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 Indl. Estate, Off Veera 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 & Clopidogrel Bisulphate Capsules

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

EDITORIAL

Reticulocyte Hemoglobin Content (CHR): The Gold Standard for Diagnosing Iron Deficiency
MB Agarwal, Swati Pai ................................................................. 11

ORIGINAL ARTICLE

Reticulocyte Hemoglobin Vis-À-Vis Immature Reticulocyte Fraction, as the earliest Indicator of Response to Therapy in Iron Deficiency Anemia
Sudhir Mehta, Laxmikant Goyal, Debashish Kaushik, Sandhya Gulati, Nidhi Sharma, L Harshvardhan, Naveen Gupta ... 14

Clinical Profile and Treatment Outcome of Drug Resistant Tuberculosis Patients of Western Maharashtra, India Sachin S Dole, VN Waghmare, AM Shaikh ........................................... 18

APO B/APO AI Ratio with Coronary Artery Disease with Normal Lipid Profile in the Indian Population Ranjan Modi, VA Kothiwale, Suresh Patted, PC Halkati .................. 22

A Bidirectional Observational Study of Concomitant Chemoradiotherapy in Adenocarcinoma Stomach Vishesh Gumdal, Prashant Kumbhaj, Yadlapalli C Deepak, Ankur Punia, Rakesh Taran, Prakash Chitalkar.................. 28

Association between QTd, Tp-e/QT Ratio and In-hospital Prognosis in Thrombolysed Acute STElevation Myocardial Elevation (STEMI) Patients G Ravi Kiran, K Ramesh, V Chandrashekhar ................. 34

Pulmonary and Ear, Nose and Throat (ENT) Involvement in ANCA-Associated Vasculitis at Diagnosis-Experience from a Tertiary Care Centre in North India Aman Sharma, Arjun Lakshman, Ram V Nampoothiri, Roshan Verna, Manish Rathi, Godali SRSNK Naidu, Benzeeta Pinto, Kusum Sharma, Varun Dhir, Ritambhara Nada, Ranjana Mirz, Naresh Pared, Sanjay Jain ........................................ 40

Insulin Myths and Impact of Round-Tree Group Education Programme on Acceptance of Insulin in Persons with Diabetes: A Study from the Himalayas Jitender Mokta, Kiran Mokta, Parmod Sinha, Asha Ranjan, Deepika, Rahul Gupta ............................................................. 48

Efficacy, Safety and Immunogenicity Study of Intravenous Infusion of Rituximab (Hetero) and Reference Medicinal Product (Rituximab Roche) in Indian Patients of Follicular Lymphoma Preliminary report (HERILY) Suresh Advani, Shubhadeep Sinha, Pankaj Thakur, Neetu Naidu, Sreenivas Chary, Ghanashyam Biswas, Vamsi Krishna Bandi ............................................................. 58

A Pan-India Study to Assess the Quality of Life, Symptom Profile and Management Trends in Patients with Migraine: A Cross-Sectional Study Sumit Singh, Kushal Sarda, Rashmi Hegde ........................................ 63

POSITION STATEMENT


STATISTICS FOR RESEARCHERS

An Introduction to Meta-Analysis
NJ Gogtay, UM Thatte ................................................................. 78

PICTORIAL CME

Frank’s Sign
VA Arun, Shrutiraj ................................................................. 86

Fascinating World of Windpipe: A Case with Variation and Implications
Kranti Garg, Varinder Saini .......................................................... 87

CASE OF THE MONTH

Dyskeratosis Congenita with Acute Myeloid Leukemia, Cryptogenic Liver Fibrosis and Portal Hypertension Prasan Kumar Panda, Rita Sood, Kewal Kanabar, Ranveer Jadon, Arundhati Sharma, Sweta Birla, Pravas Mishra, Tarun Kumar .......... 88

CASE REPORT

Scleroderma-like Initial Presentation of Multiple Myeloma Ayan Basu, Santanu Kundu, Mehebubar Rahman, Yogiraj Roy, Rama Prasad Goswami ................................................................. 93

Parathyroid Causing Acute Severe Pancreatitis
Anil Pal, Amey Sonavane, Ritesh Agrawal, Pravin Rathi .......... 95

Lemierre’s Syndrome in Pregnancy Secondary to Retropharyngeal Abscess
Joe James, NK Thulaseedharan, NV Jayachandran, P Geetha ...... 97

MEDICAL PHILATELY

Swine Flu (H1N1) Epidemics & Pandemics
Jayant Pai-Dhungat ................................................................. 101

CORRESPONDENCE

Extent of Implementation of Screening Tuberculosis Patients for Diabetes Component of the Tuberculosis Control Programme in an Urban Setting in South India Banurekha Velagutham, Tarun Bhatnagar, Swaminathan Savithri, Natarajan Dinesh Kumar, Boopathi Kangusamy, Sanjay Mehendale ................................................................. 102

