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

ARISTO Pharmaceuticals Pvt. Ltd.
23-A, Shah Indi. Estate, Off Veersa Desai Road,
Andheri (W), Mumbai - 400 053.
In Dyslipidemia

Revostat®
Rosuvastatin Tablets IP 5/10/20mg

The Revolutionary statin

₹ 7 / Tab

₹ 4 / Tab

₹ 13 / Tab

Launching Soon
Revostat GOLD 10/20
Rosuvastatin Calcium, Aspirin & Clopidgrel Bisulphate Capsules

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

EDITORIAL

Factors Affecting Outcome and the Role of Plasmapheresis in Guillain-Barré Syndrome
Satish Khadilkar, Bhagyodhan Patel.................................................. 11

ORIGINAL ARTICLE

Impact of Electrophysiological and Clinical Variants, and Timing of Plasmapheresis on Outcome of Guillain-Barré Syndrome
Bipin Amin, Himanshu Mehnath, MD Gajjar, Tarak Patel,
Jignesh Vanani, Nidhi Gupta, Anil Chauhan................................. 14

Evaluation of Cerebral Venous Thrombosis by CT, MRI and MR Venography
Pratibha Issar, Sirasapalli Chinna, Sanjeev Kumar Issar........ 16

A Comparative Study of In-Hospital Outcome of Patients with ST-Segment Elevation Myocardial Infarction with and Without Diabetes Mellitus, after Thrombolytic Therapy: In Government Hospital of Rajkot, Gujarat, India
Varshit Hathi, Meghal Anandkat....................................................... 22

Osteoporosis in Postmenopausal Females with Primary Knee Osteoarthritis in a Vitamin D Deficient Population
Pooja Dhaon, Siddharth Kumar Das, Ragini Srivastava,
Akash Asthana, Girdhar Agarwal...................................................... 26

Knowledge, Attitudes, Beliefs and Practices of Physicians Regarding Idiopathic Pulmonary Fibrosis and the Impact of a Continuing Medical Education Program
Sahajal Dhooria, Inderpal Singh Sehgal, Ritesh Agarwal,
Ashutosh Nath Agarwal, Digambar Behera................................. 30

High Prevalence of Obstructive Sleep Apnea among People with Type 2 Diabetes Mellitus in a Tertiary Care Center
Vijay Viswanathan, Indira Priyadarshini Ramalingam,
Nagarajan Ramakrishnan................................................................. 38

Study of Association of Thyroid Hormone in Pre-Eclampsia and Normal Pregnancy
L Harshwardhan, SS Dariya, Aradhana Sharma, Lalita Verma 44

Etiology and Outcomes of Lower Limb Ulcers in Non-Diabetic Patients: An Experience from Government Hospital in Western India
Yojana Gokhale, Amal Raut, Divya Kunal Lala,
Rushabh Kothar, Lalana Kalekar, Amol Kamble..................... 47

High Prevalence of Hypovitaminosis D in Patients Presenting with Proximal Muscle Weakness:
A Sub-Himalayan Study
Jatinder Mokta, Balraj, Kiran Mokta, Asha Ranjan, Ivan Joshi,
Mahak Garg......................................................................................... 55

A Cross-sectional Study of Cardiovascular Involvement in Systemic Lupus Erythematosus in an Urban Indian Tertiary Care Centre with Emphasis on 2-D Echocardiography
Seema Kini, Chetan Yekhade, Vikram Londhey.......................... 59

REVIEW ARTICLE

Communication Adaptations for a Diverse International Patient Population
Aditya Ghosh, Shashank Joshi, Amit K Ghosh............................. 65

Novel Regimens in the Treatment of Paracetamol
(Acetaminophen) Poisoning
R Dilip Kumar, Umalakshmi Premnath................................. 71

Heart Failure and the Iron Deficiency
Amey Beedkar, Rohan Parikh, Pradeep Deshmukh.............. 79

STATISTICS FOR RESEARCHERS

Common Statistical Errors and how to Avoid them
NJ Gogtay, UM Thatte................................................................. 81

PICTORIAL CME

Giant Intrapericardial Neurocysticercosis
Krishnan Mugundhan, N Balamurugan, P Chandrasekar,
S Sivakumar, MC Vasif Mayan, PD Nidhin................................. 85

Crochetage Sign
Pratibha Himrol, Susheal Kudial, Kailash Nath Sharma,
Jitender Kumar................................................................. 86

CASE OF THE MONTH

Life-threatening Medical Complications Due to Ovarian Hyperstimulation Syndrome: A Hidden Etiology
Prerana N Bhavsar, Namita J Padwal, Madhura Bhide,
Santosh P Ghagare, Anagha R Joshi, Niteen D Karnik......... 87

CASE REPORT

Invasive Aspergillus Pseudomembranous and Obstructive Tracheo-bronchitis in an Immuno-competent Patient
Ramesh S Pal, Sonam Spalgais, Amit Kumar Murar,
Umesh Chandra Ojha................................................................. 92

Mandibular AV Malformation: A Rare Cause of Massive Bleeding from Mouth Managed with Multiple Vessel Embolization
Rajeev Bhardwaj, Rajesh Sharma................................................ 94

Unusual Presentation of Injection Site Adverse Effect
Ranjana Sahasrabudhe, Tejas Limaye, Vidyak Ghokale........ 96

Thyrotoxic Channelopathies
Pankaj Singhai, Shruti Krishnan, Vikram Uttam Patil............ 98

MEDICAL PHILATELY

Medical Symbols: Part I
Jayant Pai-Dhungat................................................................. 101

CORRESPONDENCE

Painless Krait Bite in a Sleeping Victim: Delayed Diagnosis and High Mortality
Vivek Chauhan, Suman Thakur.................................................. 102

Thrombocytopenia as Harbinger of Graves’ Disease: A Rare Presentation
Rudrajit Paul, Rathindranath Sarkar, Debadiya Roy,
Indranil Thakur, Gautam Lahiri, Tanmay Jyoti Sau,
Ratul Ghosh.................................................................................. 102

ANNOUNCEMENTS

The CME & Annual Conference 2017-18.................................... 21

TAPICON 2017................................................................. 29
Manage HbA1c, Blood Pressure & Cholesterol of CV AD

For your T2DM patients, Think metformin, Use metsmall the smart decision

For Dyslipidemia in T2DM Patients

In Hypertensive Patients

Stamlo®
Amblofen 2.5 mg / 5 mg / 10 mg tabs.

leader at heart

In Diabetic Hypertensives uncontrolled on Monotherapy

Stamlo-T®
Amlodipine 5 mg + Telmisartan 40 mg tabs.

Powerful & Consistent BP Control

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
## Association of Physicians of India

**GOVERNING BODY (2017-2018)**

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
<th>City</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>President Elect</td>
<td>Pritam Gupta</td>
<td>Delhi</td>
<td>2018</td>
</tr>
<tr>
<td>President</td>
<td>BR Bansode</td>
<td>Mumbai</td>
<td>2018</td>
</tr>
<tr>
<td>Past President</td>
<td>Gurpreet Singh Wander</td>
<td>Ludhiana</td>
<td>2018</td>
</tr>
<tr>
<td>Vice Presidents</td>
<td>Girish Mathur</td>
<td>Kota</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>BB Rewari</td>
<td>New Delhi</td>
<td>2019</td>
</tr>
<tr>
<td>Hon. General Secretary</td>
<td>Mangesh Tiwaskar</td>
<td>Mumbai</td>
<td>2019</td>
</tr>
<tr>
<td>Jt. Secretary (HQ)</td>
<td>Ashit M Bhagwati</td>
<td>Mumbai</td>
<td>2019</td>
</tr>
<tr>
<td>Hon. Treasurer</td>
<td>Charu K Jani</td>
<td>Mumbai</td>
<td>2020</td>
</tr>
<tr>
<td>Members</td>
<td>Vijay Viswanathan</td>
<td>Chennai</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>MPS Chawla</td>
<td>New Delhi</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>Sekhar Chakraborty</td>
<td>Siliguri</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>DP Singh</td>
<td>Bhagalpur</td>
<td>2018</td>
</tr>
<tr>
<td>Zonal Members</td>
<td>RM Chhabra</td>
<td>New Delhi</td>
<td>2020</td>
</tr>
<tr>
<td></td>
<td>Rajinder K Bansal</td>
<td>Ludhiana</td>
<td>2020</td>
</tr>
<tr>
<td></td>
<td>Prabhat Pandey</td>
<td>Durg</td>
<td>2020</td>
</tr>
<tr>
<td></td>
<td>Narayan Deogaonkar</td>
<td>Nasik</td>
<td>2020</td>
</tr>
<tr>
<td>Invited Member</td>
<td>Sandhya Kamath</td>
<td>Mumbai</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chairman</td>
<td>ICP House Committee</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Siddharth N Shah</td>
<td>(Mumbai)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Editor-in-Chief, JAPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Milind Y Nadkar</td>
<td>(Mumbai)</td>
<td></td>
</tr>
<tr>
<td>Ex-Officio Member</td>
<td>Dean, ICP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rohini Handa</td>
<td>(Delhi)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Director, PRF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>YP Munjal</td>
<td>(Gurgaon)</td>
<td></td>
</tr>
<tr>
<td>Co-opted Members</td>
<td>Jt. Secretary (President’s place)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nihar Mehta</td>
<td>(Mumbai)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Armed Forces, Medical Services</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maj. Gen. (Dr.) A.K. Hooda, (New Delhi)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Organising Secretary, APICON 2018</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P Chandrasekhar</td>
<td>Bengaluru</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Organising Secretary, APICON 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shashank R Joshi</td>
<td>(Mumbai)</td>
<td></td>
</tr>
</tbody>
</table>

## Indian College of Physicians

**FACULTY COUNCIL (2017-2018)**

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
<th>City</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chairman</td>
<td>BR Bansode</td>
<td>Mumbai</td>
<td>2018</td>
</tr>
<tr>
<td>Dean</td>
<td>Rohini Handa</td>
<td>New Delhi</td>
<td>2018</td>
</tr>
<tr>
<td>Hon. Gen. Secretary</td>
<td>Mangesh Tiwaskar</td>
<td>Mumbai</td>
<td>2019</td>
</tr>
<tr>
<td>Past Dean</td>
<td>A Muruganathan</td>
<td>Tirupur</td>
<td>2018</td>
</tr>
<tr>
<td>Vice Deans</td>
<td>RK Goyal</td>
<td>Ajmer</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>Kamlesh Tewary</td>
<td>Muzaffarpur</td>
<td>2019</td>
</tr>
<tr>
<td></td>
<td>NP Singh</td>
<td>New Delhi</td>
<td>2020</td>
</tr>
<tr>
<td>Jt. Secretary (H.Q.)</td>
<td>Ashit M Bhagwati</td>
<td>Mumbai</td>
<td>2019</td>
</tr>
<tr>
<td>Jt. Secretary (Dean’s place)</td>
<td>AP Misra</td>
<td>New Delhi</td>
<td></td>
</tr>
<tr>
<td>Hon. Treasurer</td>
<td>Charu K Jani</td>
<td>Mumbai</td>
<td>2020</td>
</tr>
<tr>
<td>Elected Members</td>
<td>Rakesh Gupta</td>
<td>New Delhi</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>Jayanta Kumar Panda</td>
<td>Cuttack</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>Y Satyanarayana Raju</td>
<td>Hyderabad</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>Shiriram V Kulkarni</td>
<td>Khopoli</td>
<td>2018</td>
</tr>
<tr>
<td>Invited Members</td>
<td>President Elect</td>
<td>(New Delhi)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Editor-in-Chief, JAPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pritam Gupta</td>
<td>(Mumbai)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Director - PRF</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>YP Munjal</td>
<td>(Gurgaon)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sandhya Kamath</td>
<td>(Mumbai)</td>
<td></td>
</tr>
</tbody>
</table>

## Physicians Research Foundation

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

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
<th>City</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chairman</td>
<td>BR Bansode</td>
<td>Mumbai</td>
<td>2018</td>
</tr>
<tr>
<td>Jt. Secretary (Director’s Place)</td>
<td>Ghan Shyam Patey</td>
<td>New Delhi</td>
<td>2018</td>
</tr>
<tr>
<td>Hon. Treasurer</td>
<td>Charu K Jani</td>
<td>Mumbai</td>
<td>2020</td>
</tr>
<tr>
<td>Hon. General Secretary</td>
<td>Mangesh Tiwaskar</td>
<td>Mumbai</td>
<td>2019</td>
</tr>
<tr>
<td>Members</td>
<td>Soumitra Ghosh</td>
<td>Kolkata</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>AK Mukherjee</td>
<td>Kolkata</td>
<td>2018</td>
</tr>
<tr>
<td>Invited Members</td>
<td>Editor-in-Chief, JAPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Milind Y Nadkar</td>
<td>(Mumbai)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rohini Handa</td>
<td>(New Delhi)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sandhya Kamath</td>
<td>(Mumbai)</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, Pelletable Syrup

(Feric Ammonium Citrate)

The Masterpiece in Hematinics

- Pregnancy & Lactation
- General Weakness
- Menopausal
- Chemotherapy Induced Anemia
- High Blood & Iron deficiency
- Loss of Appetite
- Chronic Haemorheal Blood Loss
- Chronic Kidney Disease
Factors Affecting Outcome and the Role of Plasmapheresis in Guillain-Barré Syndrome

Satish Khadilkar¹, Bhagyadhan Patel²

Guillain Barre syndrome (GBS) is a heterogeneous group of inflammatory polyradiculoneuropathies clinically exhibiting a monophasic course of acute flaccid quadriparesis and/or cranial neuropathies. Based on clinical and electrophysiological features, various forms of GBS have been designated. GBS can progress up to a period of 4 weeks and 25-30% of patients require artificial ventilation. Natural recovery occurs slowly over a period of months and incomplete recovery can leave behind residual deficits. Hence, treatment of GBS with immunomodulation such as plasma exchange (PE) or intravenous immunoglobulin (IVIg) becomes crucial in reducing mortality and morbidity, particularly in patients with rapidly progressive weakness.¹

PE and IVIg have been extensively studied in GBS. Class I evidence exists for the effectiveness of PE in treatment of GBS when the condition is severe enough to impair independent walking or require mechanical ventilation. Even in patients with mild weakness who are able to walk independently, rapid improvement has been noticed after initial 2 cycles of PE. Studies have shown further benefit of 4 and 6 cycles of PE over the initial 2 sessions but there is no added advantage of 6 PE sessions over 4. Five PE sessions (each exchange sessions of 2-3 litres of plasma volume or 1-1.5 times of colloid volume according to weight) over 2 weeks is generally considered to be a beneficial protocol. Currently, there are no studies to demonstrate the superiority of IVIg over PE or vice versa. Benefits of PE have been documented when it is used within 4 weeks from the onset of weakness. Some studies support that the benefit of PE is larger when used within 7 days after onset of weakness when compared to patients in whom PE was initiated between 8 and 28 days after onset. Thus, studies support the hypothesis of ‘time is nerve’ similar to ‘time is brain’ in acute ischaemic stroke. Efficacy of PE in patients with GBS who continue to progress after 4 weeks is unclear. Such patients with electrophysiological evidence of demyelination and progression more than 4 weeks are often termed as acute-onset chronic inflammatory demyelinating polyneuropathy (A-CIDP) or subacute idiopathic demyelinating polyneuropathy (SIDP). In absence of evidence supporting the efficacy of PE, use of PE should be individualised in such cases. Longer the duration of progression of illness beyond 4 weeks, more is the likelihood of CIDP. Such patients benefit from corticosteroids or alternative immunomodulation.¹³

Electrophysiological tests help to confirm the diagnosis of GBS, detect its subtype (i.e. axonal or demyelinating) and hence, hint at the prognosis. Few important points need to be considered while interpreting nerve conduction study (NCS) findings in patients with GBS.

- NCS can be normal in early cases and it takes up to 2 weeks or longer, before characteristic changes become fully established. Hence, it is important for clinicians to understand that absence of abnormalities on NCS in early cases, particularly within 1 week does not rule out diagnosis of GBS. NCS can be repeated after few days to confirm the sub-type of GBS.

- Abnormality of the sural response is one of the earliest changes encountered in peripheral neuropathies. Sparing of sural responses with profound affection of upper limb sensory potentials is characteristic of non-length dependent neuropathy like GBS.

- Presence of low compound muscle action potentials (CMAP) < 20% amplitude of normal, suggests poor recovery pattern.

- Demyelinating variety of GBS is the most frequently reported sub-type from all around the world. But in clinical practice, axonal GBS is also encountered frequently in India and other Asian countries.

IVIg and PE have been found to be equally effective in all subtypes of GBS such as acute axonal motor neuropathy (AMAN), acute axonal sensory motor neuropathy...
and evaluate the impact of clinical

in this issue of JAPI aims to analyse

studied. The study by Jignesh et al

recovery pattern has not been

the 7 days window period on the

impact of earlier use of PE within

days of onset of illness. However,

well when PE is initiated within 7

crucial as patients tend to fare

- Respiratory insufficiency
- CMAP amplitude less than 20%
- Medical research council sum
- Age more than 50 years
- Preceding cytomegalovirus
- Initial rapid progression of
- CMAP amplitude less than 20% of normal
- Respiratory insufficiency

The timing of PE is always

variants, electrophysiological

subtypes and timing of PE on

outcome in patients with GBS. As

this study was conducted in Asian

subcontinent, it is not surprising

that axonal GBS (AMAN + AMSAN)

constituted a major bulk (60%)

of GBS. Amongst all subtypes,

patients with AMSAN had worse
disability score (Hughes functional
grading scale) at presentation

while patients suffering from MFS

and AIDP had lowest disability

ratings. Total recovery time was

significantly reduced and number

of patients achieving functional

independence at 6 months was

significantly higher in patients

who underwent PE within 7 days

delay in onset. Patients who were

treated within 4 days had lower total

recovery time than patients who

received PE after 4 days of disease

onset. But this improvement didn’t

reach statistical significance in this

study. The mean disability score as

calculated by Hughes functional

grating scale was more than 3 in

all subtypes. Hence, it is important

for clinicians to recognise that

all patients with deficits severe

enough to hamper independent

ambulation should be treated as

early as possible. This may have a
direct impact in reducing the days

of morbidity and provide better

functional outcome. One area of

concern is the typing of GBS in

this study. As highlighted earlier,

it may not be possible to accurately

characterise patients with GBS into

axonal and demyelinating forms

on electrophysiology, particularly

in initial days of illness and a

significant proportion of patients

may not exhibit any abnormalities

in the first few days of the clinical

symptoms. Physicians need to

appreciate that GBS largely remains

a clinical diagnosis in initial stages

and other diseases presenting with

acute flaccid quadripareisis should

be ruled out. From authors’ point

of view, following features can help
to rule out GBS mimics (Table 1).

Various variables can affect the

outcome in patients with GBS.

Such variables can be studied

systematically by stratifying patients

into different subgroups based

on timing of PE after disease

onset. While the present study

by Jignesh et al makes a good

beginning, a large, multicentric

effort will be necessary in

further assessing various

clinical, electrophysiological and

therapeutic factors that can affect

the prognosis in patients suffering

from GBS.

References

Impact of Electrophysiological and Clinical Variants, and Timing of Plasmapheresis on Outcome of Guillain-Barré Syndrome

Bipin Amin1, Himanshu Meghnathi2, MD Gajjar3, Tarak Patel4, Jignesh Vanani5, Nidhi Gupta6, Anil Chauhan5

Abstract

Introduction: Guillain-Barré syndrome (GBS) is an autoimmune polyneuropathy causing acute flaccid paralysis and it is known to improve with plasmapheresis.

Objective: To study effects of electrophysiological type of GBS, clinical variant of GBS and time taken for initiation of plasmapheresis on outcome of disease.

Methods: 50 consecutive patients of GBS attending tertiary care hospital underwent clinical examination and electrophysiological studies. Disability grade was calculated and patients were observed for full functional recovery for 6 months.

Results: In this study, patients in whom plasmapheresis was started within 7 days (n=39) were observed to have significantly better improvement in terms of smaller peak disability and rapid functional recovery compared to those in whom plasmapheresis was started after 7 days (n=11). (p<0.002). Demyelinating pattern on electrophysiology was observed to have better outcome in terms of all parameters compared to axonal. AIDP variant was observed to have best outcome and AMSAN variant was associated with worst outcome.

Conclusions: Rapid institution of plasmapheresis is the most important outcome determining factor. Irrespective of the variant specific comorbidity, early plasmapheresis improves outcome in all parameters.

Introduction

Guillain-Barré syndrome (GBS) is an autoimmune inflammatory polyradiculoneuropathy. After eradication of polio, it is increasingly becoming commoner cause of acute flaccid paralysis.1 It causes sudden onset weakness of limbs which reaches a plateau over a period of days. Even though most patients recover, some requires mechanical ventilation and substantial mortality and disability are observed among them. Timely institution of IVIG or plasmapheresis significantly affects the outcome in terms of morbidity and mortality.2

Many studies have observed epidemiology, clinical profile and outcome, but studies determining prognostic factors and their impact on outcome parameters are very few. In this study we determine correlation of disease related factors on outcome of GBS.

Aims and Objectives

To study correlation of following Guillain-Barré syndrome related factors on recovery and prognosis of patients:
1. Electrophysiological type of GBS
2. Clinical Variant of GBS
3. Time of initiation of plasmapheresis

Material and Methods

Fifty patients with Guillain-Barré syndrome, who attended Civil hospital, Ahmedabad between Sept, 2014 to Aug, 2015 were studied. They fulfilled the clinical criteria for the disease.3

Patients disability was evaluated with the Hughes functional grading scale.4 Peak disability score, time
**Results and Discussion**

Among electrophysiological criteria of Ho et al. according to the electrodiagnostic as either demyelinating or axonal disease. Patients were classified within 15 days of the onset of the done using conventional procedures even at the end of 6 months.

**Table 1:** Comparison of electrophysiologic type of GBS

<table>
<thead>
<tr>
<th>EMG NCV finding</th>
<th>Total patients (n=50)</th>
<th>Peak disability score (mean)</th>
<th>Disability score improvement by 1 grade (mean)</th>
<th>Full functional recovery (n=47)</th>
<th>Full functional recovery time (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demyelinating</td>
<td>19</td>
<td>3.4</td>
<td>10.3 days</td>
<td>19</td>
<td>62 days</td>
</tr>
<tr>
<td>Axonal</td>
<td>25</td>
<td>3.8</td>
<td>11.3 days</td>
<td>24</td>
<td>78 days</td>
</tr>
<tr>
<td>Combined</td>
<td>6</td>
<td>4.2</td>
<td>14 days</td>
<td>4</td>
<td>90 days</td>
</tr>
</tbody>
</table>

**Table 2:** Comparison of clinical variants of GBS

<table>
<thead>
<tr>
<th>Variant</th>
<th>Total patients (n=50)</th>
<th>Peak disability Score (mean)</th>
<th>Disability score improvement by 1 grade (mean)</th>
<th>Full functional recovery at 6 months (n=47)</th>
<th>Full functional recovery time (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDP</td>
<td>19</td>
<td>3.4</td>
<td>10.3 days</td>
<td>19</td>
<td>62 days</td>
</tr>
<tr>
<td>AMAN</td>
<td>18</td>
<td>3.7</td>
<td>11.5 days</td>
<td>17</td>
<td>75 days</td>
</tr>
<tr>
<td>AMSAN</td>
<td>12</td>
<td>4.3</td>
<td>12 days</td>
<td>10</td>
<td>86 days</td>
</tr>
<tr>
<td>MFS</td>
<td>1</td>
<td>3</td>
<td>16 days</td>
<td>1</td>
<td>98 days</td>
</tr>
</tbody>
</table>

**Table 3:** Comparison according to initiation time of plasmapheresis

<table>
<thead>
<tr>
<th>Initiation of plasmapheresis after onset of disease</th>
<th>No. of patients (n=50)</th>
<th>Type of variant</th>
<th>No. of patients</th>
<th>Disability Score improvement by 1 grade (mean)</th>
<th>Full functional recovery at 6 months (n=47)</th>
<th>Total recovery time (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 days</td>
<td>19</td>
<td>AIDP</td>
<td>7</td>
<td>9.9 days</td>
<td>19</td>
<td>63 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMAN</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMSAN</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-7 days</td>
<td>20</td>
<td>AIDP</td>
<td>9</td>
<td>11.3 days</td>
<td>19</td>
<td>75 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMAN</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMSAN</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>11</td>
<td>AIDP</td>
<td>3</td>
<td>13.4 days</td>
<td>9</td>
<td>88 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMAN</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMSAN</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Taken for improvement in disability score by 1 grade after institution of treatment and total functional recovery time were calculated. In present study, three patients did not achieve full functional recovery even at the end of 6 months.

Nerve conduction studies were done using conventional procedures within 15 days of the onset of the disease. Patients were classified as either demyelinating or axonal according to the electrodiagnostic criteria of Ho et al. Patients were categorized into Acute inflammatory demyelinating neuropathy (AIDP), Acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN) or Miller-Fisher syndrome according to clinical and electrophysiological profile of patients. All patients were treated with five cycles of plasma exchange using Baxter-CS 3000 continuous cell separator using double lumen femoral catheter.

Our study shows that different electro physiological profile and clinical variant have different recovery patterns. AIDP variants are associated with rapid and complete clinical recovery while AMAN and AMSAN have slightly longer clinical course. Irrespective of type of variant, rapid institution of plasmapheresis had significant impact on outcome irrespective of type of variant patient was having.

**Conclusion**

Early diagnosis and aggressive approach of management by plasmapheresis can significantly improve outcome and reduce morbidity and long term disability for patients.

**References**

Evaluation of Cerebral Venous Thrombosis by CT, MRI and MR Venography

Pratibha Issar¹, Sirasapalli Chinna², Sanjeev Kumar Issar³

Abstract

Objective: To study and compare cerebral parenchymal changes and sinuses involvement in CT with MRI and MRV in Cerebral Venous Thrombosis patients.

Method: This study was carried out in the Department of Radiodiagnosis, JLN Hospital and Research Center, Bhilai, Chhattisgarh from October 2012 to Nov 2014 and includes fifty patients of all age groups presenting with clinical symptoms of CVT, admitted in Neurology, Neurosurgery, Medicine, Pediatric, obstetric and Gynecology wards. CT, MRI and MRV findings were noted and statistical analysis was done using SPSS (Statistical package for Social science) 17.0 software. Categorical variables are expressed as frequencies and percentages. Sensitivity, Specificity, PPV and NPV of CT were calculated with respect to MRI in the diagnosis of cerebral venous thrombosis and associated brain parenchymal changes.

Result: Out of fifty cases of cerebral venous thrombosis, thirty-one were females and nineteen were males. Age range was newborn to seventy-one years with female predominance in young age. Majority of the patients presented with headache (78%) followed by seizures (32%). Out of the total 50 cases, superior sagittal sinus were involved in 24 cases, left transverse sinus in 22 cases, right transverse in 12 cases, left sigmoid in 20 cases, right sigmoid in 13 cases, left internal jugular vein in 12 cases, right internal jugular vein in 7 cases, straight sinus in 5 cases, superficial cortical veins in 6 cases, vein of Galen in 3 cases and internal cerebral veins in 2 cases. Cerebral parenchymal changes were associated with thrombosis in 26 patients, hemorrhagic infarct in 13 cases, only hemorrhage in 4 cases and only infarct in 5 cases. CT scan was able to diagnose sinus abnormality in 36% and parenchymal abnormality in 42% of cases as compare to 100% and 52% in MRI.

Conclusion: In the emergency setting CT scan plays an important role in evaluating patients clinically suspected CVT, whereas MRI combined with MR Venography is the best imaging technique for diagnosis of CVT in patients with equivocal findings on CT.

Introduction

Cerebral venous thrombosis is a relatively uncommon but serious neurologic disorder that is potentially reversible with prompt diagnosis and appropriate medical care. Because the possible causal factors and clinical manifestations of this disorder are many and varied, imaging plays a primary role in the diagnosis.¹ Whenever, clinically suspected, prompt investigation by noninvasive imaging Magnetic resonance (MR) or advanced modalities such as MRV (MR Venography) will helpful in prompt diagnosis and treatment.²

Cerebral venous thrombosis (CVT) is responsible for 1-2% of all strokes in adults and affects all age groups.² Estimated annual incidence is 3-4 cases per million people and a mortality rate of 8 %.³ Accurate and prompt diagnosis of cerebral venous thrombosis is crucial, because timely and appropriate therapy can reverse the disease process and significantly reduce the risk of acute complications and long-term sequel. A high index of suspicion for CVT and specific venous imaging are required to make a diagnosis. This is especially true for neonates, who have nonspecific presentations that consist solely of seizures in the majority.⁶,⁷

In our study we evaluated the...
findings of CVT on plain head CT scan, conventional MRI sequences, DWI, GRE, SWI sequences and MRV to arrive at the diagnosis of cerebral venous thrombosis, to know the extent of sinus involvement and to study the brain parenchymal changes associated with it.

**Method**

The present study was conducted in patients of all age groups presenting with clinical symptoms of CVT, admitted in Neurology, Neurosurgery, Pediatric, obstetric and Gynecology wards of J.L.N Hospital and Research Centre, Bilai during the time span from October 2012 to Nov 2014.

Inclusion criteria were patients willing to take part in the study and given written informed consent. Patients sent for diagnosis of CVT to Radiodiagnosis in our hospital who are clinically suspected as CVT and are not associated tumor or inflammation causing brain parenchymal or venous sinus changes. Exclusion Criteria were patients not willing to take part in the study, having previously diagnosed as CVT or past history of CVT and those who are claustrophobic. Patients with contraindication for MRI (Metal in eye, aneurismal clip, pace maker etc.) are excluded from study.

Fifty patients were included in the study. Statistical analysis was done using SPSS (Statistical package for Social science) 17.0 software. Categorical variables are expressed as frequencies and percentages. Sensitivity, Specificity, PPV and NPV of CT were calculated with respect to MRI in the diagnosis of cerebral venous thrombosis and associated brain parenchymal changes.

Ethical clearance to conduct the research was sought and obtained from Ethical Review Committee (ERC) and followed the national ethical guideline.

The study was conducted in patients presenting with clinical symptoms of CVT of all age groups with evaluation on CT, MRI and MRV for diagnosis of CVT and brain parenchymal changes associated with it.

Consent was taken from the patients before the procedure, CT, MRI and MRV. Care was taken not to get in to any sort of conflict of interest in the community. The patient and the concerned doctor were informed about the evaluation of the procedure as soon as the procedure was done.

All the patients first underwent plain head CT scan which was done on a GE FXI HI SPEED helical CT machine (single slice). This was followed by conventional MRI sequences and 2D TOF MRV with 1.5 Tesla GE SIGNA EXCITE MR System. MR sequences were axia IT1, T2 Weighted, T2 Flair, Sag T1 Flair, Coronal T2, DWI, GRE, SWI and 2D TOF VENO.

**Result**

This study includes fifty cases of cerebral venous thrombosis, from neonates up to seventy years. Age and sex wise distribution of
Individuals are given in Table 1. Highest numbers of patients are seen in the age group 21-30 which is 15 (30%) with female predominance in younger age. Various etiology associated with CVT are given in Table 2. The main clinical presentation was headache followed by seizure as given in Table 3. Various sinus and parenchymal abnormality are given in Table 4 with maximum number of patients presenting with edema on CT scan (Figures 2 a, b, c, d). On GRE images, 13 (26%) showed parenchymal hemorrhage and 32 (64%) sinus abnormality. Out of the 25 patients in whom SWI sequences are done, 14 cases had shown parenchymal hypointensity due to hemorrhage (Figures 3 a, b, c, and d) cases presented with hypointensity on SWI sequences which did not show any parenchymal abnormality on GRE sequences. Comparative study of sinus and parenchymal abnormality on CT and MRI is given in Table 6.

### Table 4: Sinus and Parenchymal abnormality on CT scan

<table>
<thead>
<tr>
<th>Sinus abnormality on CT scan</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Absent</td>
<td>32 (64)</td>
</tr>
</tbody>
</table>

### Table 5: Cortical vein and sinus abnormalities on MRI/MRV

<table>
<thead>
<tr>
<th>Sinus involved</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior sagittal sinus</td>
<td>24 (48)</td>
</tr>
<tr>
<td>Right transverse sinus</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Left transverse sinus</td>
<td>22 (44)</td>
</tr>
<tr>
<td>Right sigmoid sinus</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Left sigmoid sinus</td>
<td>20 (40)</td>
</tr>
<tr>
<td>Straight sinus</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Right internal jugular vein</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Left internal jugular vein</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Vein of gallen</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Internal cerebral vein</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Superficial cortical veins</td>
<td>6 (12)</td>
</tr>
</tbody>
</table>

Percentages count more than 100 because of multiple sinus involvement.

Discussion

Thrombosis of the dural sinus and/or cerebral veins (CVT) is an uncommon form of stroke; usually affect young individuals.\(^8\) Thrombosis of the cerebral veins and sinuses is a distinct cerebrovascular disorder that, unlike arterial stroke, most often affects young adults and children. The symptoms and clinical course are highly variable. During the past decade, increased awareness of the diagnosis, improved neuroimaging techniques, and more effective treatment have improved the prognosis. More than 80 percent of all patients now have a good neurologic outcome.\(^9\)

Fifty patients with clinical suspicion of cerebral venous thrombosis were included in this study. The patients were first examined with plain head CT scan and then were evaluated by MRI and MRV. Sinus and brain parenchymal changes associated with it are evaluated by both CT and MRI and MRV.
In our study all age groups from newborn till 70 years age group patients were there in the study. Majority of the patients were female patients (62%). The number of patients in the age group 21-40 is 46%, which implies a slightly higher occurrence of CVT in younger age group.

