflected in the metabolic signature. Tubercular lesions contain caseous material with mobile lipids in them and hence exhibit strong lipid resonances.9 Approach to ring enhancing lesions in the brain is explained in the form of a flow chart in Figure 8.10

During the hospital stay, our patient developed urinary tract infection (UTI) which resolved with broad spectrum antibiotic coverage of appropriate duration. She also developed leucocytopenia and significant thrombocytopenia. The leucocyte count had improved subsequently. However, thrombocytopenia was persistent. She received multiple platelet transfusions as she had severe bruising and bleeding gums. There was marked improvement in her sensorium within one week of starting antituberculous therapy. Her hypercalcemia responded to the treatment and her renal dysfunction also resolved. She was discharged one week after starting antituberculous treatment along with steroids.

Rarely, granulomatous diseases have been known to cause hypercalcemia.11 Among them tuberculosis and sarcoidosis are most common.12-15 The mechanism involves increased extra renal 1-alpha hydroxylase activity by the activated macrophages present in the granulomas. This leads to a non-parathormone (PTH) mediated increase in calcitriol levels.16-18 The diagnosis of tuberculosis was further established in our case by the MR spectroscopy and whole body PET imaging as well as by the remarkable clinical response to anti tuberculous therapy. Treatment of hypercalcemia in granulomatous diseases including tuberculosis consists of dietary and pharmacological measures along with the treatment of the underlying disease when possible. Dietary measures are aimed at minimizing the intestinal calcium absorption and calcitriol synthesis. These can be achieved by reducing calcium intake, elimination of dietary vitamin D supplements, and avoidance of sun exposure. Pharmacological measures include low dose glucocorticoids, bisphosphonates, and chloroquine.19-21

There have been case reports of tuberculosis presenting with lytic
bone lesions including the skull.\textsuperscript{6,22}
Elevated beta 2 microglobulin is used as a prognostic marker in several malignancies including multiple myeloma. Increased levels are also known to occur in infections such as tuberculosis.\textsuperscript{23,24}

There have also been case reports of simultaneous occurrence of tuberculosis and multiple myeloma.\textsuperscript{25,26} This is probably the first case of disseminated tuberculosis in itself simulating full blown manifestations of multiple myeloma namely, hypercalcemia, renal dysfunction, anemia, lytic lesions in the skull as well as plasma cells in the bone marrow and elevated beta 2 microglobulin.

**Conclusion**

Hypercalcemia and lytic
lesions occurring together does not always mean malignancy. Granulomatous diseases such as tuberculosis can also present with similar presentation. Our case report highlights the importance of systematic and thorough work up in order to clinch the correct diagnosis. The diagnosis of multiple myeloma requires the presence of ≥ 10% clonal proliferation of plasma cells along with one of the CRAB criteria or elevation of any one of the myeloma defining biomarkers. Having a high index of suspicion and thorough work up is of paramount importance in such cases before embarking on treatment as the diagnosis is not always straightforward forward.

References

24. The Implication and Significance of Beta 2 Microglobulin: A Conservative Multifunctional Regulator [Internet]. [cited 2017 Jul 19]; Available from: http://www.cmj.org/article.asp?issn=0336-6999;year=2016;volume=129;issue=4;spage=448;epage=455;aulast=Li
Two Cases of Early Morning Neuroparalytic Syndrome (EMNS) in the Tropics - Masquerading as Brain Death

RK Anadure¹, CS Narayanan², V Hande³, A Singhal⁴, G Varadaraj⁵

Abstract
Neurotoxicity from elapid bite may masquerade as early morning neuroparalytic syndrome (EMNS). We are reporting a series of two cases who presented as EMNS without brain stem reflexes, mimicking brain death. The first case was being considered for potential organ retrieval when the diagnosis was revised, and he recovered completely with anti-snake venom (ASV). The second patient developed severe anaphylaxis to ASV, which made continuation of the empirical therapy in a comatose patient very tricky. She gradually tolerated a low dose ASV infusion under steroid and adrenaline cover, with reversal of paralysis and coma. Both the patients showed excellent recovery post ASV treatment. A simple bedside Neostigmine challenge test and timely ASV therapy can save many helpless patients of EMNS from certain death.

Introduction
Snake bite is a common problem seen in India, especially in rural parts, and is associated with a high rate of mortality if not diagnosed and treated in time. Neurotoxicity from elapid bite may masquerade as early morning neuroparalytic syndrome (EMNS) and diagnosis at the initial stage is challenging as these patients seldom have bite marks or history of being bitten. We are reporting a series of two cases who presented as EMNS without brain stem reflexes, mimicking brain death. After ruling out other causes of similar clinical presentations and based on a positive Neostigmine challenge test, both patients were empirically treated with a standard regimen of anti-snake venom (ASV), along with other supportive measures. Both the patients showed excellent recovery post ASV treatment. These cases highlight the need to watch out for Elapid bites, especially Krait, in unusual neuroparasisis and coma, in a tropical country like ours.

Case - 1
A 38-year-old driver, with no previous co-morbidities, was on leave at his hometown Aligarh. He had an alcohol binge with his friends in the evening and fell asleep in the courtyard at home around 11 pm. He woke up at morning 3 am complaining of abdominal pain and vomiting which was attributed to alcohol by his wife and managed with lemon juice and antacids at home. However, he could not go back to sleep and remained restless throughout the night. By 6 am he complained of difficulty in swallowing and double vision and was taken to a local doctor. There he was noted to have neck muscle weakness and respiratory distress and was referred to nearby Medical college in Aligarh. He became stuporous during the road journey and was intubated on arrival at the Medical college as he was found drowsy with a low GCS of 8/15 along with pupillary abnormalities and was desaturating despite oxygen therapy. His initial hematological and biochemical parameters were normal and a CT head did not reveal any abnormality. He was managed with broad spectrum antibiotics, antimalarials, and ventilatory support. However, over the next two days he became deeply comatose with a GCS of 3/15, dilated fixed pupils and absent respiratory efforts.

He was transferred to a tertiary care hospital in Delhi Cantt on day three, on a portable ventilator with a diagnosis of Brain Death (cause unknown). At presentation, the patient was comatose with GCS of 3/15 on CMV mode ventilation. He had pyrexia of 100°F, pulse of 120/min regular and blood pressure of 140/78 mm of Hg. There was no skin rash or bite marks noted. Neurologic examination revealed normal ocular fundi with a soft neck but absent superficial and deep tendon reflexes and mute plantar response. All brain stem reflexes were absent (both pupil 8mm dilated and non-reactive, no reflex ocular movements, and absent corneal/pharyngeal reflex).

Chest examination revealed good air entry bilaterally (on Ventilator) with vesicular breath sounds and scattered coarse crackles in right infrascapular and axillary region. Cardiovascular and abdominal examination were not contributory. Urgent capillary glucose by glucometer was 151 mg% and ECG was normal. Arterial blood gas showed pH of 7.36, pO₂: 163 mmHg, pCO₂: 55.3 mmHg, HCO₃: 30.7 mEq/L, Na⁺:142 mEq/L, K⁺:3.9 mEq/L. An urgent CECT head was normal and he was admitted to ICU on ventilator for further evaluation of the cause for acute encephalopathy. He remained in the same neurologic state for next 24 hrs and only positive investigation being, elevated TLC of 16,700/cu mm with 90% polymorphs and chest X ray showing non homogenous soft alveolar opacities in right lower zone, suggesting a probable health care associated pneumonia. His CSF study showed proteins of 20 mg% and no cells. CSF
India ink stain and latex agglutination for cryptococcal antigen were negative. CSF HSV PCR was also negative. CSF ADA levels were normal. Serologic studies for HIV, HBsAg and HCV were negative. A broad differential diagnosis was considered at this stage including AIDP/ Myasthenic crisis with hypoxic encephalopathy, paralytic forms of rabies, poisoning with psychotropic agents and neuroparalytic snake bite. In the mean while an overzealous transplant team member initiated dialogue for further brain death testing and organ donation considering a young healthy patient with clinical diagnosis of Brain death. However this error was quickly corrected. Since the patient did not have a clear cause of brain stem dysfunction and had normal neuroimaging, he did not meet the first basic criteria for potential brain death testing. Since the first two diagnoses of HIE carried a poor prognosis and a toxicology screen would take time to obtain, it was decided to give a simple bedside neostigmine challenge to look for reversible neuromuscular blockade. Immediately after 1.5 mg IV neostigmine, the patient for the first time showed eyelid movements along with few weak inspiratory efforts on the ventilator tracing. This raised the suspicion of a possible elapid bite with severe neuroparalysis. Although the complete absence of brain stem reflexes was very odd. However a quick literature search and review confirmed similar case reports of unexplained neuromuscular and severe brain stem depression in elapid bites from India and Sri Lanka. It was thus decided to give him polyvalent anti-snake venom (ASV). He was given 100 ml of reconstituted ASV every 8th hourly for next 72 hrs along with Inj Neostigmine 1.5 mg IM 6th hourly. He showed progressive improvement in muscle power with return of spontaneous limb and respiratory movements over next 3 days. He was weaned off ventilator five days after starting ASV and regained full consciousness, when he was shifted to medical ward. He confirmed the high incidence of elapid snakes in his area and also having slept outdoor on the floor after alcohol binge, increasing many fold the risk of snake bite. While he gradually regained grade 4/5 muscle power over the next four weeks and started walking without support, his pupils remained dilated and fixed at 8 mm. He was sent on leave for six weeks which was uneventful and he regained grade 5/5 power with return of pupillary reflexes when examined after sick leave. He went back to full duties within 3 months of being declared brain dead and being on the list of transplant team for organ donation!