Acute Respiratory Failure and ICU Acquired Weakness in an Adult Patient with Dengue Infection-Successful Weaning from Mechanical Ventilation after 67 Days Arun Agarwal, Mudit Agrawal ................................................................. 102

Sensory Ataxia as First Manifestation of Sjogren’s Syndrome Rathindranath Sarkar, Rudrajit Paul, Rajesh Pandey, Debadipta Roy, Tanmay Jyoti Sau, Avinash Mani, Aditya Vikram Ruia, Ayandip Nandi ................................................................. 104

ANNOUNCEMENT

17th International Symposium on Diabetes ......................................... 17

Submission of API Awards Nomination ........................................ 27

Award Sessions ......................................................................... 62

Dr. Vishalrao Nadgouda All India Best Annual Thesis Award .......... 85

Election Results of API, PRF and ICP ........................................ 105

OBITUARY ........................................................................ 52
Manage HbA1c, Blood Pressure & Cholesterol of CV AD

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

For Dyslipidemia in T2DM Patients
ROZAT™
Lead the Lipid Revolution

In Hypertensive Patients
Stamlo™
leader at heart

In Diabetic Hypertensives uncontrolled on Monotherapy
Stamlo-T
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
JOURNAL OF THE ASSOCIATION OF PHYSICIANS OF INDIA
Editor-in-Chief: Prof. Milind Y Nadkar

Editorial Board (2017-2018)

Emeritus Editors: VR Joshi • Shashank R Joshi
Editor-in-Chief: Milind Y Nadkar
Executive Editor: Siddharth N Shah
Associate Editors: Sandhya A Kamath • Gurpreet Singh Wander
Assistant Editors: RR Chaudhary • Falguni Parikh
Members: Shubhendu Ghosh • Niteen Karnik • SV Kulkarni
Ex-Officio: BR Bansode • Mangesh Tiwaskar
Jt. Secretary: Shobha M Itolikar

Advisory Board (2017-2018)

Philip Abraham
MB Agarwal
Rakesh Aggarwal
MS Amraesan
DN Amrapurkar
S Arulraj
Smrati Bajpai
Sripad Banavali
Amal Kr Banerjee
Sandeep Bawdekar
D Behera
Rakesh Bhandare
Ashit M Bhagwati
Sudhir Bhandari
Shobna Bhatia
Smita M Chakote
Sekhar Chakraborty
Anil Chaturvedi
VP Chaturvedi
MPS Chawla
M Chenniappan
RM Chhabra
AR Chogle
RR Choudhary
SN Chugh
Sidhartha Das
Alaka Deshpande
Subhhangi V Dhakde
Vithal N Dhakde
SB Ganguly
Liyakat Ali Gauri
K Ghosh
Soumitra Ghosh
Nithya Gogtay
Yojana Gokhale
SK Goyal
Virender Kr Goyal
Pritam Gupta
Vishal Gupta
Ashutosh Halder
Rohini Handa
L Harshvardhan
NK Hase
DK Hazara
Shivkumar Iyer
Charu K Jani
Bhavin Jankharia
RV Jayakumar
SK Jindal
Kavita Joshi
Shilpa S Joshi
Mala Kaneria
SV Khadilkar
Uday Khopkar
Renuka Kulkarni
Vrinda Kulkarni
Vikram Lele
Charulata V Londhey
SV Madhu
BK Mahavarkar
Sanjiv Maheshwari
M Maiya
JK Maniar
Arvind Mathur
Girish Mathur
Kalpana Mehta
Sudhir Mehta
AP Misra
Isaac C Moses
K Mugundhan
YP Muljaj
JMK Murthy
A Muruganathan
Sita Naik
Velu Nair
SN Narasingan
G Narsingul
CL Nawal
Rajan Nerurkar
Jyotirmoy Pal
Jayant K Pandurkar
Vijay Panikar
KK Pareek
Rajesh Patil
Deepak Patkar
Anuruddha Phadke
Munish Prabhakar
Anupam Prakash
YSN Raju
C Venkata S Ram
Praveen K Rathi
Neelam N Redkar
BB Rewari
Mrinal Kanti Roy
Banshi Saboo
Rakesh Sahay
Anjan Saikia
Santosh Salagre
SA Sangle
K Sarat Chandra
SK Sarin
RN Sarkar
Nalini Shah
Raman Sharma
SK Sharma
Asht Sheth
NP Singh
SK Singh
Surjit Singh
Archana Sonawale
NK Soni
Uma Sundar
Anvish N Supe
Rakesh Tandon
Kamlesh Tewary
BB Thakur
Urmila Thatte
AG Unnikrishnan
V Vahia
Prema Varthakavi
Subhash Verma
Vijay Viswanathan
Gurpreet S Wander

Subscription Information
Journal of The Association of Physicians of India is published monthly. The annual subscription is ₹ 10,000 (India) and US $ 500 (other countries). The Journal is dispatched within India by surface mail and to other countries by sea mail.