Gustavo S, Fernando B, et al.⁶ and Gregory P.⁸ reported in their study that cerebral venous thrombosis is an uncommon form of stroke, usually affecting young adults. In our study a total of 62% patients were female patients. Among them 58% of the patients (18 patients) belong to reproductive age group. Ameri A, Bousser MG.⁹ in their study reported a female to male ratio of 1.29:1 in CVT and that 61% of women were between the age group 20-35 years.

Headache is the most common presentation (78%) in our study followed by seizures in 32%, vomiting in 26% and focal neurological deficit in 24% patients. Mohapatra S, Manjari B, Jayashree M.¹⁰ reported in their study that headache is the most common symptom present in more than 80% cases, seizures 35-40% cases, focal neurological signs 30-35% cases and vomiting 30% cases.

The time period between the onset of clinical symptoms and presentation to our department for imaging and diagnosis of thrombosis done was acute (0-5 days) in 32%, subacute (6-15 days) in 56% and chronic (more than 15 days) in 12% of cases. Similar findings were reported by Leach J, Fortuna R, Jones B.¹¹ reported that focal brain parenchymal abnormalities are visualised in 57% of cases. Edema without hemorrhage was reported in 8% cases on CT scan and 25% cases on MRI. Hemorrhage was reported in one third of the cases.

The sinus abnormality on T1and T2 sequences of MRI were isointense and hypointense in acute phase, both T1and T2 hyperintense in subacute phase and T1 isointense and T2 isointense to hypointense in chronic phase. Pipat C, Siriwan P, Niphon P.² in their study reported that in the acute stage, thrombus is usually isointense on T1WI and hypointense on T2WI. In the late subacute stage thrombus is usually hyperintense on both T1 and T2. In chronic stage it is hyperintense on T2 and isointense on T1.

Diffusion weighted imaging (DWI) can detect changes in water diffusion associated with cellular dysfunction and can be used to detect ischemic lesions of the brain within the first few hours of stroke onset. The application of DWI in diagnosing acute arterial stroke is well established. It shows an early decrease and late increase or normalization, of the apparent diffusion coefficient (ADC). DWI

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus abnormality</td>
<td>18 (36%)</td>
<td>50 (100%)</td>
</tr>
<tr>
<td>Parenchymal abnormality</td>
<td>21 (42%)</td>
<td>26 (52%)</td>
</tr>
<tr>
<td>Edema</td>
<td>21 (42%)</td>
<td>26 (52%)</td>
</tr>
<tr>
<td>Hemorrhagic infarct</td>
<td>11 (22%)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Only infarct</td>
<td>2 (4%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0</td>
<td>4 (8%)</td>
</tr>
</tbody>
</table>

Regarding brain parenchymal abnormality, CT could detect edema in 15 (30%) of cases and MRI in 26 (52%) of cases. Hemorrhagic infarct was seen in 26% of patients on MRI as compare to 22% on CT. Leach J, Fortuna R, Jones B.¹¹ reported that focal brain parenchymal abnormalities are visualised in 57% of cases. Edema without hemorrhage was reported in 8% cases on CT scan and 25% cases on MRI. Hemorrhage was reported in one third of the cases.

The sinus abnormality on T1 and T2 sequences of MRI were isointense and hypointense in acute phase, both T1 and T2 hyperintense in subacute phase and T1 isointense and T2 isointense to hypointense in chronic phase. Pipat C, Siriwan P, Niphon P.² in their study reported that in the acute stage, thrombus is usually isointense on T1WI and hypointense on T2WI. In the late subacute stage thrombus is usually hyperintense on both T1 and T2. In chronic stage it is hyperintense on T2 and isointense on T1.
can be used to discriminate between different types of edema, assess tissue viability, detect subclinical abnormalities, deliver time-saving information for early diagnosis and facilitate basic imaging research of the pathophysiology of CVT.\textsuperscript{11,12} In hemorrhagic infarct 16% of cases showed increased ADC and 10% of cases decrease ADC value whereas in non hemorrhagic infarct 2% of patients showed increase ADC and 8% decrease ADC value. Areas without dimnishment in ADC value may primarily represent vasogenic edema due to venous hypertension. Complete or near complete resolution of edema in patients with decreased ADC values in CVT are also reported.

Susceptibility-weighted imaging (SWI) is a new technique that exploits susceptibility differences in different tissues, to provide a different type of tissue contrast. It is particularly suited for vascular imaging, especially in cerebral ischemia. It is exquisitely sensitive to blood products, even more than the gradient-echo (GRE) technique. It also provides a unique tissue contrast, similar to blood oxygen level–dependent (BOLD) imaging. It can provide important diagnostic information and also provide insights into etiopathogenesis.\textsuperscript{13} SWI sequence was done in 25 cases. Of the 14 patients that were showing blooming on SWI, 4 patients did not show any parenchymal abnormality on GRE sequence.

SWI has become a useful method to evaluate CVST by demonstrating venous stasis and Mittal S, Wu Z, Neelavalli J, Haacke EM\textsuperscript{14} in their study reported collateral slow flow. Dural sinus thrombosis causes an increase of deoxyhemoglobin concentration in the involved veins. This appears as prominent hypointense signal intensity on SWI. SWI can assist in directing the radiologist to look for CVST while the patient is in the acute stage. SWI is so sensitive to such a small amount of hemorrhage that even conventional GRE images can fail to show the remnant hemorrhage after stroke.

GRE T2* weighted sequences are superior to spin echo techniques in detecting CVST and small haemorrhages. Paramagnetic compounds such as deoxyhemoglobin, intracellular methemoglobin, and hemosiderin behave as naturally occurring contrast agents for MRI. Thirteen patient showed hemorrhage on GRE sequences, out of which 2 patients didn’t show any hemorrhage on CT scan. Thirty two patients in our study had showed sinus GRE abnormality as hypointensity. Of the 32 patients who showed sinus hypointensity, 5 patients did not show any abnormality on conventional T1 and T2 sequences and all these patients were of acute presentation. Tang M, Chen T, Zhang X, Huang X\textsuperscript{14} in their study reported that GRE T2* WI has a higher detection rate than conventional MRI sequences and CT examinations for cerebral hemorrhages, taking advantage of its ability to detect small bleeding lesions. Compared with a conventional sequence, the GRE T2* WI sequence not only improves the detection rate of microbleeds but also reveals the progression of the bleeding lesion.

Sensitivity, specificity, PPV and NPV of CT scan was respectively 80.7%, 100%, 100%, 82.7% for edema and 84%, 100%, 100% and 94.9% for hemorrhage which is similar to Linna J, Pfefferkornb T, Ivanicovaa K, et al\textsuperscript{15} who reported that the sensitivity and specificity values of NCCT were 93.7% and 98% for intracerebral edema and 94.8% and 98.7% for intracerebral hemorrhages respectively.

In our study out of the 26 patients showing brain parenchymal changes, 21 patients showed correlation with the sinus involved. However, in 5 patients the sinus involvement and parenchymal abnormality did not correlate. All the patients with deep venous system thrombosis showed correlation with brain parenchymal changes. All the 5 patients who did not show correlation with the brain parenchymal changes showed thrombosis of the superficial venous system.

Colin S, Ja-Kwei C, Amar S, Michael H, John W\textsuperscript{16} in their study reported that the location of the infarction with respect to the expected course of venous drainage may give a clue to the venous structure involved. Thrombosis in the sagittal sinus often leads to impaired venous drainage and, therefore, parenchymal change in the parasagittal region. Thrombosis in Labbe’s vein should lead to infarction in the temporal lobe. Bilateral or unilateral infarction in the thalami, basal ganglia, and internal capsule is typically seen in deep venous thrombosis.

As noted from the above studies our study showed correlation of brain parenchymal with sinus involved in thrombosis in majority of the cases, particularly in deep venous sinus thrombosis.

**Conclusion**

CVT presents with variable clinical presentation in all the age groups and both sexes, though more common in young female patients. In the emergency setting, CT scan plays an important role in evaluating patients clinically suspected CVT, and all the patients who showed hyperdense sign on plain head CT scan were found to have CVT on MRI and MRV. For patients with equivocal findings on CT scan, MRI combined with MR Venography is the best imaging technique for the diagnosis of cerebral venous thrombosis.

GRE imaging showed sinus abnormalities better than
conventional MR sequences in acute and subacute presentation. SWI was found to be superior to both GRE sequence and CT scan imaging in detecting hemorrhage, particularly microhemorrhages.

References

A Comparative Study of In-Hospital Outcome of Patients with ST-Segment Elevation Myocardial Infarction with and Without Diabetes Mellitus, after Thrombolytic Therapy; In Government Hospital of Rajkot, Gujarat, India

Varshit Hathi¹, Meghal Anadkat²

Abstract

**Background:** Diabetes mellitus is considered as a major health problem and an epidemic throughout the world. The mortality of patients with diabetes is almost twice that of non-diabetic. The outcome of in-hospital patients with myocardial infarction with and without diabetes after thrombolytic therapy is presented here.

**Aim:** To compare the outcome of patients with myocardial infarction after thrombolysis in diabetics and non-diabetics in government hospital of Rajkot, India.

**Methods:** A retrospective, observational study was carried out between the period of March-2014 to April-2015. Patients who presented with acute myocardial infarction having ST-elevation as MI picture, were admitted to the emergency room of medicine department. All these patients were treated with streptokinase as a thrombolytic agent. Baseline ECG was taken on admission and the one after 60 minutes of thrombolysis. The study group involved two types: (i) diabetic (ii) nondiabetics.

**Results:** A total of 395 patients were included in the study. Out of them around 104 were females and 291 were males. ST-segment resolution in non-diabetic patients was found in 180 patients out of 186 and in diabetics it was found in 174 patients out of 208. Complications related to post fibrinolytic therapy was more prevalent in diabetics 148 patients (71.15%) as compared to those in non-diabetics 47 patients (25.26%). Mortality was observed only with diabetics (23.52%) as compared to no mortality in non-diabetics.

**Conclusion:** Overall, morbidity and mortality of diabetic patients with Acute Myocardial Infarction was found to be greater as compared to non-diabetics; post thrombolysis.

Editorial Viewpoint

- Mortality in diabetic patients with STEMI is almost twice than that in non-diabetics.
- This study finds mortality only in diabetics with STEMI.
- Post-thrombolytic complications were also more prevalent in diabetes.

Acute Coronary Syndrome which includes various conditions like: unstable angina, non ST-segment elevation MI (NSTEMI) and ST-segment elevation MI (STEMI). Apart from other conditions like dyslipidaemia, smoking, hypertension, any suggestive family history of atherosclerotic disease in the family, Diabetes Mellitus is considered as one of the major risk factor leading to MI. Diabetes Mellitus is a metabolic disorder which enhances the atherosclerotic rate of vascular occlusion. Even after prompt thrombolysis, outcome of patients with diabetes is worse as compared to those without diabetes indicating impaired cardiac function post

Introduction

Acute myocardial Infarction is considered as one of the major epidemic of mankind. In a developing country like India, coronary artery disease incidence is rising. There is an entity called

¹Senior Resident, ²Associate Professor in Medicine, Pandit Deendayal Upadhyay Medical College, Rajkot, Gujarat
Received: 26.05.2016; Accepted: 16-06-2017
In MI, for early and complete myocardial reperfusion, prompt thrombolysis is carried out. Changes of complications increase when there is incomplete or failed reperfusion. After fibrinolytic therapy, coronary reperfusion can be assessed by noting ECG changes pre and post thrombolysis in the form of ST-segment resolution. Micro vascular reperfusion can be better judged by ST-segment resolution whereas epicardial reperfusion can be better judged by coronary angiogram. Although epicardial reperfusion serves as a good marker for prognosis, micro vascular flow correlates more strongly with good clinical outcome. Therefore, ST segment is considered as a better prognostic tool, and it provides information which cannot be assessed by coronary angiogram alone. In one of the study done by Schroeder et al., it was reported that absence of ST-segment resolution is one of the powerful predictor of early mortality. In order to identify candidates for early invasive procedures like PTCA, ST-segment non-resolution is considered as an important tool after thrombolytic therapy. In a developing country like India, it becomes very important to establish the effectiveness and importance of ECG for assessing reperfusion as it is widely available everywhere. ECG will offer cheapest alternative for judging myocardial salvage and recovery. This study aims at establishing correlation between post thrombolytic complications with diabetics when the diagnosis is made by ST-segment elevation found on ECG in patients with Acute Myocardial Infarction (AMI) then in those with non-diabetics.

### Patients and Methods

This retrospective study was done at government civil hospital Rajkot, India, from March 2014 to April 2015. All cases with ST-Elevation acute myocardial infarction were included. Following factors were considered in diagnosis:

1. ECG changes i.e. ST-elevation >0.2mv in atleast two contiguous chest leads or >0.1mv in atleast two contiguous limb leads.
2. Elevated CPK-MB levels more than twice the reference values
3. Positive trop-t test done from kits available commercially.

These patients were presented within 12 hours and were given streptokinase as a thrombolytic agent.

The exclusion criteria followed were those patients presented after 12 hours of chest pain and those suffering from diabetes mellitus type-1.

The study population was divided in 2 groups:

- **Group-A :- Diabetic**
- **Group-B :- Non-diabetic**

Group B included only those patients who were known cases of diabetes or who were declared diabetic after repeated glucose testing or random blood sugar tests, during their in-hospital stay.

History, in detail was taken regarding age, sex, address, smoking history, any family history of atherosclerotic disease, hypertension. Pulse and blood pressure were noted on admission of patient to the emergency ward along with the entire clinical check-up. Daily follow-up was done. Any complications, ECG changes or pulse abnormalities were noted and checked regularly till discharge or death of the patient.

Exact time of onset of chest pain, its presentation and nature were noted through the history. Patients’ ECG were recorded and looked for ST-segment elevation. The segment showing maximum elevation was recorded in millimetres and treatment of thrombolysis was started. Streptokinase injection was given to all patients with the dose of 1.5 million units, diluted in 100 ml normal saline, over one hour.

ECG was repeated after almost 60 minutes of thrombolytic therapy by streptokinase and the lead with the maximum ST-segment elevation was observed for ST-resolution. Here we define resolution of ST-segment when the elevation has reduced to >50%. Informed written consent was obtained from all the patients included in the study. Routine follow-up and check-up of all the vitals and RBS was done daily and noted, as far as the in-hospital patients were concerned.

In order to differentiate between stress hyperglycaemia and non-diabetic, fasting blood sugar was done in stable condition at the time of discharge.

Assessment related to complications was also made, which mainly included: hypotension due to streptokinase, arrhythmia, chest pain-non relieving type and sometimes death.

### Results

A total of 394 patients were taken as a study population, out of them 208 were found diabetic and 186 were non-diabetic. The following table shows the demographic distribution of our study population.

Smoking was the most common associated risk factor found to be involved according to this study, even hypertension was also associated with increased co-morbidity. The average age group involved in case of diabetics was about 54-56 years whereas in

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Diabetic (n=208)</th>
<th>Nondiabetic (n=186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (yrs.)</td>
<td>54-56</td>
<td>60-62</td>
</tr>
<tr>
<td>Male</td>
<td>166 (79.81%)</td>
<td>124 (66.66%)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (20.19%)</td>
<td>62 (33.33%)</td>
</tr>
<tr>
<td>Time to thrombolysis (hrs.)</td>
<td>7.8 ± 1.2</td>
<td>6.84 ± 1.5</td>
</tr>
<tr>
<td>H/o smoking</td>
<td>110 (52.88%)</td>
<td>102 (54.83%)</td>
</tr>
<tr>
<td>HT</td>
<td>56 (26.92%)</td>
<td>98 (52.68%)</td>
</tr>
</tbody>
</table>
case of non-diabetics was around 60-62 years. Average time taken to thrombolysis all these patients presented at the emergency department from the time of onset of chest pain to thrombolysis was around 7 hours and 6.8 hours from the onset of chest pain in diabetics and non-diabetic, respectively.

Out of 395 patients investigated, 355 patients showed resolution of ST-segment elevation and remaining 40 patients showed non resolution of ST-segment elevation. These are the patient who were thrombolyzed within about 60-180 minutes on arrival by streptokinase. Out of these 395 patients, 208 patients were found diabetic, either a known case or denied. It is mostly hypothesized that type-2 diabetes interferes with reperfusion. Its importance as a good prognostic factor cannot be denied. It is mostly hypothesized that type-2 diabetes interferes with the effectiveness of thrombolysis intravenously, which may be established by ECG or angiographic findings.

Table 2: Comparison between two groups and its correlation with complications

<table>
<thead>
<tr>
<th></th>
<th>Diabetic (N=208)</th>
<th>Non-Diabetic (n=186)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Complete ST resolution</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>42 (28)</td>
<td>28 (16.09%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12 (09)</td>
<td>09 (5.17%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>86 (71)</td>
<td>71 (40.80%)</td>
</tr>
<tr>
<td>Death</td>
<td>08 (00)</td>
<td>00 (00)</td>
</tr>
</tbody>
</table>

In that diabetic population about 86 (41.34%) patients suffered from chest pain, whereas in non-diabetic population the figure reduced to 21 (11.29%). Similarly, second most common complication encountered in both group of population was arrhythmias of different types, where again afflection rate of diabetics was 20.19% whereas that of non-diabetics was 11.82%. Incidence of arrhythmias in diabetics was more (16.09%) as compared to other related complications. Overall mortality post-thrombolysis is very much less. In the present study, mortality is seen in diabetics only (23.52%).

**Discussion**

The time taken for reperfusion after presentation and complete reperfusion plays a key role in fibrinolysis. In cases of STEMI, ST-segment resolution indicates reperfusion. Its importance as a good prognostic tool cannot be denied. It is mostly hypothesized that type-2 diabetes interferes with the incidence in the patients dying of acute myocardial infarction, complete ST-segment resolution was seen in 180 patients and 6 patients' showed failed resolution of ST-segment; and in case of diabetics 174 patients’ showed complete resolution and 34 patients’ showed failed ST-resolution.

In the present study, we observed that in non-diabetic patients with acute myocardial infarction, complete ST-resolution was seen in 180 patients and 6 patients’ showed failed resolution of ST-segment; and in case of diabetics 174 patients’ showed complete resolution and 34 patients’ showed failed ST-resolution.

**Onset of complications post-thrombolysis** was observed more in diabetics (71.15%) as compared to those in non-diabetics (25.26%).

This is in support of one study which stated that complications were more prevalent in diabetics as compared to non-diabetics.7

As shown in another study, there was found a positive correlation between diabetic patients with increased morbidity as well as mortality after thrombolization. In context of ischemia, there is one another study mentioning the residual lesion in the infarct related artery was greater in diabetics post fibrinolytic therapy; thereby leading to higher rate of recurrent ischemia.8

Post myocardial infarction, heart failure remains one of the most important prognostic factor. Here in the present study, heart failure is found to be associated with diabetic to a greater extent than non-diabetic. Any patient showing signs of heart failure post thrombolysis are considered in the category. In one of the study, it was found that in-hospital heart failure among diabetics was more common.9 In that study, heart failure developed in 9% diabetics and 4.3% non-diabetics (p=0.001)

Arrhythmias are also found to be associated with post fibrinolytic therapy. Their incidence is more in case of diabetics (20.2%) as compared to non-diabetic (11.82%). It indicates that arrhythmias are more common in diabetics than in non-diabetics, which is supported by another study which also showed positive correlation between arrhythmias and diabetics(p<0.0001)3 In another study, it was observed that the incidence in the patients dying of AV-block or LBBB was almost three times more common in diabetic patients’ as compared to non-diabetics.10

In the present study, mortality associated with diabetics, post fibrinolytic therapy was found to be about 3.8% of total diabetic population. It was associated with failed ST-resolution post therapy. No mortality was observed in non-
The study has limitations due to small sample size and inadequate and irregular follow-up after discharge of the patient. As hospital is equipped with the equipment to deal with various medical emergencies, in-hospital death ratio is overall less. The results of the study are supported by another similar study carried out by Muhammad AK et al7 their study also indicated significant correlation between mortality and failed ST-resolution in diabetics (7.4%) as compared to non-diabetics with failed ST-resolution. In another study, carried out by Timmer JR et al,11 it was found that diabetes is associated with increased 30-day mortality.

In previous study, it was shown that there was a close negative association of diabetes with outcome of STEMI patients. As diabetes is associated with increased mortality after thrombolysis in case of ST-segment Elevation Myocardial Infarction, there arises a necessity to revise new treatment modalities and revised reperfusion methods.12 In another study it was proved that fibrinolysis may be less effective in diabetic patients.13 Angeja et al14 showed that micro vascular flow reduced in diabetic patients post-fibrinolytics therapy. May be, it is due to increased aggregation of platelets and its reduced ability to induce endothelium-mediated vasodilation.15 There is a possibility that PCI can be a better option of treatment in diabetics presenting with ST-segment elevation MI. Moreover, other associated risk factors and recovery at the left ventricular level are also to be considered as far as long term outcome for diabetics is talked about. Several preventions like vigorous glycaemic control, strict management of hyperlipidaemia also plays a vital role in good prognosis of diabetes patients.

In the present study, we have our own limitations regarding age, sex, geographical location and other risk factors, which could not be assessed properly in order to clearly point out the cause leading to mortality.16 for that multi-variate analysis is to be performed. During acute phase of myocardial infarction, there are chances of stress hyperglycemia, which may give misleading records of hyperglycemia, but it can be certainly differentiated after the acute phase of infarction passes, which takes almost 7 days and by that time the patient is discharged from the hospital. This comes as a major limitation of the study. Moreover our study is a single centre study with limited sample size.

Conclusions

Overall, morbidity and mortality of diabetic patients with Acute Myocardial Infarction was found to be greater as compared to non-diabetics; post thrombolysis. Post thrombolization, frequency of various complications are more in failed ST-resolution then successful reperfusion, in both diabetic and non-diabetic populations. In diabetes with acute myocardial infarction, abnormality in vascular flow may contribute to the poorer outcome.

References

Osteoporosis in Postmenopausal Females with Primary Knee Osteoarthritis in a Vitamin D Deficient Population

Pooja Dhaon¹, Siddharth Kumar Das², Ragini Srivastava², Akash Asthana³, Girdhar Agarwal³

Abstract

Aim and Objective: To find prevalence of osteoporosis (OP) in postmenopausal females with primary knee osteoarthritis (OA) in India, where there is widespread Vitamin D deficiency (VDD).

Material and Methods: 75 postmenopausal women (PMW) fulfilling ACR criteria for Knee OA between 40 - 60 years of age, having OA grade 2 or more as per Kellgren Lawrence grade on anterior-posterior radiograph of the right knee were enrolled. 34 PMW of the same age with normal right knee radiograph were taken as controls. Bone mineral density (BMD) of lumber spine (L1-L4), total hip and left forearm was performed using DXA in all patients and controls. The results were expressed in absolute values (g/cm²) and as per WHO criteria – Osteoporosis: T score < -2.5, Osteopenia: T score between -1 and -2.5. Vitamin D Level was done by ELISA.

Results: Body mass index (BMI) of patients was significantly higher than controls (p 0.006). There was no difference in BMD between patients and controls at any site. Forty percent patients and 53% controls had osteopenia (p ns), while 34.6% patients and 41.1% controls had osteoporosis at any site (p ns). When this comparison was made at each site there was no difference between patients and controls.

Conclusion: Prevalence of osteoporosis in PMW with primary knee OA is similar to that in general population.

Background

Due to increase in longevity and changing lifestyle of Indian women, menopausal and postmenopausal health has now become an important concern. It was expected that by the year 2015, India would have about 150 million females who will live beyond menopause.¹ Morbidities associated with long term changes in ovarian hormonal levels include osteoporosis (OP) and osteoarthritis (OA). The prevalence and severity of OA and OP increase in postmenopausal women (PMW).² A study from western India which assessed 500 PMW, reported that 51.6% females had OA while 62% females had OP. Vitamin D deficiency (VDD) which is rampant in India in all age groups, increases in severity in PMW. This may be due to a number of factors – dietary deficiency, undetected fat malabsorption, reduced cutaneous synthesis. VDD is also related to both osteoarthritis and osteoporosis.³,⁴

Literature coming from the west has found an inverse relationship between OA and OP.⁵–⁸ Local factors such as osteophyte formation and subchondral sclerosis can increase measured values from the bone density assessments of the spine and hip done by DEXA (Dual Energy X ray Absorptiometry). However the study of osteoporotic fractures provided data on women with severe OA. According to that study, BMD (bone mineral density) increased at remote sites such as proximal and distal sites of the radius and calcaneous relatively more in patients with OA compared to individuals without OA.⁹ Some data from the west suggest that the prevalence of OP in OA is same as in general population.⁹ There is paucity of Indian data in

¹Department of Medicine, HIMS, Safedabad, Barabanki, Uttar Pradesh; ²Department of Rheumatology, KG Medical University, Lucknow, Uttar Pradesh; ³Department of Statistics, Lucknow University, Lucknow, Uttar Pradesh

Received: 19.08.2016; Revised: 01.04.2017; Accepted: 05.07.2017
Table 1: Demographic and disease variables in patients and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=75) Mean ± SD</th>
<th>Controls (n=34) Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51 ± 5.3</td>
<td>50.1 ± 5.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>151 ± 5.7</td>
<td>152.7 ± 6.0</td>
<td>0.15</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.5 ± 10.6</td>
<td>62.1 ± 13.2</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
<td>29.1 ± 4.6</td>
<td>26.4 ± 4.8</td>
<td>0.006*</td>
</tr>
<tr>
<td>S. Calcium (mg/dl)</td>
<td>9.4 ± 1.3</td>
<td>9 ± 2.2</td>
<td>0.23</td>
</tr>
<tr>
<td>S. Alkphos (IU/L)</td>
<td>200 ± 90.2</td>
<td>220 ± 90.6</td>
<td>0.28</td>
</tr>
<tr>
<td>Vitamin D (ng/ml)</td>
<td>17.3 ± 19.4</td>
<td>19 ± 6.8</td>
<td>0.62</td>
</tr>
</tbody>
</table>

* Significant p value

This study was performed parallel to the Rheumatology OPD, identified to have primary knee osteoarthritis on the basis of clinicoradiological ACR criteria of 1987, were studied. Thirty-four (34) postmenopausal females of similar age were taken as controls. All the patients and controls provided written informed consent. None of the patients and controls had inflammatory joint disease, medical renal disease, metabolic bone disease, hyperparathyroidism or were on any drugs like steroid which affect the bone health. The control population was representative of the general population. A complete history was taken and examination was done for each subject. Demographic variables were noted for all subjects.

Radiographs of the right knee were taken and evidence of knee OA was studied as per the Kellgren and Lawrence (KL) grade 1- 4. Osteoarthritis was classified as present, if KL grade of 2 or more was present while controls had normal x-rays. Bone mineral density (BMD) of lumbar spine (L1-L4), total hip and left forearm was performed using dual x-ray energy absorptiometry (DXA) using Lunar prodigy Densitometer 12165 (GE medical systems) in all patients and controls. All BMD results were expressed in absolute values (g/cm2) and T-Score i.e. number of standard deviation above or below the mean results of young female adults. [Reference population - USA (Combined NHANES (Ages 20-30)/ Lunar (ages 20-40)]. Osteoporosis was defined as per the WHO guidelines T score < -2.5 and osteopenia between -1 and -2.5.

Blood samples were collected from all patients and controls. Serum calcium was done by the OCPC method (LYPHOZYME-BEACON diagnostics); Serum alkaline phosphate was done by DGKC-SCE method (Agappe diagnostics). Vitamin D analysis was done by Enzyme immunoassay (Immuno diagnostic systems). The following cut-off values, as mentioned with the kit, were used: deficient: <20 ng/ml, Suboptimal – between 20 -30 ng/ml and optimal- >30 ng/ml.

Statistical Analysis

For the comparison of baseline characteristics between the groups independent sample t-test was used. The BMD among the groups, adjusted for the significantly different baseline characteristics, were compared using Analysis of Covariance (ANCOVA). The analysis was performed using SPSS software version 20.0.

Results

75 patients and 34 controls were enrolled in the study. The demographic variables and disease variables are as shown in Table 1. Among the demographic variables, there was a significant difference in the body mass Index (BMI) between patients and controls (p 0.006). Among the other variables, there was no difference between patients and controls. Out of the 75 patients, 43 (57%) had grade-2 OA, 26 (35%) had grade 3- OA, while 6 (8%) had grade-4 OA. The mean BMD at the three sites is shown in Table 2. There was no significant difference in the body mass Index (BMI) between patients and controls at any site. There was no relationship between BMD and severity of OA. There was no difference between BMD of patients and controls at any site even after adjusting it for BMI (Table 2). As per BMD T-score, 26 (34.6%) patients and 14 (41.1%) controls had osteoporosis at any site, while 30 (40%) patients and 18 (53%) controls had osteopenia at any site (p ns). When this comparison was made at individual sites, no difference was found between patients and controls (Figure 1).
Vitamin D Deficiency

70 (93.4%) patients and 32 (94%) controls had suboptimal vitamin D levels (p ns). Amongst the patients, 44 (59%) had vitamin D deficiency, while 26 (34.6%) had vitamin D insufficiency. Among the controls, 20 (59%) had vitamin D deficiency, while 12 (35%) had vitamin D insufficiency. Out of the 26 patients with suboptimal vitamin D, 9 (34.6%) had osteoporosis and 13 (50%) had osteopenia at any site. Out of the 9 controls with suboptimal vitamin D, 9 (75%) had osteoporosis while 3 (25%) had osteopenia at any site. Out of the 44 patients with vitamin D deficiency, 15 (34%) had osteoporosis and 16 (36.3%) had osteopenia at each site. When the comparison was made at each site, controls with suboptimal vitamin D were significantly more osteoporotic at forearm compared to the patients (Table 3). When the absolute BMD values were compared in patients and controls, the difference was not found to be significant (Table 4).

Discussion

The results of the study show that there is no relation of OA and OP in VDD post menopausal women. There was a significant difference between patients and controls with suboptimal vitamin D at forearm. But as the sample size of the study is too small, it is very difficult to interpret whether this difference proves any relation between OA and OP. The result is similar to the study by Ghosh et al. The study had 98 cases and 108 age- matched controls. VDD was present in 55% patients and 34% controls. In the present study almost all the subjects had low vitamin D. The reason for this difference may be because Ghosh et al. had also included males and pre-menopausal females, while the present study only had post menopausal females. Even though varying degree of VDD is rampant in India among all age groups, according to various studies published earlier, VDD gets aggravated after menopause because of traditional clothing pattern and these females often remain indoor. In multiple studies from various parts of India the prevalence of VDD in postmenopausal females ranges from 50 – 80%,.

In the study by Ghosh et al., almost 80% patients and controls had low BMD. The result of the present study is similar. Another study from north India which looked for prevalence of primary

Table 3: Comparison of osteoporosis and osteopenia in patients and controls with low vitamin D

<table>
<thead>
<tr>
<th>Site</th>
<th>Osteoporosis (T&lt;-2.5)</th>
<th>Osteopenia (T between -1 and -2.5)</th>
<th>Chi square (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient n-44</td>
<td>Patient n-20</td>
<td>Control n-20</td>
<td>Patient n-26</td>
</tr>
<tr>
<td>AP spine (L1-L4)</td>
<td>8 (18%)</td>
<td>3 (15%)</td>
<td>23 (52.2%)</td>
</tr>
<tr>
<td>Total hip</td>
<td>4 (9%)</td>
<td>1 (5%)</td>
<td>15 (34%)</td>
</tr>
<tr>
<td>Left forearm</td>
<td>11 (25%)</td>
<td>3 (15%)</td>
<td>13 (29.5%)</td>
</tr>
<tr>
<td>Any site</td>
<td>15 (34%)</td>
<td>5 (25%)</td>
<td>16 (36.3%)</td>
</tr>
</tbody>
</table>

Table 4: Comparison of BMD absolute values between patients and controls with low Vitamin D

<table>
<thead>
<tr>
<th># BMD in g/cm2</th>
<th>Vitamin D &lt;20 ng/ml</th>
<th>Vitamin D between 20 and 30 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td># BMD in g/cm2</td>
<td>Patient n-44</td>
<td>Patient n-26</td>
</tr>
<tr>
<td>AP spine (L1-L4)</td>
<td>0.99 ± 0.15</td>
<td>1.0 ± 0.17</td>
</tr>
<tr>
<td>Total hip</td>
<td>0.90 ± 0.13</td>
<td>0.87 ± 0.24</td>
</tr>
<tr>
<td>Left forearm</td>
<td>0.77 ± 0.29</td>
<td>0.80 ± 0.13</td>
</tr>
</tbody>
</table>

**# p ns**
osteoarthritis in postmenopausal females, reported prevalence of OP to be 37.8% with maximum at spine and minimum at femur. In the present study maximum OP was at forearm and minimum at hip. Ghosh et al found VDD to be associated with both OA and OP, but did not find any relation between the two conditions.

In the present study also there was no relation between OA and OP, where almost all subjects had low vitamin D. This means that OA does not provide protection for development of OP. Osteopenia and osteoporosis does occur in patients with knee OA. There are some clinical implications of this. Some patients with knee OA may require a knee replacement in future. So early detection and treatment of OP in patients of knee OA might improve the outcome of joint replacement surgery.

This sample size of this study is too small to know the exact relation between the two. So this may be considered a pilot study and a multi-centric study with a large sample size must be planned on this to know the exact relation between OA and OP in India.