**Case - 2**

A 27 year old mother, nursing 6 month old twin babies, was rushed to emergency room in a comatose state at 0730 h in the morning. She had slept normally the previous day at 2330 h and did not get up at night to feed her babies. She continued to sleep beyond 6 am which was her usual time of awakening. At 0700 h, she was noticed by her mother to have heavy breathing and in an unresponsive state. She was immediately brought to emergency department of our hospital. On arrival at emergency room, her GCS was 6/15 (E1V2M3) with blood pressure 130/80 mm Hg, heart rate 102/min, respiratory rate 28/min and random capillary glucose level was 112 mg/dL. She was immediately shifted to ICU. She had optimal oxygen saturation despite tachypnea, but her GCS deteriorated to 5/15 (E1V2M2) over the next hour in ICU. There was no skin rash or injury marks or any signs of meningial irritation. Her ECG was normal and arterial blood gas showed normal parameters. Her Ryles tube (RT) aspirate was clear and there was no smell of OP compounds or alcohol. She was kept on continuous RT aspiration to keep stomach empty. Her urine examination for beta HCG and toxicology screening were negative.

On detailed CNS evaluation she had depressed brain stem reflexes, pupils were 8 mm and only sluggishly reacting to light, corneal reflex and doll’s eye were absent and pharyngeal gag reflex was absent. She had generalized hypotonia with depressed deep tendon reflexes and bilateral plantar showing extensor response. She had normal vesicular breathing in all chest areas. Cardiovascular and abdominal examination were normal. Her baseline investigations showed normal hemogram and biochemical parameters. An urgent NCCT head was also normal. She was managed with anti-epileptics, antivirals (Acyclovir), considering seizures with post ictal state or viral encephalitis as possibilities. She underwent MRI and MRA brain to look for any signs of encephalitis or posterior circulation stroke/CVT, but no abnormality was found. Her urgent EEG showed diffuse background slowing, but no epileptiform discharges.

Every investigation only added to the mystery of her encephalopathy. A lumbar puncture and CSF examination was also normal. Meanwhile, her GCS dropped further to 4/15 with laboured breathing and pupils became non reactive to light. She was intubated and put on SIMV mode of ventilation, about six hours after coming to hospital with no diagnosis. Considering the authors previous experience with a similar case, Elapid bite was strongly considered at this stage as a cause of rapidly evolving EMNS and absent brain stem reflexes mimicking brain death.

She was subjected to a neostigmine challenge test and for the first time since admission, she showed eyelid movements along with lifting of eyebrows. This indicated the strong possibility of neuro-paralytic snake bite (Elapids). A literature review confirmed case reports of krait bite from South Mumbai, where she was staying, although viper bites were by far more common. In view of absence of an alternate explanation and strong clinical suspicion, it was decided to offer her empirical polyvalent anti-snake venom (ASV).

A standard test dose of 01 ml of diluted ASV was given IV, however it triggered sudden tachycardia (130-140 beats/min) and fall in blood pressure (80/60 mm Hg systolic) along with a diffuse erythematous skin rash. She responded to IV hydrocortisone and pheniramine. Clearly she was reacting to the ASV, and we had to decide on continuing an empirical therapy which was triggering hemodynamic instability and anaphylaxis. However considering the lack of other therapeutic options and our strong clinical suspicion we took the NOK into confidence and started a very low dose ASV infusion at the rate of 0.5 ml/h (reconstituted ASV) under steroid and anti-histamine cover with adrenalin as stand by. ASV infusion had to be stopped thrice in the first four hours due to hemodynamic instability and adrenaline was used once due to sudden fall in BP. But she started tolerating the very low dose infusion after 06 hours. Infusion rate was gradually doubled every hour thereafter to a maximum of 10 ml/h.
She opened eyes about 20 hours after starting ASV. She showed steady motor recovery in the form of spontaneous limb movements by 24 hours when ASV was stopped (Total about 250 ml). She regained her sensorium and was extubated 36 hours after ASV. She started walking with support after 72 hours and thereafter showed steady improvement in clinical status. On further enquiring, she gave history of visit to the society park and a long walk in grass without footwear, the evening prior to her hospitalization. She was not sure about any bite. She was discharged home with twins in her arms, 6 days after being clinically brain dead, and responding to ASV therapy, which almost killed her due to anaphylaxis!!

**Discussion**

Snake-bites are well-known medical emergencies in many parts of the world, especially in rural areas. India is estimated to have the highest snake bite mortality in the world. Agricultural workers and children are the most affected. World Health Organisation (WHO) estimates place the number of bites to be 83,000 per annum with 11,000 deaths. In India, the common species of snakes seen are the Elapidae which includes common cobra, king cobra and krait, Viperidae which includes Russell’s viper, pit viper and saw-scaled viper and Hydrophidae (the sea snakes).

There have been various case reports on neurological manifestations mimicking brain death in krait bite - “Is the patient brain dead” by R Agarwal et al., “Snake bite mimicking brain death” by Joseph John et al., “Early morning neuroparalytic syndrome” by Mohd Haneef, “Suppression of brain stem reflexes in snake bite” by JP Goyal et al., and two cases of locked in syndrome in snake bite reported by S Prakash et al.

Neuroparalysis in a snake bite occurs as a result of blockade of neuromuscular transmission. Toxins from cobra venom act mainly postsynaptically whereas those of krait venom act mainly presynaptically. Neurotoxicity following krait bite is common, manifesting frequently as respiratory muscle paralysis. The krait venom competes with acetylcholine at the neuromuscular junction post-synaptic receptors leading to neuromuscular paralysis (Figure 1). The venom by its direct neurotoxic effect on the brain could produce alteration of level of consciousness ranging from drowsiness to deep coma. Neurotoxicity from the elapid bite may manifest as early morning neuroparalytic syndrome (EMNS) or even as locked-in syndrome. Patients presenting as EMNS do not have bite marks on their body and hence the diagnosis may be complicated. The time lag between the bite and onset of paralysis is usually 4–12 hours. The earliest manifestation is ptosis followed by external ophthalmoplegia. Paralysis then progresses to involve muscles of palate, jaw, tongue, larynx, neck, and muscles of deglutition - usually but not strictly in that order. The proximal muscles of the limbs are involved earlier than distal, and there can be complete quadriplegia and ‘locked-in’ state. Patients with acute respiratory failure are categorised as severe envenomation. Recovery starts in the reverse order and the median time of onset for recovery of respiratory failure is 2 days.

Patients, like the first case we have presented, with ‘locked-in’ state and absent pupillary reflexes are uncommon. Internal ophthalmoplegia seen in these patients can plausibly be attributed to the autonomic dysfunction. It is important that emergency physicians recognise the ‘locked-in’ syndrome, so as to prevent the dangerous error of diagnosing brain-death. The diagnosis of brain-death requires a clear and evident cause of CNS insult/ disease, along with documentation of coma, absence of brain-stem reflexes, and unresponsive apnea, in the absence of conditions that mimic brain death like severe electrolyte and acid-base disturbances, drug intoxication, neuromuscular blocking agents, etc. In fact, confirmatory tests like cerebral angiography, electroencephalography, etc, are recommended in situations like ‘locked-in’ syndrome, where a diagnosis of brain death is difficult to establish.