Copyright and Photocopying
No part of this publication may be reproduced, or transmitted in any form or by any means, electronic or mechanical, including photocopy without written permission from the Hon. Editor.

Business Correspondence
Enquiries concerning subscription, advertisement, etc. should be addressed to Prof. Milind Y. Nadkar, Editor-in-Chief, JAPI, No. 006 & 007, Turf Estate, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai-400 011. Tel.: (022) 66662324, 24912218 Tel/Fax: 2492 0263 E-mail: onlinejapi@gmail.com / api.hdo@gmail.com

Printed, Published and Edited by Prof. Milind Y. Nadkar, on behalf of The Association of Physicians of India, Journal of The Association of Physicians of India, Turf Estate, Unit No. 006 & 007, Opp. Shakti Mill Compound, Off Dr. E. Moses Road, Near Mahalaxmi Railway Station (West), Mumbai-400 011. Editor-in-Chief: Prof. Milind Y. Nadkar.

Advertorial Enquiry:
Prof. Milind Y. Nadkar,
Editor-in-Chief, JAPI,
No. 006 & 007, Turf Estate, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai-400 011. Tel.: (022) 6666 3224 / 2491 2218 Mobile : 77381 85750 E-mail: onlinejapi@gmail.com / api.hdo@gmail.com

Printed at Shree Abhyudaya Printers, A210, Shah & Nahar Industrial Estate, Lower Parel (West), Mumbai 400 013. Tel.: (022) 2494 5893 * urvi@urvi.cc

JAPI App: myJAPI
www.japi.org
### Governing Body (2017-2018)

**President Elect**
- Pritam Gupta (Delhi) (2018)

**President**
- BR Bansode (Mumbai) (2018)

**Past President**
- Gurpreat Singh Wander (Ludhiana) (2018)

**Vice Presidents**
- Girish Mathur (Kota) (2018)
- BB Rewari (New Delhi) (2019)

**Hon. General Secretary**
- Mangesh Tiwaskar (Mumbai) (2019)

**Jt. Secretary (HQ)**
- Ashit M Bhagwati (Mumbai) (2019)

**Hon. Treasurer**
- Charu K Jani (Mumbai) (2020)

**Members**
- Vijay Viswanathan (Chennai) (2018)
- MPS Chawla (New Delhi) (2018)
- Sekhar Chakraborty (Siliguri) (2018)
- DP Singh (Bhopalpur) (2018)

**Central Zone**
- Shriram V Kulkarni
- Satyanarayana Raju
- Jayanta Kumar Panda
- Rakesh Gupta

**North Zone**
- Ashit M Bhagwati
- Girish Mathur
- K Mugundhan
- Maj. Gen. (Dr.) A.K. Hooda

**South Zone**
- Rohini Handa
- SB Ganguly
- Atul Bhasin
- Udai Lal

**Mid East Zone**
- Suman Bhandari
- A K Mukherjee
- YK Mitra
- Shyam Sundar

**Mid South Zone**
- AR Mehta
- AK Mukherjee
- JK Mitra
- Sandhya Kamath

**East Zone**
- PS Karmakar
- YJ Mehta
- M R Chhabra
- Charu K Jani

**West Zone**
- Prabhat Pandey
- Narayan Deogaonkar
- R M Chhabra
- Devi Ram

**Regional Members**
- Alok Dhar
- Maj. Gen. (Dr.) A.K. Hooda
- Maj. Gen. (Dr.) A.K. Hooda
- Charu K Jani

**Ex-Officio Members**
- Editor-in-Chief, JAPI
- Milind Y Nadkar (Mumbai)

**Invited Members**
- Ashit M Bhagwati
- Girish Mathur
- K Mugundhan
- Maj. Gen. (Dr.) A.K. Hooda

**Co-opted Members**
- YP Munjal (Gurgaon)

**Zonal Members**
- North Zone: RM Chhabra (New Delhi) (2020)
- North West Zone: Rakesh Gupta (New Delhi) (2020)
- Central Zone: Prabhat Pandey (Durg) (2020)
- West Zone: Narayan Deogaonkar (Nasik) (2020)