References

Knowledge, Attitudes, Beliefs and Practices of Physicians Regarding Idiopathic Pulmonary Fibrosis and the Impact of a Continuing Medical Education Program

Sahajal Dhooria¹, Inderpaul Singh Sehgal¹, Ritesh Agarwal², Ashutosh Nath Aggarwal², Digambar Behera³

Abstract

Background: Significant deficiencies have been identified previously in the knowledge of physicians regarding the current diagnosis and management of idiopathic pulmonary fibrosis (IPF). Whether a continuing medical education (CME) program helps in overcoming these deficiencies has never been studied.

Methods: This was a questionnaire-based study performed to assess the knowledge, attitudes, beliefs and practices of physicians regarding IPF before and after attending a CME program at a tertiary care teaching Institute in northern India. A questionnaire comprising of 18 questions on knowledge, attitudes, beliefs and practices regarding IPF (designed by Delphi method) was self-administered by the participants prior to (pretest) and after (posttest) attending the program. The pretest and posttest knowledge and belief scores (maximum achievable score 17) were compared.

Results: Of the total 98 physicians who agreed to participate, 84 completed the pretest questionnaire. The mean (SD) total score for knowledge and beliefs questionnaire was 10.7 (3.5). The mean (SD) pretest and posttest scores of 52 subjects, who completed both the questionnaires were 10.3 (3.4) and 11.1 (2.9) respectively with a mean increase of 0.8 (p=0.048). The proportion of participants who scored >50% increased (p=0.046) from 41 (78.8%) to 48 (92.3%) between the pretest and posttest questionnaires. Only 54.8% and 47.6% of the participants responded correctly to the questions on CT features and drugs useful for IPF, respectively.

Conclusions: Significant deficiencies were noted in the knowledge of IPF among a small group of physicians attending a CME. A CME program with didactic lectures helps improving the knowledge only marginally.

Editorial Viewpoint

• Significant deficiency in knowledge of physicians regarding IPF was noted.
• This deficiency was marginally improved by CME in a small group of physicians.

In the United States, the prevalence estimates of IPF range from 14-43 per 100,000 population. Although these estimates are not available for India, studies from referral centers suggest that 29-48% of the patients presenting with DPLDs had IPF. Despite being commonly diagnosed in tertiary care centers, IPF remains under-recognized at primary care.

Four professional societies including the American Thoracic Society published a joint guideline statement on IPF in 2011 which was recently updated. These guidelines provide comprehensive evidence-based recommendations on the diagnosis and treatment of IPF. Important diagnostic and management issues including the role of high resolution computed tomography (HRCT) scan of the chest and surgical lung biopsy in the diagnosis of IPF, and its treatment with immunosuppressive and anti-fibrotic agents have been addressed along with the best available evidence. Whether the knowledge and beliefs of physicians in India are...

¹Assistant Professor, ²Professor, ³Professor and Head, PGIMER, Chandigarh
Received: 04.08.2016; Accepted: 05.07.2017
Table 1: Knowledge and belief questions along with the correct answers and method of scoring

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>Correct option(s)</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knowledge questions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1  The terms interstitial lung disease and idiopathic pulmonary fibrosis can be used interchangeably</td>
<td>A. Yes</td>
<td>B</td>
<td>1 point for correct answer</td>
</tr>
<tr>
<td></td>
<td>B. No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2  The mean age at diagnosis is between</td>
<td>A. 20-30 years</td>
<td>D</td>
<td>1 point for correct answer</td>
</tr>
<tr>
<td></td>
<td>B. 30-40 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. 40-50 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D. 50-70 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3  IPF is more common in</td>
<td>A. Males</td>
<td>A</td>
<td>1 point for correct answer</td>
</tr>
<tr>
<td></td>
<td>B. Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4  Risk factors for the occurrence of IPF (indicate all that apply)</td>
<td>A. Smoking</td>
<td>A, D</td>
<td>1 point for each correct option marked</td>
</tr>
<tr>
<td></td>
<td>B. Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. Connective tissue disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D. Gastroesophageal reflux disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5  Median survival in IPF is</td>
<td>A. 1 year</td>
<td>B</td>
<td>1 point for correct answer</td>
</tr>
<tr>
<td></td>
<td>B. 3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D. 7 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6  The diagnosis of IPF requires</td>
<td>A. Can be diagnosed on HRCT</td>
<td>A</td>
<td>1 point for correct answer</td>
</tr>
<tr>
<td></td>
<td>B. Transbronchial forceps biopsy in all cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. Surgical lung biopsy in all cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7  Histopathological diagnosis should be obtained in all cases if possible</td>
<td>A. Yes</td>
<td>B</td>
<td>1 point for correct answer</td>
</tr>
<tr>
<td></td>
<td>B. No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8  The features of IPF on HRCT of the chest include (indicate all that apply)</td>
<td>A. Upper lobe distribution</td>
<td>B, C</td>
<td>1 point for each correct option marked</td>
</tr>
<tr>
<td></td>
<td>B. Reticular abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. Honeycombing and traction bronchiectasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D. Subpleural sparing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9  Drugs found to be effective in long term management of IPF (indicate all that apply)</td>
<td>A. N-acetylcysteine</td>
<td>D, E</td>
<td>1 point for each correct option marked</td>
</tr>
<tr>
<td></td>
<td>B. Prednisolone plus azathioprine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. Prednisolone plus azathioprine plus N-acetylcysteine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D. Pirfenidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E. Nintedanib</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F. Gefitinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>G. Erlotinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H. Deflazacort</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Belief questions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 IPF has a strong familial basis</td>
<td>A. Yes</td>
<td>B</td>
<td>1 point for correct answer</td>
</tr>
<tr>
<td></td>
<td>B. No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 IPF occurs only in smokers</td>
<td>A. Yes</td>
<td>B</td>
<td>1 point for correct answer</td>
</tr>
<tr>
<td></td>
<td>B. No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 IPF occurs in those with connective tissue diseases</td>
<td>A. Yes</td>
<td>B</td>
<td>1 point for correct answer</td>
</tr>
<tr>
<td></td>
<td>B. No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Lung transplantation is the only definitive management option for advanced IPF</td>
<td>A. Yes</td>
<td>A</td>
<td>1 point for correct answer</td>
</tr>
<tr>
<td></td>
<td>B. No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Can IPF and emphysema be present in the same patient?</td>
<td>A. Usually</td>
<td>B</td>
<td>1 point for correct answer</td>
</tr>
<tr>
<td></td>
<td>B. Sometimes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. Extremely rarely</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D. Never</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HRCT-high resolution computed tomography, IPF-idiopathic pulmonary fibrosis

in conformity with these guidelines remains unclear. There have been a few surveys on the knowledge and practices of physicians on DPLDs and IPF prior to the advent of the new guidelines. A recent large survey of French physicians (post guidelines) revealed that although 67% of them knew about the 2011 international guidelines, yet only 36% utilized multidisciplinary discussion in the management of IPF, and 49% continued to treat their patients with corticosteroids. Similarly, in an Australasian
survey, it was found that 33% of the physicians used corticosteroids and/or azathioprine in the management of their IPF patients. Thus, there seems to be an unmet educational need among physicians with regards to IPF. Whether a continuing medical education (CME) activity would help in meeting this need has never been studied.

The American College of Chest Physicians (ACCP) recommends that CME activities should be used to improve physician knowledge. A continuing medical education program is organized every year at our center, a tertiary care teaching institute in the northern part of India. The attendees are physicians drawn predominantly from the surrounding regions and have various levels of qualifications. To improve the general understanding of interstitial lung diseases (ILDs) and IPF among the attendees, the theme of this year’s CME was selected as ‘Diffuse parenchymal lung diseases’. We hypothesized that the CME attendance would improve their knowledge and belief scores.

In this study, we aimed to assess the knowledge, attitudes, beliefs and practices regarding IPF of physicians attending the CME activity at our center. We also sought to determine the impact of the CME on the knowledge, attitudes, and beliefs of the attendees.

**Subjects and Methods**

This was a questionnaire-based study with a pretest-posttest design and without a control group. The study was exempted from a full ethical review by the Institute Ethics Committee.

Study subjects and intervention: The study population comprised of attendees at the CME program at our center based on the theme ‘Diffuse parenchymal lung diseases’ held on October 18, 2015. The CME activity had a didactic content comprised of lectures, an academic pro-con debate, case presentations, and panel discussion. The content covered several aspects of diagnosis and management of IPF including the clinical, radiologic, and pathologic features, role of lung biopsy, drug treatment, and the role of transplantation. The speakers of the program were reputed academic pulmonologists. The CME program was approved by the Regional Medical Council and was accredited for four CME hours.

Study questionnaire: Attendees at the CME were informed of the purpose of the survey and were invited to complete the study questionnaire if they consented to participate. The same questionnaire was self-administered by the participants before (pretest) and after (posttest) attending the CME. While the pretest was completed by all attendees before entering the venue, the posttest was administered to only those attendees who attended the entire event. Those who came late (joined after the start of the programme) or left early (before completion of the programme) were not given the posttest questionnaire. The questionnaire (Table 1) consisted of 18 items (9 knowledge, 5 belief, 3 attitude, and 1 practice question). Each question was accompanied by 2-8 possible answers (with single or multiple options being correct). The items of the questionnaire were designed by the Delphi method by all the authors. The questionnaire was tested in a pilot assessment on five subjects undergoing training in internal medicine at our institute to estimate the face validity. These subjects were not enrolled in the current study.

The knowledge and belief questions were designed to test the participants’ knowledge on the epidemiology, pathogenesis, diagnosis and treatment of IPF. The knowledge and belief questions (14 questions) were scored (Table 1) as they were objective (had definite correct and incorrect answers). One point was awarded for each correct answer. Three questions (Table 1, items 4, 8, and 9) had more than one correct option and a point was awarded for each correct option marked. The total score obtainable for the knowledge and beliefs questionnaire ranged from 0 to 17. The attitude and practice questions were more subjective and were not scored.

Data were also collected on the educational qualifications, designation, professional setting of the participating physicians and the type of practice (type of patients encountered). It was defined a priori that only those questionnaires would be considered complete and included in the analysis which carried all the demographic details and a response to >80% (15/18) items.

The mean change in the score on knowledge and beliefs questionnaire after attending the CME program was calculated. The change in the proportion of participants with a score of 8 or more (i.e. more than 50% correct answers) between the pretest and posttest questionnaires was also assessed.

Statistical analysis: Qualitative data are expressed as number (percentage) while quantitative data are expressed as mean (standard deviation [SD]) or median (interquartile range). The categorical data regarding the proportion of correct responses to each individual question and the proportion of participants with a score of 8 or more were compared between the pretest and posttest using the (one sided) chi-square test. Mann Whitney U test was used for comparisons of scores between two independent groups. The pretest and posttest scores were compared using the Wilcoxon signed ranks test. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 22, IBM, Armonk, NY) and StatsDirect version 2.8.0. A p value <0.05 was
considered statistically significant.

**Results**

A total of 98 physicians agreed to participate in the study; 84 pretest questionnaires were completed and included in the analysis. The qualification of a majority (64%) of participants was either a postgraduate course in internal medicine or pulmonary medicine (pursuing or completed), while a reasonable proportion (18%) mentioned fellowship in pulmonary medicine as their qualification (Table 2). Most of the participants were either students or practitioners and more than a half (56%) worked in a public sector hospital.

The mean (SD) total score for knowledge and beliefs questionnaire for the entire cohort (n=84) was 10.7 (3.5) with a range from 3 to 17. Sixty nine (82.1%) participants scored 8 or more (i.e., >50% correct responses) in the knowledge and beliefs questionnaire. Of the entire cohort, the posttest questionnaires were completed by 52 participants.

The mean (SD) pretest and posttest scores of these 52 participants were 10.3 (3.4) and 11.1 (2.9) respectively (p=0.048) with a mean increase of 0.8. The proportion of participants who scored >50% increased significantly (p=0.046) from 41 (78.8%) to 48 (92.3%) between the pretest and posttest questionnaires. In the entire cohort of 84 participants, 54.8% of the participants responded correctly (both correct options marked) to the question on HRCT features of IPF (Table 3, item 8), while 47.6% responded correctly to the question on the drugs useful for long term management of IPF (Table 3, item 9). Thirty-three (39.3%) and 27 (32.1%) participants considered steroids and azathioprine effective in the long term management of IPF, respectively.

A majority (55%) of the participants responded that they would diagnose and treat patients with suspected IPF themselves (Table 4). A majority (66%) also said that they would tell their patients with IPF that the disease had a guarded prognosis and treatment may or may not benefit them. The proportion of participants strongly disagreeing with the idea that ‘resources for education should not be directed towards IPF as it is rare in the country’ increased from 35% to 52% after the CME. More than half the participants (57%) communicated that the last time they saw a patient with suspected IPF, they had diagnosed IPF on HRCT chest and referred the patient to a higher center.

### Table 2: Demographic characteristics of the 84 participants who completed the pretest questionnaire

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualification</td>
<td></td>
</tr>
<tr>
<td>Medical graduates</td>
<td>7 (8.3)</td>
</tr>
<tr>
<td>Postgraduate course in pulmonary medicine</td>
<td>32 (38.1)</td>
</tr>
<tr>
<td>Postgraduate course in internal medicine</td>
<td>30 (35.7)</td>
</tr>
<tr>
<td>Fellowship in pulmonary medicine</td>
<td>15 (17.9)</td>
</tr>
<tr>
<td>Designation</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>36 (42.9)</td>
</tr>
<tr>
<td>Practitioner</td>
<td>38 (45.2)</td>
</tr>
<tr>
<td>Faculty in a teaching institute</td>
<td>10 (11.9)</td>
</tr>
<tr>
<td>Practice setting</td>
<td></td>
</tr>
<tr>
<td>Office based</td>
<td>4 (4.8)</td>
</tr>
<tr>
<td>Corporate hospital</td>
<td>33 (39.3)</td>
</tr>
<tr>
<td>Public sector hospital</td>
<td>47 (56.0)</td>
</tr>
<tr>
<td>Type of practice</td>
<td></td>
</tr>
<tr>
<td>General medicine clinic</td>
<td>26 (31.0)</td>
</tr>
<tr>
<td>General medicine clinic with predominantly chest disease patients</td>
<td>25 (29.8)</td>
</tr>
<tr>
<td>Chest clinic</td>
<td>33 (39.3)</td>
</tr>
</tbody>
</table>

### Table 3: Participant responses to knowledge and belief questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Correct responses, number (percentage)</th>
<th>Entire cohort (N=84)</th>
<th>Pre CME (N=52)</th>
<th>Post CME (N=52)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 The terms interstitial lung disease and idiopathic pulmonary fibrosis can be used interchangeably</td>
<td>60 (71.4)</td>
<td>37 (71.2)</td>
<td>42 (80.8)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>2 The mean age at diagnosis is between</td>
<td>33 (39.3)</td>
<td>19 (36.5)</td>
<td>23 (44.2)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>3 IPF is more common in</td>
<td>52 (61.9)</td>
<td>34 (65.4)</td>
<td>36 (69.2)</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>4 Risk factors for the occurrence of IPF</td>
<td>1 correct: 33 (39.3)</td>
<td>1 correct: 22 (42.3)</td>
<td>1 correct: 27 (51.9)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>5 Median survival in IPF</td>
<td>36 (42.9)</td>
<td>20 (38.5)</td>
<td>19 (36.5)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>6 The diagnosis of IPF requires</td>
<td>71 (84.5)</td>
<td>44 (84.6)</td>
<td>43 (82.7)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>7 Histopathological diagnosis should be obtained in all cases if possible</td>
<td>43 (51.2)</td>
<td>25 (48.1)</td>
<td>25 (48.1)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>8 The features of IPF on HRCT of the chest include</td>
<td>1 correct: 35 (41.7)</td>
<td>1 correct: 27 (51.9)</td>
<td>1 correct: 23 (44.2)</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>9 Drugs found to be effective in long term management of IPF</td>
<td>1 correct: 31 (36.9)</td>
<td>1 correct: 23 (44.2)</td>
<td>1 correct: 21 (40.4)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>10 IPF has a strong familial basis</td>
<td>43 (51.2)</td>
<td>26 (50.0)</td>
<td>20 (38.5)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>11 IPF occurs only in smokers</td>
<td>68 (81.0)</td>
<td>42 (80.8)</td>
<td>40 (76.9)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>12 IPF occurs in those with connective tissue diseases</td>
<td>32 (38.1)</td>
<td>19 (36.5)</td>
<td>17 (32.7)</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>13 Lung transplantation is the only definitive management option for advanced IPF</td>
<td>68 (81.0)</td>
<td>40 (76.9)</td>
<td>46 (86.5)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>14 Can IPF and emphysema be present in the same patient?</td>
<td>62 (73.8)</td>
<td>35 (67.3)</td>
<td>39 (75.0)</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

*One-tailed t values for comparisons between pretest and posttest responses. CME—continuing medical education, HRCT—high resolution computed tomography, IPF—idiopathic pulmonary fibrosis.
Table 4: Participant responses to attitude and practice questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attitude questions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Entire group</strong></td>
<td>Pretest (N=52)</td>
</tr>
<tr>
<td>1 What would you do if a patient with suspected IPF presents to you?</td>
<td></td>
</tr>
<tr>
<td>I would refer all patients of suspected IPF to a tertiary care center</td>
<td>12 (14.3)</td>
</tr>
<tr>
<td>I will establish the diagnosis of IPF and then refer</td>
<td>24 (28.6)</td>
</tr>
<tr>
<td>I will diagnose and treat the patient myself</td>
<td>46 (54.8)</td>
</tr>
<tr>
<td>Did not respond</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>2 What will you tell your patient about the prognosis of IPF?</td>
<td></td>
</tr>
<tr>
<td>I will tell the patient he will completely recover with treatment</td>
<td>0</td>
</tr>
<tr>
<td>I will tell the patient that the disease is self-limiting and he will completely recover</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>I will tell the patient that he has a progressive disease with a guarded prognosis and that treatment will definitely benefit him</td>
<td>25 (29.8)</td>
</tr>
<tr>
<td>I will tell the patient that he has a progressive disease with a guarded prognosis and that treatment may or may not benefit him</td>
<td>55 (65.5)</td>
</tr>
<tr>
<td>I will tell the patient that he has a fatal disease and not offer him any treatment</td>
<td>0</td>
</tr>
<tr>
<td>Did not respond</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>3 Resources for education should not be directed towards IPF as it is rare in the country</td>
<td></td>
</tr>
<tr>
<td>Strongly agree</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Somewhat agree</td>
<td>12 (14.3)</td>
</tr>
<tr>
<td>Disagree</td>
<td>38 (45.2)</td>
</tr>
<tr>
<td>Strongly disagree</td>
<td>27 (32.1)</td>
</tr>
<tr>
<td>Did not respond</td>
<td>5 (6.0)</td>
</tr>
</tbody>
</table>

**Practice question**

1 The last time I saw a patient with suspected IPF: | Entire group (N=84) |
| Referred him/her to a higher center straightaway | 4 (4.8) |
| Obtained an HRCT of the chest and referred him/her to a higher center | 15 (17.9) |
| Diagnosed IPF on HRCT of the chest and referred him/her to a higher center | 48 (57.1) |
| Obtained a surgical lung biopsy and managed him/her further | 14 (16.7) |
| Did not respond | 3 (3.6) |

HRCT-high resolution computed tomography, IPF-idiopathic pulmonary fibrosis

**Discussion**

The study demonstrates that a CME activity consisting of didactic training leads to only a marginal improvement in the knowledge and belief scores of the attendees on IPF. Whether this small increase in the scores actually translates into improvement in their clinical practice cannot be discerned from the current study. To the best of our knowledge, this is the first study to evaluate the knowledge, beliefs, attitudes and practice of physicians regarding IPF in India. This is also the first study ever to evaluate the impact of a CME program on the knowledge of physicians on IPF.

Most (82%) attendees at the CME scored reasonably (>50% correct responses) on the pretest knowledge and belief questionnaire. The proportion obtaining a score >50% increased significantly after the event. However, on a closer look, the gaps in practically useful knowledge become evident. About 28.6% of the physicians thought that the terms ILD and IPF can be used interchangeably. Further, about 45% of the participants could not identify the two important features of IPF on HRCT correctly (Table 3). Similarly, about 52% of the participants could not point out correctly that the drugs that have been found useful in the long term management of IPF are pirfenidone and nintedanib. About 39% and 32% of the respondents considered steroids and azathioprine, respectively to be useful in the long term management of IPF. This is similar to an older US survey and a recent French study, in which 39% and 49% of the respondents treated their IPF patients with corticosteroids. The low level of awareness regarding IPF among physicians may be attributed to a number of factors. First, our understanding of the various entities clubbed under DPLDs and IPF in particular has evolved considerably in recent times. Novel techniques for diagnosis (e.g., transbronchial lung biopsy with a cryoprobe) and novel treatments have become available only in the past decade. Practising physicians who received medical education years ago might not be familiar with the latest advances in knowledge. Second, IPF is a relatively rare disease and few physicians encounter IPF patients routinely. Due to the lack of knowledge at the primary care level, the median delay in diagnosis of IPF may be about 1.5-2 years.

In a European study, more than half of the patients with IPF had visited three or more physicians before receiving an IPF diagnosis. Further, due to a high prevalence of tuberculosis and its sequelae in this country, interstitial lung diseases are often misdiagnosed as post tuberculosis lung fibrosis. Third, there is a lack of facilities for high quality HRCT of the chest and a dearth of well-trained pulmonary radiologists. Therefore, radiologists often report the thoracic CT of IPF patients as just ILD without further mentioning...
the specific type. Multidisciplinary discussions are not held commonly as recommended for the diagnosis of idiopathic interstitial pneumonias. In the French study, only in 36% of the cases, management of IPF resulted from a multidisciplinary discussion. Finally, although pirfenidone has been available in the country for the past 5 years, its appropriate use is still not known to many physicians; nintedanib is not yet available in the country.

The absolute increase in the knowledge scores of the physicians after attending the CME was only marginal, although statistically significant. This indicates that a CME offering a single exposure to didactic training may not be adequate to significantly improve the knowledge of the participants. According to the ACCP educational guidelines, multiple instructional techniques and multimedia CME interventions are preferable to single-medium and single technique interventions during CME programs. Holding workshops designed to train the attendees in the application of diagnosis and management guidelines with one-to-one interaction between the instructor and the participants might be an effective alternative. Repeated exposures may further enhance the effectiveness of educational interventions.

On a more positive note, most physicians (95.3%) were aware of the progressive nature and guarded prognosis of the disease and were ready to communicate to their patients just the same. An interview based study demonstrated recently that there was a need to convey more information regarding the progression of IPF to patients and their caregivers and develop palliative interventions. This requires concerted efforts on the part of physicians to establish a good relationship with their patients. A majority (77.3%) of physicians in the current study also disagreed with the idea that ‘resources for education should not be directed towards IPF as it is rare in the country’. Further, the CME also had an impact on their attitude so much so that the proportion of physicians ‘strongly disagreeing’ with this notion increased from 35% to 52%. A majority of the physicians (57%) in the current study referred their patients to higher centers for management higher than the proportion (35%) reported in a previous study. About 81% believed that lung transplantation was the only definitive management for advanced disease as compared to 61% observed in a previous study.

The study has important implications both at the national and global level. Being the first study of its kind on IPF, it raises questions on the awareness of physicians regarding the uncommon disease entity of IPF. It also draws attention to the fact that despite the availability of international guidelines on IPF, the reach of consensus statements to physicians far and wide may not be adequate. Similar studies need to be performed in different regions of this country and in other countries to identify the knowledge gaps among physicians across the world. There is also a need for focused CME programs and workshops to bridge these gaps.

The study has several important limitations. The questionnaire used in the study was investigator-designed and has not been formally validated. However, a validated questionnaire to assess physician knowledge on IPF is not available. In the absence of a validated questionnaire, previous large studies have also used investigator designed non-validated survey instruments. Most of the attendees at the CME had received postgraduate education or were enrolled in postgraduate medical programs. Thus, the findings cannot be generalized to a broad population of physicians as most primary care physicians in India especially in rural areas are medical graduates. There was no control group in this study. However, numerous studies using a similar design without controls have shown the effectiveness of CME in enhancing the knowledge of participants.

In conclusion, significant deficiencies were identified in the knowledge of physicians attending a CME regarding IPF. A CME program with didactic lectures helps in improving the knowledge only marginally. Further studies from different regions are needed to identify the knowledge gaps. Finally, there is a need for focussed interactive workshops to fill in these gaps.

References


High Prevalence of Obstructive Sleep Apnea among People with Type 2 Diabetes Mellitus in a Tertiary Care Center

Vijay Viswanathan¹, Indira Priyadarshini Ramalingam², Nagarajan Ramakrishnan³

Abstract

Purpose: Untreated obstructive sleep apnea (OSA) is a risk factor for hypertension and cardiac events, and is associated with increased mortality. Recent studies indicate that majority of people with type 2 diabetes also has OSA. The aim of this study was to assess the prevalence and severity of OSA and risk factors contributing to it among people with chronic and severe type 2 diabetes.

Methods: A total of 203 people with type 2 diabetes (mean age: 54±8 years, 145 males, 58 females, HbA1c ≥7% [53mmol/mol]) attending a diabetes specialty hospital were included in the study; all were subjected to comprehensive diabetic evaluation and Apnea Hypopnea Index (AHI) was used to evaluate OSA.

Results: 23.65% of the study subjects had OSA (AHI ≥15). OSA was more prevalent among men compared to women. BMI, was significantly higher among subjects with OSA (P=0.01). People with OSA had higher percentage of diabetic complications such as cardiovascular disease (CVD), retinopathy and neuropathy. Hypertension was identified as independent predictors of OSA.

Conclusions: Prevalence of OSA was higher in this study compared to Indian studies hitherto. Since OSA is treatable, people with diabetes should be screened for this condition to reduce their CVD risk.

Introduction

Sleep apnea refers to breathing abnormalities that occur during sleep and comprises mainly of obstructive sleep apnea, central sleep apnea and mixed sleep apnea. OSA is characterized by repetitive upper airway obstructions leading to intermittent hypoxia and sleep fragmentation. Due to poor sleep quality, those with OSA experience day-time fatigue, sleepiness, functional impairment and overall reduction in quality of life. OSA is a common disorder found in people with obesity, diabetes, hypothyroidism and CVD. According to the reports of National Sleep Foundation, the prevalence of sleep apnea among adult population of the U.S.A is approximately 18 million.¹ Though there are no nation-wide studies on the prevalence of OSA, in Indian population cross sectional studies conducted across various sub-populations reported a prevalence of 13.7% among adults² and 7.5% among urban middle-aged men.³

Type 2 diabetes has attained the status of an epidemic and in India with more than 62 million individuals currently diagnosed with the disease.⁴ It has been reported that the majority of people with type 2 diabetes also have OSA.⁵ Since intermittent hypoxia has been shown to exert adverse effects on glucose metabolism, OSA not only increases the risk of developing type 2 diabetes but also contributes to poor glycemic control in people with existing diabetes.⁶ A recent follow-up study in Chinese population has shown that poor sleep quality and short sleep duration contributed substantially to increased risk for type 2 diabetes which is an independent of the potential confounders such as age, obesity, family history of diabetes.

¹Head & Chief Diabetologist, M.V. Hospital for Diabetes & President, Prof. M. Viswanathan Diabetes Research Centre, Chennai, Tamil Nadu; ²Clinical Research Associate, Prof. M. Viswanathan Diabetes Research Centre, Chennai, Tamil Nadu; ³Senior Consultant and Director, Nithra Institute of Sleep Sciences, Chennai, Tamil Nadu

Received: 08.01.2016; Revised: 26.05.2017; Accepted: 05.07.2017
and so on. Moreover, European Sleep Apnea Cohort Study has shown that people with diabetes with severe OSA had higher HbA1c levels compared to non-apneic people with diabetes. Moderate to severe OSA is also a significant risk factor for cardiovascular events. Both diabetes and OSA contribute independently to incidence of cardiovascular events, and the co-existence of both conditions may promote cardiovascular morbidity and mortality among such individuals.

While few investigators have studied the prevalence of OSA among certain Indian populations based on age and gender, studies on the prevalence of OSA among people with diabetes in India is sparse. The Chennai Urban Rural Epidemiology Study has reported that the age-standardized prevalence of diabetes in Chennai, an urban metro located in Tamil Nadu, is 14.3% and that the prevalence has increased by 72.3% within a span of 14 years. There are no studies from this part of India on the prevalence of OSA among people with diabetes, especially among those with severe and chronic diabetes. Hence we conducted a study to assess the prevalence and severity of OSA and risk factors contributing to it among people with inadequately controlled type 2 diabetes.

Methods

The study was conducted at a tertiary care diabetes hospital in Chennai according to Declaration of Helsinki and its later amendments. The study was approved by the Institutional Ethics Committee and informed consent was obtained from all the participants. 275 subjects of both sex attending the hospital with HbA1c ≥7% [53mmol/mol], and willing to participate in the study were considered. Subjects taking sleep medicines were excluded from this study. Subjects were screened for OSA by ResMedApneaLink™ Plus (ResMed Germany Inc., Germany). Apnea Hypopnea Index (AHI) was used to determine OSA (overnight evaluation, minimum duration: 5:30 hours) and daytime sleepiness was assessed using Epworth Sleepiness Scale (ESS).

According to the American Academy of Sleep Medicine (AASM) a threshold of 15 events (AHI or RDI) per hour with or without symptoms or 5 events per hour with symptoms were considered as OSA. In the present study type 4 polysomnography has been used and AHI has been used for diagnosis of OSA with a cut off of 15. Oxygen desaturation index (ODI) was measured using oximetry. ESS score of >10 was considered to be abnormal, indicative of overnight sleep disturbances. The result obtained by Apnea Link was correlated with ESS. Subjects whose evaluation time was less than the minimum stipulated duration were excluded from the study. At the end, 203 subjects satisfying inclusion criteria (145 males, 58 females) were included in this study.

Anthropometric measurements including height, weight, BMI, waist circumference, hip circumference and neck circumference were recorded (the mean of two consecutive measurements was considered for each variable). Other clinical data collected included history of hypertension, duration of diabetes, current medication and presence of complications of diabetes such as retinopathy, neuropathy, nephropathy, peripheral vascular disease (PVD), CVD (known history of myocardial infarction, coronary artery bypass graft, coronary angioplasty) and stroke. Self-reported snoring habit and presence of dental deformities were documented. Dental deformity refers to the presence of malocclusions (crooked or crowded teeth), and this was identified by a dentist. Lipid profile, liver function test parameters and renal function test parameters were estimated in blood using BS-400 Mindray Chemistry Analyzer and HbA1c was estimated by HPLC (Biorad).

Data was analyzed using SPSS 19.0. The categorical variables are represented as percentages and measurable variables as mean ± standard deviation. Chi square test was done to compare categorical variables, whereas t test was done to compare quantitative variables between subjects with and without OSA. ANOVA was done to compare the variables between subjects categorized into different groups based on the severity of OSA (normal, mild, moderate and severe). P value <0.05 was considered significant in all analyses. Multiple logistic regression analysis was used to identify the confounders.

Results

Clinical characteristics

The mean age of the total study subjects was 54±8 years. The mean duration of diabetes was 12±8 years and 72.1% of subjects had a family history of diabetes. 78.8% were non-smokers and 80.3% of them did not consume alcohol. Their mean BMI was 28.3±5.2 kg/m², waist circumference was 100.5±12 cm, hip circumference was 100.4±13.3 cm and neck circumference was 38.6±5.4 cm. 75.8% of the subjects reported that they had snoring habit and 29.1% were identified to have dental deformities. Mean HbA1c% was 9.6±2.0 (81±15 mmol/mol), [range: 7 - 19.4 (53 - 189 mmol/mol)] and dyslipidemia was prevalent among 70% of these subjects. On comparing the anthropometric measurements of men and women, BMI and hip circumference were significantly higher among women, whereas height and neck circumference were higher among men (P<0.001, Table 1).

Prevalence of OSA and confounders

Prevalence of OSA was found to be 23.65% among the study subjects. OSA showed weak
positive correlation with ESS score (r = 0.29). IAHIAA OSA was more prevalent among men compared to women (73.46% vs. 26.53%). Among habitual snorers, 83.33% had OSA, whereas only 16.66% subjects had OSA among those who did not snore (P = 0.013). The prevalence of OSA among those subjects with dental deformities was not significantly higher compared to those without dental deformities (P = 0.34). The percentage of hypertensive’s among subjects with OSA was higher (79.16%) but their number did not differ significantly between the two genders. While the co-existence of diabetic complications and OSA were analyzed, it was seen that 66.6% of subjects with neuropathy, 37.5% with nephropathy, 37.5% with retinopathy and 25% with CVD had OSA.

The mean age of subjects with OSA was higher than those without OSA (P = 0.020). Weight, BMI, and waist circumference were also significantly higher among subjects with OSA (P = 0.004, 0.002, and 0.001 respectively). Biochemical parameters analyzed such as HbA1c, liver enzymes - alanine aminotransferase (ALT) and aspartate aminotransferase (AST), serum urea, serum creatinine, total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol did not differ significantly between those with and without OSA (Table 2).

Multiple logistic regression analysis showed that BMI, contributing to OSA among our study subjects (P = 0.01). When separate analysis was done for both genders, it was found that presence of hypertension were associated with OSA among men (0.03) and BMI among women (0.05).