Anti-snake venom (ASV) is a specific antidote to snake venom actions, however, there are no clear guidelines on the optimal dose in management of patients with severe envenomation and doses as high as 1400 mL have been used empirically in the hope of early recovery. Some studies have addressed the issue of ASV dosage, but not specifically in patients with severe neuroparalytic envenomation. The use of ASV is generally safe and only rarely have fatalities been reported. The incidence of reactions to ASV has varied from 4–8%. The reactions can range from pyrogenic reactions (mild) to anaphylactic shock (severe) and can be prevented by premedication with subcutaneous adrenaline, intravenous hydrocortisone, and anti-histamines. It is important to remember that anaphylaxis does not mean stopping ASV, but giving it slowly and carefully with monitoring under steroid and adrenaline cover. We used a similar low dose empirical regimen in our second case, which she tolerated and then responded very well despite initial severe anaphylaxis.

In our two cases, initially the possibility of brain death secondary to prolonged hypoxia prior to
hospitalisation was considered, as patient had rapidly evolving neuroparalyis followed by coma, absence of brainstem reflexes and apnea. However a high index of suspicion, with a positive neostigmine challenge and residence in a snake infested region, helped make the diagnosis of snake bite.

Case 1 is the first case report where the patient was diagnosed as brain dead and almost went under the transplant surgeon’s knife before timely diagnosis and recovered steadily after starting ASV with complete reversal of neuroparalysis in six weeks. Case 2 highlights the need to continue empirical ASV therapy even when no history of snake bite is available. Early and energetic ASV therapy even in patients with anaphylaxis to ASV, is associated with excellent outcomes.

**References**


### “Three in One” - Polyautoimmunity with Multiple Autoimmune Syndrome

**Arun Agarwal¹, Amit Sanghi², Manisha Agarwal³, Mamta Agarwal⁴**

**Abstract**

Autoimmune disease (AD) may well start off as a single diagnosis and over the years develop into polyautoimmunity and even multiple autoimmune syndromes (MAS) seen in the same patient, as new clinical symptoms and laboratory finding show up in the course of disease. We present a case of MAS who was initially diagnosed to have autoimmune thyroid disease (AITD) – hypothyroidism. She was then evaluated for persistent mild to moderate iron deficiency anemia, unintentional weight loss along with skin rash and diagnosed to have celiac disease and undifferentiated connective tissue disease (uCTD).

**Introduction**

Autoimmunity is an immune response directed against an antigen within the body of the host whereas autoimmune disease is a pathologic condition caused by the adaptive autoimmune response. The first step in the diagnosis of these diseases is usually the demonstration of autoantibodies. However, the mere presence of autoantibody does not necessarily establish a cause-and-effect relationship, since the autoantibodies may be the result, not the cause, of the disease process. The antibodies may present many years before the clinical appearance and diagnosis of many connective tissue diseases. Combined with genetic information or family history, the presence of autoantibodies may be highly predictive of the later onset of an autoimmune disorder.¹,²

Polyautoimmunity which encompasses the concept of a common origin of these diseases, is defined as presence of more than one AD in a single patient. When three or more ADs coexist, it is called multiple autoimmune syndrome (MAS), which represents the best example of polyautoimmunity as well as the effect of a single genotype on diverse autoimmune phenotypes.

This is a clinical case of a mature adult female patient, now 26 years old with a family history of Type 2 diabetes mellitus (T2DM) and hypertension in both parents and autoimmune thyroid disease (AITD) in sibling and mother. In 2012 she was initially diagnosed with hypothyroidism and has by now diagnosed with Celiac disease and early uCTD.

¹Senior Consultant and Head, Department of Internal Medicine, ²Consultant, Department of Gastroenterology, ³Consultant, Department of Pathology, Narayana Multispeciality Hospital, Jaipur, Rajasthan; ⁴Senior Consultant In Radiodiagnosis, Malviya Nagar Clinic and Sonography Centre, Malviya Nagar, Jaipur, Rajasthan

Received: 12.01.2016; Accepted: 06.09.2017
Table 1: Thyroid function, Levothyroxine dosage, hemoglobin and body weight

<table>
<thead>
<tr>
<th>Date</th>
<th>FT3 (ng/dl)</th>
<th>FT4 (mIU/L)</th>
<th>TSH (mIU/L)</th>
<th>L-Thyroxine dosage</th>
<th>Hb (gm/dl)</th>
<th>HCT (%)</th>
<th>Body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>06.09.2012</td>
<td>0.65</td>
<td>7.04</td>
<td>100ug</td>
<td>4.00</td>
<td>0.80</td>
<td>11.70</td>
<td>150 ug</td>
</tr>
<tr>
<td>02.05.2013</td>
<td>0.78</td>
<td>12.98</td>
<td>125ug</td>
<td>8.6</td>
<td>11.12.2013</td>
<td>0.96</td>
<td>2.130</td>
</tr>
<tr>
<td>11.12.2013</td>
<td>0.91</td>
<td>0.90</td>
<td>125ug</td>
<td>9.7</td>
<td>8.6</td>
<td>27.7</td>
<td>40.4</td>
</tr>
<tr>
<td>06.09.2012</td>
<td>1.00</td>
<td>1.32</td>
<td>125ug</td>
<td>7.0</td>
<td>29.08.2016</td>
<td>0.65</td>
<td>7.04</td>
</tr>
<tr>
<td>02.05.2013</td>
<td>0.78</td>
<td>12.98</td>
<td>125ug</td>
<td>39.6</td>
<td>10.10.2016</td>
<td>1.00</td>
<td>0.92</td>
</tr>
<tr>
<td>27.04.2016</td>
<td>0.91</td>
<td>6.73</td>
<td>100ug</td>
<td>13.6</td>
<td>28.11.2016</td>
<td>1.26</td>
<td>0.472</td>
</tr>
<tr>
<td>06.09.2012</td>
<td>0.65</td>
<td>1.32</td>
<td>125ug</td>
<td>12.5</td>
<td>29.08.2016</td>
<td>1.01</td>
<td>12.5</td>
</tr>
<tr>
<td>02.05.2013</td>
<td>0.78</td>
<td>12.98</td>
<td>125ug</td>
<td>39.6</td>
<td>28.11.2016</td>
<td>1.26</td>
<td>0.472</td>
</tr>
<tr>
<td>06.09.2012</td>
<td>0.65</td>
<td>1.32</td>
<td>125ug</td>
<td>12.5</td>
<td>28.11.2016</td>
<td>1.26</td>
<td>0.472</td>
</tr>
</tbody>
</table>

Abbrreviations with normal range: FT3 (Free Triiodothyronine); FT4 (Free Triiodothyronine): 0.61-1.32; TSH (Thyroid stimulating hormone): 0.35-5.60; Hb (Hemoglobin): 12-15; HCT (Hematocrit): 41-46

Table 2: Other investigations

<table>
<thead>
<tr>
<th>Tests</th>
<th>Report</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticulocyte count</td>
<td>0.8%</td>
<td>0-5-1.5</td>
</tr>
<tr>
<td>Serum Ferritin</td>
<td>4.68 ng/ml</td>
<td>6.24-137</td>
</tr>
<tr>
<td>TPO antibodies</td>
<td>204.4 IU/ml</td>
<td>0-34</td>
</tr>
<tr>
<td>Serum Iron</td>
<td>31 ug/dl</td>
<td>37-145</td>
</tr>
<tr>
<td>Vit. B12</td>
<td>516 pg/ml</td>
<td>187-883</td>
</tr>
<tr>
<td>ESR</td>
<td>104 mm 1st hour</td>
<td>0-12</td>
</tr>
<tr>
<td>PBF</td>
<td>RBC show anisopoikilocytosis, microcytosis, hypochromic anemia. Tear cells, target cells, cigar type cells seen.</td>
<td></td>
</tr>
<tr>
<td>rTg IgA antibody</td>
<td>&gt;800 AU/ml</td>
<td>&lt;8</td>
</tr>
<tr>
<td>ANA-IFA</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Primary dilution</td>
<td>1:40</td>
<td></td>
</tr>
<tr>
<td>Primary Intensity on IF</td>
<td>3+</td>
<td></td>
</tr>
<tr>
<td>ANCA pattern</td>
<td>Speckled</td>
<td></td>
</tr>
<tr>
<td>End point titre</td>
<td>1:320</td>
<td></td>
</tr>
<tr>
<td>ANCA (c and p ANCA)</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>UGIE</td>
<td>Oesophagus and stomach show normal mucosa. D1 and D2 part shows paucity of folds and scalloping and D2 biopsy done.</td>
<td></td>
</tr>
<tr>
<td>Duodenal biopsy</td>
<td>Features suggestive of malabsorption syndrome-Celiac disease (Modified Marsh Grade 3b).</td>
<td></td>
</tr>
<tr>
<td>Stool test (routine)</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Antibodies to extractable nuclear antigens (ENA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti Ro(SS-A) antibodies</td>
<td>Positive (+++)</td>
<td></td>
</tr>
<tr>
<td>Anti centromere antibodies</td>
<td>Borderline (+)</td>
<td></td>
</tr>
<tr>
<td>C-Reactive proteins</td>
<td>0.44 mg/L</td>
<td>0-6</td>
</tr>
</tbody>
</table>