### Indian College of Physicians

**Faculty Council (2017-2018)**

**Chairman**
- BR Bansode (Mumbai) (2018)

**Dean**
- Rohini Handa (New Delhi) (2018)

**Dean Elect**
- G Narasimulu (Hyderabad) (2018)

**Hon. General Secretary**
- Mangesh Tiwaskar (Mumbai) (2019)

**Past Dean**
- A Muruganathan (Tirupur) (2018)

**Vice Deans**
- RK Goyal (Ajmer) (2018)
- Kamlesh Tewary (Muzaffarpur) (2019)
- NP Singh (New Delhi) (2020)

**Jt. Secretary (H.Q.)**
- Ashit M Bhagwati (Mumbai) (2019)

**Jt. Secretary (Dean’s place)**
- AP Misra (New Delhi)

**Hon. Treasurer**
- Charu K Jani (Mumbai) (2020)

**Elected Members**
- Rakesh Gupta (New Delhi) (2018)
- Jayanta Kumar Panda (Cuttack) (2018)
- Y Satyanarayana Raju (Hyderabad) (2018)
- Shriram V Kulkarni (Khopoli) (2018)

**Ex-Officio Members**
- Rakesh Gupta (Mumbai) (2018)
- YP Munjal (Gurgaon)
- Sandhya Kamath (Mumbai)

### Physicians Research Foundation

**Board of Directors (2017-2018)**

**Chairman**
- BR Bansode (Mumbai) (2018)

**Hon. General Secretary**
- Mangesh Tiwaskar (Mumbai) (2019)

**Jt. Secretary (Director’s Place)**
- Ghan Shyam Panjwani (New Delhi)

**Hon. Treasurer**
- Charu K Jani (Mumbai) (2020)

**Members**
- Soumitra Ghosh (Kolkata) (2018)
- AK Mukherjee (Kolkata) (2018)

**Invited Members**
- Ashit M Bhagwati
- Rohini Handa

**Co-opted Members**
- YP Munjal (Gurgaon)
- Sandhya Kamath (Mumbai)
Have a Cough Free Conversation

In Dry and Allergic Cough

Grilinctus® Syrup
(Dextromethorphan HBr 5 mg,
Chlorpheniramine Maleate 2.5 mg,
Guaifenesin 50 mg and NH4Cl60 mg/5 ml)

In Productive Cough

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

Grilinctus®-L Syrup
(Levoclopoxetine Fenofibrate Eg, to
Levodopaferine HCl20 mg /5ml)

FRANCO-INDIAN PHARMACEUTICALS PVT. LTD.
11, Dr. D. Wades Road, Mumbai 400 011.
Once-daily TRESIBA® U L T R A - L O N G
DURATION OF ACTION

Journal of The Association of Physicians of India • Vol. 65 • October 2017

GET HbA1c DOWN WITH CONTROL

- Successful reductions in HbA1c
- Lower risk of nocturnal hypoglycaemia versus glargine
- Flexibility in day-to-day dosing time when needed
...delivered in a once-daily dose.


Reticulocytes are newly produced, relatively immature red blood cells (RBCs). Reticulocyte count is not a part of standard CBC. It has to be ordered and used along with CBC. Reticulocyte count in the blood reflects bone marrow (BM) function or activity. These cells are 25% higher in volume in comparison with mature RBCs. Mature RBCs have no nuclei, but reticulocytes still have some remnant genetic material i.e. RNA. As reticulocytes mature, they lose the last residual RNA and fully develop into RBCs. Reticulocyte count or percentage is an indicator of ability of person’s bone marrow to produce adequate RBCs (Erythropoiesis).

Reticulocytosis reflects responsive marrow. It is seen in acute or chronic bleeding, hemolysis and following treatment of deficiency anemias. Reticulocytopenia suggests non-functional bone marrow i.e. Aplastic anaemia etc.

Reticulocyte count is, traditionally, performed manually. With refinement of technology and the principles of fluorescence, modern cell analyzers incorporate automated reticulocyte counting. Automated reticulocyte counts have greater precision, accuracy, and reproducibility than manual counts. The reference range for reticulocyte count for adults is 0.5%-1.5%.

Corrected reticulocyte count (CRC) or Reticulocyte Index (RI) are calculated (formula underneath) and these give a more accurate assessment of marrow function. The reference range for CRC in adults is 0.5%-1.5%.

RI = Reticulocyte count (%) x (measured hematocrit / normal hematocrit).\(^1\)

Reticulocyte Production Index (RPI) is another calculation (formula underneath) & it corrects for the degree of reticulocyte immaturity. An increased RPI (>3) is seen with hemorrhage, hemolysis and response to hematinics.

\[ RPI = RI \times \left( \frac{1}{\text{maturation time}} \right) \]

Immature Reticulocyte Fraction (IRF) is a quantitative measurement of the RNA content of reticulocytes. It is a ratio of immature reticulocytes to the total number of reticulocytes. Younger reticulocyte contains a higher RNA. IRF is automatically reported by modern blood cell analyzers capable of doing reticulocyte count testing. It is a much better indicator of responsive marrow than total reticulocyte cell count.\(^1\) Increased IRF reflects early marrow recovery and it precedes increase in absolute reticulocyte count.