Discussion

OSA is characterized by fragmented sleep due to micro-arousals causing non-refreshing sleep owing to poor quality of sleep. OSA and diabetes share several risk factors such as advancing age, obesity etc. Much data exists in various populations to prove the link between OSA and diabetes, and there are studies that have shown the adverse impact of reduced sleep duration on glucose metabolism even among normal subjects. Different pathophysiological mechanisms such as high sympathetic nervous system activity, intermittent hypoxia, dysregulation of hypothalamus-pituitary axis etc. have been proposed to cause this alteration. Our study focused on the prevalence and associated factors of OSA among people with poorly controlled type 2 diabetes mellitus. The prevalence of OSA in this study was higher than those reported among people with diabetes from other parts of India. This could be because we studied a population with chronic and severe diabetes, and glycemic status has been shown to be highly correlated with OSA. A hospital-based study conducted by Ekka et al., showed that among 325 subjects with type 2 diabetes in North India, the prevalence rate for OSA was 24.3%. Yet another study from West India among people with diabetes, with a smaller sample size (n=33), showed that OSA was present among 27% of its study population. The highest prevalence of OSA reported so far, 86%, was from a study done among obese subjects with type 2 diabetes mellitus in USA. Higher prevalence of OSA among men compared to women has been long recognized by different researchers internationally. This holds true

Table 1: Comparison of anthropometric data of men and women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gender</th>
<th>Mean ± SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>Men</td>
<td>167±6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>153±9</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>163±9</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Men</td>
<td>76.7±12.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>73.0±19.15</td>
<td>0.12</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>75.7±14.36</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Men</td>
<td>27.4±4.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>30.7±5.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>28.3±5.22</td>
<td></td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>Men</td>
<td>100.0±12.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>101.5±11.92</td>
<td>0.44</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>100.4±12.00</td>
<td></td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>Men</td>
<td>98.3±11.73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>105.5±15.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>100.4±13.32</td>
<td></td>
</tr>
<tr>
<td>Neck (cm)</td>
<td>Men</td>
<td>39.9±5.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>35.2±2.70</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>35.8±5.40</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Comparison of anthropometric measurements and biochemical estimations between subjects with and without OSA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without OSA (≤15)</th>
<th>With OSA (≥15)</th>
<th>95% CI of the difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>27.7±4.9</td>
<td>30.5±5.7</td>
<td>-4.57</td>
<td>-1.06</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>98.6±12.15</td>
<td>106.5±14.8</td>
<td>-11.92</td>
<td>-4.00</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>99.5±12.86</td>
<td>103.7±14.8</td>
<td>-4.00</td>
<td>0.42</td>
</tr>
<tr>
<td>Neck (cm)</td>
<td>38.5±5.77</td>
<td>38.8±4.44</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>ESS</td>
<td>5.6±3.15</td>
<td>6.4±5.46</td>
<td>-2.33</td>
<td>0.70</td>
</tr>
<tr>
<td>HbA1c % (mmol/mol)</td>
<td>9.6±2.19</td>
<td>9.2±3.19</td>
<td>-0.26</td>
<td>1.16</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>25.7±29.98</td>
<td>24.2±17.88</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>31.4±25.24</td>
<td>28.4±20.14</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>32.4±23.27</td>
<td>37.1±26.24</td>
<td>0.75</td>
<td>3.18</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1±0.79</td>
<td>1.2±0.87</td>
<td>0.36</td>
<td>0.16</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>165.6±51.77</td>
<td>165.8±51.58</td>
<td>0.12</td>
<td>0.09</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>184.3±191.2</td>
<td>153.5±78.85</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>38.9±9.64</td>
<td>41.28±7.08</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>90.9±31.25</td>
<td>93.8±34.68</td>
<td>0.64</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD: Standard deviation, CI: Confidence interval, kg/m²: kilogram per square metre, cm: centimetres, mmol/mol: millimoles per mol, U/L: International units per litre, mg/dL: milligrams per decilitre, mmol/L: millimoles per litre

Note: *P value men vs women

SD: Standard deviation, cm: centimetres, kg: kilograms, kg/m²: kilogram per metre square; P value men vs women
among Indian population also, and the results of our study agree with these findings.

Snoring has been established to be a symptom or confounding factor for OSA. There are several studies that have shown that habitual snoring causes irregularities in the glucose metabolism such as decreased insulin sensitivity and elevated HbA1c levels. It should be noted in this context that a high proportion of our study subjects had all the three inter-related conditions, i.e., snoring, OSA and poorly controlled diabetes. Also, a high percentage of men who reported habitual snoring in this study had OSA. The relationship between duration of diabetes and OSA has not been well studied. Our results indicate that severity of OSA may increase with longer duration of diabetes, which agrees with the results from the study by Ekka et al. Hypertension was present among 76.16% of subjects with OSA in this study. Previous investigations report that hypertension prevails among approximately 60% of subjects with OSA and OSA can lead to persistent systemic hypertension. The Wisconsin Sleep Study has reported that this relationship is independent of other confounding variables like BMI. Hypertension was found to have independent association with OSA, and it was gender-related in our study. There is paucity of data in both international and Indian population on the prevalence of diabetic complications among people with diabetes and OSA. Those with severe OSA had higher prevalence of chronic diabetic complications, particularly CVD, in this study. An 11 year prospective study from California shows that the death rate due to CVD was approximately double among people with moderate to severe OSA compared to those with mild or no OSA. Treating OSA among subjects with CVD would be beneficial as such people are at higher risk to experience severe cardiovascular consequences and mortality.

The mean age of subjects with OSA was higher in this study and it has been proven that the prevalence of any type of sleep apnea (central or obstructive) increases with age, though an independent relationship is not well established. The positive association between OSA and factors such as BMI, neck circumference and waist circumference was seen among the subjects of this study. BMI had high association with OSA among women, whereas no such relationship was observed among men. Obesity is an obvious risk factor for OSA and high proportion of subjects with OSA have high BMI. Mayer et al in their study among OSA and non-OSA subjects showed that upper airway anatomy differs considerably among people with high BMI, which contributes to breathing abnormalities in them while sleeping. An earlier study by our group has shown that OSA was highly prevalent among people with type 2 diabetes (28%) even when their BMI were low. Waist circumference, a confounding factor for obesity, was significantly higher among women subjects of this population. Visceral adiposity has been shown to be linked independently with OSA among men, but not among women previously.

Our study has some major limitations. The study was conducted among subjects with inadequately controlled diabetes, and thus the results may not be applicable directly to a population with good or fair glycemic control. Though the study provides some useful insights on OSA among people with diabetes, being a hospital-based study, the results cannot be generalized. We did not use the gold standard, polysomnography, for evaluating OSA among our study subjects that might have affected the accuracy of the test results.

Conclusions

Our study shows that OSA is highly prevalent among people with type 2 diabetes with in adequate glycemic control. High rate of OSA observed among our study subjects warrant that people with diabetes should be screened and treated for OSA since the co-existence of these two conditions increase their CVD risk. BMI, neck and waist circumference, male gender, presence of hypertension etc. have been identified as the risk factors contributing to OSA in this population. Prospective studies in this direction are required to know if improving blood pressure control, BMI, neck and waist circumference would reduce the incidence of OSA among people with diabetes.

Compliance with Ethical Standards

Conflicts of interest: The authors declare that they have no conflict of interest.

Research involving Human Participants: The study was approved by Institutional Ethics Committee and has been performed in compliance with the Declaration of Helsinki and its later amendments.

Informed consent: All participants gave informed consent for this study.

Acknowledgement

The authors wish to thank Mr. Sriram Ramachandran and Sabitha Palazhy for statistical analysis of data and Baby Priya Surulimuthu for helping in data collection.

Funding

This study was funded internally by Prof. M. Viswanathan Diabetes Research Centre.

References

3. Udwadia ZF, Doshi AV, Lonkar SG, Singh CI.


27. Vijay V, Ramakrishnan N, Sunanina S, Vigneswari A, Satyavani K. Subjects with type 2 diabetes may have obstructive sleep apnoea even at lower BMI values. *Ind J Sleep Med* 2012; 7:45-47.


Study of Association of Thyroid Hormone in Pre-Eclampsia and Normal Pregnancy

L Harshvardhan¹, SS Dariya², Aradhana Sharma³, Lalita Verma⁴

Abstract

Aim: The aim of the study was to assess association of thyroid hormone in preeclampsia and normal pregnancy.

Material and Method: This was a hospital based observational case control study. Total 100 women were included, out of them 50 normal pregnant women in control group and 50 pre-eclamptic women in case group were included.

Result: In this study no significant difference was found in FT3 (p value 0.085) and FT4 (p value 0.065) in control and case group. TSH and Anti TPO levels in control and case group were statistically significant (p value <0.001 and <0.000).

Conclusion: We observed that thyroid hormones (TSH and Anti TPO) have statistically significant relation in pre-eclamptic women.

Introduction

Preeclampsia is the leading cause of maternal mortality in developing countries and is associated with a five-fold increase in perinatal mortality.¹ Preeclampsia is defined by National High Blood Pressure Education Program working Group as if blood pressure after 20 weeks of gestation is raised to 140/90 mm of Hg or more or have mean B.P. (diastolic+1/3rd pulse pressure) of more than 110 mm of Hg. The increase in B.P. have to be present on at least two occasions 6 hour apart along with presence of proteinuria and /or oedema.²

Pregnancy is associated with many hormonal changes which includes increase in estrogen, human chorionic gonadotropin, human chorionic somatotropin, prolactin and decrease in thyroxine.³ It has long been recognized that maternal thyroid hormone excess or deficiency can influence maternal and fetal outcome at all stages of pregnancy and can interfere with ovulation and fertility.⁴

The mechanism and clinical significance of hypothyroidism in preeclampsia is controversial and may be related to decreased plasma protein concentrations and increased endothelin level.⁵

Owing to various changes in thyroid profile of patients with preeclampsia and in normal pregnancy, an attempt was made to study the comparison of serum levels of FT3, FT4, TSH and Anti TPO in preeclampsia and normal pregnancy.

Material and Methods

After taking informed consent and clearance from institutional ethical committee, 100 women were included for the study. This is a hospital based observational study having a case control design. It was performed on 50 normal pregnant women and 50 pre-eclamptic women who were admitted in the department of obstetrics and gynecology SMS medical college Jaipur.

Inclusion criteria for women

1. Patients of preeclampsia in third trimester of pregnancy.
2. All consecutively diagnosed cases of preeclampsia.
3. No previous history of thyroid disease in pregnancy and postpartum period.
4. No previous history of congenitally malformed baby.

The equal number of matched healthy normotensive pregnant women in the third trimester attending the antenatal clinic during the study period, labeled as control group.

If anytime during the antenatal period, follow-up control group developed hypertension, they were...
were followed up all through their antenatal, intrapartum and postpartum period. They were especially observed for the development of the symptoms and signs of hypo and hyperthyroidism. The normal values used in our study are

- Serum FT3 =1.8-4.2 pg/ml
- Serum FT4 =0.89-1.76 ng/ml
- Serum TSH =0.4-4.0 µIU/ml
- Serum Anti TPO =Upto-35 IU/ml

P value less than 0.05 was considered as significant.

**Observation and Results**

Total 100 women were included, out of them 50 normal pregnant women in control group and 50 preeclamptic women in case group, were enrolled.

The mean age of cases was 25.60 ± 4.36 years and the mean age of control was 24.40 ± 3.30 years (p value=0.124).

Thyroid function testing was major variables of study, and our study shows that mean Free Triiodothyronine (FT3) in case was 2.24±0.82 pg/ml and in control was 1.99 ± 0.60 pg/ml (p value=0.085). Mean Free Thyroxine (FT4) in cases was 1.13±0.45 ng/dl and in control was 1.00±0.20 ng/dl (p value=0.065). Mean Thyroid Stimulating Hormone (TSH) in cases was 5.36±2.66 µIU/ml and in control was 3.48±1.83 µIU/ml (p value<0.001). Mean Anti Thyroid Peroxidase (Anti TPO) in cases in was 46.12±14.56 IU/ml and in control was 22.66±17.39 IU/ml (p value<0.001)

There was no significant difference in FT3 (p 0.085) and FT4 (p 0.065) in control and case group. TSH and Anti TPO levels in control and case group were increased significantly (p value<0.001 and < 0.000) (Table 1) and (Figures 1 and 2).

**Discussion**

Preeclampsia is a leading cause of maternal and fetal/neonatal mortality and morbidity worldwide. The purpose of study to determine thyroid dysfunction in pre-eclamptic women at tertiary care centre. The study was carried out on 100 pregnant woman (50 preeclamptic as casesand 50 normal pregnancy as control) who presented at SMS medical college and attached group of hospitals Jaipur (Rajasthan). The pregnant women were without any comorbid illness. Various studies have sought to determine the relation between deranged thyroid function and preeclampsia. In present study group we observed that there is high prevalence of hypothyroidism approximately 46% in preeclamptic women as compared to 14% in control. These findings supported the report that preeclamptic woman had higher incidence of biochemical hypothyroidism compared with normotensive pregnant woman (Kumar et al. 2005 40% v/s 12.2%).

We observed serum TSH level were

**Table 1: Comparison in thyroid hormone in case and control group**

<table>
<thead>
<tr>
<th></th>
<th>Case Mean ± SD</th>
<th>Control Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>25.60 ± 4.36</td>
<td>24.40 ± 3.30</td>
<td>0.124</td>
</tr>
<tr>
<td>BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>149.52 ± 6.66</td>
<td>121.36 ± 3.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>94.48 ± 3.95</td>
<td>80.16 ± 1.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FT3</td>
<td>2.24 ± 0.82</td>
<td>1.99 ± 0.60</td>
<td>0.085</td>
</tr>
<tr>
<td>FT4</td>
<td>1.13 ± 0.45</td>
<td>1.00 ± 0.20</td>
<td>0.065</td>
</tr>
<tr>
<td>TSH</td>
<td>5.36 ± 2.66</td>
<td>3.48 ± 1.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti TPO</td>
<td>46.12 ± 14.56</td>
<td>22.66 ± 17.39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Fig. 1: Thyroid hormone in normal and preeclamptic women with 3 level of mean BP

Fig. 2: Comparison in thyroid hormone in case and control group
significantly higher in the study group as compared to controls (mean TSH 5.36±2.66 µIU/ml P<.001). These findings are in concordance with kumar et al, Lao et al,⁶ Tehrani et al,⁷ Larijani et al.⁸ On the other hand Khadim et al,⁹ Qublan et al¹⁰ observed insignificant TSH value.

The elevated estrogen levels lead to increased TBG levels in pregnancy. This can explain the elevated TT3 and TT4 levels observed in some studies. However FT3 and FT4 levels remain normal. In pre-eclampsia it is postulated that conversion of T4 to T3 in the liver is hampered which can account for low FT3 levels observed in pre-eclamptic patients. Also it is thought that pre-eclampsia causes a Sick Euthyroid state which leads to low FT3 levels in the presence of normal FT4 and TSH levels.

Also observed in our study were significantly elevated Anti Thyroid Peroxidase (Anti TPO) levels in the study group (46.12 ± 14.56 v/s 22.66 ±17.39 ; p<0.001). This is in concordance with the observation of Alavi et al.¹¹ It has been seen that pregnant women with raised Anti TPO levels carry a higher risk of miscarriage, although the mechanism by which it occurs is not clearly understood.

Conclusion

Thyroid diseases are predisposing factors for development of preeclampsia. We observed statistically significant higher numbers of preclamptic women who has abnormally high TSH levels and Anti TPO levels. A statistically significant higher numbers of cases with pre-eclampsia were also observed (46%) in pregnant women as compared to (14%) in control group. TSH is above 5µIU/ml, than risk of developing preeclampsia is 4-5 times higher. This high risk is potent marker to develop preeclampsia needs further investigation because of small number of subjects in this study. A multicenter study may reveal the association and mechanism of thyroid abnormalities in pre-eclamptic women in different geographical regions.

Such a study helps us to identify thyroid abnormalities and take appropriate therapeutic action to correct them. It may lower the incidence and severity of morbidity and mortality associated with preeclampsia.

References

Etiology and Outcomes of Lower Limb Ulcers in Non-Diabetic Patients, An Experience from Government Hospital in Western India

Yojana Gokhale¹, Amol Raut², Divya Kunal Lala³, Rushabh Kothari², Lalana Kalekar⁴, Amol Kamble⁵

Abstract

Aim: To study the Etiology and Outcomes of Lower Extremity Ulcer in Non-Diabetic Patients.

Method: A total number of 40 patients were collected from Rheumatology services (Department of Medicine), Venous Clinic (Department of Surgery) and Dermatology Clinic (Department of Dermatology) of a tertiary care hospital in Mumbai over a period of 48 months from January 2013 to December 2016. The study included serial recruitment of lower limb ulcer fulfilling inclusion criteria.

Results: Patients with lower limb ulcers presented with a wide range of pathology. Ulcers due to Vasculitis was the most common etiology (40%) and affected females predominantly (12/16). Venous ulcers were the second most common etiology and predominantly affected men (8/10).

Conclusion: It is important to consider differential diagnosis of Vasculitic ulcer in chronic non healing ulcers as they show rapid response to treatment with immunosuppressant. If such ulcers are not promptly diagnosed and treated properly, systemic vasculitis can cause end organ damage or even endanger patient life.

Introduction

A n ulcer is defined as a breach in the continuity of skin and mucous membrane. Chronic ulceration of the lower limb including the foot is a frequent condition leading to pain, social discomfort and generating significant cost implications. Prevalence number (all ulcers) range from 1 % in the adult population to 3-5 % in the population over 65 years of age.1,2 It has been reported that lower limb ulcers related to venous insufficiency constitutes 70% of cases, arterial disease 10%, ulcer of mixed etiology 15% and 5% of leg ulcers occur due to lesser known pathophysiological causes.3 Thus, the later group comprises of considerable diagnostic challenge.

For, a rationale approach towards patients with leg ulcers, it is important to have detailed knowledge about clinical picture, pathogenesis, diagnostic possibilities and treatment modalities of common causes, but at the same time to be aware of the large differential diagnosis of leg ulceration. Because an incorrect diagnosis usually leads to incorrect treatment and crucial time is lost leading to complications. Since numerous factors lead to lower leg ulceration, it is essential that health professionals adopt an interdisciplinary approach to the systematic assessment of the individual in order to ascertain the pathogenesis, a definitive diagnosis and early treatment.

Method

This prospective and retrospective study was conducted for a period of 48 months (Between January 2013 to December 2016) in a tertiary care hospital in Mumbai. Patients of both sex, older than 18 years, and with lower leg ulcer of more than 4-week duration was included in the study. Patients having diabetes and traumatic ulcers were excluded from the study. Details of History and Clinical Parameters were noted with predefined parameters.

¹Professor, ²Registrar, Department of Medicine, ³Fellow in Rheumatology, ⁴Associate Professor, ⁵Lecturer, Department of Medicine, Lokmanya Tilak Municipal Hospital, Mumbai, Maharashtra
Received: 18.04.2017; Revised: 06.06.2017; Accepted: 03.07.2017
Table 1: Baseline characteristic of study population and site of leg ulcer (N=40)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous</td>
<td>10</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>16</td>
</tr>
<tr>
<td>Arterial</td>
<td>4</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>4</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2: Etiology of leg ulcer (N=40)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous</td>
<td>10</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>16</td>
</tr>
<tr>
<td>Arterial</td>
<td>4</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>4</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>3</td>
</tr>
</tbody>
</table>

Result

The Table 1 outlines the baseline characteristics of the study population and site of ulcer. Out of 40 patients (with 50 ulcers) 23 were males and 17 females. The mean age of study population was 44.9 years ranging from 18 to 81 year. The average duration of leg ulcer at the time of presentation was 4.6 months (4 weeks to 52 weeks). The most common site of ulcer was Gaiter area (15 out of 50 i.e, 30%). Out of these 15 ulcers 7 were venous, 6 due to vasculitis, 1 arterial and 1 tuberculosis. The findings imply that even an ulcer on gaiter area, which is conventionally thought to occur due to venous insufficiency needs detailed history and investigation for other probable etiology.

Table 2 outlines the etiology of ulcer in our study population. Out of 40 patients 10 had venous ulcers (M:8, F:2) and 8/10 (80%) had history of of varicose vein, 16 had ulcers due to vasculitis (F:12, M:4), 4 had arterial ulcer, 4 due to Pyoderma gangrenosum, 2 Tuberculosis, 1 malignancy (cutaneous T cell lymphoma) and for 3 patients cause could not be found out.

Table 3 depicts investigation. Rheumatoid factor was positive in 2, Anti-CCP antibody positive in 2. Antinuclear antibody positive in 6 (4 SLE patient, 1 systemic sclerosis and 1 Dermatomyositis. ANCA positive in 4 patients (3 p-ANCA positive and 1 c-ANCA positive). Patient with cANCA also had antibodies to PR3 and was diagnosed as Granulomatosis with polyangiitis. 1 Patient with p ANCA and positive anti-MPO antibodies was diagnosed as microscopic polyangiitis, whereas 2 patients with p ANCA did not have anti MPO but were ANA positive, which was the cause for perinuclear pattern in immunofluorescence (false positive pANCA). Lupus Anticoagulant was positive in 1 patient, 1 patient was HIV positive and etiology of ulcer was tuberculous. Mycobacterium tuberculosis was detected in this ulcer. 4 patients had documented hematuria/proteinuria. ESR was raised in 27 patients (67.5%) out of which 16 were vasculitis, 3 venous, 2 arterial, 2 tuberculosis, 2 idiopathic, 1 malignancy and 1 pyoderma. Infectious ulcers with surrounding skin shows signs of inflammation like warmth and edema have a high ESR. Thereby, implicating that patients with high ESR but without any inflammation of surrounding skin should further be evaluated for etiology like systemic vasculitis, tuberculosis and malignancy. CRP was raised in 25 patients (65%), out of which 16 were vasculitic ulcer, 2 idiopathic, 1 arterial, 2 pyoderma gangrenosum, 3 venous and 1 malignancy. Biopsy performed in 35 patients, 23 leaded to diagnosis as vasculitis:16, pyoderma gangrenosum: 4, Tuberculosis:2, malignancy: 1 and 12 were unyeilding. Nerve conduction study was performed on 9 patients with burning pain in their feet and lack of proprioception to ulcer. 4 were abnormal, 2 patients had small fibre sensory neuropathy and 2 PAN.1 sensory axonal neuropathy was later diagnosed as MPA and 1 as axonal neuropathy diagnosed as PAN. Doppler abnormalities in 15 out of 40 (10 venous, 4 arterial, 1 DVT). The patient with calf vein DVT had ulcer on lateral malleolus and was diagnosed to be Granulomatosis with polyangiitis, 10 patients had either superficial or deep vein incompetence, 2 patients had thrombus in popliteal artery and 2 had fibrofatty plaque occluding vessel lumen leading to ulcer so it makes arterial and
venous study of bilateral lower limb an important diagnostic tool for ulcers.

The Table 4 depicts types of vasculitis and ulcer. Out of total 16 patients of vasculitic ulcer, 2 had medium vessel vasculitis suggestive of Polyarteritis nodosa, 1 had microscopic polyangiitis, 1 had Granulomatosis with Polyangiitis, 4 had Leucocytoclastic vasculitis, 4 Systemic lupus erythematous (3 SLE vasculitis and 1 secondary APLA), 2 were rheumatoid arthritis, 1 had systemic sclerosis and 1 had Dermatomyositis. Out of 4 patients of SLE 2 were diagnosed case and 2 were diagnosed in our clinic. Patients diagnosed as SLE who presented with ulcer were having clinical manifestations suggestive of SLE which in any case would have been diagnosed without a biopsy. They did have clinical features of SLE but were missed by local care givers. Out of 2 RA both patients had history of polyarthritis but were not on DMARDs, they were on alternative medication and correlation of RA with ulcer was detected in our hospital. In a study conducted by Hafner et al on management of ulcer in RA, 9-10% of patients with rheumatoid arthritis were reported to have leg ulcer.4

Table 5 shows nature of surrounding skin of ulcer. 10 patients with venous ulcer (100%) presented with skin changes associated with varicose vein, surrounding skin being hyperpigmented with atrophic blanche and eczema while 12 patients with vasculitic ulcer had normal skin, 3 patients with purpura around ulcer and 1 with gangrenous surrounding skin.

The Table 6 depicts healing of lower limb ulcer in 6 months. Out of 16 patients of vasculitic ulcer, 12 had complete healing, 4 with 50% healing and none required amputation. Whereas ulcers of other etiology like venous 1 healed completely at 6 months, 2 with 50% healing, 3 with 25-50% healing, 3 were non healing ulcers and 1 patient was lost to follow up. 1 patient with tuberculosis had more than 50% healing and 1 was had 25-50% healing. 1 patient with malignancy and 1 with arterial ulcer required amputation. Out of pyoderma gangrenosum 1 healed completely in 6 months and 3 more than 50%.

**Discussion**

Etiology of leg ulcer is varied and depends on the department in which the study was conducted. A study from Australia in 1992 by department of surgery showed that venous ulcer was found to be the most prevalent cause of ulcer in 66.9% of patients, arterial in 27.6%, both arterial plus venous in 14%, Rheumatoid arthritis in 11.2% and diabetes in 12%, in 3.5% cases cause could not be found out.5 Korber et al from Germany in the year 2010 conducted a study on etiology of ulcers with patients from Dermatology department. Their results showed venous insufficiency was dominating factor for ulcer in 47.6% cases, arterial in 14.5%, 17.6% due to combined arterial and venous etiology, vasculitis 5.1%, pyoderma gangrenosum, 3% infection, 1.4% neoplasia, 1.1% drug induced, 1.1%

---

**Table 3: Investigation in study population**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>No. of patients tested positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid factor</td>
<td>2</td>
</tr>
<tr>
<td>ANTI-CCP</td>
<td>2</td>
</tr>
<tr>
<td>ANA</td>
<td>6</td>
</tr>
<tr>
<td>SLE</td>
<td>4</td>
</tr>
<tr>
<td>SSc</td>
<td>1</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>1</td>
</tr>
<tr>
<td>ANCA</td>
<td>4</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>3</td>
</tr>
<tr>
<td>c-ANCA</td>
<td>1</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>1</td>
</tr>
<tr>
<td>Anti-cardiolipin antibody (IgM and IgG)</td>
<td>0</td>
</tr>
<tr>
<td>ESR (more than 20)</td>
<td>27</td>
</tr>
<tr>
<td>CRP (more than 6)</td>
<td>25</td>
</tr>
<tr>
<td>Urine Routine (Proteinuria / Haematuria)</td>
<td>4</td>
</tr>
<tr>
<td>Doppler (n=40)</td>
<td>15</td>
</tr>
<tr>
<td>NCV (n=9)</td>
<td>4</td>
</tr>
<tr>
<td>Biopsy yield (n=35)</td>
<td>23</td>
</tr>
<tr>
<td>HIV</td>
<td>1</td>
</tr>
<tr>
<td>HBsAg</td>
<td>0</td>
</tr>
<tr>
<td>HCV</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4: Types of vasculitis and ulcer**

<table>
<thead>
<tr>
<th>Types of vasculitis</th>
<th>No. of pts. (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic polyangiitis</td>
<td>1</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>2</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>1</td>
</tr>
<tr>
<td>Leucocytoclastic vasculitis</td>
<td>4</td>
</tr>
<tr>
<td>Systemic lupus erythematosis with vasculitis</td>
<td>3</td>
</tr>
<tr>
<td>Rheumatoid arthritis with vasculitis</td>
<td>2</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Secondary APLA syndrome with SLE</td>
<td>1</td>
</tr>
<tr>
<td>Dermatomyositis with vasculitic ulcers</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 5: Nature of surrounding skin of ulcer**

<table>
<thead>
<tr>
<th>Types of ulcer / surrounding skin</th>
<th>Normal</th>
<th>Hyperpigmented</th>
<th>Inflamed</th>
<th>Gangrenous</th>
<th>Purpuric patches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vasculitic</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Arterial</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 6: Healing at 6 months**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Complete &gt;50%</th>
<th>50-25%</th>
<th>Non-healing</th>
<th>Amputation</th>
<th>Lost to follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>12</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arterial</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tuberculos</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
calciphylaxis. Another study from Sweden in 1991 by department of vascular surgery revealed cause of ulcer to be venous in 72%, arterial 12%, ischemic 6% and for 10% no cause could be elicited. A study from India from department of surgery in year 2005 shows that etiology of chronic wounds included systemic conditions such as diabetes, atherosclerosis, tuberculosis, and leprosy. Other major causes included venous ulcers, pressure ulcers, vasculitis, and trauma.

Venous ulcers are caused due to incompetence of valves in veins of lower limb especially, perforators. It usually occurs in medial distal leg (Figure 1) (Gaiter area) and can be very painful. The risk factors for venous ulcers include obesity, old age, history of leg injury and prolonged standing. The skin surrounding the ulcer is edematous and fibrinous exudates leads to fibrosis of subcutaneous tissue. Lymphedema usually results from obliteration of superficial lymphatics. There is hypertrophy of overlying epidermis giving polypoid appearance known as lipodermatosclerosis.

In ulcers due to vasculitis which is a systemic disease patient usually complains of fever, weight loss, fatigue, joint pain, rash and is associated with increase in acute phase reactants like ESR and CRP. Positive serological test for ANCA, ANA etc. are usually present. The skin surrounding vasculitic ulcer is normal prior to the onset of ulcer and also after ulcer develops. This makes an important clue to diagnosis differentiating it from venous ulcers.

In our study, we have excluded patients with diabetic foot and traumatic ulcers. All patients were extensively investigated and subjected to biopsy from the ulcer edge, therefore we found different etiology of leg ulcers. In our total study population of 40 the average duration of leg ulcer was 4.6 months which may be due to delay in seeking medical care or being treated in peripheral health care. One patient 48/F (Figure 2) presented as non healing ulcer over right lateral malleolus and was admitted in surgery ward. She developed gangrene of toes a week later for which she was referred to rheumatology services. On further enquiry she had history of low grade fever, sudden onset bilateral hearing loss since 4 months which revealed non tuberculous granuloma. On investigation patient’s creatinine was 3.2, ESR 112, proteinuria and hematuria in urine routine, right calf vein DVT on Doppler and positive c ANCA and anti pr3. patient was treated with steroid and iv cyclophosphamide and ulcer healed in 4 months and at 1 year hearing improved.

This patient would have been missed if not evaluated and investigated extensively. Thus with this example we want to point the importance of and recommend complete evaluation of a patient of lower extremity ulcer in terms of detailed medical history (fever, joint pain, oral ulcers, neuropathic pain, rash, cough, hemoptysis, hearing loss), past history, thorough clinical examination and investigation (urine r/m, ESR, CRP, CBC, creatinine) serological investigations (RA, anti-CCP, ANA, ANCA, LA, ACA, HBsAg, anti HCV), arterial and venous Doppler study, NCV and biopsy of ulcer.

Conclusion

In non diabetic leg ulcer it is important to differentiate vasculitic ulcer from venous ulcer by looking for features of systemic disease like fever, joint pain, rash, site of ulcer other than gaiter area, associated neuropathy, raised ESR, active urinary sediments, serology and biopsy to confirm diagnosis. It should also be remembered that many patients take alternate medicines/steroids on demand basis from family physicians which mask symptoms like fever, joint pain and rash.

References

Your Trust Matters the Most for Our
Teneligliptin

In Type 2 Diabetes...

GLYPTEN
Teneligliptin 20 mg

Trust... Transition... Teneligliptin
In **Type 2 Diabetes**
with **High PPHG**

**Choose the No. 1 brand**

- **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)
High Prevalence of Hypovitaminosis D in Patients Presenting with Proximal Muscle Weakness: A Sub-Himalayan Study

Jatinder Mokta1, Balraj2, Kiran Mokta3, Asha Ranjan4, Ivan Joshi5, Mahak Garg5

Abstract

Background: Hypovitaminosis D has emerged as a major public health problem and 25-50% of patients encountered in clinical practice are deficient in vitamin D. This study was conducted to estimate the prevalence of hypovitaminosis D among patients presenting with proximal muscle weakness.

Study Design: It was a cross-sectional study done on patients ≥18 years presenting in outdoor clinic from May 2008 to April 2013, with difficulty in standing and going up stairs/ diffuse musculoskeletal pains. Proximal muscle weakness due to other causes were excluded through investigations and those taking steroids and/or indigenous drugs were also excluded. Vitamin D levels measured by radioimmunoassay (RIA) in all eligible patients and individuals included in the study were those with hypovitaminosis D (<30ng/dl) and proximal muscle weakness. Patients reassessed after supplementation with vitamin D at 2 and 6 months.

Results: 99 patients with hypovitaminosis D associated proximal myopathy included in study. Of these 55 (55.55%) were males and 44 (44.44%) were females. Age ranged from 22 to 82 years with a mean of 52.84 ± 12.6 years. Of 99 patients, 55 (55.55%) were from the rural area and 44 (44.44%) from urban area. Mean duration of symptoms was 22.7 months (range 6-60 months). The level of 25(OH) Vitamin D ranged from 2.0 ng/dl to 35.7 ng/dl with the mean level of 13.18 ± 5.80 ng/dl (males = 12.76± 4.85ng/dl and females = 13.60±6.70ng/dl). Hypovitaminosis D was present in 98.98%. A direct relationship was found between the vitamin D levels (<10 ng/dl) and severity of weakness. Of 83 patients, who reported at the end of two and six months of treatment, 71 (85.54%) patients were able to stand-up from squatting position.

Conclusion: Muscle weakness is common among vitamin-D deficient individuals. Our study indicates that more focus should be on muscle symptoms in at risk population groups. The vitamin D deficiency related myopathy should not be missed due to its potential reversibility with vitamin D supplementation.