Abbreviations: TPO: Thyroid peroxidase; ESR: Erythrocyte sedimentation rate; PBF: Peripheral blood film; rTg: Tissue transglutaminase; ANA-IFA: Anti nuclear antibody-Immunoflourescence assay; ANCA: Anti neutrophil cytoplasmic antibody; Anti Ro(SS-A): Anti sjogrens syndrome related antigen A

Case Report

A 23 year female, was diagnosed with thyropric hypothyroidism and moderate anemia in June 2010 and has a history of not gaining weight. She weighed 34 kg then with a body mass index (BMI) of 14.2 kg/m². She was started on 50ug of Levothyroxine with regular monitoring of thyroid functions and has been taking iron-vitamin and calcium supplements intermittently for persistent anemia and body-aches. Despite titrating her levothyroxine dosage she always had low FT4 and raised TSH. Her thyroid functions, levothyroxine dosage, hemoglobin, hematocrit and actual body weight are tabulated in Table 1.

She has a family history of AITD-hypothyroidism (mother/sister), along with T2DM and Hypertension in both parents. She attended clinic on 22.08.2016 with complaints of weakness, loss of appetite, diffuse aches, un-intentional weight loss of around 8 kg in last 2-3 months, and developing erythematous and itchy skin on exposure to sun. She has mild pallor and normal skin clinically. She had no history of Raynaud phenomenon, inflammatory arthritis, dryness in oral cavity or chronic cough. Her vital parameters and systemic examination were essentially normal. She was evaluated and had moderate iron deficiency anemia with high TGT and TPO antibodies. She was admitted on 22.08.2016 for parenteral iron therapy and upper GI endoscopy (UGIE) with duodenal biopsy. Her other reports are mentioned in table 2. Figure 1 shows findings on histopathology of duodenal biopsy and UGIE. Her X-ray chest, ultrasound of whole abdomen, bone mineral densitometry and routine urine examination were normal. She was diagnosed with Celiac disease and AITD. In view of her skin rash and aches she was further investigated for other possible concurrent ADs and was confirmed to have early undifferentiated Connective tissue disease (eUCTD) with positive ANA, SS-A and Anti centromere antibodies. In follow up after 3 months, she has gained 10 kg in body weight, her levothyroxine dosage has been reduced to 100ug with normal thyroid functions, and hemoglobin has improved to 13.6g/dl. She refused for a repeat UGIE.

Discussion

Herein, we have reported a case of polyautoimmunity, a term that was used for the first time by Sheenan and Stanton-King. There is strong evidence that ADs share several clinical signs and symptoms, pathophysiological mechanisms, environmental and genetic factors, and this fact indicates that they have a common origin, which has been called the autoimmune tautology. Polyautoimmunity may influence on the severity of ADs. Familial autoimmunity and female gender are confirmed risk factors for polyautoimmunity.

Celiac disease (CD) is frequently accompanied by a variety of extra digestive manifestations, thus making it a systemic disease rather than a disease limited to the gastrointestinal tract. It is a permanent intolerance of dietary gluten leading to mucosal damage in the proximal small bowel in genetically susceptible individuals, characterized by inflammation, crypt hyperplasia and villous atrophy which regress on withdrawal of gluten from the diet. The clinical presentation of CD has now moved from overt malabsorption in childhood towards milder symptoms or atypical features in adult life. Clinicians must remember that CD may present...
with extra intestinal manifestations, and associated illnesses may appear both at the time of diagnosis and throughout the evolution of the disease. The case discussed has been diagnosed with Hypothyroidism 6 years back and despite titrating levothyroxine dosage had persistently low FT4 and high TSH. She also had persistent mild to moderate anemia and unintentional weight loss (despite hypothyroidism) and malabsorption/CD was never thought.

CD has been found at an increased rate in patients with autoimmune thyroid disease with a prevalence ranging from 2% to 7%. The decrease of the thyroid antibodies after 2 or 3 years or the normalization of thyroid function after 1 year of gluten free diet (GFD) has been reported and these results may depend on longer duration of GFD in treated patients with CD. Such associations of AD’s may lead to adverse effects on the growth, metabolism, and fertility. The coexistence of CD and AITD has been explained by several mechanisms such as common genetic predisposition and the association of both diseases with the gene encoding cytotoxic T-lymphocyte-associated antigen-4, a gene conferring susceptibility to thyroid autoimmunity. In addition, it has also been demonstrated that tTG antibodies react with thyroid tissue, and this binding could contribute to the development of thyroid disease in CD.5

Presence of diffuse aches and rash on exposure to sun made us to evaluate her for other associated ADs including CTD. Unclassifiable symptoms, no physical examination findings, and serological results suggestive of a CTD lead to diagnoses of an early UCTD. UCTD are those in which signs and symptoms are consistent with a CTD but that do not fulfill the classification or diagnostic criteria for any one of the defined CTDs. In order to fulfill the criteria for UCTD, ANA must be present, along with disease duration of at least 3 years. Cases with a shorter duration should be described as early UCTD. The case discussed had positive ANA and antibodies to Ro/SS-A and centromere. Women with anti-Ro/SS-A antibodies are at increased risk for having a child with neonatal lupus syndrome. Anti-Ro/SS-A antibodies may also be the first detectable auto antibodies that precede the development of SLE in asymptomatic individuals.

There are three phases of UCTD. The initial phase of UCTD may occur many years prior to diagnosis, during which time the patient may be asymptomatic and may lack serum auto antibodies. In the second phase, auto antibodies may appear in the serum despite an absence or paucity of symptoms. The interval between autoantibody appearance and significant symptom onset is highly variable among individual patients and the specific auto antibodies. Finally in the third phase signs and symptoms of the autoimmune disease appear, leading to a definitive diagnosis. A clinical diagnosis of early UCTD may be made in the second phase, and some of these cases may evolve into a definite CTD or may remain undifferentiated. Our patient also evolved into second phase of UCTD over these years. Some antibodies have greater diagnostic value. Among them antinuclear and anti-Ro/SS-A antibodies have greater diagnostic value. Among them antinuclear and antinuclear antibodies and is advised to take hydroxychloroquine tablets and to avoid sun exposure. Finally she will evolves into which AD or remain undifferentiated, cannot be commented at this moment.

The implementation of a gluten-free diet (GFD) improves the overall clinical course and influences the evolution of the associated diseases. In this case, she has gained weight, her thyroid status has normalized and iron deficiency anemia has disappeared.

Conclusions

Diverse ADs in the same patient including organ specific and systemic ADs, are true associations as a part of the autoimmune tautology rather than the chance findings.

One should search for well-defined phenotypes by looking for clusters of ADs in the same individual and try to explain their existence by sharing of the same etiopathogenesis rather than a secondary disease. Polyautoimmunity is the term proposed for this association of disorders.

Treatment of CD with a gluten-free diet reduces the recognized complications of this disease (such as malabsorption, and infertility), provide benefits in general health and perhaps life expectancy, improves glycemic control in patients with type 1 diabetes mellitus, enhances the absorption of medications for associated hypothyroidism, iron deficiency anemia and osteoporosis.

A premature diagnosis of one of the discrete rheumatic diseases should be avoided, since the undifferentiated nature of the syndrome usually persists. Among those destined to develop a defined connective tissue disease, which is more common than resolution of the syndrome, evolution generally occurs within two to five years.