Reticulocyte hemoglobin content (CHr) is a measurement of hemoglobin inside the reticulocyte. It correlates directly with the functional availability of iron in the marrow. Today, it is called as the gold standard for diagnosing iron deficiency.

Any laboratory test to be called a perfect test, it should be accurate, simple & inexpensive. It than acquires clinical utility. Many tests are described to assess iron deficiency (ID), however, no single test fulfills all these criteria. Usually, simultaneous measurements of a group of tests is needed. These include: Hb, reticulocyte count, RBC indices, S. iron (SI), total iron binding capacity (TIBC), S. Ferritin (SF), soluble transferrin receptor (sTfR) assay etc.

Modern automated particle cell counters utilize flow-cytometry technique and measure reticulocyte cellular characteristic i.e. IRF, CHr (or Ret-He). These are proposed as a surrogate marker to predict early response to iron therapy. Flow cytometry assesses the maturity of reticulocytes separating them in to 3 areas according to the degree of fluorescence i.e. low-fluorescence reticulocytes (LFR), middle-fluorescence reticulocytes (MFR) & high-fluorescence reticulocytes (HFR), LFR being the most mature one. If the HFR having more RNA that corresponds to the earliest of reticulocytes and hence indicates erythropoietic activity following treatment of anemia. In various studies, HFR or CHr have been applied to predict early response to hematinics.

IRF increases in response to treatment with Erythropoiesis Stimulating Agents (ESAs) much before an increase of reticulocyte count and hence can be used in clinical practice for quick assessment during treatment of renal anaemia with ESA.\(^5\)

The IRF has been also proposed as an early marker of engraftment in bone marrow or hematopoietic stem cell transplantation and bone marrow regeneration following chemotherapy.\(^6\)

Also, in patients of myelodysplastic syndrome and

---

1 Prof & Head, Dept of Hematology, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra; 2 Consultant, Laboratory medicine, Manipal Hospital, Bengaluru, Karnataka
dyserythropoietic anaemias, IRF is increased without reticulocytosis.\textsuperscript{7}

IRF has also been used to diagnose hereditary spherocytosis (HS). In HS, there is high reticulocyte count without equally elevated IRF.\textsuperscript{8}

CHr constitutes the most valuable screening tool for identifying iron deficiency (ID) with or without anaemia. Decreased CHr (cutoff value of 25 pg) stands for accurate diagnosis of functional iron deficiency with sensitivity of 94\% & specificity of 80\%.\textsuperscript{9,10}

Due to increased hepcidin production, in patients with inflammatory disorders, systemic infections and malignancies, iron is trapped in reticuloendothelial system (RES) and also poorly absorbed from GI tract leading to functional iron deficiency resulting in anaemia of systemic disease (ASD). This is also a hypochromic microcytic anaemia and it mimics iron deficiency anaemia (IDA). Also, in the presence of ASD, it is difficulty to diagnose underlying IDA. Such patients have high or normal S. Ferritin despite iron deficiency (acute phase response). In this situation, CHr differentiates ID from ASD. The discriminatory power of CHr, both with respect to sensitivity and specificity, is better then MCV and Ferritin.\textsuperscript{3}

While treating anaemia, one is curious to know the response to treatment at the earliest. This confirms that the treatment is on correct line, and also avoids in advertent hazards of over treatment. It takes weeks to observe a significant response to hematinsics (oral or I.V. Iron, vitamin B12 or folic acid) by looking at hemoglobin (Hb), Packed cell volume (PCV) or hematocrit and erythrocyte indices. The main reason for late response is the long lifespan of mature RBC. Hence there is a need to seek an earlier, more sensitive and reliable marker for assessing the response. Over last decade or more, there is a growing body of evidence suggesting that reticulocyte, the newly produce erythrocyte may be the solution. Its cellular characteristics can be measured by modern automated particle cell counters. These parameters provide early information which is sensitive, accurate and reproducible both for diagnosis and assessing therapeutic response.

Both IRF & CHr have been used as early response to treatment following Intravenous (IV) iron therapy in diverse patient populations, including pediatrics, geriatrics, pregnancy & chronic kidney disease (CKD).\textsuperscript{11-16}

Mehta et al in their study published in this issue of JAPI have shown that CHr is superior to conventional erythrocyte and iron metabolism indices including IRF. CHr serves as an earliest predictor of response to treatment & hence it is of great clinical utility.

No test is free from flaws. Mean cellular volume (MCV) is used for calculating CHr. That is its biggest diagnostic limitation. CHr is low in subject with thalassaemia and hemoglobinopathies without iron deficiency. Similarly, it is elevated in iron deficiency subjects with confounding megaloblastic anaemia because of high MCV. Therefore, it is important that CHr is interpreted in the context of patient’s overall erythrocyte physiology including co-existing megaloblastic anaemia, presence of thalassaemia/hemoglobinopathies or blood transfusion.