Introduction

Hypovitaminosis D has emerged as a major public health problem worldwide affecting about 1 billion people and knows no geographical boundaries, with males and females of all ages and ethnic background equally affected.1 About 25-50% or more of patients encountered in clinical practice are deficient in vitamin D, however the extensive array of symptoms and gradual evolution of the course of hypovitaminosis D makes it difficult to diagnose.2

Myopathy have been known to be part of osteomalacic symptom complex, and lately it has been documented that myopathy in hypovitaminosis D individuals can occurs before the bone involvement and precedes the bone disease.3 Myopathy, is a common symptom of hypovitaminosis D and in one third of patients, it is the presenting symptom. Most often it remains unrecognized or misdiagnosed because muscle weakness develops insidiously over years and patients

1.Medicine, Professor, Deptt. of Medicine, 2. Associate Professor, Deptt. of PSM, 3. Assistant Professor, Deptt. of Microbiology, 4. Senior Resident, 5. Junior Resident, Deptt. of Medicine, IGMC, Shimla, Himachal Pradesh

Received: 30.06.16; Accepted: 07.07.2017
are mostly referred to different medical specialists for more common non-specific symptom-diffuse musculoskeletal pain.\(^3\) Large antigravity muscles of lower limbs, which maintain the postural tone, are most commonly affected group of muscles in vitamin D deficiency and increases the susceptibility of falls in elderly.\(^3\)

Himachal Pradesh is a small mountainous state of India located in the southern Himalayas. Three-fourth of the state falls in the temperate or sub temperate climatic zone and its location is between latitude 30° 22′ 40″ N to 33° 12′ 40″ N and longitude 75° 45′ 55″ E to 79° 04′ 20″ E.\(^4\) Culturally, people of the state wear clothes covering whole of the body throughout the year and are less likely to be exposed to the sun. Moreover, most of the field work in the rural area (>90% of people live in the rural areas and depend on agriculture for their livelihood) is either done in the morning hours (5am-9am) or late afternoon (4pm-7pm) and urban people mostly remain housebound (either in the office or at home). Hence, this study was conducted to estimate the prevalence of hypovitaminosis D among patients presenting with proximal muscle weakness in the outdoor clinic. Objective: The aim of the study was estimate the prevalence of hypovitaminosis D in patients presenting with proximal muscle weakness and to determine the effect of vitamin D supplementation for the preservation of muscle strength.

**Study Design and Study Setting**

It was a cross-sectional study. All patients ≥18 years (non-pregnant) who presented to the outdoor clinic of the department of Internal Medicine, Indira Gandhi Medical College, Shimla, a tertiary care teaching institution from May 2008 through April 2013, with complaints of difficulty in standing up from squatting position and going up stairs or with diffuse musculoskeletal pains and found to have proximal muscle weakness on examination were included in the study. Patients were identified in the outdoor clinic by asking them to standup from the squatting position unaided (were asked to sit on the floor and keep both hands on the top of head). Except for proximal muscle weakness detailed neurological examination was normal. Complete heamogram, fasting blood glucose, electrolytes, liver and renal function tests, calcium, phosphorous, alkaline phosphatase, creatinine phosphokinase, ANA and thyroid function tests were done. Patients were excluded if their proximal muscle weakness was deemed secondary to diabetes, thyroid disorders, anemia, electrolyte abnormalities and renal insufficiency. Patients taking steroids and/or indigenous drugs were excluded. Patients suffering from chronic diseases of liver, skin, lung, heart, malnutrition and with history of alcohol abuse were also excluded. Thus, individuals included in the study were those with hypovitaminosis D (either insufficiency or deficiency) and proximal muscle weakness. Patients were reassessed after supplementation with vitamin D at 2 and 6 months. For financial reasons, repeat serum 25-hydroxyvitamin D levels and parathyroid hormone assays were not done. Data was analyzed using Microsoft Excel and were presented as means with SD when needed. We calculated prevalence (%) of different grades of vitamin D deficiency. We considered p-value of 0.05 and below as statistically significant for association with different predictors of vitamin D deficiency.

**Treatment and follow-up**

We obtained a written informed consent from each participant before subjecting him/her to clinical examination and laboratory investigations. Patients found to have hypovitaminosis D were treated with oral cholecalciferol 60,000 IU once a week for 8 weeks followed by 60,000 IU every four weekly\(^2\) and were asked to come for review at 2 and 6 months to evaluate the treatment outcome. Patients with concomitant hypocalcemia were treated with elemental calcium supplementation 1000 mg/day. In the observation period, no other treatment that could influence muscle power was given. Especially, no muscle training was given.

**Operational Definitions:** We grouped the hypovitaminosis as below.\(^2\)

- Normal → Serum 25 (OH) D level > 30 ng/dl
- Hypovitaminosis → Serum 25 (OH) D level < 30 ng/dl
- Insufficiency → Serum 25 (OH) D level between 20-30 ng/dl
- Deficiency → Serum 25(OH)D level < 20 ng/dl.

**Sample Collection:** After obtaining informed consent, a detailed history, a through general physical examination and a focused systemic and neurological examination was done to rule out neurological disorders. Morning blood samples were obtained from the patients after an overnight fast, for routine tests (complete hemogram, liver and kidney functions, electrolytes, calcium, phosphorous, alkaline phosphatase, ANA, blood glucose and thyroid functions) and 25(OH) D vitamin D. All biochemical tests were performed with auto-analyzer (Hitachi, Tokyo, Japan) on the same day of sample collection. Samples for 25(OH) vitamin D were stored at -20°C till analysis and were measured by radioimmunoassay (RIA).

**Results**

After exclusion, we found 99 patients with hypovitaminosis D associated proximal myopathy.
Of these 55 (55.55%) patients were male and 44 (44.44%) patients were female. The age of the study participants ranged from 22 to 82 years with a mean of 52.84 ± 12.6 years. Of 99 patients, 55 (55.55%) were from the rural area and 44 (44.44%) from urban area. Thirty-four patients (34.34%) presented with difficulties in standing from sitting position unaided or ascending upstairs whereas sixty-five patients (65.65%) presented with diffuse musculoskeletal pains and proximal muscle weakness on clinical examination. The mean duration of symptoms was 22.7 months (range 6-60 months). Of the 99 patients, 37 (37.37%) sought consultation for the first time while 62 (62.62%) had 2 to 5 prior consultations with other care providers over past 2 to 5 years before presenting to this institution and were previously treated with various drugs like multivitamins, vitamin B12 injections, pain killers and antidepressants.

The level of 25(OH) D ranged from 2.0 ng/dl to 35.7 ng/dl with the mean level of 13.18 ± 5.80 ng/dl (males = 12.76 ± 4.85 ng/dl and females = 13.60 ± 6.70 ng/dl). There was no difference in the mean 25(OH) D levels by gender (p = 0.474), between rural and urban (p = 0.554) and in patients aged above 50 years and less than 50 years (p = 0.970). Hypovitaminosis D [25(OH) D] <30 ng/dl was present in 98.98%. Only one (1.01%) patient had normal 25 (OH) D levels higher than 30 ng/dl. Whereas 90.90% of patients were, deficient and 8.08% of patients had insufficient levels of vitamin D. Of all patients, 31.31% had severe (<10 ng/dl) deficiency of vitamin D (Figure 1). We did not find any association of 25 (OH) D levels with age, sex and place of residence (Table 1, 2 and 3). However, a direct relationship was found between the vitamin D levels (<10 ng/dl) and severity of weakness. Average corrected serum calcium was 8.96 ± 67 mg/dl (normal 8.5 -10 mg/dl) and only 16 (16.16%) patients had serum calcium levels below normal range. Serum total alkaline phosphatase (TAP) was mildly raised in 30 (30.30%) of patients. Of 83 patients, who reported at the end of two and six months of treatment with oral cholecalciferol, 71 (85.54%) patients were able to stand-up from squatting position. The response to treatment was observed at the end of two months (could stand from squatting position with minimal support) with maximum response seen at the end of six months (could get-up unaided from the squatting position, Table 4). A strong inverse correlation between levels of vitamin D and response to treatment was observed in this study.

**Discussion**

We found a very high prevalence of hypovitaminosis D (98.98%) in patients presenting with proximal muscle weakness, two third of the patients remained undiagnosed for 2-5 years despite repeated consultations. In this study, no association of hypovitaminosis D with age (<50 and >50yrs), gender and place of residence (urban/rural) was noticed. India, being a tropical country with abundant sunshine, high prevalence of hypovitaminosis D (insufficiency/deficiency) has been observed from different regions of the country. However, all studies that examined the association between hypovitaminosis D and proximal muscle weakness were conducted outside India and among different study populations. Results of this study extended support to earlier studies showing high prevalence of hypovitaminosis D in patients presenting with proximal muscle weakness. Skaria et al showed that myopathy is the presenting symptom in 30% of patients and is clinically detectable in 96.7% of patients with hypovitaminosis D. Our study further support the previous observations that hypovitaminosis D myopathy is most often undiagnosed or misdiagnosed for several years as two thirds of patients in this study had multiple consultations for 2-5 years before hypovitaminosis D related myopathy was diagnosed. Our results showed a positive relationship between muscle power and serum 25 (OH) D levels and an inverse relationship between serum 25 (OH) D levels and response to the vitamin D supplement.
This study extend support to the previous study that weight bearing lower limb muscles are primarily affected in vitamin D deficiency and response to vitamin D treatment should be assessed by measuring the muscle strength of these antigravity muscles. There results demonstrated that voluntary contractions of large muscle of lower limbs could be a good test in the absence electrical stimulation facilities for muscle contraction. Like various previous studies, this study favours that the clinical (symptom and sign) assessment and measurement of serum 25 (OH) D remains the most reliable method for early detection of hypovitaminosis D related muscle weakness in at risk individuals as myopathy may precede the development of biochemical abnormalities (low calcium and raised alkaline phosphatase). Moreover, muscle enzyme creatinine kinase elevates only in minority of patients with vitamin D related muscle weakness and muscle biopsy shows non-specific muscle fiber atrophy. The ultimate evidence of diagnosis rests on the response to therapy as more than four-fifths of hypovitaminosis D related myopathy responded to vitamin D treatment in this study. Previously muscle weakness in vitamin D deficiency was described only when bone involvement is marked. However, like Glerup et al we demonstrated no significant correlation between muscle power and bone involvement (most common used markers of bone involvement TAP was raised only in 30.30% and calcium decreased in only 16.16%). Moreover, no difference in the muscle power between patients with elevated TAP and patients with normal TAP was noted and muscle power was equally decreased in both groups.

**Conclusion and recommendations**

We conclude that muscle weakness is common among vitamin-D deficient individuals and vitamin D myopathy precedes the development of biochemical signs of bone involvement. Our study indicates that more focus should be on muscle symptoms in at risk population groups. The vitamin D deficiency related myopathy should not be missed due to its potential reversibility with vitamin D supplementation. To avoid vitamin D deficiency myopathy, a serum 25(OH)D levels >20 ng/dl should be maintained in the population. Probably the best solution to the problem in the absence of fortification of food items would be supplementation of vitamin D for at risk individuals. Additional research preferably by means of controlled randomized trials is needed to confirm these findings.

**References**

A Cross-sectional Study of Cardiovascular Involvement in Systemic Lupus Erythematosus in an Urban Indian Tertiary Care Centre with Emphasis on 2-D Echocardiography

Seema Kini¹, Chetan Vekhande², Vikram Londhey³

Abstract

Background: Cardiovascular manifestations are responsible for considerable morbidity and mortality in patients with SLE. A wide range of manifestations due to active lupus, like pericarditis, valvular affection, myocarditis, and less commonly pulmonary hypertension, are described. This study was undertaken to study cardiovascular manifestations in SLE, with a focus on echocardiography findings, in an urban Indian setting.

Methodology: Fifty consecutive cases of SLE following up in the Rheumatology Clinic of TNMC and BYL Nair Charitable hospital, an Indian tertiary care hospital were studied. They were subjected to an echocardiographic examination if not already done. Detailed history, examination, study of past medical records and investigations were carried out, especially related to cardiovascular system. Treatment details, flares, other systemic involvement were noted. Serial echocardiography if done previously were noted down. The data was analysed using descriptive statistics.

Results: An echocardiographic abnormality was noted in 25 (50%) of the 50 subjects. Pulmonary hypertension in 21 (42%); valvular abnormalities in 16 (32 %); pericardial effusion in 9 (18%) and diastolic dysfunction in 6(12%) were the echocardiography findings. Six out of the 7 cases with moderately to severe pulmonary hypertension seemed to be responding to immunosuppressive therapy clinically as well as on echocardiography; 1 did not respond. At least 1 traditional risk factor for atherosclerosis was present in 58% of cases.

Conclusions: Screening echocardiography may be recommended, especially at presentation, during SLE flare, or in the presence of cardiac symptoms. Moderate to severe pulmonary hypertension can develop any time in the course of the disease. It may be responsive to immunosuppression. Further detailed studies including multiple echocardiographic parameters and right heart catheterisation need to be undertaken to study the responsiveness of pulmonary hypertension to immunosuppressive therapy.

Editorial Viewpoint

• SLE can affect the heart in numerous ways.
• 2D Echo is a good screening tool to pick up the same.
• Pulmonary hypertension (PH) may occur anytime during the course of SLE.
• PH with SLE may be responsive to immunosuppression.

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease that predominantly affects young females of the child-bearing age group. The disease has a wide spectrum of presentations and manifestations. From an involvement of a single system, to permutations and combinations of multiple system affection, remissions of unpredictable durations and relapses, the management of SLE remains a great challenge for the clinician.

Butterfly rash, discoid rash, photosensitivity, oral ulcers, polyarthritis, polyserositis,
nephrotic syndrome, seizures, psychosis, hemolysis and cytopenias are the well known manifestations of SLE. Besides the well known cardiac manifestation of pericarditis, we do come across valvular abnormalities, myocarditis, conduction abnormalities, impairment of systolic and diastolic function, pulmonary or peripheral arterial hypertension and microcirculatory problems.¹

Cardiovascular disease has been recognised as an important cause of morbidity and mortality in SLE.

We conducted a cross-sectional, observational study of 50 consecutive cases of SLE following up in the Rheumatology OPD of BYL Nair Charitable Hospital between June 2012 to June 2013, after ethics committee approval. All the cases, diagnosed as per the American College of Rheumatology Criteria for SLE, were included after a written, informed consent. The clinical history, examination and investigations were recorded. The past medical records were reviewed for any cardiovascular abnormalities, electrocardiograms, chest radiographs, 2D-echocardiography reports, flares, and treatment administered. Besides the routine investigations, 2-D echocardiography was done in all patients who had not done it before. Serial echocardiographic findings were noted if available. Those with other associated rheumatologic diseases, rheumatic heart disease or congenital heart disease were excluded. We noted the presence of traditional risk factors for atherosclerosis in our subjects, but did not perform carotid intima/media thickness due to financial constraint. Descriptive statistics and Chi square test were applied to get the results.

### Results

A total of 50 patients of SLE were studied. Table 1 gives some characteristics of the study population. The immunologic profile of the study population is reflected in Table 2. Other systemic involvement besides cardiovascular is mentioned in Table 3. Single system involvement was seen in only 10 cases. Of the remaining forty, 25 were having two systems involved, 11 had 3 systems involved and 4 had 4 systems involved. Thus 40 (80%) patients had multi-system involvement.

In this study 2D echo was done in each of 50 SLE patients at some point of time during the study period.

### Methodology

We conducted a cross-sectional, observational study of 50 consecutive cases of SLE following up in the Rheumatology OPD of BYL Nair Charitable Hospital between June 2012 to June 2013, after ethics committee approval. All the cases, diagnosed as per the American College of Rheumatology Criteria for SLE, were included after a written, informed consent. The clinical history, examination and investigations were recorded. The past medical records were reviewed for any cardiovascular abnormalities, electrocardiograms, chest radiographs, 2D-echocardiography reports, flares, and treatment administered. Besides the routine investigations, 2-D echocardiography was done in all patients who had not done it before. Serial echocardiographic findings were noted if available. Those with other associated rheumatologic diseases, rheumatic heart disease or congenital heart disease were excluded. We noted the presence of traditional risk factors for atherosclerosis in our subjects, but did not perform carotid intima/media thickness due to financial constraint. Descriptive statistics and Chi square test were applied to get the results.

### Results

A total of 50 patients of SLE were studied. Table 1 gives some characteristics of the study population. The immunologic profile of the study population is reflected in Table 2. Other systemic involvement besides cardiovascular is mentioned in Table 3. Single system involvement was seen in only 10 cases. Of the remaining forty, 25 were having two systems involved, 11 had 3 systems involved and 4 had 4 systems involved. Thus 40 (80%) patients had multi-system involvement.

In this study 2D echo was done in each of 50 SLE patients at some point of time during the study period.

### Methodology

We conducted a cross-sectional, observational study of 50 consecutive cases of SLE following up in the Rheumatology OPD of BYL Nair Charitable Hospital between June 2012 to June 2013, after ethics committee approval. All the cases, diagnosed as per the American College of Rheumatology Criteria for SLE, were included after a written, informed consent. The clinical history, examination and investigations were recorded. The past medical records were reviewed for any cardiovascular abnormalities, electrocardiograms, chest radiographs, 2D-echocardiography reports, flares, and treatment administered. Besides the routine investigations, 2-D echocardiography was done in all patients who had not done it before. Serial echocardiographic findings were noted if available. Those with other associated rheumatologic diseases, rheumatic heart disease or congenital heart disease were excluded. We noted the presence of traditional risk factors for atherosclerosis in our subjects, but did not perform carotid intima/media thickness due to financial constraint. Descriptive statistics and Chi square test were applied to get the results.
significantly contributed to the PH. Of the remaining 7 with moderate to severe PH, without any other significant contributing factor, during the period of documentation of PH, 1 case of lupus nephritis (LN) was on MMF and 6 received cyclophosphamide either for LN, CNS lupus or symptomatic PH itself. At the time of analysis of this study, 4 had received greater than 1.5 years of MMF/Cyclophosphamide; their PH had normalised in 3 of the 4; and not responded in 1. The remaining 3 had completed 6-8 months of Pulse cyclophosphamide; their PH had reduced and they became asymptomatic. Thus 6 of 7 cases with moderately severe symptomatic PH seemed to be responsive to immunosuppression. All those with mild PH, remained clinically stable and asymptomatic for PH at the time of the analysis, since the time of detection of PH. There was no significant association of pulmonary hypertension with disease duration of greater than or less than 5 years, presence or absence of Raynaud’s phenomenon, other systemic involvement. Antiphospholipid antibodies were not available in all the patients to study the association.

Valvular abnormalities were found in 16 (32%) patients. All of these were regurgitant lesions; none were stenotic. Valvular lesions were as follows: Only mitral regurgitation (MR): 4; Only Aortic regurgitation (AR): 2; Both MR and AR: 4; significant tricuspid regurgitation: 4; aortic sclerosis: 2cases. Only half of the 16 with valvular affection were symptomatic.

The most common risk factor for atherosclerosis (Figure 3) found in this study was dyslipidemia found in 20 (40%) of the patients followed by hypertension found in 17 (34%). Longer duration of SLE was significantly associated with the presence of hypertension (Point Biserial coefficient $r_{pb}=-0.37; p$ value=0.007). Eleven course of the disease. Abnormal echocardiography was found in 25 (50%). The remaining had a normal echo. The most common echocardiographic finding was pulmonary hypertension (PH) [cases with Pulmonary arterial systolic pressure (PASP)>35 mm Hg were considered to have PH] found in 21 (42 %) of the patients; followed by valvular abnormalities in 16 (32 %); pericardial effusion in 9 (18%) and diastolic dysfunction in 6 (12%) (Figure 1).

Twelve patients had pulmonary hypertension (Figure 2); 17 of these were detected at the initial presentation, when the SLE was active. Out of 21 patients with pulmonary hypertension, 11 were found to be asymptomatic. They all had mild PH (PASP36-50mmHg). The 10 with symptomatic PH had moderate to severe (PASP >50 mmHg) PH. Of these 10, one had severe ILD and 2 had renal failure when PH was detected. Both these conditions would have
(22%) of the patients were found to be overweight. Diabetes was found in none. Family history for hypertension was found to be significant in only one patient. None of them were smokers. Twenty-nine cases had either dyslipidaemia, HT or they were overweight. Of these, 11 had 2 risk factors and 2 of them had 3 risk factors. Though all of the above are traditional risk factors for ischaemic heart disease (IHD), only one patient was documented to have IHD. She had unstable angina, with a normal 2D echo. Coronary angiography and cardiac stress test, could not be done due to lack of consent.

Pericardial effusion was found in 10 (20%) patients. Quantifying, 8 of them have mild effusion and 2 had moderate effusion. However all were asymptomatic with no evidence of chest pain, haemodynamic compromise or cardiac tamponade. A single case had pericarditis without effusion.

Diastolic dysfunction was found in 12% and systolic dysfunction in 8% of patients. None of the patients had regional wall motion abnormalities suggestive of IHD.

ECG abnormalities were seen in 11 (22%) of the patients of which ST-T changes and q waves in anterior leads were seen in 2 patients each. However all these patients were clinically asymptomatic. LVH was seen in 6 patients; all of them were hypertensive. P-pulmonale with or without RVH was seen in 8 patients, all of whom were having pulmonary hypertension.

The chest radiograph showed normal heart in 40 of the 50 cases. Of the remaining 10, four had cardiomegaly and 7 had a prominent pulmonary conus (One had cardiomegaly with prominent pulmonary conus).

**Discussion**

Many of the commonly described cardiovascular manifestations of SLE have been seen in our study. There was a high prevalence of echocardiographic abnormalities 25 cases (50%). Majority of the patients were asymptomatic. So screening 2D Echo in all cases of SLE seems necessary.

A striking finding was the detection of pulmonary hypertension during the course of SLE, in a large number of cases. There is a possibility of over-diagnosis by 2D echo as compared to the gold standard, right-heart catheterisation. We were unable to perform the same due to cost and invasiveness of the procedure. There are studies on the accuracy of echocardiography being used for the assessment of PH and the results are contradictory.6,8 There have been prior studies on PH in connective tissue disorders in which PH was based on echocardiographic features, mainly PASP to quantify PH; Western as well as Indian.11-13

In our study the PASP by TR jet seemed to correlate with the WHO class functional class of the patient and the ECG and X-ray Chest findings. The ones with moderate to severe PH (PASP>50mmHg) had functional class II, III or IV, but those with mild PH were asymptomatic. Of the 10 cases with moderate to severe PH, 8 had P-pulmonale with or without RVH on ECG and 7 had a prominent pulmonary conus on X-ray. Hence in our set-up where right heart catheterisation is not feasible, 2-D echocardiography, along with ECG and chest radiograph may be the best way to diagnose and monitor the level of PH. But the possibility remains that at least some of the asymptomatic PH cases may have got excluded after a right heart catheterisation. So it remains a limitation of the study; that right heart catheterisation was not done to confirm the presence of pulmonary hypertension, as in most Indian studies on PH in connective tissue diseases.15

Our study did show a high number of cases with PH. This may be due to the fact that we considered them to have had PH any time during the course of the illness and not only at the time of the study assessment. So the figure does not indicate the prevalence in a cross-section of our SLE patients. Also there is a possibility of selection bias as a symptomatic individual would be more likely to have an echocardiography report than an SLE without cardiac symptoms. Various studies have reported highly variable rates of PH in SLE due to varying methods of assessing PH, varying cut-offs for PH or varying methodologies. As per a recently published review,15 the prevalence of PH in SLE is 8-17.2% in Caucasians and 35.3-49% in Asians. Thus Asians do have a higher prevalence of PH in SLE as compared to Caucasians.

Most of cases had mild PH that did not seem to progress, but even normalise with the control of SLE disease activity. Of the ones with moderate to severe PH, and without ILD or renal failure (both of which contribute to causing PH), immunosuppression with pulse cyclophosphamide or MMF seemed to show benefit, clinically as well as on echocardiographically. However we cannot make a definitive conclusion, as the number of cases of SLE with PH was small; their follow-up duration was short and confirmatory right heart catheterisation was not done. There are some previous studies that support the use of immunosuppression in the treatment of PH in SLE.10,16,17 All these studies have the limitation of having small numbers. A single Indian study by Kommireddy S, et al11 studied 24 cases of SLE with PH and observed their response to immunosuppression in the form of monthly cyclophosphamide pulses for 6 months. They found an improvement in a significant proportion of patients. However in this study too, right heart catheterisation to confirm PH, was not performed.
(pulmonary vasodilators vs immunosuppression) prospective studies with larger study group are needed to confirm the usefulness of immunosuppression in PH with SLE, based on our pilot findings. Also multiple parameters for assessment of PH on echocardiography, hemodynamic parameters should be serially assessed in a pre-planned manner.

Recent articles show a major concern about premature atherosclerosis in patients with SLE. In our study, peripheral vascular involvement seemed to be clinically due to vasculitis or antiphospholipid antibody syndrome; and not due to atherosclerosis. We did not evaluate the coronary status nor peripheral dopplers in all the patients. Only a single patient had documented IHD with unstable angina. This would make one think whether atherosclerosis is a theoretical concern in SLEs. However we cannot conclude thus as we have not evaluated the coronary status nor the intima-media thickness of carotids. Also, only 4 cases from our study population were above the age of 40. Survival from disease activity and opportunistic infections still may be a bigger concern in SLE than that of atherosclerosis.

Several studies including Asian studies have documented the concern for atherosclerosis in SLE to be true. In an Indian postmortem study by Panchal, et al, it was shown that death due to cardiovascular cause seen in 8 of 27 SLEs; this was second to death due to renal disease (13 of 27). Thromboses/embolism, vasculitis and severe coronary atherosclerosis were seen in nine, five and one of the 27 subjects, respectively. Thus we must make all efforts to monitor for and aggressively treat the traditional risk factors of atherosclerosis. Dyslipidemia was the most common risk factor for atherosclerosis in our study. In another Indian study, Bhatt SP et al, have shown that dyslipidemia is a significant risk factor for peripheral vascular disease in SLE. In our study hypertension is the second commonest risk factor and was associated with longer disease duration, possibly due to steroids. However dyslipidemias did not show the same relationship. Inability to perform Carotid intima media thickness was also a limitation of this study.

The nontraditional factors for cardiovascular disease in SLE are disease-specific like renal disease manifestation as lupus nephritis (LN), presence of pro-inflammatory cytokines, some of inflammatory mediators, antiphospholipid antibodies, anti-oxLDL (anti oxidised low density lipoprotein) antibodies, corticosteroid uses and cumulative dose of glucocorticoids. Svenungsson E, et al, have proven the distinct influence of these factors by studying 3 age-matched groups: SLE with cardiovascular event, SLE controls and population controls. Hence disease activity control and at the same time early introduction of steroid-sparing regimens may need to be emphasised.

Limitations of our Study
- Possible selection bias enrolling cases of SLE who already had a 2DEcho report.
- Echocardiographies done by more than 1 operator.
- Lack of confirming the diagnosis of PH with a right heart catheterisation when PASP was found to be higher than 40.
- The number of those who had PH does not represent the prevalence as it was noted during the course of SLE and not at enrolment.
- Carotid intima-media thickness was not performed as a marker of atherosclerosis.
- Antiphospholipid antibodies were not evaluated for in all the cases.

Conclusions
- Echocardiographic abnormalities are common in SLE. They may be related to disease activity like, pericardial effusion, pulmonary hypertension, diastolic dysfunction. Majority were detected at initial presentation and most were asymptomatic.
- Screening of all cases of SLE with echocardiography is recommended, especially at presentation, during SLE flare, or in the presence of cardiac symptoms.
- Moderate to severe pulmonary hypertension can develop any time in the course of the disease. It may be responsive to immunosuppressive therapy if there are no other contributing causes. However these are just pilot observations. Further research is needed to prove the usefulness of immunosuppressives for pulmonary hypertension in SLE.
- Traditional risk factors for atherosclerosis like dyslipidemias, hypertension, diabetes and overweight are prevalent in over half of the cases of SLE. These need to be regularly monitored for and treated.
- Steroid therapy may increases the risk of atherosclerosis further as per literature. Hence steroid sparing therapies should be initiated early in the disease course.

References


Abstract
We live in an age of hyper connectivity, people from around the world are looking outside their own national borders to receive medical care. As more people are learning about the quality that the elite Indian hospitals provide at a competitive, and often more affordable, price compared to other institutions around the world, they are becoming increasingly interested in receiving their medical care in Indian hospitals. It is for this exact reason that it is very important to learn the importance of communicating effectively with people from a diverse background. Over the next decade, the number of international patients that Indian hospitals will provide care for is set to dramatically increase. In this new age of medicine in India, it is imperative that doctors are adequately equipped with the communication skills to appropriately connect with patients coming from very different cultural backgrounds. The interaction with an international patient can be tremendously deepened through effective communication that adheres to the cultural beliefs of the patient. In this article, we detail how to effectively communicate with people from different backgrounds. We explore how to speak with patients and connect on a deeper level and respect the cultural differences that exist. We will also discuss how to avoid offending your patients or miscommunicating your plans to them. Overall, improved awareness of cultural differences will ensure higher patient satisfaction as well as an improved doctor patient interaction.

Introduction
We live in an age of hyper connectivity, where people from around the world are looking outside their own national borders to receive medical care. As more people are learning about the quality that the elite Indian hospitals provide at a competitive, and often more affordable, price compared to other institutions around the world, they are becoming increasingly interested in receiving their medical care in Indian hospitals. The changing demographics of the patients, improved economy of India will to the private and public sector with opportunities for tremendous growth.1

In October 2015 the medical tourism sector in India was estimated to be worth US$ 3 billion. By 2020 this number is projected to be around $7-8 billions. The Medical Tourism Market report 2015 as found India to be one of the “lowest cost and highest quality of all medical tourism destinations as it offers a wide variety of medical procedures at one-tenth the cost of similar procedures in United States.”2

According to the CII- Grant Thornton report (2015) the patients from Bangladesh and Afghanistan comprise 34% of all foreign patients, while Russia and Commonwealth of Independent States (CIS) account for 30%. Other sources of patients include Africa, Middle – east particularly patients coming from Persian Gulf countries.3

Hospitals will need to develop new capabilities, business models to deal with the new opportunities of dealing with international patients. It is for this exact reason that it is very important to learn the importance of communicating effectively with people from a diverse background. Over the next decade, the number of international patients that Indian hospitals will provide care for is set to dramatically increase.3

In the following review, we will help physicians understand the essential concepts of intercultural communication. Although these concepts will be discussed through

1Director of Research Division, GlobeHealer, Philadelphia, Pennsylvania, USA; 2Endocrinologist, Joshi Clinic, Lilavati & Bhatia Hospital, Mumbai, Maharashtra; 3Professor of Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA
Received: 10.11.2016; Accepted: 15.03.2017
The Importance of Cultural Awareness in the Medical Field

Cultural beliefs are the lens through which patients process new information, forms memories, and react to external stimuli. “Culture is an organized group of learned responses, a system of ready-made solutions to problems people face that is learned through interactions with others in the society.”^4^ Cultural shapes an individual’s response to illness and treatment. Awareness to patient’s culture and sensitivity to basic premises is essential in providing high quality treatment to a patient.

As a population gets more diverse, patient’s continuously move across states and country boundary lines, awareness and acknowledgement of cultural differences remains an essential skill for everyone associated with healthcare. Cultural sensitivity is defined as “The knowledge and the interpersonal skill that allows providers to understand, appreciate, and work with individuals from cultures other than their own. It involves an awareness an acceptance of cultural differences, self-awareness, knowledge of a patient’s culture and adaption of skills”^5^.

A brief training of cultural sensitivity has been shown to improve the continuity of care and increase patient satisfaction.\(^6\)

Medical practices that are known to understand and respond appropriately to cultural differences tend to be popular with patients and have been shown to have increased net earnings. Seibert and his colleagues\(^7\) have suggested a check list to identify readiness for Cultural sensitivity and awareness in a hospital could be helpful. This list includes:

1. Identifying patient’s preferred communication methods.
2. Identifying language barriers.
3. Identifying cultural differences.
4. Double checking with patients regarding their comprehension of illness.
5. Identifying any unique religious and spiritual beliefs.
6. Does the patient trust the health provider?
7. Assess any cultural or cultural-specific dietary considerations.
8. Identifying our own biases and prejudices.

Contextual Differences Among Cultures

It has been recognized that communication usually happens within a cultural context which includes a pattern of cultural and environmental cues and an implicit understanding that conveys a meaning between two members of the same culture. Hall\(^8\) has described cultures as high context or low context based on the difference of their communication styles (Table 1).