References

SLE in a Male Patient Presented Initially as Rowell’s Syndrome

Ayan Basu¹, Yogiraj Ray², Pratik Bhowmik³, Mehebubar Rahman⁴, Rama Prosad Goswami⁵

Abstract

A 22 year old male Indian patient presented with high grade fever, multiple joint pain, low back pain, generalized body ache since 6 months and erythematous pruritic rashes and atypical annular target like lesions over face, arm, leg and back and ulcers on hard palate and buccal mucosa for 2 months. Laboratory investigations showed a speckled pattern anti-nuclear antibody with a titer >1:160 and positive SS-A, dsDNA auto-antibodies and Rheumatoid factor. Diagnosis of Rowell’s syndrome was made based on clinical and laboratory finding and the patient was treated with oral prednisolone (50 mg/day), hydroxychloroquine (200 mg q12h) and pulse cyclophosphamide (700 mg) chemotherapy. Majority of skin lesions and oral ulcerations subsided after 4 weeks of therapy. Till date only 11 male patients out of the total 71 cases of Rowell’s syndrome were reported in the world’s literature.

Introduction

SLE (Systemic lupus erythematosus) is a systemic autoimmune disorder which may present with several skin manifestations like malar rash, discoid rash, photosensitivity, subcutaneous lupus erythematosus, oral ulceration etc. But SLE patient presenting with erythema multiforme like skin lesions is very unusual. Rowell first described this association in 1963. Rowell’s syndrome is a rare presentation of lupus erythematosus (LE) with erythema multiforme like lesions associated with positive antinuclear antibody (ANA), anti-La (SS-B)/anti-Ro (SS-A) antibodies and rheumatoid factor.¹ Till date only 11 male patients out of the total 71 cases of Rowell’s syndrome were reported in the world’s literature.² Here we describe a male patient whose clinical picture is consistent with so-called Rowell’s syndrome.

Case Report

A 22 year old non-smoker, non-alcoholic unmarried male Indian patient without any history of high risk sexual behavior was admitted to our hospital with high grade fever, multiple joint pain, low back pain, and generalized body ache since 6 months and erythematous pruritic rashes throughout the trunk, extremities and face since 2 months (Figures 1 and 2). Sometimes fever was associated with chill and rigor without burning sensation during micturition. Patient also had oral ulceration during the course (Figure 3). There was no similar type of past illness or history of prolonged medication. There was no history suggestive of chilblain too.

On clinical examination patient was normotensive, had mild pallor, multiple soft, non-tender, non-matted discrete cervical, axillary and inguinal lymph nodes. Skin examination revealed well-defined, erythematous papules and plaques, mostly annular, some with scales that coalesced into large, confluent lesions which were present on the nose, malar areas, ears, back, arms, legs, palms and soles. Patient had few atypical annular target like or erythema multiforme-like lesions over face, arm, leg and back. Patient also had ulcers with surrounding erythema on hard palate and buccal mucosa. Musculo-skeletal system examination revealed swollen and tender small joints of hands, wrists and knees and tenderness over arms and thighs with proximal muscles weakness. Laboratory investigations showed mild anemia (Hb-10.4 gm %). Liver function test was normal except elevated enzymes: ALT - 246 IU/L, AST - 469 IU/L and Alkaline Phosphatase - 514 IU/L. Anti-nuclear antibody test was found to be positive - titer was >1:160 with a speckled pattern. Subsequent investigations revealed positive dsDNA (+++, signal intensity-30) and SS-A (+++, signal intensity-87) auto-antibodies. Rheumatoid factor was also positive. C3 level was decreased (52 mg/dl) and C4 level was normal. A comprehensive metabolic

Fig. 1: Numerous erythematous, annular plaques that coalesced on the face, hemorrhagic crusting on the lips

Fig. 2: Erythematous targetoid lesions on back

Fig. 3: Erosion on the oral mucosa
panel (urea, creatinine, fasting plasma glucose and lipid profile), erythrocyte sedimentation rate, C-reactive protein, CPK, coagulation profile, thyroid profile and urinalysis were normal. Ultrasonography revealed mild hepatomegaly. Chest radiograph was normal. Right axillary lymph node FNAC report was suggestive of reactive hyperplasia. Skin and renal biopsy could not be done as the patient did not give consent. Based on clinical and laboratory investigations, diagnosis of Rowell Syndrome was made. Majority of skin lesions and oral ulcerations subsided after 4 weeks of oral prednisolone (50 mg/day), hydroxychloroquine (200 mg q12h) and one pulse injection of cyclophosphamide (700 mg) chemotherapy (Figures 4 and 5). Other symptoms also subsided except pain lower limbs. Routine biochemical tests also normalized. Patient was then maintained on low dose alternate day prednisolone and hydroxychloroquine and monthly pulse cyclophosphamide chemotherapy for 6 months.

The patient is now in our regular follow up with oral azathioprine 50 mg daily and prednisolone 7.5 mg on alternate day. His quality of life has improved and he has joined his normal duties.

Discussion

The first described association between LE and erythema multiforme was made by Scholtz in 1922. In 1963, Rowell et al. reported a new syndrome characterized by LE, erythema multiforme-like lesions, a positive test for rheumatoid factor, speckled ANA and a saline extract of human tissue for rheumatoid factor, speckled ANA for rheumatoid factor, speckled ANA pattern of ANA. Minor criteria were chilblains, positive rheumatoid factor and anti-Ro or anti-La antibody. All three major criteria and at least one minor criterion are required for the diagnosis of Rowell’s syndrome. A review of 18 case reports of Rowell’s syndrome between 1963 and 2000 showed that the speckled ANA pattern was the most consistent feature of Rowell’s syndrome and was described in about 88 percent of the cases, whereas rheumatoid factor was the least preserved feature and is present in only 41 percent. Anti-Ro/La antibodies were detected in 53 percent of the cases. Although chilblains had been described in all four of Rowell’s original cases, this feature was found in only five of the 15 cases reported between 1982 and 2008. A more clinically relevant question and resulting controversy concern whether Rowell’s syndrome truly merits distinction as a unique clinical entity. The speckled ANA pattern, which correlates with antibodies to various ribonucleoproteins, is not unique to Rowell’s syndrome; it is also positive in SLE, mixed connective-tissue disease, and scleroderma. Similarly, anti-Ro/La antibodies can be detected in SCLE (70%), Sjögren syndrome (80%), SLE (20–60%), rheumatoid arthritis, and scleroderma; they are strongly associated with photosensitivity and vasculitis in SLE. These two antibodies contribute to the formation of the ANA speckled pattern. Therefore, the concomitant appearance of this pattern with positive anti-Ro or anti-La antibody can be expected. Also, rheumatoid factor positivity can occur in DLE (17%), SLE (40%), scleroderma (40%), SCLE, and Sjögren syndrome. In view of the lack of specific features Kuhn et al. suggested that Rowell syndrome is probably not a distinct entity and is now widely considered to be a variant of SCLE. The therapeutic regimen, responses, and prognosis in Rowell’s syndrome are similar to those of SLE or DLE that occur alone. Most of the reported cases showed good responses to mid-to-high doses of prednisone with azathioprine or antimalarials, such as chloroquine or hydroxychloroquine. However, male patients with these characteristic clinical and immunological features very rarely reported in the world literature and here we have described a male patient whose clinical picture was consistent with so-called Rowell’s syndrome.

Conclusion

SLE is rare in male and initial presentation with erythema multiforme is even more rare. So high degree of suspicion is clue to the diagnosis of SLE in this situation. We like to report the case to make the physicians aware about the possibility of SLE in a case of erythema multiforme with systemic features like fever and joint pain.

References

Percutaneous Transcatheter Treatment of Lutembacher Syndrome

Rohit Mathur¹, Sanjeev Sanghvi², Anil Baroopal³

Abstract

Lutembacher syndrome is a rare cardiac abnormality characterized by a combination of congenital atrial septal defect (ASD) and acquired rheumatic mitral stenosis (MS). Here we report a case of 18-year-old male with Lutembacher syndrome successfully treated percutaneously with transcatheter Accura balloon valvuoplasty and Amplatzer septal occluder device closure.

Introduction

Lutembacher syndrome was first described by Rene Lutembacher in 1916.¹ Percutaneous transcatheter treatment can be done in selected cases, although surgery is the preferred treatment for these patients. In a patient of Lutembacher syndrome with severe pulmonary hypertension, Ruiz et al² did first combined transcatheter treatment by ASD closure with Lock’s clamshell occluder and balloon mitral and aortic valvotomies.