In conclusion, reticulocyte hemoglobin content (CHr) is an extremely valuable recent addition to an expanding list of biomarkers that can be used to differentiate iron deficiency from other causes of anaemia. In olden days, stainable marrow iron was used as a gold standard for diagnosing iron deficiency. After that, soluble transferrin receptor (sTfR)-Ferritin index was used for this purpose. Today, CHr can be called as the gold standard replacing both of these.

It is a pity that despite its simplicity and utility, it is rarely used in clinical practice.

References

In Hypertension, 

Zilarbi™

Azilsartan Medoxomil 40/80 mg Tablets

Drop in BP, as it should be...

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

METPURE-XL

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

Because Heart Matters

Offers high cardioselectivity & Beta-1 blockade over 24 hours

1. Indian Medical Gazeteer 2006: 72-75  

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

Emcure Pharmaceuticals Ltd.
Survey No 255/2, Phase -1, M.I.D.C., Hirjewadi, Pune- 411057(India)
Tel: +91 20 39821000 I Fax: +91 20 39821019 I www.emcure.co.in I www.chiral EMCure
Reticulocyte Hemoglobin Vis-À-Vis Immature Reticulocyte Fraction, as the earliest Indicator of Response to Therapy in Iron Deficiency Anemia

Sudhir Mehta¹, Laxmikant Goyal², Debasish Kaushik³, Sandhya Gulati⁴, Nidhi Sharma⁵, L Harshvardhan⁶, Naveen Gupta³

Abstract

Aim: To evaluate reticulocyte hemoglobin (RET-Hb) vis-à-vis immature reticulocyte fraction (IRF) as an earliest indicator of response to iron therapy in iron deficiency anemia (IDA), by assessing change in RET-He and IRF at 48 hours after initiation of intravenous iron therapy.

Material and methods: A hospital based interventional, analytic study was conducted among 144 patients (age group 15-65 years) with newly diagnosed and untreated IDA admitted in medicine ward and not suffering from any inflammatory disorders (excluded by C-reactive protein). Patient having other forms of anemia/hemoglobinopathies/ malignancy, MCV >80 fL and pregnant female were excluded. All patients were subjected to automated CBC, RET-He, iron studies and iron staining of bone marrow aspirates. Then intravenous iron sucrose was given along with oral antioxidants. After 48 hours, CBC, RET-He and IRF were repeated for each patient.

Result: Total 144 patients were included. Of these, 42 patients were excluded due to aparticulate bone marrow aspirate. Remaining 102 patients were classified in to Group A (grade 0 and 1- depleted iron stores) and Group B (grade 2 and 3 - functional iron deficiency). RET-He and IRF increased significantly at 48 hours after initiation of intravenous iron therapy (post therapy) as compared to baseline (pre therapy) in both the two groups as well when all patients were considered together. Post therapy, the mean increase in RET-He was significantly smaller in magnitude in group B than in group A. The increase in IRF was not significantly different between the two groups.

Conclusion: RET-Hb, a real time indicator of iron supply (hemoglobinization) to the developing RBC’s, is the earliest marker of response to iron therapy as compared to IRF (representative of reticulocyte count).

Introduction

Iron deficiency is one of the most common nutrient deficiencies and a leading cause of anemia worldwide.¹ The challenge in iron deficiency anemia (IDA) is not only to diagnose it early but also to monitor and evaluate its response to iron therapy at the earliest. Response to iron therapy is classically assessed by increase in peripheral blood Reticulocyte count which occurs in 3-4 days and rise in hemoglobin within the first week.² Automated counters form an integral part of modern day hematology. Immature Reticulocyte Fraction (IRF) is one of the newer parameters of automated haematology analyzers and is a sensitive measure of erythropoiesis.³ However, in certain situations like bleeding, IRF will increase despite no improvement in Haemoglobin (Hb). Moreover, IRF does not give any information on the incorporation of iron into developing red blood cells.

A newer reticulocyte parameter Ret-He is a measure of hemoglobin content of the freshly produced red blood cells and offers real-time information on iron supply for erythropoiesis.³ RET-He is not an acute phase reactant and has been found to be useful in detecting

¹Senior Professor, ²Assistant Professor, ³Former Registrar, Department of Medicine, ⁴Professor, ⁵Assistant Professor, Department of Pathology, ⁶Professor, Department of Medicine, SMS Medical College, Jaipur, Rajasthan
Received: 28.11.2016, Accepted: 15.08.2017
response to iron therapy, changing as early as 3rd–4th days. IRF denotes fraction of developing RBC’s (reticulocytes) which have high content of mRNA with least maturity. The utility of IRF in monitoring anemia has been reported in various studies. This study was undertaken to evaluate Ret-Hb vis-à-vis IRF as an earliest indicator of response to iron therapy in iron deficiency anemia (IDA), by assessing change in reticulocyte haemoglobin (RET-He) and IRF at 48 hours after initiation of intravenous iron therapy.