In high-context cultures, people rely less on verbal communication and more on the context of nonverbal actions and environmental settings to convey meaning. In high-context cultures, the rules of everyday lives are less explicit; instead, individuals grow to learn how to recognize situational cues in the form of gestures and tone of voice and know how to respond as expected. In high-context cultures, the executive offices could be shared and open to all colleagues and other managers would not require or expect detailed information. Information is shared with everyone. Subjective relationships are varied of objective data, and social as well as business relationships would overlap. Position and status are more valued much more than competence. Meetings could be called in a short notice and key people always accept. The primary role of communication is building a relationship and not exchanging information in most of these cases.\(^8\)

In low-context cultures, people rely heavily on written agreements and interpret laws strictly, whereas high-context cultures view adherence to laws as being more flexible. The primary task of communication in low-context cultures is exchanging information. In low-context cultures, executive officers

---

Table 1: Communication styles between high and low context cultures. Developed from reference\(^8\)

<table>
<thead>
<tr>
<th>High context culture</th>
<th>Low context culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect and implicit message</td>
<td>Direct simple and clear message</td>
</tr>
<tr>
<td>Increase use of non-verbal communication</td>
<td>Low use of non-verbal communication</td>
</tr>
<tr>
<td>Low reliance on written communication</td>
<td>High reliance on written communication</td>
</tr>
<tr>
<td>Use feelings and intuition to make decisions</td>
<td>Use data and evidence to make decisions</td>
</tr>
<tr>
<td>Long-term relationships</td>
<td>Short-term relationships</td>
</tr>
<tr>
<td>Relationships are more important than schedules</td>
<td>Schedules are more important than relationship</td>
</tr>
<tr>
<td>Strong distinction between in-group and out-group</td>
<td>Flexible and open</td>
</tr>
<tr>
<td>Polychronic*</td>
<td>Monochronic**</td>
</tr>
</tbody>
</table>

Polychronic* - like to do multiple things at one time; Monochronic** - like to do one thing at one time.
are separated with controlled access. Workers rely on details and background information. Information is highly centralized and controlled. Objective data is valued over subjective relationship. Business and social relationships are often discreet. Confidence is valued as much as position and status. Meetings have fixed agenda with plenty of advanced notice.

Hence, high-context differences become more apparent in situations which involve decision making, problem solving, and negotiating. While in low-context cultures, individuals tend to focus on the results of the decisions they face, and there is increased focus on the decisions they face. In comparison, the high-context cultures emphasize the means of the method by which a decision will be made. Building and protecting a relationship is equally important as facts and information in high-context cultures and is used often in making decisions. Hence, physicians from a low-context culture have to be more direct and explicit while dealing with a patient from a high-context culture.9

High-context cultures include Italian, Spanish, Greek, Arabic, Chinese and Japanese and Indian patients while low-context cultures include British, American, Scandinavian, German, and Swiss patients (Figure 1).

Opportunities and Challenges of Communication in a Diverse World

Diversity includes all characteristic that define people as individuals.10 Intercultural communication is a process of sending and receiving messages between culturally diverse individuals that could lead to different interpretation of the verbal and nonverbal messages. There is a need to grasp cultural differences because efforts to recognize and bridge cultural differences will open up physicians practice opportunities while maximizing contributions of all employees in a diverse workforce.

There are several advantages of diverse workforce.11 They include (i) broad range of views and ideas, (ii) better understanding of diverse, fragmented markets and (iii) a broad pool of talent from which to recruit. Current physicians and hospital managers need to communicate with people from other cultures throughout their career. A hospital’s cultural diversity affects how its messages are conceived, composed, delivered, received and interpreted.

Culture influences everything about communication including: (i) language, (ii) nonverbal signals, (iii) meaning of words, (iv) time and space issues and (v) rules of human relationships.12

It is important to keep in mind, while we encode our message according to our culture, others decode our message based on their background.

Cultural differences have led to development of cultural myopia like ethnocentrism and stereotyping. Ethnocentrism is the tendency to judge other groups according to standards, behaviors and customs of one’s own group.13 This has led to the feeling of superiority complex in one’s own group. On the other hand stereotyping is the tendency to assign generalized attributes to an individual on the basis of their belonging to a particular group. The most appropriate trait in current day environment is accepting cultural pluralism which is a practice of accepting multiple cultures as it is without one’s own personal biases.14 This would include avoiding assuming that all people will react similarly to the same message, avoid making premature judgments when people act differently and acknowledging the differences among various cultures.

Classifications of Cultural Differences

When it comes to knowing how people of various cultures would like to be treated it is essential to understand the eight variations15 in cultures namely (i) Contextual, (ii) Legal and ethical, (iii) Social (iv) Nonverbal, (v) Age, (vi) Gender, (vii) Religious and (viii) Ability.

i. Contextual Differences:
   - Cultural context: physical cues, environmental stimuli and implicit understanding that conveys meaning between members of the same culture
   - High context: rely less on verbal communication and more on nonverbal and environmental stimuli (i.e. Chinese speaker will not spell out all the details in a speech)
   - Low context: value written agreements and interpret laws strictly (i.e. spelling out the rules through verbal communication)

ii. Legal and Ethical differences16
   - Actively seek mutual ground
   - Send and receive messages without judgement
   - Send messages that are honest
- Show respect for cultural differences

iii. Social differences
- Formal rules of etiquette are explicit and well-defined, but informal rules are learned through observation and imitation
- Respect and rank are reflected differently from culture to culture in the way people are addressed and in working environment
- The rules of polite behavior vary from country to country
- Attitudes toward times, such as adherence to meeting schedules vary throughout the world
- Cultures around the world exhibit degrees of openness toward outsiders and people whose identities don’t align with prevailing social norms

iv. Nonverbal differences
- The meaning of nonverbal signals vary from culture to culture so don’t make assumptions and rely on them

- What to study about the way people behave in a culture?
  - Greetings
  - Personal space
  - Touching
  - Facial expression
  - Eye contact
  - Posture
  - Formality

v. Age differences
- Culture view on youth and aging affect how people communicate with one another
- Different generation labels (based on year of birth)
  - Baby boomers (1946-1964)
  - Generation X (1965-1985)
  - Generation Y (born after 1980)

vi. Gender Differences
- Men emphasize content in message, women emphasize relationship management
- Different cultures have different norms when it comes to gender

vii. Religious Differences
- In many countries like US the law requires employers to accommodate employee’s religious beliefs to a reasonable degree
- Important in business to decide on policies
  - Either “check faith at the door”
  - Or allow religion-based support groups to be formed
- Want to avoid friction developing between employees

viii. Ability differences
- There are several assistive tech companies and national organizations, that help companies to create a more workplace benefiting individuals with physicians or cognitive challenges. These companies provide devices and system that help with verbal and visual communication and allow individuals to have increased mobility in the workplace.

Adapting Our Approach to Other Cultures

To understand and adapt to other cultures we need to recognize the influences that our own culture has on our communication habits. This allows us to be aware of our habits. Unlike the golden rule of...
in the previous section or taking a course on cultural difference can be help considerably.

Every large hospital leadership needs to realize that the need for members of their team to be fluent in other languages. While English is prevalent internationally as the patients travel globally we cannot assume that everyone understands it or speaks it the same way. As the business of medicine around the world grow, so too does the demand of multi-lingual communicators.

Hospital staff needs to respect the preference of patients regarding their communication style

Communication style varies widely from culture to culture by (i) level of directness, (ii) Degree of formality and (iii) preferences for written vs. spoken communication. We will describe some guidelines for written and spoken communication and the increasing role of having language interpreters and translators in taking care of patients from across other cultures. Watching and learning the patient communicate is the best way to adapt to their style and improve your skills.

1. While sending written communication to patients from a different culture one should be aware of the following facts.
   i. Clarity and simplicity essential when writing to someone who doesn’t share your native language
   ii. Use simple, clear language
   iii. Be brief: write short sentences
   iv. Use transitional elements: allow them to follow your train of thought (use words like first, second, third, last)
   v. Address international correspondence carefully
      a. Addressing appropriate salutations used in other countries

2. Speaking and Listening Carefully
   i. Speaking clearly and getting frequent feedback are 2 keys to successful intercultural conversations
   ii. Listen more effectively in intercultural communities by letting others finish what they are saying and accepting what you hear without judgement.
      a. Steps to effective communication
      iii. Speak slow and clear
   iv. Don’t rephrase unless necessary, gives the person your communicating with more phrases to try and understand
   v. Look for and ask for feedback to make sure your message is coming across
   vi. Don’t talk down by over enunciating or oversimplifying sentences
   vii. At the end of the conversation, make sure you and the listener agree on what has been said and decided

3. Using interpreters, translators, and translating software
   i. For important business, use a professional interpreter (for oral communication) or a translator (for written communication)
   ii. Can help avoid embarrassing blunders in international business
   iii. Translation software helpful with individual words or short sentence, can give an overall gist of the message
      i. Still not as good as a professional interpreter
   iv. Help other adapt to your culture, respectfully
      i. Doing so will create a more productive workplace and will help you understand their cultures as well

Conclusion

Over the next decade, the number of international patients that physicians in India will provide care for is set to dramatically increase. In this new age of medicine in India, it is imperative that doctors are adequately equipped with the communication skills to appropriately connect with patients coming from very different cultural backgrounds. The interaction with an international patient can be tremendously deepened through effective communication that adheres to the cultural beliefs of the patient. Overall, improved awareness of cultural differences will ensure higher patient satisfaction as well as an improved doctor patient interaction.

References

2. Laurie Goering, “For big surgery, Delhi is dealing,” The Chicago Tribune, March 28, 2008
3. “Indian medical tourism industry to touch


Introduction

Acetaminophen poisoning is the most common cause of fulminant hepatitis and drug induced liver injury worldwide. Even though it is not the commonest cause of fulminant hepatitis in India, poisoning is still common and confusions prevail regarding the optimum and modern regimens in Indian population. Acetaminophen poisoning may occur either as a result of acute ingestion or following cumulative effects. The important steps in management include hemodynamic stabilization, decontamination, and administration of N-acetylcysteine-the specific antidote. The duration of treatment with N-acetylcysteine depends on the type of ingestion and the presence of transaminits.

The novel regimens for the management of acetaminophen poisoning is been discussed here.

Management Protocol

The management of the patient depends widely on the time after consumption at which the patient presents. Most of them who present in the initial 24 hours of presentation will be asymptomatic, while a few may need treatment for the symptoms caused by the co-ingestants.

As symptoms pertaining to acetaminophen poisoning are uncommon in the first few hours of presentation, the severity of the event is assessed by plotting the Rumack-Mathew normogram (Figure 1)

The normogram chart will be useful only if the patient presents within 24 hours of ingestion. It is not useful for those who present after 24 hours of acute ingestion, unknown time of ingestion, or those who have a staggered overdose.

Symptoms and signs of acetaminophen poisoning usually occur between 24 and 72 hours after consumption. Patients may present with nausea, vomiting, jaundice, abdominal pain, renal injury, coagulopathy (eg, gastrointestinal bleeding), hepatic encephalopathy, cerebral edema, or hypotension. The presence of the above necessitates maintaining hemodynamic stability, including airway management, fluid resuscitation, ionotropes, renal replacement therapy as and when required, or management of raised intracranial pressure.

Gastrointestinal Decontamination

This finds role in those patients who present following an acute ingestion of toxic dose of acetaminophen of >7.5 grams. Activated charcoal, 1g/kg (upto a maximum dose of 50 g) can be all patients who presenting within the first 4 hours of consumption as a means of reducing the absorption.

The toxic dose in children <6 years is 200mg/kg or more within an 8 hour period, while in adults it is 200mg/kg or 10 g whichever is less over a single 24 hour period or 6g or 150mg/kg whichever is less within a single 24 hour period. For individuals at risk, like pregnant women, prolonged fasting, chronic alcoholism or chronic isoniazid use, the threshold for referral would be 4 g or 100 mg/kg within a 24 hour period.

It may be withheld in those whose airway is compromised, like in unconscious patients, as they stand a chance of aspiration, unless they are intubated. However, intubation is not warranted with the sole purpose of administering charcoal or when the patient presents later than 4 hours after consumption.

Studies have proved that activated charcoal has reduced the risk of exposure considerably:

- Studies have revealed that those treated with activated charcoal had a higher decrease in serum acetaminophen levels than those who are not. When compared to those treated with gastric lavage and antiemetics.
- Observation studies have also proved that administration of activated charcoal has lowered the toxicity that can result from it.
- Further, a retrospective study involving 981 patients following an acute acetaminophen overdose revealed that the requirement of N-acetyl treatment was less for those who were pretreated with...
The aim of management is to start N Acetyl Cysteine much earlier than the rise in the alanine aminotransferase, which can be safely achieved within 8 hours of ingestion.

The mechanism by which NAcetyl cysteine has shown to reverse the hepatotoxicity is by restoring the glutathione stores.

So far no randomized placebo controlled trials have been done to evaluate the efficacy of N Acetyl Cysteine due to ethical reasons. Further, it has also been shown that late administration after hepatotoxicity has set in, has reduced the mortality and has helped in improving the hepatic and cerebral function.17,19

However, some queries remain with respect to mode of administration of N Acetyl Cysteine following an acute ingestion. The two protocols commonly followed are the 20 hour intravenous (IV) protocol15 and the 72 hour oral protocol17 which have been reviewed here.

There are also studies showing reports that hepatotoxicity continues following ingestion of massive doses of acetaminophen (ingestion >30 g, or serum concentration >500 mg/L [3300 Î¼mol/L]) despite early administration of N A Cysteine.20,21 Many of these cases were those in which diphenhydramine was co-ingested and the patients had raised acetaminophen concentrations at the end of the intravenous 20 hour protocol. Pharmacokinetic models suggest that a higher dose of N-acetylcysteine treated for a longer duration may be beneficial in such cases.22,23 In such occasions, consultation with a toxicologist who is familiar with the management of acetaminophen overdose may be sought.

Indications — Indications for N-acetylcysteine therapy include:
- Serum level of acetaminophen concentration at four hours or more following acute ingestion above the “treatment” line of the nomogram for acetaminophen poisoning (Figure 1)
- In a suspected case of consumption of 150 mg/kg (7.5 g total dose regardless of weight) or more for a patient whose serum acetaminophen levels may not be available for at least the first 8 hours of consumption.
- A patient with serum acetaminophen concentration of more than or equal to 10 microgram/ml (66 µmol/L) following an acute ingestion.
- Patient with a history suggestive of acetaminophen overdose and evidence of hepatotoxicity.
- Those with a delayed presentation of more than 24 hours and having laboratory evidence of liver injury (ranging from mild transaminitis to fulminant hepatic failure) with a history of excessive acetaminophen ingestion. Patients with delayed presentation and hepatic injury should be managed in consultation with a regional poison control center (1-800-222-1222 in the United States) or a medical toxicologist.

20 hour IV protocol — The 20 hour intravenous (IV) protocol for N-acetylcysteine treatment has commonly been used since the 1970s.

The approved 20 hour IV dosing regimen may be complicated and is performed as follows:
- An initial loading dose of 150 mg/kg in 200 ml diluent is given over 15 to 60 minutes (we recommend 60 minutes)
- This is followed by a 4 hour infusion at 12.5 mg/kg per hour IV (ie, total of 50 mg/kg over 4 hours) in 500 ml of diluent.
- Finally, at a rate of 6.25 mg/kg per hour IV (ie, total of 100 mg/kg over 16 hours) in 1000 ml diluent over 16 hours.
In children between 20-40 kgs
• loading dose of 150mg/kg in 100 ml diluents over 1 hour,
• then 50 mg/kg /hour in 250 ml of diluent over 4 hours
• then 100mg/kg in 500 ml diluent over 16 hours.
In children <20 kgs,
• 150mg/kg into 3ml/kg diluents in 1 hour
• Then 50mg/kg into 7 ml/kg diluents over 4 hours
• Finally 100 mg/kg into 14 ml/kg diluents into 16 hours.

This treatment protocol provides a total of 300 mg/kg over 20 to 21 hours.\(^{15}\)

The duration of treatment may be extended if the patient presents following large doses and has evidence of hepatotoxicity.

**Simplified 20 hour IV protocol** — The results of a large retrospective study and experience at some hospitals suggest that non-allergic anaphylactic reactions during treatment with IV N-acetylcysteine can be reduced by using a two-bag regimen instead of the traditional three-bag regimes. In the study, non allergic anaphylactic reactions occurred in 10 percent of the 389 patients treated with the standard regimen versus 4.3 percent of the 210 patients treated with a modified two-bag regimen (odds ratio [OR] 2.5; 95% CI 1.1-5.8).\(^{24}\)

Another randomized trial using a slightly different protocol that also slowed the initial infusion rate reported similar decreases in the rate of adverse events.\(^{25}\) While further trials are needed to confirm the improved safety of the two-bag regimen, it is believed to be a reasonable treatment approach in adults and older adolescents.

The two bag regimen can be given in the following manner:

- First, administer a 4 hour infusion at 50 mg/kg per hour IV (ie, total of 200 mg/kg over 4 hours)
- Next, administer a 16 hour infusion at 6.25 mg/kg per hour IV (ie, total of 100 mg/kg over 16 hours)

**72 hour oral protocol** — The 72 hour oral (PO) dosing protocol for N-acetylcysteine treatment has been used successfully for more than 30 years, and consists of the following:
- A loading dose of 140 mg/kg PO, followed by
- A dose of 70 mg/kg PO every four hours for a total of 17 doses.

No dose adjustment is needed if the patient has been treated with activated charcoal.

The incidence of hepatotoxicity for patients treated within eight hours of ingestion is less than 10 percent, but increases to approximately 40 percent if treatment is delayed beyond 16 hours. In the largest study of oral N-acetylcysteine, no deaths occurred among patients treated before the onset of transaminase elevation.\(^{11}\)

**Other protocols** — A 12-hour protocol for N-acetylcysteine treatment of APAP overdose has been described.\(^{23}\) This protocol involves the administration of 100 mg/kg of N-acetylcysteine over two hours as a loading dose, and then administration of 200 mg/kg over 10 hours. In a randomized trial, this protocol resulted in fewer adverse effects than the standard 20-hour protocol. However, the study was not large enough to draw conclusions about efficacy.

For patients with recurrent supratherapeutic ingestion or unknown time of ingestion, serum acetaminophen and transaminases should be measured, and NAC must be started until serum acetaminophen levels are below 10 micrograms /ml or until the transaminases normalize.

**IV versus oral** — There have been no trials comparing patients who have been treated with the 20 hour IV and the 72 hour oral routes. The best available data suggest that both routes are effective and differences are minimal.\(^{26,27}\) In most patients, either the oral or IV route is acceptable. IV administration is preferred in the following:

- Vomiting
- Contraindications to oral administration (ie, pancreatitis, bowel ileus or obstruction, bowel injury)
- Hepatic failure
- Patients who refuse oral administration

Patients showing evidence of hepatic failure require IV therapy.

However, in children dilutional hyponatremia and seizures from free water load associated with infusion have been reported in some cases. Massive doses may also cause raised intracranial hypertension, cerebral edema and status epilepticus.

**Effect of patient weight on dosing** — In the United States, dosing depends on the weight of the individual. However, the maximum dose is based upon a weight of 100 kg for IV therapy and 110 kg for oral therapy.\(^{28,29}\) The basis for this has not been proved however it has been showed that dosing above this has not resulted in increased efficacy.\(^{31}\) However, in a large observational study, clinicians often based dosing on actual weight with a low rate of adverse events.\(^{31}\)

**Adverse reactions** — Dosing errors may occur during common IV N-acetylcysteine administration,\(^{32}\) however significant adverse events arising from such miscalculations are rare. The most common adverse drug reaction described with intravenous preparation has been non IgE mediated anaphylaxis (anaphylactoid reactions), while that associated with oral administration has been vomiting.

Anaphylaxis (anaphylactoid...
reaction) — Prospective studies suggest that between 10 to 20 percent of patients treated with IV N-acetylcysteine develop a hypersensitivity reaction (ie, anaphylaxis that is not IgE-mediated, formerly known as an anaphylactoid reaction).\textsuperscript{33,34} Reactions may not be very severe and most individuals are able to tolerate the infusion when it is resumed. However, patients receiving IV N-acetylcysteine need close monitoring and medications handy so as to counteract the adverse drug reactions including airway management.

These include oxygen, antihistamine medication (eg, diphenhydramine), salbutamol, noradrenaline (1:1000 for intramuscular use), steroid (eg, methylprednisolone), a resuscitation cart, and emergency airway management equipment. Even those restarted on N-acetylcysteine infusion after anaphylactoid reaction must be monitored in a critical care setting for the remainder of the infusion.

Limited observational evidence is available regarding the continuation of N-acetylcysteine in patients with anaphylaxis.

Based upon one small case series, the following approach is suggested:\textsuperscript{35}

- Patients who experience flushing without pruritus or urticaria don’t need interruption of the infusion, which can be continued, unless more severe signs develop. There is no convincing evidence that slowing the infusion rate would reduce the risk of hypersensitivity reactions.
- Patients who develop urticaria should have the infusion discontinued temporarily and they must be administered norepinephrine, as well as diphenhydramine and a glucocorticoid. The infusion may be restarted once urticaria resolves.

- The same protocol applies to those who develop angioedema or respiratory symptoms and if wheezing is present, nebulization is needed. The infusion may be resumed after the symptoms abate and an hour after epinephrine is administered.
- Patients who develop hypotension or other signs of systemic anaphylaxis after IV N-acetylcysteine therapy should have the infusion stopped and receive treatment for anaphylaxis in such situations. Restarting IV N-acetylcysteine should not be resorted to as it may be hazardous. Oral N-acetylcysteine therapy should be provided as an alternative, which may be tolerated by most of them.

Vomiting — Approximately 33 percent of subjects treated with oral N-acetylcysteine develop nausea and vomiting.\textsuperscript{37} The palatability of N-acetylcysteine may be improved by converting it into a juice form.

It is reasonable to administer an antiemetic to nauseated patients or patients who have vomited prior to receiving oral N-acetylcysteine. 5-HT\textsubscript{3} receptor antagonists (eg, ondansetron) are effective antiemetics that are widely used in this setting.\textsuperscript{37}

If a patient vomits within an hour of oral dose of N-acetylcysteine, the dose be may be repeated. Persistent vomiting despite oral anti-emetic is an indication for intravenous administrations.

Duration of treatment — While the efficacy of IV and oral administration is similar, controversy persists about the optimal duration N-acetylcysteine therapy. The current treatment protocols approved by the Food and Drug Administration (FDA) are time-based (20 and 72 hours).

Many authors recommend that therapy be tailored to each patient, using clinical endpoints rather than time to determine duration.\textsuperscript{38-40} We suggest the following approach for three common clinical scenarios based upon the type of ingestion and the clinical status of the patient:

- Following an acute ingestion with treatment started before transaminitis or within eight hours of ingestion - Administer IV or oral N-acetylcysteine for a minimum of 20 hours (which may be extended if oral route is administered).\textsuperscript{41}

The aminotransferase must be checked regularly and particularly as the treatment duration is coming to an end (approximately 18 hours after starting treatment). If transaminitis is present or serum acetaminophen is detected, treatment with N-acetylcysteine at 6.25 mg/kg per hour (for IV protocol) or 70 mg/kg every four hours (for oral protocol) must be continued and ALT and serum acetaminophen concentration must be rechecked every 12 hours. PT INR must also be measured as it is an indicator of acute liver injury.

Treatment may be stopped when the serum acetaminophen is <10 microgram/ml, INR<1.3 and there is no increase in aminotransferases. There is no uniformly accepted definition of “clearly decreasing.” One conservative definition is a decrease of more than 50 percent from the peak measurement or three consecutive decreasing values, all below 1000 international units/L.

Monitoring during treatment — Some authors recommend that once N-acetylcysteine is initiated within 8 hours of ingestion, further evaluation of aminotransferases may not be warranted. However, others say that it is advisable to check the levels as some individuals might develop liver injury during the treatment period also which might necessitate extension of the treatment.\textsuperscript{43}
measurement is also recommended during the end of treatment in order to guide if treatment duration needs to be extended.20,38,39

Some guidelines recommend measuring serum aceterminophen, INR, serum bicarbonate, and serum creatinine at the end of treatment and continuing treatment if any value is abnormal.44 The ALT is used to monitor the degree of hepatic injury and the other tests are used to determine the need for liver transplant.45

Measuring the ALT and INR every 12 hours for any patient who develops ALT elevation is beneficial. If the patient has an ALT greater than 1000 international unit/L, coagulopathy (ie, INR >1.5), or encephalopathy, then the serum bicarbonate, glucose, and creatinine should also be measured every 12 hours. Intense monitoring is required as a need for transplantation may arise.

Side effects — Both therapeutic serum concentrations of N-acetylcysteine and high concentrations of acetaminophen can elevate the INR. These elevations are usually mild (INR should not be greater than 1.5), occur between 4 and 20 hours post ingestion, and resolve as treatment is continued.46

### Antidote Treatment in Special Circumstances

**Treatment in hepatic failure** — In the face of hepatic failure, N-acetyl Cysteine must be given as it improves the hepatic microcirculatory functions.

There is no role of oral N-acetylcysteine in hepatic failure. The dosing protocol is the same as the 20 hour regimen used for the prevention of hepatic injury, except the final infusion rate (6.25 mg/kg per hour) is continued until the patient receives a transplant OR the hepatic encephalopathy resolves2,6,17 and the international normalized ratio (INR) is less than two.44,47

Additional supportive therapies for the management of acute hepatic failure and its complications (including encephalopathy, coagulopathy, and acute renal injury) are started as indicated.

The following is King’s college criteria that is used as a guide to know the indication for liver transplantation in paracetamol poisoning.

**Treatment in pregnancy** — Management of acetaminophen poisoning in pregnancy doesn’t differ significantly from the general population. However, intravenous administration is preferred to ensure rapid delivery to the fetus and to prevent vomiting.

As acetaminophen crosses the placenta, maternal overdose may also cause fetal compromise and there are case reports of fetal and neonatal death from hepatic necrosis following maternal overdose.48,49 However, most cases of pregnant women with an acetaminophen overdose are uneventful.49,50

The risk of hepatotoxicity also doesn’t change in pregnancy hence Rumack-Mathew normogram may also be used in pregnant population.14

In pregnant patients with repeat or chronic ingestions, serum acetaminophen and transaminase concentrations should be measured. Treatment with N-acetylcysteine is indicated if the serum acetaminophen concentration is greater than 20 mcg/mL or a serum transaminase concentration is elevated (>50 international unit/L).42 Dosing and the duration of treatment do not differ in the pregnant patient.

Though there are several reports of good outcomes among mothers with hepatic injury following acetaminophen overdose,51,52,53 it is likely that maternal toxicity increases the risk for adverse pregnancy outcomes. The incidence of fetal malformations have not shown to be to be increased following acetaminophen overdose if treatment is started on time, but data are limited.50,54

The most important intervention to avoid toxic effects of acetaminophen poisoning is timely treatment with N-acetylcysteine. In a prospective observational study of 60 pregnant women with acetaminophen overdose, increasing time to N-acetylcysteine administration was associated with an increased risk of miscarriage and fetal death.48 Multiple case reports describe similar findings.55-57

As against what many claim both IV and oral routes have been used successfully to treat pregnant patients with acetaminophen overdose, and oral formulations may be used when IV N-acetylcysteine is not available. Oral administration produces therapeutic N-acetylcysteine concentrations in cord blood.55

Standard laboratory studies and monitoring should be performed in pregnant patients with acetaminophen overdose.

**Other Treatments**

**Cimetidine and other medications** — Several other treatments have been suggested as possible adjuncts for the prevention...
of acetaminophen-induced liver injury. The most commonly cited is cimetidine, an inhibitor of acetaminophen metabolism.\(^{59-63}\) While this treatment was useful in animal models, it had no effect in a clinical trial where patients were treated with N-acetylcysteine.\(^{64}\) Other substances have also been evaluated in animal models, but none is considered standard care in humans.\(^{65-68}\)

Older studies evaluated therapies such as methionine, mand dimercaprol,\(^{13,69,70}\) but these treatments were limited by adverse effects and play no role in current management.

Extracorporeal removal — Although acetaminophen overdose is cleared by hemodialysis,\(^{71,72}\) the safety and efficacy of N-acetylcysteine leaves no role for dialysis in the standard management of acetaminophen poisoning when N-acetylcysteine is available. Extracorporeal removal may be useful in treating acetaminophen overdose if N-acetylcysteine is not available, but there are no systematic studies to evaluate the effectiveness of this treatment. Hemodialysis should never be considered an alternative to N-acetylcysteine therapy.

If acetaminophen overdose is complicated by acute kidney injury, hemodialysis may be necessary. For patients with a massive overdose and evidence of mitochondrial dysfunction (such as presence of severe lactic acidosis without liver failure), some experts advocate early hemodialysis in addition to N-acetylcysteine.\(^{73}\) However, this recommendation is based on expert opinion and there are many reported cases of recovery with acetylcysteine therapy alone. While hemodialysis is a reasonable treatment, it should not be considered a standard therapy for these cases.

Of note, hemodialysis removes N-acetylcysteine as well as acetaminophen, so some toxicologists recommend doubling the standard dose during hemodialysis.\(^{74,75}\) However, it is not clear that the amount of N-acetylcysteine removed affects clinical outcomes, so increasing the rate is not universally recommended and should not be considered.

### Prognosis

The outcome of acetaminophen intoxication is almost always good as long with timely administration of N-Acetyl cysteine, particularly when given within the first 10 hours.\(^{10,11,76}\) A study of around 333 cases of acetaminophen overdose found that hepatotoxicity was reported in only 4 percent of patients and mortality rate was less than 1 percent when NAC was rapidly administered.\(^{77}\) Hence, fulminant hepatic failure and death from acetaminophen poisoning result from inability to recognize poisoning, or delayed initiation of management.

Studies are ongoing in order to find out some biomarkers that can predict the risk of hepatotoxicity early at the time of presentation following acetaminophen overdose.\(^{78,79}\)

### References


the hepatoprotective action of N-acetylcysteine in mice treated with toxic doses of paracetamol. Toxicology 1997; 121:122.


66. Reisman SA, Alexunes LM, Klaassen CD. Oleanolic acid activates Nrf2 and protects from acetaminophen hepatotoxicity via Nrf2-dependent and Nrf2-independent processes. Biochem Pharmacol 2009; 77:1273.


Heart Failure and the Iron Deficiency

Amey Beedkar¹, Rohan Parikh¹, Pradeep Deshmukh²

Abstract
Iron deficiency anemia is a significant problem worldwide and more so in developing countries, like India. The prevention and treatment of iron deficiency is a major public health goal in India.

It is now well recognized that iron deficiency has detrimental effects in patients with coronary artery disease, heart failure, and pulmonary hypertension, and possibly in patients undergoing cardiac surgery. Around one-third of all patients with HF, and around one-half of patients with pulmonary hypertension, are affected by iron deficiency.¹

Introduction
Anaemia is a frequent finding in patients with heart failure (HF) and can worsen cardiac function, myocardial contractility, renal function, exacerbate symptoms and worsen quality of life. It is being increasingly recognised that patients with an underlying cardiac disease (especially elderly individuals and those with chronic diseases) can present with signs and symptoms of cardiac failure in absence of clinically apparent anaemia. These patients should be evaluated for an underlying iron deficiency (during early iron deficiency, anaemia is typically absent), as prompt initiation of parenteral iron can result in symptomatic improvement and even reverse the cardiac failure. Improved exercise capacity has been demonstrated after iron administration in patients with pulmonary hypertension.³

Absolute ID was defined as ferritin < 100 µg/L, functional ID was defined as ferritin 100–299 µg/L and transferrin saturation (TSAT) < 20%.⁴

Iron Deficiency and Heart Failure-Drug Trials

The Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency (FAIR-HF) study analysed the impact of intravenous iron therapy with Ferric Carboxymaltose in 459 patients with heart failure and iron deficiency, and found an improvement in functional class, 6-minute walk test distance and quality of life in Ferric Carboxymaltose -versus placebo-treated patients.⁵ Similar results were recently obtained in the Ferric Carboxymaltose evaluatIoN on perFormance in patients with IRon deficiency in coMBination with chronic Heart Failure (CONFIRM-HF) study.⁶ Treatment with intravenous ferric carboxymaltose in patients with chronic heart failure and iron deficiency, with or without anemia, improves symptoms, functional capacity, and quality of life with an acceptable the side-effect profile.¹

Doses in Heart Failure

Oral versus parenteral iron
The choice between oral and parenteral iron depends on a number of factors including the severity of the anaemia and rapidity of correction needed, cost and availability of different iron preparations, as well as the ability of the patient to tolerate oral iron preparations. However in cardiac patients, where rapid correction of the iron deficiency is desirable, we prefer to use parenteral iron. With the availability of IV iron formulations with improved toxicity profiles and minimal adverse effects, intramuscular (IM) iron which is painful, stains the buttocks, and has variable absorption is generally avoided.

Dose calculation
Generally, the dose of parenteral iron is calculated based on body weight, current hemoglobin level, and amount of elemental iron per milliliter of the iron product.

-Volume of product required (mL) = [weight (kg)x (14 - Hgb) x (2.145)] / C + correction of stores

Where C= concentration of elemental iron (mg/ml) in the product being used. Iron carboxymaltose contains 50 mg iron/mL solution for injection.

In practice, there is no evidence that total doses above 1000 mg of elemental iron are clinically useful. Often a fixed dose of approximately 1000 mg, is generally sufficient to treat anemia and provide additional storage iron without causing iron overload.

Choice of IV formulation
The choice of the formulation will depend on the cost, availability, and number of visits/ time required to administer the full dose. The different parenteral forms of iron available are Ferric carboxymaltose , Iron Sucrose, Iron dextran, Ferumoxytol , Ferric pyrophosphate citrate and Ferric gluconate. With the exception of Iron dextran, the incidence of severe anaphylactic reactions is exceedingly rare but merits a vigilant attitude

¹Registrar, ²Associate Professor, Goverment Medical College and Superspeciality Hospital, Nagpur, Maharashtra
Received: 17.04.2016; Accepted:12.09.2017
as it can be life threatening. IV iron should be avoided in patients with active infections. Unlike iron sucrose and ferrous gluconate which need frequent low doses to be administered in multiple settings, Ferric carboxymaltose (FCM) which is a colloidal iron hydroxide complex can be administered in one or two visits. This is highly desired in settings where rapid correction of the iron deficiency is indicated. Also, unlike with iron dextran, the risk of anaphylactic reactions is minimal.