Case Report

A 18-year-old male presented to us with six month history of dyspnea on exertion and palpitations. Patient gave history suggestive of rheumatic heart disease, diagnosed at peripheral hospital three years back and was on penicillin prophylaxis. His blood pressure was 94/60 mm Hg with a regular heart rate of 76 beats per minute. On auscultation loud first heart sound, fixed splitting of second heart sound, grade 3/6 ejection systolic murmur at pulmonary area and middiastolic murmur at apex was heard. Routine laboratory investigations were within normal limits. His electrocardiogram showed sinus rhythm, tall P waves, right ventricular hypertrophy and incomplete right bundle branch block. X-ray chest showed cardiomegaly with pulmonary plethora (Figure 1). Transthoracic echocardiogram was performed which revealed dilated right atrium and right ventricle. There was rheumatic mitral stenosis with mitral valve area of 1.1 cm² by planimetry, a large ostium secundum ASD with left to right shunt and adequate rims. Left ventricular function and all other valves were normal. Transesophageal echocardiogram (TEE) was done to rule out left atrial appendage clot and evaluation of ASD. In TEE it was found to be a 30 mm ASD with superior vena cava rim of size 12 mm and inferior vena cava rim of size 7 mm (Figure 2) and no left atrial or left atrial appendage clot. There was no mitral regurgitation (MR).

Diagnosis of Lutembacher syndrome was made and the patient was stabilized with diuretics. Percutaneous transcatheter treatment was planned. Right ventricular catheterization study showed normal right ventricular and pulmonary arterial pressures indicating adequate diuresis. Percutaneous trans-luminal mitral commissurotomy (PTMC) was done using 28 mm Accura balloon catheter introduced through ASD (Figure 3). Pre and post PTMC hemodynamic and oximetry parameters are shown in Table 1. The ASD closure was done with 38 mm size Amplatzer ASD closure device (Figure 4). The whole percutaneous transcatheter procedure of Accura balloon mitral commissurotomy and Amplatzer ASD device closure was done in a single stage under general anaesthesia. Post procedure transesophageal and transthoracic echocardiogram showed ASD device in situ with no residual shunt. Mitral valve was opening well with mitral valve area of 1.8 cm² by planimetry, without mitral regurgitation (Figures 5, 6). The patient was then discharged after two days in stable condition.

Discussion

Lutembacher syndrome is more common in females due to female preponderance of both ASD and MS. The incidence of MS in patients with ASD is 4% and the incidence of ASD in patients with MS is 0.6-0.7%.³ Altered clinical and hemodynamic features are observed in Lutembacher syndrome because combined ASD and MS affect each other. MS augments the left to right shunt.

Fig. 1: X-ray chest shows cardiomegaly with pulmonary plethora

Fig. 2: Pre procedure transesophageal echocardiogram showing (1) Superior vena cava rim of size 12 mm; (2) Inferior vena cava rim of size 7 mm and; (3) 30 mm ASD
atrial septal defect and presence of adequate rims (< 5 mm) around the left atrial thrombus, (2) absence of contraindications are: (1) presence of pulmonary hypertension). The Eisenmenger syndrome (irreversible hypertension, except in patients with PTMC, (3) any degree of pulmonary stenosis, (4) mitral valve morphology favorable for transcatheter treatment of Lutembacher area.

Table 1: Pre and post PTMC hemodynamic and oximetry parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre PTMC</th>
<th>Post PTMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LA pressure</td>
<td>20 mm Hg</td>
<td>6 mm Hg</td>
</tr>
<tr>
<td>Aorta pressure</td>
<td>110/70 mm Hg</td>
<td>118/70 mm Hg</td>
</tr>
<tr>
<td>LV pressure</td>
<td>100/6 mm Hg</td>
<td>110/6 mm Hg</td>
</tr>
<tr>
<td>Mitral valve area</td>
<td>1.1 cm²</td>
<td>1.8 cm²</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Heart rate</td>
<td>76/min</td>
<td>74/min</td>
</tr>
<tr>
<td>Sa O₂</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Mv O₂</td>
<td>72%</td>
<td>72%</td>
</tr>
<tr>
<td>Pv O₂</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Pa O₂</td>
<td>91%</td>
<td>86%</td>
</tr>
<tr>
<td>Mid RA O₂</td>
<td>92%</td>
<td>87%</td>
</tr>
<tr>
<td>Qp/Qs</td>
<td>3.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Sa O₂, Mv O₂, Pv O₂, Pa O₂, and RA O₂ are systemic arterial, mixed venous, pulmonary venous, pulmonary arterial and right atrial blood oxygen saturations, respectively. Qp and Qs are pulmonary and systemic blood flow respectively.

Even when the ASD and mitral valve fulfill the required criteria for interventional management, at times it may be difficult due to some problems that may be encountered during procedure such as– (1) floating of PTMC catheter due to large ASD, hence the inability of delivery wire to go through stenosis to the left ventricle; (2) tendency to mitral restenosis: because of this, some authors advise to allow a lapse of a 24–48 hours after PTMC prior to ASD closure to give room for mitral valve assessment; (3) embolization or slippage of septal occluder probably due to large size ASD; (4) persistent ASD after mitral valvuloplasty either due to presence of tail of balloon atrial septum during inflation (increasing atrial septostomy) or inadequate deflation of balloon prior to withdrawing it. Despite these problems, percutaneous treatment of Lutembacher syndrome overcomes the complications associated with open surgery, with rapid recovery and shorter hospital stay. The case reported by us was treated successfully by Accura balloon mitral commissurotomy and Amplatzer ASD device closure in a single stage. Therefore percutaneous transcatheter treatment of Lutembacher syndrome is reasonable and effective in selected group of patients, avoiding complications associated with open heart surgery.

References

Adult Onset Still’s Disease Masquerading as Sepsis in an Asplenic Patient

Ramadoss Ramu¹, Vivek Arya², Rajesh Satyapal Taneja², Mohammad Ali³

Abstract
Adult onset Still’s disease (AOSD) is a rare inflammatory disorder of unknown etiology. It is a diagnosis of exclusion. We report a case of post-splenectomised man, presented with high grade fever, joint pain and body ache. Since Overwhelming Post Splenectomy Infection (OPSI) was the initial probable diagnosis, empirical antibiotic therapy was initiated. Evaluation to find a septic focus, autoimmune diseases ad malignancies was carried out which showed negative results. Since alternative diagnoses were excluded and the Yamaguchi’s criteria for AOSD was fulfilled, the patient was treated with IV steroids which resulted in rapid resolution of his symptoms. AOSD with asplenia is a unique condition because immunosuppressive therapy for AOSD may increase the risk of OPSI in such a patient. This is the first case report of AOSD in an asplenic patient from India.

Introduction
Adult onset Still’s disease (AOSD) is an auto-inflammatory disorder of unknown etiology with a prevalence of less than 1/100,000 people. It can manifest in multiple forms like pyrexia of unknown origin, serositis, aseptic meningitis, myocarditis, hemophagocytic syndrome and septic arthritis.¹ We report a case of an asplenic patient who presented with fever and polyarthralgia in whom AOSD was diagnosed. Immunosuppressive therapy was needed for the treatment of AOSD but the patient was on high risk of developing opportunistic infections because of his asplenic status. But the patient was treated successfully with intravenous steroids. This is the first case report of AOSD in an asplenic patient from India.

Case Report
A 39 year old man presented to our hospital with complaints of joint pain, body ache and intermittent high grade fever for one month and sore throat for four days. The joint pain involved both large and small joints. Despite analgesics there was no relief in pain. He also had swelling of the right knee and small joints of the hands. The patient had no other co-morbid illnesses. He had undergone splenectomy ten years ago following blunt injury to abdomen. Details of vaccination following AOSD were not available.

On examination, the patient was conscious and oriented. He had a temperature of 101°F and blood pressure of 130/72 mmHg, with a regular pulse of 102/minute and respiratory rate of 15/minute. There was no rash or lymphadenopathy. Throat was found to be congested. Examination of abdomen revealed a left paramedian scar and no organomegaly. Locomotor examination showed tenderness over multiple joints (spine, shoulders, wrists, metacarpophalangeal joints, hip, knee and ankles). Swelling was noted in the small joints of hands and right knee. Rest of the systemic examination was normal.