Materials and Methods

This hospital based interventional, analytic study was conducted at a tertiary care center in Rajasthan, during September 2013 to December 2014, after obtaining due permission from Research Review board/ Institutional Ethics committee and informed written consent of the study participants. Hundred forty four patients (age group 15-65 years) with newly diagnosed and untreated iron deficiency anemia admitted in medicine wards and not suffering from any inflammatory disorders (excluded by C-reactive protein) were included in this study. Patients having other forms of anaemia/ hemoglobinopathies/ any malignancy/having MCV >80 fL and pregnant females were excluded from this study.

Blood samples from patients were drawn in EDTA vials for CBC including RET-He, IRF and peripheral blood smear; and in plain vials for serum ferritin, serum iron and TIBC. Patients having microcytic hypochromic anemia, serum ferritin below 20 ng/ml and transferrin saturation < 20% were selected. Patient’s clinical history, findings of physical examination and other relevant data, including lab test results, were recorded in structured forms. CBC, RET-He and IRF were tested on Sysmex XT 4000i automated analyzer. Serum ferritin was measured on IMMULITE 2000 Systems analyzer using a solid-phase, two-site chemiluminescent immunometric assay. Serum iron was measured using colorimetric assay. TIBC was measured using saturation – precipitation method. Transferrin saturation (TSAT) was calculated as TSAT = (serum iron/TIBC) x100 and expressed as percentage.

Under strict aseptic precaution bone marrow aspirates were obtained from posterior iliac crest and sent for Wright – Giemsa staining along with Prussian blue staining for estimation of iron store.

The patients were then started on intravenous iron sucrose (300mg dissolved in 250 ml Normal Saline IV infusion over 4 hours on Day 0 and Day 1) along with oral antioxidants. After 48 hours, CBC, RET-He and IRF were repeated for each patient.

Statistical Analysis

Microsoft Excel® and SPSS® 20 for Windows® were used for data storage and analysis. The qualitative data were expressed in percentages and quantitative data were expressed as mean ± standard deviation. Student’s t test was used to determine statistical difference between variables. Results were considered significant if P < 0.05.

Results

A total of 144 patients were included in the study. Of these, 42 (29.2%) patients were excluded from final statistical analysis as their bone marrow aspirates were aparticulate and therefore, their iron stores could not be assessed. From the bone marrow aspirates of remaining 102 patients, Prussian blue stained films were examined and graded.

These 102 study participants had mean age 35.63 ± 15.96 years (range 15 to 65 years) with male: female ratio 1:1.83. Of the 102 patients, 73 (71.6%) had no stainable iron in bone marrow (grade 0), 10 (9.8%) had grade 1 stainable iron, 8 (7.8%) had grade 2 stainable iron and 11 (10.8) had grade 3 stainable iron. Based on the grading of bone marrow iron store, the patients were classified into Group A (grade 0 and 1- depleted iron stores) and Group B (grade 2 and 3 -functional iron deficiency).

In comparison to Group B, patients of Group A had significantly lower RET-He (Group A 17.84 ± 2.39 vs. Group B 25.08 ± 4.42; P< 0.0001) and lower serum ferritin (Group A 8.68 ± 2.80 vs. Group B 15.61 ± 4.68; P < 0.0001) before start of iron therapy (Table 1).

RET-He and IRF increased significantly at 48 hours after initiation of intravenous iron therapy (post therapy) as compared to baseline (pre therapy) in both the two groups as well when all patients were considered together (Table 2).

Post therapy, the mean increase

<table>
<thead>
<tr>
<th>Table 1: Comparison of various parameters between storage iron deplete (Group A) and functional iron deficiency (Group B) patients before start of iron therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
</tr>
<tr>
<td>MCV (fL)</td>
</tr>
<tr>
<td>MCH (pg)</td>
</tr>
<tr>
<td>RDW-CV (%)</td>
</tr>
<tr>
<td>TIBC (µg/dl)</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
</tr>
<tr>
<td>Iron (µg/dl)</td>
</tr>
<tr>
<td>TIBC (µg/dl)</td>
</tr>
<tr>
<td>TSAT (%)</td>
</tr>
<tr>
<td>IRF</td>
</tr>
<tr>
<td>@ Significant</td>
</tr>
</tbody>
</table>
Response to iron therapy could be detected at an earlier stage, when RBC indicators are still as pretreatment level but the iron stores are sufficient to the point of affecting hematopoiesis and inducing production of a certain percentage of reticulocytes with increased Hb content, resulting in a progressive increase of RET-He.11-14

The current study revealed that RET-He and IRF increase significantly after intravenous iron therapy as early as 48 hours after initiation of treatment irrespective of the status of the iron stores (deplete or functional iron deficiency). The mean increase in RET-He (3.8133 ± 0.3966 vs. 1.4947 ± 2.1309, P < 0.01) was of significantly smaller magnitude in group B than in group A. The increase in IRF was not significantly different than in group A. The increase in RET-He (3.8133 ± 0.3966 vs. 1.4947 ± 2.1309, P < 0.01) was of significantly smaller magnitude in group B than in group A. The increase in IRF was not significantly different than in group A.