All the iv preparations of iron are equally effective in treating iron deficiency. However, some studies have found Ferric carboxymaltose (FCM) to be better than other iron formulations.³

Table showing comparative efficacy of Iron dextran Iron sucrose Ferric carboxymaltose ³

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Iron dextran</th>
<th>Iron sucrose</th>
<th>Ferric carboxymaltose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SD) haemoglobin increase g/dL</td>
<td>1.4 (0.9-1.9)</td>
<td>2.4 (1.99-2.74)</td>
<td>2.7 (2.30-3.03)</td>
</tr>
<tr>
<td>Mean (± SD) MCV increase (fl)</td>
<td>5.8 (4.0-7.6)</td>
<td>5.6 (2.9-8.3)</td>
<td>7.0 (4.6-9.7)</td>
</tr>
<tr>
<td>Mean (± SD) ferritin increase (mcg/dL)</td>
<td>149 (93-205)</td>
<td>109 (84-133)</td>
<td>149 (99-200)</td>
</tr>
</tbody>
</table>

Managing adverse reactions

Adverse reactions are exceedingly rare with FCM.

Like any iron preparation, FCM can also cause myalgia, muscle weakness, arthralgia, nausea, vomiting and headache.

Transient fever, arthralgias, myalgias, or flushing are generally seen in approximately 0.5 to 1 percent of infusions. In absence of associated hypotension, tachypnea, tachycardia, wheezing, stridor, or periorbital edema, the infusion should be temporarily withheld and the patient observed. If symptoms resolve, the infusion can be resumed. Antihistaminics should not be administered as they can actually worsen the symptoms. If symptoms persist unchanged, 125 mg intravenous methylprednisolone should be administered, then wait for 30 minutes, and reinitiate the iron infusion; a short course of oral methylprednisolone also may be administered.

A short course of nonsteroidal anti-inflammatory drugs (NSAIDs), if appropriate may be initiated.

Patients with more serious or true anaphylactic reactions should be treated according to standard protocols. Any adverse effect with parenteral iron administration should be reported.

Monitoring and hemoglobin/iron targets

Effective treatment of iron deficiency results in resolution of symptoms, a modest reticulocytosis (peaking in 7 to 10 days), and normalization of the hemoglobin level in six to eight weeks. For IV iron, hemoglobin is to be re-assessed four to eight weeks after the iron has been administered. The iron parameters should not be repeated for at least four weeks, because IV iron interferes with most assays of iron status.

Future Strategies

Future studies are needed for defining the role of blood transfusions; treatment heart failure patients and the patients with stable, asymptomatic or symptomatic ischemic heart disease.

Conclusions

Anemia is common in patients with heart disease and now we have the evidence base to support a role for iron therapy for anemia correction. Iron treatment helps ameliorate symptoms in patients heart failure. The role of blood transfusions remains understudied and unclear.

References

Common Statistical Errors and how to Avoid them

NJ Gogtay, UM Thatte

“To consult the statistician after an experiment is finished is often merely to ask him to conduct a post mortem examination. He can perhaps say what the experiment died of.” – R. A. Fisher

Introduction

Researchers should ensure publication of work done as papers that do not see the light of the day have wasted precious time and resources of all stakeholders and will have failed to advance Evidence Based Practice. Getting the statistics right in the publication is crucial. There is evidence both from India and elsewhere about inappropriate reporting of statistics in papers. For example, Jayakaran and Yadav [2011] analyzed n=196 articles in two Pharmacology journals published from India and found that 78.1% articles had inappropriate descriptive statistics, 31.1% used the wrong statistical test for between group comparisons and only 1% reported statistical assumptions.

Researchers can commit errors at two levels, both of which can affect statistics in the manuscript. The first is errors that occur during the process of research [such as errors in planning and/or implementation of the study] and the second is those that occur during data analysis, interpretation and presentation of results [either in the form of a manuscript or podium/poster presentations]. This paper will describe errors with the latter. It is important to point out here that more often than not, errors during the planning and conduct of research cannot be easily identified by a journal editor [who only sees the final manuscript] and hence any study should be done with utmost care and attention to detail. This is because errors of omission or commission that occur during the process of research are detrimental to the most important stakeholder in research – the patient one whose quality of life we hope to improve through the research process.

Common Statistical Errors

Before we proceed to common statistical errors, let us understand why it is important that we carry out data analysis meticulously. Data analysis is a process that seeks to identify relationships, associations, differences, variance or trends that may exist within the data. The purpose is to see if the results can be generalized to the population or in other words “how true” or real these findings are. It is useful remember the following before data analysis- 1) Organize all collection forms, and material used to record the data in one place 2) Check the data for completeness and accuracy 3) Note missing data if any and decide whether or not to remove from the analysis and document this 4) Assign unique identifiers to the data 5) Feed the data into an appropriate software [Microsoft Excel, SPPS are two examples] and do a thorough quality check of the fed data by someone independent of the study.

The subsequent sections describe common statistical errors. The list given is not intended to be all encompassing but rather cover some of the more common errors made by authors and often missed by editors.

Errors in Data analysis

The choice of Parametric versus non-parametric methods and the importance of assumptions

Statistics as a discipline uses models and assumptions. Prior to applying any parametric test, the researcher needs to check if the assumption of normality is met as these tests are to be used only when the data is normally distributed. Also, it is a common myth that parametric tests are more powerful than non-parametric tests. In fact, they are powerful only to the extent that the assumptions are met, [see later for assumptions for the unpaired t-test] Else, they miss differences or relationships, which would have been otherwise picked up by non-parametric tests.2

Using the wrong statistical test

Statistical tests are not only numerous, but also have similar sounding names. Each test is to be used only if certain assumptions are satisfied. For example, the student’s t-test is a widely used parametric test that is of two types- the unpaired [also called the two-sample t test] and the paired t test and data needs to be normally distributed for its use. For the unpaired t-test, in
addition, observations need to be independent and the variances in the two groups equal. This test cannot be used for multiple group comparisons. Williams found that among articles published in the American Journal of Physiology that used either the unpaired or the paired t-test, 17% used the test inappropriately for multiple comparisons.

The need to address confounding and effect modification

Confounding: This occurs when the effect or association between an exposure and outcome is distorted by the presence of a third variable. This variable is one that is linked to both the exposure and the outcome, but does not lie in the causal pathway. Confounders are viewed as the “nuisance” factor/s that distort the association one way or the other [positive or negative]. Let us understand this with an example. One study that compared pet owners versus non-pet owners found that the former had significantly lower systolic blood pressure relative to the latter despite coming from similar socioeconomic backgrounds and having similar body mass index. One possible reason is that pet owners [dog owners in particular] tend to get more exercise relative to non-pet owners and thus exercise here becomes the confounder or confounding variable.

Effect modification: This occurs when the exposure has a different effect on different groups of patients leading to differential outcomes in sub groups. Let us understand this with an example of the use of perioperative beta blockers and association of their use with mortality after non-cardiac surgery in a retrospective cohort study of 663,635 patients. The authors stratified patients based on the Revised Cardiac Risk Index (RCRI); which is a tool used to estimate a patient’s risk of perioperative cardiac complications. The Odds ratios for different levels of risk are presented in Table 1.

The table shows that when beta blockers are given to patients with high RCRI scores [2, 3 or 4 and more], there is a reduction in mortality. However, at lower scores of 1 or 0, this effect is attenuated or even lost and thus RCRI here acts as the “effect modifier”.

Sub group analyses

When two group comparisons are made, the result is an average effect of the two interventions [and the difference between them] in a heterogenous group of patients. The practicing clinician would however like to know if the better treatment is likely to work in the individual patient that he is treating. This is because each individual patient has certain characteristics that define him/her- for example gender, severity of the disease, age [young/middle aged/elderly], alcohol [presence/absence], smoking [presence/absence], diabetes and so on. The clinician may want to know that given a certain set of characteristics, what is the probability of response. This is what is essentially addressed by sub group analyses, which are defined as “analysis of treatment effects with subgroups of patients enrolled in a study/trial. The fundamental idea with these analyses is to uncover interesting relationships that could be explored further. Their disadvantage lies in the fact that 1) the differences or associations uncovered could be spuriously positive [Type 1 error] 2) They may not able to pick up a difference due to smaller numbers of patients in each group [beta error/false negative error] 3) be difficult to interpret. Let us understand both their utility and difficulties with two examples.

The IRESSA Survival Evaluation in Lung Cancer (ISEL) was a phase III study that compared the efficacy of Gefitinib versus placebo in patients with refractory advanced non-small cell lung cancer (NSCLC). The study did not yield a significant difference in survival between the two groups of patients. However, when a planned sub group analysis of n = 342 patients of Asian origin was done, [n= 235 received Gefitinib and n= 107 received placebo], it was seen that Gefitinib significantly improved survival among the Asian patients [HR 0.66, 95% CI [0.48, 0.91], median survival 9.5 months versus 5.5 months, p <0.01]. At the other end of the spectrum, a sub group analysis of men versus women [a meta-analysis that included n = 6 studies] concluded that the effects of use aspirin for primary prevention reduced myocardial infarction significantly in men but not in women. These findings were however not confirmed by two other meta-analyses [where trials of both primary and secondary prevention were included] and it was concluded that gender did not really affect the efficacy of aspirin. Sub group analysis at best, should be hypothesis generating and the best ones that
those that are specified a priori. Post-hoc sub group analysis when done should be transparently reported.

**Understanding and addressing bias**

Bias can very simply be defined as any deviation from the truth. Since the purpose of research is to arrive at the truth, researchers must have a good grasp of bias and minimizing it. Bias can be broadly classified as – 1) Selection bias [for example prevalence- incidence bias, admission rate bias and non-responder bias] and 2) Information bias [for example misclassification bias and Hawthorne effect].

Let us understand how bias can affect study results (and interpretation) with an example of a paper by Redelmeier and Singh who reported that Academy Award-winning actors and actresses lived almost 4 years longer than those who did not receive an Oscar. It was later shown that the statistical method used for the analysis actually conferred an unfair advantage to the Oscar winners, a type of bias called as “immortal time bias” and the difference in survival was just one year and not statistically significant. Another and oft quoted example is that of a study by Coren and Halpern [1991] which reported that left handers died much earlier than right handed people. This questionnaire based study did not take into account the fact that in the early part of the 20th century, many parents forced children who were naturally inclined to be left handed to use the right hand resulting in groups that were not clearly only left handed or right handed.

**Presenting Data Appropriately**

**Quantitative data - use summary measures appropriately**

When quantitative data [height, weight, blood pressure for example] are presented, both means and medians can be reported as summary measures. It is important that the mean is always accompanied by the standard deviation [SD] which gives the extent of variability seen in the data and written as mean [SD]. The standard error of mean [which is much smaller than the SD and is given by SD/√n] should not be given as it is a population parameter and not sample statistics and will always be smaller than the SD. Jaykaran and Yadav for instance showed that 78.1% papers had inappropriate descriptive statistics and use of mean ± SEM rather than mean ± SD was the most common presentation error seen. The median is used to present skewed data and when used, it must always be accompanied by the range. Alongside the median, graphical depictions of skewed data such as the box and whisker plot giving the inter-quartile range are useful visual aids that help understand variability in the data better.

**Presentation of categorical data**

Categorical variables may be dichotomous or binary [for example -male and female] or non-binary [mild, moderate and severe pain]. These are described as proportions of the total number of participants [along with 95% Confidence Intervals]. They can also be expressed in the form of a bar or pie chart. Often times, binary categorical data is best presented as a 2 x 2 table. This is particularly done when there are two group comparisons and helps in the calculation of several metrics such as the relative risk, odds ratio, hazard ratio. It is also useful when diagnostic tests are being evaluated for the calculation of sensitivity, specificity, positive and negative predictive values and the diagnostic odds ratio. In addition, tests such as the Chi-square test, Fisher’s exact probability test and the McNemar’s test are best understood and interpreted with the 2 x 2 table.

**Outliers and their reporting**

An outlier is essentially an abnormal value that lies far away from the rest of the values in the sample. Outliers are important are they can have a significant impact and alter results of the analysis dramatically. They could be true outliers, a typographical error that resulted during data entry [which needs to be corrected], or a wrong measurement. All outliers need to be carefully considered. Given that here is little consensus on how outliers are to be analyzed, it is important that are outliers are reported with honesty and where appropriate an analysis with and without the outlier be performed and reported.

**Reporting only P values, not reporting the exact p value and confusing it with the effect size and not reporting Confidence Intervals**

The p value that is usually set at 5% essentially tells you whether the results are consistent with being due to chance. It does not by itself provide a good measure of evidence. It must always be accompanied by the effect size [the magnitude and direction of the difference when two group comparisons are made] and the 95% CI of the difference [the confidence interval gives the range in which we expect the true population value to lie]. The p value, the effect size and the confidence intervals of the effect size must be viewed in tandem for drawing meaningful conclusions.

**Interpreting Data Correctly**

**Correlation and Causation**

A common mistake is to assume that just because we find a correlation between two variables, one causes the other. This is often described in statistical parlance as “Correlation does not imply causation”. An often-quoted example in this regard is the “Correlation” of Sun Signs in Astrology with outcomes by the researchers of the Second International Study of Infarct Survival Trials Collaborative Group [ISIS-2]. Overall, the study showed a significant benefit of aspirin over
Clinical versus Statistical significance

Statistical significance can be mistaken by both authors and readers with clinical significance. Let us understand this with an example of blood pressure reduction after the use of two anti-hypertensive drugs. Say that Drug A produces a greater reduction in blood pressure than Drug B and the difference is 2 mm Hg which is reported as \( p < 0.05 \) and the 95% CI is.\(^1\)\(^6\) This means that when Drug A is used in the population, the reduction maybe as low as 1 mm or as high as 6 mm Hg, 95% of the times. Thus, whether this 2 mm of Hg [which is the average reduction] is significant enough to alter a change in prescription from Drug B to Drug A must be well thought through as this difference may really not be clinically meaningful.

Conclusions

In summary, it is useful to remember that the process of research and its subsequent publication is fraught with the potential for making errors and all efforts must be made to minimize if not eliminate them.

References

Giant Intraparanchymal Neurocysticercosis

Krishnan Mugundhan¹, N Balamurugan¹, P Chandrasekar¹, S Sivakumar², MC Vasif Mayan³, PD Nidhin³

38 yrs old male presented with 4 months history of headache, vomiting and right focal seizures of one week duration. On examination, patient was conscious, oriented, pupil 3 mm equally reacting to light on both sides. Fundus was normal. No weakness of limbs noted. CT Brain showed Small cystic lesion with surrounding edema seen in right parietal lobe. Large cyst in left frontal lobe. Small calcified granuloma in left parasagittal parietal lobe (Figure 1). MRI Brain showed Cystic lesion with small mural nodule seen in occipital lobe (Figure 2). Diagnosis of neurocysticercosis was made. Patient was treated with albendazole, steroids and antiepileptics. Patient was free from headache, vomiting and seizures.

On follow up, after 6 months he developed headache, vomiting and right focal seizures. On examination, patient was drowsy, pupil 3 mm equally reacting to light on both sides. Fundus was normal. Weakness of right upper and lower limbs was noted.

Repeat CT Brain showed Previous cystic lesion in right parietal lobe is calcified. Left frontal lobe cystic lesion is increased in size compared to previous scan (Figure 3). CT Brain(Contrast) showed mild contrast enhancement of periphery of cyst in left frontal lobe with ipsilateral compression of lateral ventricle (Figure 4). Patient was taken up for surgery in view of raised intracranial pressure. Craniotomy was done. The cyst was excised. Patient’s sensorium improved. Weakness of right upper and lower limbs was also improved.

CT Brain Post operative image, showing left parietal craniotomy with excision of left frontal lobe cystic lesion (Figure 5). Histopathology of the cystic lesion showed cross-section of a parasite with brood capsule and scolices in the inner cuticular layer. The above features are characteristic of cysticercosis (Figure 6).
subcuticular layer shows cellular layer. The above features are characteristic of cysticercosis (Figure 6). At 6 months follow up, patient recovered completely (Figure 6).

Giant intraparenchymal cysticercosis is a relatively rare presentation of neurocysticercosis (NCC) and only few reports have been published. Clinical presentation of NCC is variable and depends on the location, growth, size, number of cysts, stage of cyst and host immune response. Diagnosis of NCC is mostly based on the clinical and radiological methods. MRI is the radiological modality of choice to determine the pathological stage of the cyst. The stage of the cyst determines the the MRI cyst morphology. Viable cysts show neither enhancement nor perilesional edema, and are hypointense to brain parenchyma. Large cysticercus in NCC causing elevated intracranial pressure are commonly seen in subarachnoid space. NCC is usually managed medically. Surgery is usually recommended for Intraventricular cysts, large cisternal cysts, large parenchymal cyst and when the diagnosis is not certain in imaging studies. The outcome of the patients with parenchymal and intraventricular cyst is usually good.

This case is being presented for its rarity and highlights the need of follow up with imaging studies.

**Crochetage Sign**

Pratibha Himral¹, Susheel Kudial², Kailash Nath Sharma³, Jitender Kumar⁴

![Fig. 1: 12 lead ECG](image)

4 years primigravida presented to our outdoor department for evaluation of dyspnea of one month duration. Cardiac auscultation revealed normal first heart sound, fixed and wide split of second heart sound and an ejection systolic murmur best heard in the left upper sternal border. The ECG showed peak P wave in the limb lead II, right axis deviation, tall R wave in V1(0.9mV) and R/S in V1 >1 and a crochetage R wave in inferior limb leads II, III and aVF. Transthoracic echocardiography showed a large ostium seconum ASD with a diameter of 30 mm with left to right shunt and pulmonary hypertension.

Crochetage is a French word which means notch. The first description of notch on R wave in the electrocardiogram of the patient with atrial septal defect was given by Alvarez et al in 1959. The crochetage R wave is defined as a rapid up and down motion of the R wave tracing on its ascendant branch or near its zenith with bifid or M-shaped pattern involving initial 80 milliseconds of the QRS complex in the inferior limb leads in patients with ostium seconum or sinus venous type of atrial septal defect. The exact patho-physiology is not known. Sensitivity and specificity of this sign approaches 92-100% when present in all the three inferior limb leads.

Similar bifid pattern is also seen in right bundle branch block but this conduction defect involves the last part of the QRS complex. This bifid pattern of right bundle branch persists after surgery whereas early disappearance of crochetage R wave has been observed in 33% of operated patients.

**Acknowledgement**

We thank Dr. L. Sankar, Associate Professor of Neurosurgery and Dr. M. Thenmozhi, Professor of Pathology, Government Mohan Kumaramangalam Medical College Hospital, Salem, for their valuable academic help.

**References**

Life-threatening Medical Complications Due to Ovarian Hyperstimulation Syndrome: A Hidden Etiology

Prerana N Bhavsar¹, Namita J Padwal², Madhura Bhide³, Santosh P Ghagare⁴, Anagha R Joshi⁵, Niteen D Karnik⁶

Abstract
Ovarian hyperstimulation syndrome is usually an iatrogenic complication in women taking ovulation induction medications during assisted reproduction. We hereby report the case of a 25 years old female who presented with hypertension, polyserositis with tense ascites and large cystic ovaries. She developed sigmoid and transverse sinus thrombosis. She had undergone a clandestine ovulation induction therapy as a commercial ovum donor. She fitted in severe category of ovarian hyperstimulation syndrome.

Introduction
Serious thromboembolism in reproductive age group females warrants a search for known etiologies like systemic lupus erythematosus (SLE), antiphospholipid and anticardiolipin antibody syndrome, other thrombophilic state including factor V Leiden deficiency and congestive cardiac failure. Ovarian hyperstimulation syndrome (OHSS) is a recognized complication in females undergoing ovulation induction therapy. Most cases are mild but serious life threatening complications including death are reported.¹ It was first described in 1941 with the first fatal case having renal failure was documented in 1951.² OHSS is classified as mild, moderate, and severe³ (Table 1).

We report a case of hypertension with polyserositis complicated by sigmoid and transverse sinus thrombosis in a 25 year old female. She had a tense ascites, large cystic ovaries and had undergone a clandestine ovulation induction therapy.

Case Report and Discussion
A 24 year old woman presented with complaints of abdominal pain and distention, nausea and vomiting since 4 days with mild headache since 3-4 days. She had no history of fever, jaundice, oliguria, chest pain, heart disease or seizures. She was married since 3 years, had regular menses, was nulliparous and had undergone a medical termination of pregnancy (MTP) 2 years ago for socioeconomic reasons. Her last menstrual period (LMP) was 15 days prior to admission.

On examination, she was conscious, oriented, and afebrile with pulse- 116 beats/minute, blood pressure (BP) - 146/80 mm Hg, respiratory rate- 24/minute. She had pitting ankle edema but there was no pallor, cyanosis, clubbing or icterus. Her jugular venous pressure was 6-8 cm of water; bilateral basal crepitations were evident with right infrascapular dullness. On chest auscultation, heart sounds were normal. The abdomen was distended, tender with flank dullness and fluid thrill. There was no guarding, rigidity or hepatosplenomegaly. Neurological evaluation was normal. Hence, this was a young female with acutely distended tender abdomen with

Table 1: Categories of OHSS

<table>
<thead>
<tr>
<th>Category</th>
<th>Features</th>
</tr>
</thead>
</table>
| Mild     | Grade 1: Abdominal distension and bloating  
          | Grade 2: grade 1 disease plus nausea, vomiting, and/or diarrhea, as well as ovarian enlargement of 5-12 cm |
| Moderate | Grade 3 - Features of mild OHSS plus ultrasonographic evidence of ascites |
| Severe   | Grade 4 - Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax and breathing difficulties  
          | Grade 5 - All of the above plus a change in the blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities, and diminished renal perfusion and function |

¹Assistant Professor, ²Associate Professor, ³Speciality Medical Officer, ⁴Professor and Head, Department of Medicine, ⁵Professor, Department of Radiology, LTM Medical College and LTMG Hospital, Mumbai, Maharashtra
Received: 10.09.2017; Accepted: 15.09.2017
free fluid, stage I hypertension and polyserositis. The main differentials considered were acute Budd-Chiari syndrome, portal vein thrombosis, pancreatitis with acute lung injury, peritonitis with ruptured ovarian cyst. The cardiopulmonary differentials considered were myocarditis and/or acute pulmonary thromboembolism complicated by right heart failure. Nephrotic-nephritic syndrome and Meig’s syndrome were the other differentials.

Her investigations are outlined in Table 2. Urine analysis was normal, no red blood cells casts or proteinuria. The ECG revealed sinus tachycardia. Serum amylase was 72 units/L (normal 40-140 units/L) and lipase was 26 units/L (normal 0-50 units/L). Chest X-ray revealed bilateral pleural effusion (right > left) (Figure 1).

Mild pericardial effusion was seen on echocardiography, the left ventricular ejection fraction was 60% with normal chamber dimensions. There was no regional wall motion abnormality, dilated pulmonary artery or thrombi. Ultrasonography of abdomen and pelvis revealed tense ascites, bulky ovaries, normal portal vein dimensions and no hepatosplenomegaly. Doppler revealed normal portal and hepatic vein blood flow. A diagnostic ascitic tap was non hemorrhagic with 24 mg % protein, 4 lymphocytes, no malignant cells and normal fluid amylase.

Budd-Chiari syndrome generally presents with ascites out of proportion to edema feet, tender hepatomegaly and absent hepatojugular reflux. Though our patient had tense ascites, the hepatojugular reflux was normal. She did not have clinical or ultrasonographic evidence of hepatomegaly or hepatic vein thrombosis. Portal vein thrombosis as a cause of acute portal hypertension to explain her tender ascites would have evidence of portosystemic shunts, upper gastrointestinal bleed and splenomegaly. The absence of splenomegaly with normal portal vein dimensions and flow rules out portal vein thrombosis. Tender fluid filled abdomen with breathlessness and bilateral crepitations on auscultation could favour acute pancreatitis with acute lung injury. The presence of normal serum lipase, normal serum and ascitic fluid amylase with absence of bulky pancreas on ultrasonography ruled out acute pancreatitis. Absence of hypotension, a normal left ventricular ejection fraction with no regional or global wall motion abnormality ruled out myocarditis as a cause of heart failure. Her pulmonary artery and right and left ventricular dimensions were normal and no thrombus was visible in pulmonary artery. This makes pulmonary thromboembolism unlikely. However, her serum fibrinogen degradation product (FDP) level was high (5000ng/L) (normal 10-20 ng/L). She had stage I hypertension, basal crepitations, pleural effusion and ascites; this could suggest a fluid overload state.

Nephrotic-nephritic syndrome patients generally present with puffiness of face, anasarca and polyserositis which our patient had along with stage I hypertension. However, absence of proteinuria or red blood cell casts in urine ruled out this possibility. A ruptured ovarian cyst could be a differential.

<table>
<thead>
<tr>
<th>Table 2: Baseline investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Hemoglobin [g/dl]</td>
</tr>
<tr>
<td>WBC [cells/cc]</td>
</tr>
<tr>
<td>Platelet count [lakh/cc]</td>
</tr>
<tr>
<td>ABG [pH/PCO2/PCO2/HCO3/SpO2]</td>
</tr>
<tr>
<td>Blood urea nitrogen [mg/dl]</td>
</tr>
<tr>
<td>Creatinine [mg/dl]</td>
</tr>
<tr>
<td>Serum sodium [mEq/L]</td>
</tr>
<tr>
<td>Serum potassium [mEq/L]</td>
</tr>
<tr>
<td>Hematocrit [%]</td>
</tr>
<tr>
<td>Serum bilirubin [mg/dl]</td>
</tr>
<tr>
<td>Total protein [g/dl]</td>
</tr>
<tr>
<td>Serum albumin [g/dl]</td>
</tr>
<tr>
<td>SGOT/SGPT [U/L]</td>
</tr>
<tr>
<td>PT(sec)/INR/PTTK (sec)</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
</tr>
<tr>
<td>Antiphospholipid and anticardiolipin antibody</td>
</tr>
<tr>
<td>Serum homocysteine</td>
</tr>
</tbody>
</table>
However, her menstrual cycles were absolutely normal prior to the episode. LMP was 15 days prior to admission. The abdominal pain was generalized and not localized to either iliac fossa and ascitic tap did not reveal red blood cells. Meig’s syndrome consists of ovarian tumour with ascites and pleural effusion. Our patient had bilateral bulky ovaries with tense ascites and bilateral pleural effusion (right> left). Considering this possibility, CT scan abdomen and pelvis was planned.

She was treated with diuretics (injectable frusemide, tablet spironolactone) and given oxygen by nasal prongs (4-6 L/ min). She received intravenous ceftriaxone and metronidazole. Her breathlessness gradually settled, blood pressure stabilized to 130/80 mmHg. However, her abdominal tenderness persisted. The CT scan abdomen and pelvis done on day 4 revealed bilateral bulky ovaries with multiple varying sized hypodense cysts within them. Right ovary measured 3.8x5.5x7.1 cm (APxMLxSI), volume 78.6 cc. Left ovary measured 3.7x5.3x5.1 cm (APxMLxSI), volume 53 cc. (Figures 2, 3 and 4)

A concurrent CT pulmonary angiography ruled out complicating pulmonary thrombi (done in view of high serum FDP levels). In view of huge bulky ovaries, the differentials now narrowed down to Meig’s syndrome, carcinoma ovaries and ovarian hyperstimulation syndrome.

Meig’s syndrome is a diagnosis of exclusion only after ovarian carcinoma is ruled out. The average age of presentation is 50 years; few prepubertal cases related to benign ovarian teratoma or cystadenoma have been reported.5,6 The presenting features include fatigue, shortness of breath, increased abdominal girth, weight gain, nonproductive cough, abdominal bloating, amenorrhea (in premenopausal women) and menstrual irregularities. The physical signs include tachycardia, tachypnea with basal dullness in chest. Abdominal findings include shifting dullness, fluid thrill and palpable lower abdominal masses (left>right). The ascitic and pleural fluid is more likely to be exudative than transudative.7 Her younger age, regular menstrual cycles and CT scan suggestive of cystic ovarian masses (Figures 2, 3 and 4), as against a solid mass in Meig’s syndrome, ruled out the possibility.

Early ovarian carcinoma causes minimal signs. Most cases of carcinoma ovary are diagnosed at an advanced stage with abdominal bloating and distention, vaginal bleeding, weight loss and palpable abdominal masses. A malignant pleural effusion may be present. The average age of presentation is 5th decade onwards8 and ascitic fluid is usually hemorrhagic. Our patient was just 25 years old with a non-hemorrhagic ascitic fluid and normal CA-125 levels (12 units/ml, Normal < 35 units/ml) this makes carcinoma ovary unlikely.

Could polycystic ovarian disease be a possibility? These patients have a long standing history of irregular menses, hirsutism and weight gain with difficulty in conception. The reported ovarian volume in PCOD is usually 10 cm3 or greater.9 Though our patient was obese (weight- 68kg, body mass index-28), her menstrual history was normal, she had previously conceived naturally within 1 year of marriage and she had much larger ovarian masses. This makes polycystic ovarian disease less likely.

On day 5, patient complained...
of an excruciating right sided headache radiating to neck and had projectile vomiting. On examination she was drowsy and irritable, pulse- 68/minute, blood pressure-130/84mm Hg. There were no signs of meningeal irritation or any focal neurological deficit. Bilateral planters were extensors. The CT brain revealed right sigmoid and transverse sinus thrombosis (Figures 5, 6).

At this stage, her husband voluntarily disclosed that she had daily travelled for 2-3 hours to visit a private infertility clinic in a neighboring metro city for 10 days, a week prior to admission. She had received daily injections and tablets. It turned out that she was motivated by a close friend to act as a commercial ovum donor. The injections which she received were probably gonadotropins and tablets were clomiphene citrate. Four days prior to admission she had undergone per vaginal procedure (ovum pick up) and returned home in the evening. The private clinic had taken care not to keep any documentary evidence with the patient.

Hence, our final diagnosis was ovarian hyper stimulation syndrome (OHSS) in a commercial ovum donor with hypertension, polyserositis and extensive sigmoid and transverse sinus venous thrombosis.

Her thrombophilia and hormonal workup was sent. Her serum estradiol was 5625pg/ml (normal: 25-75 pg/ml on days 2-3 of menstrual cycle) serum progesterone: 120.6ng/ml (normal: 18-20ng/ml) and serum beta hCG: 2mIU/L (normal: <5.0 mIU/L). She was started on anticoagulation with injectable low molecular weight heparin for 3 weeks followed by oral warfarin. She needed injection mannitol for raised intracranial tension, her antibiotics were continued for 2 weeks in view of persistent abdominal tenderness. Patient was kept in hospital for almost 2 months in view of slow resolution of headache and abdominal tenderness. On discharge (day56), her abdominal tenderness had resolved, the ovarian size had reduced (ovarian volume, right 28.2 cc and left 20 cc) and repeat CT brain had shown partial resolution of sigmoid and transverse sinus thrombosis. She was advised to continue tablet warfarin for a total period of six months.

Ovarian hyper stimulation syndrome is usually an iatrogenic complication seen in women taking ovulation inducing medications during assisted reproduction. It is characterized by cystic enlargement of ovaries, hemoconcentration and hypovolemia due to third space fluid shift. The mechanisms include increased capillary permeability and ovarian neoangiogenesis. Vasoactive substances like interleukins, tumor necrosis factor-alpha, endothelin I and vascular endothelial growth (VEGF) are incriminated. During ovulation induction, the high risk groups for OHSS include patients with PCOD, age> 30 years, low body weight, previous episodes of OHSS and those having large number of follicles on ultrasonography. A steep rise in estradiol level before an HCG injection is also a predisposing factor. A retrospective study conducted in a private infertility centre in Spain reviewed complications related to ovarian stimulation and oocyte retrieval in 4052 oocyte donor cycles. Twenty two donors (0.87%) had evidence of moderate to severe OHSS; 11 required hospital admissions and 11 were managed on outpatient basis. All cases were related to HCG triggering.

Other rare etiologies for OHSS include vesicular mole and gonadotropin secreting pituitary adenoma. However, the severity is milder. After conception, pregnancy itself in these high risk patients puts them at risk for OHSS. Martin et al have reported pre HCG estradiol level >6000pg/ml and number of follicles more than 30 to be associated with >80% incidence of severe OHSS. During ovulation induction, estradiol level >20,000 picogram/ml and progesterone level > 30 ng/ml in early part of luteal phase are warning signs for developing ovarian hyper stimulation syndrome. Ovarian hyper stimulation syndrome is reported to be very rare without beta- HCG administration. The medication classes commonly used in ovulation induction include clomiphene citrate, letrozole and other aromatase inhibitors, injectable gonadotropins and FSH products, Gonadotropin releasing hormone (GnRH) pump and bromocriptine. Both GnRH agonists and antagonists are used. The ovaries are stimulated with the injectable FSH medications for about 7-12 days until multiple mature size follicles have developed. Human chorionic gonadotropin (HCG) is used to cause final maturation of the eggs. The regimen commonly used for ovulation induction is 75 IU FSH+ 75IU LH or 75 IU pure FSH intramuscular injections daily for 10 days followed by 10,000 IU of HCG on 11th day (FSH- follicle stimulating hormone, LH- leutenising hormone). Side effects include abdominal distention or discomfort, bloating sensation, mood swings, fatigue or restlessness. In most cases, the side effects are relieved by follicular aspiration.