Investigation reports at the time of admission were as follows: Hb-10.9 g/dl, TLC-24000/cu.mm, DCL-P90/L8/E2, Platelet count- 4 lakhs/cu.mm, Urea-116 mg/dl, Creatinine- 2.1 mg/dl, Na-142 mmol/l, K- 5.2 mmol/l, Total bilirubin-2.8 mg/l, ALT-212 U/l, AST- 198 U/l, ALP- 294 U/l, serum albumin-2.5 g/dl, serum globulin- 4g/dl. Creatinine kinase and lactate dehydrogenase were within normal limits.

Considering the patient’s asplenic status, Overwhelming Post Splenectomy Infection (OPSI) was the provisional diagnosis and empirical antibiotic therapy was initiated. Evaluation to find a septic focus or autoimmune diseases was done. Blood and urine cultures were sterile. Serological tests for dengue, chikungunya, EBV, hepatitis A-E, malaria, brucella, HIV and syphilis infections were negative. Tuberculin sensitivity test failed to show any significant induration. Bone marrow aspiration showed normoblastic erythropoiesis and myeloid hyperplasia. Rheumatoid factor and anti-nuclear antibodies were negative. Serum ferritin levels were 3230 ng/dl (normal: 40-200 ng/dl). Serum triglyceride and fibrinogen levels were normal. C-reactive protein (CRP) was raised (32 mg/dl). Erythrocyte sedimentation rate (ESR) was 95 mm at 1 hr. Abdominal ultrasonogram revealed no positive findings except asplenia. Radiographs of the chest, pelvis, hands and feet revealed no abnormality. No vegetations were seen on an echocardiogram.

There was no improvement in the symptoms after a week of treatment. Subsequent investigations showed persistently elevated total leukocyte count with neutrophilic predominance. Since the initial differential diagnoses were excluded, we looked for an alternate diagnosis. As the Yamaguchi’s criteria for Adult Onset Still’s Disease were fulfilled, it was decided to treat the patient with steroids. Due to the risk of OPSI, he was vaccinated against pneumococci, meningococci and hemophilus influenzab prior to treatment.

The patient was given three daily pulses of 500mg of intravenous methylprednisolone which resulted in rapid resolution of his symptoms. After a week of steroid therapy, he was discharged on 1 mg/kg of oral prednisolone and 15 mg/week of methotrexate. Investigations at the time

¹Senior Resident of Medicine, ²Professor of Medicine, ³Medical Officer of Medicine, PGIMER & Dr. RML Hospital, New Delhi
Received: 05.09.2016; Revised: 04.01.2017; Accepted: 10.10.2017
AOSD is a rare inflammatory disorder caused by an aberrant innate inflammatory pathway. It has bimodal age distribution peaks at 15-25 and 36-46 years of age. Increased release of active interleukin-1 beta is considered a major event in pathogenesis. At least seven sets of diagnostic criteria have been devised. However, the Yamaguchi criteria (Table 1) have the highest specificity and sensitivity for diagnosing AOSD.

Table 1: Yamaguchi's criteria for diagnosing adult onset Still's disease

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever of at least 39°C for Sore throat at least one week</td>
<td>Leukocytosis (10,000/ microl or greater), with granulocyte predominance</td>
</tr>
</tbody>
</table>
| Arthralgias or arthritis for at least two weeks | Normal serum ferritin level is 40-200 ng/ml. Hyperferritinemia occurs in many diseases but rarely do their levels go up as high as in AOSD. In most studies, levels of 1000 ng/ml has been used to suggest the presence of AOSD. Ferritin is also used as a marker to monitor response to treatment in AOSD. Precise mechanism behind hyperferritinemia is not known. Inflammation is associated with increased production of ferritin from histiocyte-macroage system and/or increased release from damaged hepatocytes. Also, cytokines involved in inflammatory processes may induce hyperferritinemia through increased production of nitric oxide (NO). NO induces ferritin expression.

In healthy individuals, 50-80% of ferritin is glycosylated. Several studies have shown that the level of glycosylated ferritin is low in AOSD patients (<20%). The reason behind decreased glycosylated ferritin could be the saturation of glycosylation process due to hyperferritinemia or decreased clearance of non-glycosylated proteins by histioyte-macrophage system. But as this test is not readily available, we could not get this test done in our patient.

Jaqua et al reported a similar case of AOSD in a 26 year old soldier who presented with fever and arthralgia. He had undergone splenectomy for ITP. Initially he was treated with empirical antibiotics but later developed a typical Still's rash which led to the diagnosis of AOSD. He was treated with methylprednisolone and anakinra following which he showed marked improvement.

NSAIDs, corticosteroids, and DMARDs are the cornerstones of therapy for AOSD. NSAIDs were previously considered as the first-line medication. They have now been replaced by corticosteroids. Relatively high doses of steroids (equivalent to 0.5 to 1 mg/kg/d of prednisone) are required to induce clinical remission. In patients with inadequate response to corticosteroids, methotrexate is the best choice to control disease activity. There are a few studies available which showed limited success with anti-TNF drugs, interleukin blockade and intravenous immunoglobulin in AOSD.

Our patient showed remission with steroids. In an asplenic patient, long term corticosteroids are relatively contraindicated, given the potential predisposition to infection. So, he was discharged on tapering doses of oral prednisolone. Methotrexate was started after confirming normal liver and kidney functions. In future, this patient’s fever could be indicative of OPSI or flare-up of AOSD. So he was advised to obtain medical care immediately.

Conclusion

The presentation of fever with asplenia made us focus on OPSI by an encapsulated organism. But when the patient did not improve with initial management, it made us look for alternative diagnoses thus leading to the rare diagnosis of AOSD. Keeping an open mind while evaluating the patient can prevent an unusual disease from being misdiagnosed.

References

1st time in India

Volibom
(Voglibose 0.2/0.3 mg + Metformin 500 mg)

Boost
PPHG Control

Preserve
β-cell function

Control
65% β-cell

T2DM
48% β-cell

Avior Therapeutics
A Pharmaceutical Biotechnology Company
Medical Symbols: Part-3

Jayant Pai-Dhungat

Rx of Prescriptions

Rx is an abbreviation for the Latin word “Recipere” which means “Take thou”. This Latin abbreviation is completed by some statement like “Fiat mistura” which means let a mixture be made. However, Rx symbol is believed to have evolved from Egyptian mythological Eye of Horus, an ancient Egyptian symbol associated with healing power. Horus was son of Isis (mother) and Osiris. His evil uncle Seth murdered Osiris, father of Horus. Horus then battled with Seth to avenge his father’s death. During the fight, Seth plucked out Horus’s left eye and tore it apart. Thoth (God of wisdom & magic) found the eye, pieced it together and added some magic. He returned the eye to Horus, who in turn gave it to his murdered father Osiris, thereby bringing him back to life. Thus the Eye of Horus became a powerful symbol in ancient Egypt. It was worn as an amulet to ensure good health and ward off sickness.

Horus’s eye is the origin of the pharmacist’s symbol for medications. They would mix up and compound ingredients to make drugs or remedies. Until 19th Century, the generally accepted distinction was between Apothecary/pharmacist as compounder of medicines and physician as a therapist. In 1920s, 80% of prescriptions were compounds mixed in doctor’s dispensaries. In 1940s this declined to 20%, and then to 1% or less in 1970.

Ankh-Crux ansata

Ankh is ancient Egyptian hieroglyph signifying “life,” a cross surmounted by a loop and known in Latin as a crux ansata (handle-shaped, cross). As a vivifying talisman, ankhs are often held or offered by gods and pharaohs. The Egyptian Gods are often portrayed carrying it by the loop. The ankhs may be in hands or proximity of almost every deity in the Egyptian pantheon. It appears frequently on Egyptian paintings and other arts. Egyptians carried it as an amulet either alone or in two other hieroglyphs that mean “strength” and “health”. They were also worn for protection and for fertility. Mirrors of beaten metal were perceived as decorations. Ankh also appears on copper coins from ancient Cyprus. As a cross, it has been extensively used as a symbol of the Coptic Orthodox Church.