Our patient had been a commercial ovum donor. Her symptoms started after aspiration of ovum. The abdominal bloating with ascites, pleural effusion and pericardial effusion were suggestive of fluid retention secondary to hormonal effects. On admission, she had mild elevation of blood pressure with mood swings. Her large ovarian size along with the above features were suggestive of OHSS. Her normal β hCG levels and negative urine pregnancy test ruled out an accidental pregnancy. Subsequently on day
5, her headache worsened and she developed sigmoid and transverse venous sinus thrombosis.

Patient undergoing ovarian stimulation with exogenous high dose gonadotropin administered for ovulation induction are at high risk of developing thromboembolic complications. A hypercoagulable state with secondary supraphysiological hyperestrogenemia and hemoconcentration in ovarian hyper stimulation syndrome have been proposed to induce attack of thromboembolism. Ovarian stimulation during in-vitro fertilization is associated with an increase in both fibrinogen level and clot lysis time as well as decreased in antithrombin III level. Recently, it has been shown that mutation in the prothrombin gene and the factor V gene are associated with cerebral vein thrombosis. The simultaneous presence of the above mentioned mutation and ovarian hyperstimulation syndrome might enhance the risk of cerebrovascular thrombosis. A high prevalence of thrombosis in neck (81%) and intra cranial vessels (67%) has been of thrombosis in neck (81%) and enhance the risk of cerebrovascular thrombosis. The mentioned mutation and ovarian ovarian hyperstimulation syndrome. The mutation in the prothrombin gene and the factor V gene are associated with cerebral vein thrombosis. The factor V Leiden deficiency (especially in conjunction with oral contraceptive pills), trauma and meningitis. Ovarian hyperstimulation syndrome is now a new recognized iatrogenic cause of serious venous thromboembolism in females of reproductive age group. Delayed life threatening complications as seen in our patient, warrant a close monitoring, even after ovum extraction. Such patients may directly present as medical emergencies and would need a high index of suspicion for appropriate diagnosis.

**Conclusion**

This case has been presented to increase awareness regarding OHSS presenting as polyserositis and cerebral venous sinus thrombosis in females of reproductive age group. Ovarian stimulation is a well-defined procedure in treatment of female infertility. The options later on include natural conception or assisted reproduction including in vitro fertilization with the help of donated ovum. With increasing maternal age, an ovum donor may be the only viable option. In the future, we may come across increasing number of OHSS cases in females undergoing infertility treatment as well as in commercial ovum donors.

**References**

Invasive Aspergillus Pseudomembranous and Obstructive Tracheo-bronchitis in an Immuno-competent Patient

Ramesh S Pal1, Sonam Spalgais2, Amit Kumar Murar2, Umesh Chandra Ojha1

Abstract

A 19 year female, presented with life threatening haemoptysis and cough with minimum expectoration for 3 months. Bronchoscopy showed multiple nodules in airway. The direct microscopy and culture of sputum revealed fungal elements and Aspergillus flavus respectively. Serum Galactomannan was positive. Thus diagnosis of invasive aspergillus tracheo-bronchitis made. She responded to voriconazole. Aspergillus tracheo-bronchitis is a rare form of invasive pulmonary aspergillosis in immuno-competent host. Aspergillus spp in respiratory samples should not be routinely discarded as colonization.

Introduction

Aspergillus tracheo-bronchitis is a unique feature of invasive pulmonary aspergillosis (IPA). It represents isolated invasion of tracheo-bronchial tree by Aspergillus spp. The risk factors for invasive aspergillosis in critically ill patients include neutropenia, haematological malignancy, solid organ transplant, prolonged use of corticosteroid, inherited severe immuno-deficiencies, chronic obstructive pulmonary disease, chronic liver disease, diabetes mellitus and HIV infection.1 Aspergillus tracheo-bronchitis present as obstructive, ulcerative or pseudomembranous disease; however they may coexist. Aspergillus tracheo-bronchitis may also be coexistent with other forms of aspergillos related pulmonary diseases.2 The mortality rate of invasive pulmonary aspergillosis (IPA) exceeds 50% in neutropenic patients and reaches 90% in haematopoietic stem cell transplant recipients. Aspergillus spp. can present as invasive tracheobronchitis even in immunocompetent. Cases involving patients with normal immunologic function are limited to individual reports3. We report a case of invasive tracheo-bronchitis in young immune-competent girl without involvement of pulmonary parenchyma with complete clinico-radiological improvement.

Case Report

A 19 year old female, presented with life threatening haemoptysis. She had cough with minimum expectoration for last 3 months. There was no history of any chronic illness in the past except two episodes of massive haemoptysis in last 15 days. She was admitted and treated with supportive treatment in the form of haemostats, cough suppressant, antibiotics and other symptomatic treatment. On examination her general physical examination was normal. Vitals were normal limit. On respiratory examination there was decreased movement of the chest wall in left mammary, suprascapular and interscapular regions. Breath sounds were decreased on the left axillary and infra-axillary areas. Fine crepitation in left infraclavicular area and occasional rhonchi were heard. Others systemic examination was normal. There was no history of pulmonary tuberculosis, chronic pulmonary disease, diabetes mellitus, hypertension, cancer chemotherapy, corticosteroid therapy, joint pain, recent surgery, use of antibiotic or viral fever. Her routine Haematological (Haemoglobin, TLC, DLC and platelets counts) and biochemical (KFT, LFT, blood glucose level and serum electrolytes) investigation were normal. Chest X-ray revealed collapse of left lower lobe (Figure 1). CECT chest showed sub-segmental collapse of left lower lobe with partial luminal obstruction of left main bronchus (Figures 2a and b). Fiberoptic videobronchoscopy detected multiple tiny nodules in trachea and left lower lobe bronchi with plugging of left lower lobe and dark brown intra luminal thready material protruding from it (Figures 3a, b and c). Bronchial aspirate from left lower lobe consisted of thready brownish material (Figure 3d). Cytology of bronchial aspirate showed infiltrate with fungul hyphae with septations suggestive of Aspergillus spp. Biopsy from nodules of tracheobronchial tree showed chronic non-specific inflammation. The direct microscopy from sputum also showed fungal elements while culture of sputum grew Aspergillus flavus species. Patient’s serum Galactomannan was done and showed positive result. So patient was diagnosed with invasive aspergillus tracheo-bronchitis as per ERS criteria.4 Patient was further investigated with including serological test for HIV, hepatitis B and C which were negative. Immunoglobulin level of IgG/IgA and C3, C4 complement component were also normal. Treatment was started with intravenous voriconazole for one month followed by oral voriconazole for next 2 months. She was discharged on improvement. Her chest X-ray improved with resolution of left lower collapse (Figure 4). Repeat serum Galactomannan was negative after 3 month of treatment. On follow-up for last one and half year, the patient had no history of haemoptysis.

Discussion

Aspergillus is a saprophytic filamentous fungus, wide spread in the environment. Transmission occurs via inhalation of aerosolized spores Although Aspergillus can affect any organ system, the respiratory tract is involved in more than 90% of

1Consultant, 2Senior Resident, ESI-PGIMSR New Delhi

Received: 12.03.2016; Accepted: 07.07.2017
affected patients. On reaching the alveoli, these spores germinate to give hyphae and colonization of fungi takes place, leading to infarction, necrosis, edema, and haemorrhage in distal tissue. It can give rise to various clinical conditions depending upon the host’s immunological status. Invasive pulmonary aspergillosis (IPA) is now recognized as an important cause of pulmonary morbidity with a mortality rate near 80%. Aspergillus tracheo-bronchitis (ATB) is a rare presentation of IPA occurring infrequently with absence of pulmonary parenchyma involvement. Patient affected with ATB are most often immuno-compromised secondary to hematological malignancy, HIV/AIDS, solid organ transplant or chronic steroid therapy. ATB has also been described in patients with connective tissue diseases, hepatic failure and obstructive lung disease. Many published cases of IATB have not been diagnosed until post mortem. Chest computed tomography was useful to detect bronchial obstruction and left lower collapse in present case. Performing bronchoscopy with microscopic examination of tracheal and bronchial specimen is the most sensitive diagnostic tool for early diagnosis of pseudomembranous aspergillus tracheo-bronchitis (PMATB) and obstructive airway tracheo-bronchitis (OATB). Characteristic finding on bronchoscopy includes tracheal ulcer, raised nodules and presence of pseudomembrane in distal trachea and bronchus as in this case. Mainstay of therapy remains early diagnosis and initiation of antifungal therapy.

Conclusion

Aspergillus tracheo-bronchitis is a rare form of Invasive pulmonary aspergillosis in immune-competent host. The finding of Aspergillus species in respiratory tract samples in critically ill patients should not be routinely discarded as colonization, even in immune-competent hosts.

References

Mandibular AV Malformation: A Rare Cause of Massive Bleeding from Mouth Managed with Multiple Vessel Embolization

Rajeev Bhardwaj¹, Rajesh Sharma²

Abstract

An arteriovenous malformation (AVM) is a site of abnormal connectivity between arteries and veins. Arteriovenous malformations of jaw are extremely rare conditions that can result in disastrous complications, if handled carelessly. Although various treatment modalities have been advocated in the literature, there seems to be no complete consensus on a suitable treatment in these cases. We describe a case of mandibular AVM, who presented with massive bleeding from mouth and each time, embolization of one vessel was done, it recruited new vessel.

Introduction

Arteriovenous malformation (AVM) of the mandible is rare entity and difficult to manage. These often remain undiagnosed until dramatic bleeding occurs, mostly after tooth extraction. AVMs have a high propensity to bleed, which may be life threatening.¹

Case

19 years male presented with bleeding from mouth for one month. Bleeding occurred from left side of mouth. Bleeding was continuous. Patient had learnt to keep a cotton pack inside the mouth to control bleeding. There was no history of (H/O) trauma or tooth extraction. For the last one week, he had developed swelling on left side of lower lip. There was no H/O bleeding from other sites. There was no H/O excessive bleeding after trauma. No H/O purpuric spots, ecchymotic spots or swelling of joints.

In the past history, he presented with excessive bleeding from mouth around 8 years back, after tooth extraction. Bleeding could not be controlled and he was then admitted in pediatrics department of our hospital. His bleeding could not be controlled and he was the referred to Post-Graduate Institute of medical Education and Research (PGIMER), Chandigarh. There he was investigated for bleeding disorders, but all investigations were found to be normal. He was then subjected to carotid angiography and was found to have mandibular AVM. He was twice subjected to embolization with polyvinyl alcohol (PVA) particles but bleeding continued. He then got himself discharged. One dental surgeon applied some chemical cautry at local site and bleeding stopped. He remained symptom free for around eight years.

Investigations:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB</td>
<td>7.4 Gm%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>1.3 lac /cmm</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>156%</td>
</tr>
<tr>
<td>Factor IX</td>
<td>95.7%</td>
</tr>
<tr>
<td>INR</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Fig. 1: Left facial arteriography shows AVM in mandibular region

Fig. 2: Embolization of left facial artery with vascular plug

Management

Right femoral artery approach was taken. Left common carotid artery was engaged with Right Judkin’s catheter. Then selective cannulation of right external carotid was done. Left facial artery was then engaged. Due to multiple branches and large nidus, micro catheter could not be selectively placed in the nidus. So facial artery was embolized with Amplatzer vascular plug (AVP) – (Figure 2). Next day bleeding again started. Check angio showed vascular plug in position but now the AVM was filling from right facial artery (Figure 3). Since coils or vascular plug was not available, it was embolized with PVA particles (Figure 4). Bleeding stopped and patient was discharged the next day. He again reported after one week with excessive bleeding from the same side of mouth. Check angio showed that the AVM had recruited feeders from maxillary artery (Figure 5). Also the right facial artery had recanalized. Next day, his left external carotid artery was embolized with AVP (Figure 6), as maxillary artery could not be approached due to the presence of a part of AVP in external carotid. His right facial artery was embolized with coils (Figure 7). Now...
we were certain that bleeding will not recur. After shifting to the ward, we asked the patient to remove the cotton plug from the mouth. He was very reluctant to remove it. However on our persistence, he removed the plug and immediately, he bled profusely, till he again packed his mouth with cotton plug. His blood pressure fell to 70 mmHg (Systolic) and he was given I/V fluids and 2 units of blood transfusion. Next day we called oral surgeon. He insisted that he will examine the bleeding site after removing the cotton plug. And patient again had massive bleeding and only cotton plug controlled the bleeding. We again took the patient for check angiography. The culprit vessel was now right superior thyroid artery (Figure 8). This was embolized with PVA particles (Figure 9). Bleeding stopped. Patient was discharged after removing his cotton plug, after three days. Now it is over three years, and there is no recurrence of bleeding.

Discussion

The vascular malformations (VMs) can be categorized as low flow lesions (capillary, venous, lymphatic malformations) and high flow lesions (AVMs, arteriovenous fistulae) according to blood flow characteristics. AVMs are most common high flow lesions. Intraosseous VMs of the maxillofacial region sometimes give rise to dental emergencies and may cause disfigurement, morbidity and even death. A review of fatal cases by Lamberg and others shows that in most instances, exsanguination is the result of dental extractions, the dentist being unaware of existence of the AVM.

Numerous treatments in varying combinations and various degrees of success have been employed, including ligation,5,6 embolization,7–9 radical resection,7 use of sclerosing solutions,10 curettage and packing11 and radiation.12 Embolization followed by surgical treatment is still the modern conventional approach.13 Embolization reduces blood flow, allowing excision to be performed subsequently within 48 hours–2 weeks.13,14 Embolization is also not without risk as embolic complications, allergic reactions, avascular necrosis of bone,13 delayed root development,14 defective mandibular growth have been reported. Resection of mandible can result in a variety of disabilities including impairment of speech articulation, salivary control,
difficulty in swallowing, trismus and deviation of mandible toward the surgical side during functional movement.16

As seen in our case, a seemingly complete transarterial embolization does not guarantee complete occlusion of the AV-shunt surgery zone, and recruitment of new feeding vessels resulting in recurrence and rehemorrhage.16 For successful occlusion, the embolization should be done at or near the nidus, but due to the tortuous vessels, it may not always be achieved, as was the case with us.

References

Unusual Presentation of Injection Site Adverse Effect

Ranjana Sahasrabudhe¹, Tejas Limaye², Vidya Gokhale³

Abstract
Insulin is an integral part of Type 1 diabetes management. Patient education is of utmost importance to ensure proper injection technique for getting appropriate glycaemic control and to avoid injection site adverse effects. Commonest injection site adverse effect is lipodystrophy.¹ We present a case where incorrect injection technique led to an unusual presentation of injection site adverse effect, which is resolving after correction of the injection technique.

Introduction
Diabetes control rests upon the knowledgeable participation of the patient, even more so for Type 1 diabetes. Insulin is the life line for Type 1 diabetes patients and the patient is expected to take the injections himself. Good injection technique is essential for proper effect of insulin as well as to avoid injection site adverse effects. We present a case which demonstrates a peculiar injection site adverse effect which, though resolving after correction of the injection technique, is still visible 1.5 years later.

Case Report
A boy diagnosed to have Type 1 diabetes at the age of 11 years, reported to our clinic 3.5 years later in quest of insulin pump. He was on twice a day pre-mixed human insulin (30% soluble Insulin and 70%Isophane Insulin) and Insulin Glargine at bed time. He looked sick, was nauseated and had vomits which were attributed by his parents to acidity. On examination, he was dehydrated and urine showed positive for ketones. His weight (43kg) was low for his age (25th centile – IAP guidelines).²

He gave history of persistently high blood sugars, with frequent nausea and vomiting. Fasting sugar that day was 425 mg% and postprandial 363 mg%. Hypoglycaemia had never been a problem, except 2 years ago when the blood sugar had dipped to 35 mg%. They reported to be doing home monitoring only intermittently and were unaware of the need to monitor HbA1c.

On inspection, his injection sites showed lipohypertrophy and unusual injection marks. His mother, who gave the insulin injections, explained that she held the syringe “straight” as she had been “told” at the time of diagnosis. When asked to demonstrate, it was evident that she was holding the syringe parallel to the skin, instead of perpendicular to the skin as required for subcutaneous injection. Both arms and thighs had these scar marks of varied grades of pigmentation on the hypertrophied injection sites (Figure 1).

The patient and his parents were explained and demonstrated the proper injection technique, including the

¹Associate Professor, Pharmacology, BVDU Medical College, Pune, Maharashtra; ²SRF, Diabetes Educator and Nutritionist; ³Diabetes Educator and Medical Social Worker, Diabetes Unit, KEM Hospital, Pune, Maharashtra
Received: 08.03.2016; Accepted: 10.07.2016
lead to localized cutaneous reactions like lipodystrophy, which in turn compromise the glycaemic control.6

In the case reported here, incorrect injection technique resulted in small scars with abnormal pigmentation at the injection sites, in addition to localized lipohypertrophy and poor glycaemic control. We came across two other reports of similar skin injury. One report attributed the manifestation to post-inflammatory hyperpigmentation after micro trauma caused due to repeated use of the needle.7 The other report attributed it to intradermal injections leading to localized insulin allergy with resolution of the problem after switching to subcutaneous injection.8

The scar marks in our patient have also faded after correcting the injection technique and no new marks have appeared since then. This would implicate faulty injection technique as the cause, though investigations with skin biopsy would throw more light on the etiology.

**Lesson to be Learned from this Case**

Any psychomotor skill like the injection technique needs to be taught by demonstration and actual practice under supervision. Mere verbal instructions may be misinterpreted, resulting as it did, in our patient, in injurious injections, with poor control of diabetes.

**References**

7. GU Sawatkar, S Dogra, S Kumar Insulin injection: cutaneous adverse effects. *IJEM* 2015; 19:533-4
Thyrotoxic Channelopathies
Pankaj Singhai¹, Shruti Krishnan², Vikram Uttam Patil³

Abstract
Thyrotoxic periodic paralysis (TPP), a disorder most commonly seen in Asian men, is characterized by abrupt onset of hypokalemia and paralysis. The condition primarily affects the lower extremities and is secondary to thyrotoxicosis. Early recognition of TPP is vital to initiating appropriate treatment and to avoiding the risk of rebound hyperkalemia that may occur if high-dose potassium replacement is given.

Here we present a case of 31 year old male with thyrotoxic periodic paralysis with diagnostic and therapeutic approach.

Introduction
Thyrotoxic periodic paralysis (TPP) is most common in Asian populations, with an incidence of approximately 2% in patients with thyrotoxicosis of any cause. TPP is characterized by acute onset of severe hypokalemia and profound proximal muscle weakness in patients with thyrotoxicosis.² TPP is commonly misdiagnosed in western countries because of its similarities to familial periodic paralysis. Familial periodic paralysis is an autosomal dominant disorder caused by a defect in the gene coding for L-type calcium channel 1-subunit (CACNA1S) on chromosome 1q31–32. The neuromuscular presentations of both are identical, and to enhance diagnosis of TPP, physicians need to look for subtle features of hyperthyroidism in the presence of hypokalemic periodic paralysis. Early diagnosis not only aids in definitive management with nonselective beta-blockers and correction of hyperthyroidism, but also prevents the risk of rebound hyperkalemia due to excessive potassium supplementation.

Case Report
A 31 year old South Indian man with a history of recurrent muscle weakness and hypokalemia presented in our Emergency department with generalized muscle weakness, more pronounced in his lower extremities. The patient’s symptoms started in the early morning, and he was unable to walk to the bathroom. He had had similar episodes before and took potassium supplements sporadically. His initial episode of hypokalemia and paralysis had occurred 6 years earlier. He denied use of diuretics, laxatives, alcohol, or recreational drugs. He reported intermittent palpitations and diarrhea and had no family history of periodic paralysis.

In the Emergency department, his initial potassium level was 2.4 mEq/L with normal acid-base status. His phosphorous level was 2.6mg/dL (reference range 2.7-4.5 mg/dL) and serum magnesium level was 1.9 mg/dL (reference range 1.7-2.6 mg/dL) on admission. His CPK enzyme levels were 85 U/L (reference range 51 – 294 U/L). Urine potassium per 24 hours was 2.3 mmol/day (reference range 2.5-125 mmol/day). Electrocardiogram showed atrial fibrillation with a ventricular rate of 130 beats per minute. Initial diagnosis of hypokalemic periodic paralysis was made. Patient was commenced on intravenous potassium 10mEq/hr. Oral potassium supplementation was also given. His symptoms improved the next day with the complete recovery of muscle power in the lower extremities.

On the following day, thyroid function test showed serum TSH of 0.005 µIU/ml (reference range 0.50-6.8 µIU/ml) and a free T4 level of 3.34 ng/dl (reference range 0.89-1.76 ng/dl). Patient was further evaluated for cause of thyrotoxicosis and was found to have high titres of TRab (TSH Receptor Anti-body). Tc 99m scan of the thyroid showed homogenous uptake in both the lobes, suggestive of Graves Disease (Figures 2 and 3). He was commenced on Carbimazole 10 mg twice a day and Propranolol 40mg twice daily. Patient’s serial serum potassium levels continued to remain normal without...
oral potassium supplements during his stay in hospital and he was sent home with the diagnosis of TPP secondary to Graves Disease. Patient is on regular follow up on OPD basis and there is no further episode of hypokalemia and or quadriparesis. Last Thyroid profile report is as follows – TSH of 1.067 µIU/ml and FT4 – 1.08 ng/dl.

Discussion

Even though it is commonly seen in Graves’ disease, TPP is not related to the etiology, severity, and duration of thyrotoxicosis. Family history of periodic paralysis is usually absent.

The pathogenesis of thyrotoxic periodic paralysis has long been thought related to increased Na+/K+ ATPase activity in skeletal muscle and/or hyperadrenergic activity and hyperinsulinemia. This mechanism alone, however, associated paradoxical depolarization of the resting membrane potential. Recent findings that loss of function mutations of the skeletal muscle-specific inwarding rectifying K+ (Kir) channel, Kir2.6, associate with thyrotoxic periodic paralysis provide new insights into how reduced outward K+ efflux in skeletal muscle, from either channel mutations or inhibition by hormones (adrenaline or insulin), can lead to a vicious cycle of hypokalemia and paradoxical depolarization.

Thyroid hormones can increase Na/K-ATPase activity in skeletal muscle, liver, and kidney to induce an influx of potassium into the intracellular space. Among the various Na/K-ATPase subunits, the α1-, α2-, β1-, β2-, and β4-subunits are expressed in skeletal muscles. Thyroid hormone-responsive elements (TREs) are present in the upstream region of these five genes, and thyroid hormones has been shown to increase Na/K-ATPase activity via both transcriptional and posttranscriptional mechanisms.

The enhanced β-adrenergic response in thyrotoxicosis further increases Na/K-ATPase activity and may explain why nonselective β-adrenergic blockers can abort or prevent paralytic attacks.

The events that lead to paralysis with hypokalemia and hypophosphatemia in patients with TPP are complex. They include hyperthyroidism, a genetic and racial predisposition, and an exaggerated insulin response, a hyperadrenergic state, and probably other mechanisms leading to the intracellular shift of K+. Episodes of paralysis occurred during the night in more than 80% on patients with TPP. It has been shown that plasma glucose and insulin responses to meals are markedly higher in the evening than in the control subjects. Such a phenomenon suggests the possible mechanism for the nocturnal preponderance of TPP; another explanation could be the circadian rhythmicity of many hormones reaching their peak levels during sleep.

In conclusion, the diagnosis of TPP at the initial encounter is often delayed and confused with other more familiar causes of lower extremity paralysis, partially because of the subtleness of the thyrotoxicosis and partially because of unfamiliarity with this disorder by physicians. When a young male of Asian descent is initially seen with severe lower extremity weakness or paralysis, TPP should be considered as the most likely diagnosis until proven otherwise. This is important because TPP is a curable disorder that resolves when a euthyroid state is achieved.

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
Medical Symbols: Part-1

Jayant Pai-Dhungat

Commonly used medical symbols take into account Greek mythological deities like Apollo (god of light, Sun, truth and medicine), his son Asclepius-God of healing, who was taught by Chiron- the wise Centaur. Asclepius’s first daughter was Hygeia goddess of hygiene & cleanliness (Preventive medicine). Panacea was second daughter of Asclepius and goddess of remedies (indirectly-medical research). The four main deities are used in Hippocratic Oath which has been taken by physicians for centuries. Recent Study carried out in Karnataka* (2014), to assess knowledge and awareness of true origins of medical symbols (the emblems and icons) among doctors and medical students, revealed that there was very little awareness (6%) about the main emblem of medicine i.e. rod of Asclepius and knowledge of other symbols was also lacking in medical fraternity. The present series is aimed at learning these and related interesting symbols through the medium of medical philately.

Rod of Asclepius

Asclepius, Greco-Roman God of medicine was son of Apollo (God of healing, truth and prophecy). Chiron the wise Centaur taught him the art of healing. He was renowned for his unsurpassed medical prowess. Asclepius’s rod is not like other rods used by aged, handicapped and blind. He used this thick staff to walk around the mountains to see patients. Emblem depicts a serpent entwined around a staff that is traditionally a knotty tree. This Greek icon has served as medical emblem since 2400 yrs.. The rod of Asclepius, is a befitting representation of physician’s noble art of healing, and symbolizes authority. The combination with the snake adds further meaning. The snake is widely acknowledged as a symbol of good and evil. In its positive aspect, the snake shreds its skin, after having grown a new skin underneath, suggesting restoration, regeneration and revitalization. Moreover some snake venoms are fatally poisonous and at the same time have medicinal properties, becoming nature’s molecule of life and death. Therefore the serpent is also seen as dual nature of physician’s work that involves sickness and health, life and death. It even signifies the dual power of medicine whether it will harm or heal determined by dosage and situation.

Asclepius was honored as a hero and eventually worshiped as God. He is frequently represented standing, dressed in a long cloak. The cult began in Thessaly South Greece, but spread to many other parts of Greece and beyond. In 293 BC, it spread to Rome, where he was worshipped as Aesculapius. The rod of Asclepius has become an internationally recognized symbol of medicine. During the 10th Congress of the World Medical Association held in Havana, Cuba on April 6th 1956, WHO emblem was depicted for the first time on two stamps The Association advised the medical council of each country to adopt the rod of Asclepius. In 1902 Captain of the US Medical corps proposed the adoption of Caduceus as corps’s official symbol. This misunderstanding of ancient mythology and iconography led to inappropriate popularization of the caduceus as a medical symbol. Caduceus (double snaked rod) belonged to Hermes (Asclepius’s uncle) and Greek god of commerce. The erroneous assumption was pointed out several years later. Staff of Hermes lacks substantial background and hardly evokes the connotation produced by staff of Asclepius- an emblem of noble art of healing.

Painless Krait Bite in a Sleeping Victim: Delayed Diagnosis and High Mortality

Vivek Chauhan¹, Suman Thakur²

¹Assistant Professor, Senior Resident, Dr. RPAEC Kangra, Tanda Sir,
²Assistant Professor, Professor and HOD, Resident, RMO, Department of Medicine, Medical College Kolkata, West Bengal

I read the article published in your journal ‘A Clinico-Epidemiological Profile of Neuroparalytic Snake Bite: Using Low Dose ASV in a Tertiary Care Centre from North India’ with great interest.¹ The authors have described 113 cases of neuroparalytic snake bites in this article with 18 deaths. The important factor responsible for death in this study was delay in seeking treatment. As shown by the authors, 21 people presented more than 8 hours after the bite who were all given the ventilatory support and still 18 (86%) died.¹

The authors have not given description of the type of snakes that led to neuroparalysis. As we know that in India Cobra, Krait and Russell’s viper are the ones that can cause neuroparalysis. From a carefully obtained history we can identify whether it was a Krait or a cobra that produced neuroparalysis. Cobra is known to bite humans mostly when they accidentally disturb a cobra during their work or movement while Krait on the other hand bites the humans who are sleeping indoors during night time. As is shown by the authors 41 (36%) of the bites were indoors, these should be the most probable Krait bites.

We have an extensive experience of neurotoxic bites, as this is the predominant envenomation in our region.² The activity of the victim and the time of bite are important to make a diagnosis. If the victim is in deep sleep, a Krait bite will often be missed due to its painless nature. Fang marks are not visible as Krait has very short fangs and there is no local swelling or necrosis. The victims of Krait bite thus present late, often after > 8 hours of bite, found severely paralyzed in the morning neuroparalysis and it would be interesting to know how common the Krait bites are in their region.

References

Thrombocytopenia as Harbinger of Graves’ Disease: A Rare Presentation

Rudrajit Paul¹, Rathindranath Sarkar², Debaditya Roy³, Indranil Thakur⁴, Gautam Lahiri⁵, Tanmay Jyoti Sau³, Ratul Ghosh²

¹Assistant Professor, ²Professor and HOD, ³Resident, ⁴RMO, ⁵Professor, Department of Medicine, Medical College Kolkata, West Bengal

Sir,

Graves’ disease is an autoimmune form of primary hyperthyroidism. It presents with various clinical features like eye signs, tachycardia, weight loss, skin changes etc. However, initial presentation of Graves’ disease with a haematological abnormality like thrombocytopenia is very rare.

We are reporting the case of a 32 years old woman, who presented initially to her physician with sustained heavy menstrual blood loss three months ago before presenting to us. Complete blood count done at that time revealed platelet count of 6,000/µL. Her white blood cell count and haemoglobin concentrations were within normal limits. There was no history of fever or joint-pain preceding the illness. She needed platelet transfusion at the local hospital. Next month she developed petechial rashes and needed 26 units of platelet transfusion. Once her condition stabilized, she was referred to our hospital for further evaluation.

At presentation to us she was emaciated, had mild pallor and a few old bruises over the trunk. Her pulse rate was 130/ minute and blood pressure 130/89 mmHg. There were no lymph node enlargements, hepatosplenomegaly or sternal tenderness. There were no clinical features suggestive of any rheumatological condition. There were no goitre or ocular signs. She had been administered progesterone, tranexamic acid, multivitamins and pantoprazole tablets over the last three months. She had been started on oral corticosteroids for the last two weeks before coming to us based on a provisional diagnosis of autoimmune thrombocytopenic purpura (AIPT).

Initial laboratory work up done in our hospital revealed haemoglobin of 5.9g/dl, total leucocyte count of 8,600/µL (normal differential count and no abnormal cells) and platelet count of 20,000/µL. Erythrocyte sedimentation rate was 50 mm in first hour. Serum ferritin was 12ng/ml. Antinuclear factor was negative, liver and kidney function tests were within normal limits. Ultrasonography of abdomen did not reveal any evidence of chronic liver disease or any mass lesion. Viral serology was negative. In view of her emaciated condition and tachycardia, thyroid function was requested. Her TSH 0.006 µU/ml (N: 0.5—4.5), total T3 220.05 ng/dl (N: 80—180) and total T4 14.6 (N: 4.6—12 µg/dl). Ultrasonography of neck revealed diffuse enlargement of thyroid gland with increased vascularity and technetium scan of the thyroid gland showed generalized increased uptake of the radiotracer (figure 1). She was diagnosed with Graves’ disease and started on oral carbimazole 15 mg per day along with propranolol tablets 30 mg per day. As it was still not known whether her thrombocytopenia was related to Graves’ disease, bone marrow study during follow up was planned if thrombocytopenia did not resolve.

During follow up at one month her platelet count had gone up to 80,000/µL. There had been no new bleeding episodes. Her body-weight had also increased by 3 kg. She has been on Antithyroid medication for the last three months and has maintained platelet count of 1, 20,000 to 1, 40,000/µL. Her thrombocytopenia seems to be related to Graves’ disease.

There have been case-reports of thrombocytopenia as initial presentation of Graves’ disease.¹ In some
In the work up of a case of thrombocytopenia, thyroid function test is not done unless the patient presents with florid signs like ophthalmopathy or goitre. In the absence of these signs, high degree of clinical suspicion is needed to diagnose the underlying Graves’ disease.

The underlying pathophysiology of the association of the two conditions is not clear. Cordiano et al. found that approximately 80% patients with hyperthyroidism and thrombocytopenia had platelet autoantibodies. In patients with Graves’ disease presenting with thrombocytopenia platelet count responds to anti-thyroid therapy. Our patient had a significant rise in platelet count following carbimazole therapy and became transfusion independent.

We are reporting this case to make clinicians aware of this rare association. In a case of refractory thrombocytopenia when the usual secondary causes are negated, a thyroid profile may be of help in diagnosing Graves’ disease. In this situation use of Anti-thyroid medication corrects thrombocytopenia.

References
Olmesar
Olmesartan Medoxomil 10 / 20 / 40 mg Tablets
BP control...every hour, 24 hours

Rosumac Gold
Rosuvastatin 10 / 20 mg + Aspirin 75 mg + Clopidogrel 75 mg

3D Magic

Nexovas
Citalopram 5/10/20mg Tablets
The Nex... for Cardio Renal Protection

Etizola
Etizolam 0.25 / 0.5 / 1 mg
Shorter action... Lesser side effects
Start "EARLY" in Hypertension

ZILARTA 80
Calcium Channel Blocker Tablets
24h Potency & Maximum BP Control

50% reduced price
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/10mg Tablets

CILACAR-T80
Candesartan 10mg/10mg Tablets

In Uncontrolled Hypertension with IHD

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

CILACAR-M10/50
Candesartan 10mg/10mg Tablets

In Uncontrolled Hypertension with LVH/CHD/Stroke

CILACAR-C
Candesartan 10mg/10mg/25mg Tablets

CILACAR-C
Candesartan 10mg/10mg Tablets

Triple therapy

In Uncontrolled & Complicated Hypertension

CILACAR-TC
Candesartan 10mg/10mg/25mg Tablets

CILACAR-TC
Candesartan 10mg/10mg Tablets

Enhance Quality of Life

Make a SMART MOVE to witness the Difference