The ankh seems at least to be an evolved form of, or associated with the Egyptian glyph. It would seem that the ancient Egyptians called that part of the sandal glyph. However, what the sign itself represents is often disputed. For example, Sir Alan Gardiner (1957) thought that it showed a sandal strap with the loop at the top forming the strap. Initially this theory found little favor, but this interpretation has received some acceptance in the recent times. It seems likely that the loop at the top of tau cross represents the female sexual organ and tau crosses the male. For this reason the ankh is considered a symbol of life, fertility and regeneration. Ankh along with “hand mirror” symbolized the gift of eternal life, which Gods promised to their worshippers. There are many scenes of the ankh being applied to the nostrils of the dead, to bring them back to life.
Results of Outcome of Two Pregnanacies with Imatinib

Samrat Shah1, Bhise Rohan2, B Srinivas3, Lunge Snehal4
1Graduate in Medicine, 2Medical Oncologist, 3Physician, 4Dermatologist, JN Medical College, Belgaum, Karnataka

Tyrosine kinase inhibitors provide lengthy remissions and the possible normal life expectancy in patients with Chronic Myelogenous Leukemia.1 Hence imatinib is now recommended as the first-line therapy.1 However, treatment of maternal CML with imatinib during pregnancy is not recommended because of the potential teratogenicity in animal studies.4 There are very few case reports about effect of imatinib on conception and pregnancy5 suggesting that imatinib has minimal effect on pregnancy outcome. We report results of two pregnancies in a single patient on imatinib which was continued throughout pregnancy.

A 26 year old female came to hospital with history of per vaginal leak since morning. She was booked case of 33 week 3 days of gestation on regular anti natal checkup. Patient was known case of Philadelphia chromosome positive chronic phase CML diagnosed since 2009 on tablet imatinib 400 mg/day. Patient tolerated drug well and had complete hematological and cytogenetic remission. Her Quantitativ assay for BCR-ABL in 2011 was 0.001 indicating molecular remission. Her Quantitative assay for BCR-ABL in 2011 was 0.001 (major cytogenetic response). Patient continued to take the drug during the entire course of pregnancy.

She was G2P1L0. First pregnancy was pre term vaginal delivery of male baby weighted 1kg died of prematurity. Patient had continued imatinib through out the pregnancy.

Present pregnancy was diagnosed with urine pregnancy test. She had taken folic acid supplementation. Regular check sonography was done. Anomaly scan did not reveal any malformations. Pregnancy was uneventful.

There was no history of urinary tract infection. There was no history of smoking or tobacco chewing. No invasive procedures were performed during pregnancy. She was not a known hypertensive or diabetic.

Her LMP was 9-1-2015. EDD was 16-10-2015.

On examination vitals were stable. Uterus was uniformly distended, 32 week in size, cephalic position. There was evidence per vaginal leak on speculum examination.

On investigation: CBC-normal, renal profile-normal. LFT-normal. Urine routine showed no signs of infection.

LSCS was done in view of PROM. Post section mother and baby were stable. Baby weighted 1.47 kg and was active and healthy.

Pregnancy and cancer is a complex situation. Often treatment cannot be delayed. Many cases with CML have been reported to have a successful pregnancy. However, there is a paucity of data regarding CML patients on imatinib mesylate becoming pregnant and completing pregnancy successfully. Imatinib is known to have antiangiogenic effect in animal models mediated by platelet-derived growth factor receptor (PDGFR); however, as human umbilical vein endothelial cells do not express PDGFR, effect is unknown. Animal studies have observed encephalocoele, menencephaly, and reduced and absent parietal bones as teratogenic effects at dose above 100 mg/kg.6 Female rats also experienced early fetal resorption. Due to paucity of data on these rare congenital malformations, Imatinib has not been recommended particularly during the period of organogenesis.2

However imatinib did affect course of both pregnancies in our patient. Both the pregnancies resulted in premature deliveries. There is need to follow up this child for long term effects.

Continuation of imatinib in pregnancy is a controversial issue. As there are case reports alone and no other literature available regarding continuing imatinib in pregnancy, it is difficult decision for the doctor and the patient to continue or stop imatinib during pregnancy. Further research is warranted but it’s a difficult field as the animal studies warrant stoppage of imatinib during pregnancy.

References

Remitting Seronegative Symmetrical Synovitis with Pitting Edema Associated with Gastric Carcinoma

Rathindranath Sarkar1, Rudrajit Paul2, Debaditya Roy3, Indranil Thakur3, Goutam Lahiri3, Tanmay Jyoti Sau3, Ratul Ghosh2
1Professor and HOD, 2Assistant Professor, 3Resident, RMG, 4Professor, Dept. of Medicine, Medical College, Kolkata, West Bengal

Sir,

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a rare polyarthritis syndrome affecting mainly older adults (male>female).1 We here report a case of RS3PE associated with malignancy.

A 58 year old male patient was admitted with acute onset melena for three days and chronic fatigue for two months. On examination, the patient was found to be severely pale. There was no organomegaly or lymphadenopathy. An emergency blood test revealed hemoglobin level of 3 g/dl. Hence, immediate blood transfusion was given.

After stabilization, further examination revealed pitting edema of...
dorsum of both hands with tenderness of all small joints of hands (Figure 1). The patient stated that this painful hand had started one month ago. The pain was fluctuating in severity but the swelling of the dorsum was constant and increasing. There was no pain or swelling in any other joint of the body including the feet. The patient also had difficulty in making a grip. The symptoms had started in both hands simultaneously.

Further tests revealed a microcytic hypochromic anemia with low serum ferritin. An upper GI endoscopy was done which revealed a fungating, bleeding mass in the gastric body. Ultrasonography with power Doppler study of both hands was done which revealed thickened synovium with increased blood flow, suggestive of synovial inflammation, mainly in metacarpophalangeal joints. Serum ESR was 70 mm in 1st hour. But serum rheumatoid factor was negative. Thus, in view of the clinical history and imaging features, the hand pathology was diagnosed as remitting symmetrical seronegative synovitis with pitting edema (RS3PE).

Unfortunately, before any more tests could be done, the patient had a massive bout of melena and he passed away two days later. Post-mortem, the gastric biopsy report was collected from the pathology department, which revealed poorly differentiated gastric adenocarcinoma.

RS3PE is an acute onset polyarthritis syndrome which can occur idio pathically or as paraneoplastic complication in a malignancy. Recently, a diagnostic criteria has been proposed for the syndrome, which includes sudden onset polyarthritis, bilateral hand pitting edema, age >50 years and negative rheumatoid factor. However, in many cases, the diagnosis remains purely clinical.

RS3PE has been described in association with malignancy only in a few previous reports. The commonly reported malignancies include lung cancer, leukemia and endometrial carcinoma. This has also been reported in gastric carcinoma only a handful of times.

RS3PE of idiopathic variety responds very well to low dose steroids. The role of steroids in paraneoplastic RS3PE is variable. The rheumatological symptoms may remit with successful treatment of the underlying carcinoma.

We present this case to sensitize clinicians to this rare paraneoplastic rheumatological phenomenon. Any old patient presenting with RS3PE should be evaluated for underlying malignancy.

References

Z PROTECTION at 50% reduced price

Start ‘EARLY’ in Hypertension

ZILARTA 40
ZILARTA 80

24 POTENT & EFFECTIVE BP CONTROL
Z+ Protection in Hypertension / Diabetes / CKD

CILACAR
Candesartan 10mg / 10mg / 25mg Tablets

From Hypertension Control to Superior End Organ Protection

4th Generation Dual L/N Type CCB

- Significantly reduces SBP, DBP, PR with minimal BP Variability
- Decreases Urinary Albumin / Creatinine Ratio, Reduces Proteinuria

Dual therapy

In Stage II Hypertension / Diabetic Hypertension start with

- CILACAR-T
  Candesartan 10mg Tablets

- CILACAR-T 80
  Candesartan 80mg Tablets

In Uncontrolled Hypertension with IHD

- CILACAR-M 10/25
  Candesartan 10mg / Metoprolol Succinate 25mg Tablets

- CILACAR-M 10/50
  Candesartan 10mg / Metoprolol Tartrate 50mg Tablets

In Uncontrolled Hypertension with LVH/CHD/Stroke

- CILACAR-C 8.24
  Candesartan 8.24mg Tablets

- CILACAR-C
  Candesartan 16.48mg Tablets

Triple therapy

In Uncontrolled & Complicated Hypertension

- CILACAR-TC 8.25
  Candesartan 8.25mg + Telmisartan 40mg Tablets

- CILACAR-TC 12.5
  Candesartan 12.5mg + Telmisartan 80mg Tablets

Enhances Quality of Life

Make a SMART MOVE to witness the Difference