Identifying patients who show low RET-He after IV iron therapy makes it possible to identify the patients who are not responding to IV iron. Thus these patients may be offered additional diagnostic tests and management strategies.

IRF just reflects the erythropoietic activity of bone marrow but does not show the actual incorporation of iron in developing RBC’s (hemoglobinization of mature RBC’s). RET-Hb is not only sensitive but also a real time indicator of iron supply to the developing RBC’s. In other words, RET-Hb is a real time parameter of hemoglobinization.

In our study we observed that mean increase in IRF did not show significance between the two groups (iron depleted v/s functional iron deficiency) but there was significant increase in RET-Hb which confirms that mean magnitude change in RET-Hb is a real time indicator of iron supply to the developing RBC’s.

The aim of iron therapy in IDA is to improve iron supply (Hemoglobinization) to the developing RBC’s. As the traditional parameter of treatment response – reticulocyte count and newer parameter – IRF only reflect erythropoietic activity of bone marrow and they do not reflect the incorporation of iron in maturing RBC’s, which is the primary aim of iron therapy. RET-Hb is a real time indicator of iron supply (Hemoglobinization) to the developing RBC’s and is a

### Discussion

All the patients included in our study had microcytic hypochromic anemia with low serum ferritin and low transferrin saturation. Those with grade 0 and 1 were considered to have depleted iron stores and, therefore, represented absolute iron deficiency (deplete iron store). Those with grade 2 and 3 in our study had functional iron deficiency.9

Reticulocytes are non-nucleated immature red blood cells (RBCs) in peripheral blood. Reticulocytes are sensitive in detecting erythropoietic activity as they have a more rapid turnover in circulation than mature red cells (1–2 vs. 120 days). Reticulocyte indices provide a real time evaluation of the bone marrow activity, reflecting the balance between iron and erythropoiesis of the preceding 48 hours.6,10

Response to iron therapy could be detected at an earlier stage, when RBC indicators are still as pretreatment level but the iron stores are sufficient to the point of affecting hematopoiesis and inducing production of a certain percentage of reticulocytes with increased Hb content, resulting in a progressive increase of RET-He.11-14

The current study revealed that RET-He and IRF increase significantly after intravenous iron therapy as early as 48 hours after initiation of treatment irrespective of the status of the iron stores (deplete or functional iron deficiency). The mean increase in RET-He (3.8133 ± 0.3966 vs. 1.4947 ± 2.1309, P < 0.01) was of significantly smaller magnitude in group B than in group A. The increase in IRF was not significantly different between the two groups (8.5169 ± 5.0252 vs. 8.4000 ± 5.3905, P > 0.01). Thus those patients who had depleted iron stores showed greater increase in RET-He in response to intravenous iron therapy as compared to those with functional iron deficiency. These results were similar to the ones reported by Brugnara et al.6 who showed that reticulocyte hemoglobin content (CHR) increased within 4 days of intravenous iron therapy. Mittman et al.13 had also reported similar increase in CHR within 48 hours of intravenous iron therapy. Another study also reported increase in CHR with intravenous iron therapy.16 RET-He and CHR both are comparable to each other.17

Identifying patients who show low RET-He after IV iron therapy makes it possible to identify the patients who are not responding to IV iron. Thus these patients may be offered additional diagnostic tests and management strategies.

IRF just reflects the erythropoietic activity of bone marrow but does not show the actual incorporation of iron in developing RBC’s (hemoglobinization of mature RBC’s). RET-Hb is not only sensitive but also a real time indicator of iron supply to the developing RBC’s. In other words, RET-Hb is a real time parameter of hemoglobinization.

In our study we observed that mean increase in IRF did not show significance between the two groups (iron depleted v/s functional iron deficiency) but there was significant increase in RET-Hb which confirms that mean magnitude change in RET-Hb is a real time indicator of iron supply to the developing RBC’s.

The aim of iron therapy in IDA is to improve iron supply (Hemoglobinization) to the developing RBC’s. As the traditional parameter of treatment response – reticulocyte count and newer parameter – IRF only reflect erythropoietic activity of bone marrow and they do not reflect the incorporation of iron in maturing RBC’s, which is the primary aim of iron therapy. RET-Hb is a real time indicator of iron supply (Hemoglobinization) to the developing RBC’s and is a

### Table 2: Comparison of various parameters at the time of diagnosis and at 48 hours after initiation of intravenous iron therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At diagnosis</td>
<td>Post therapy</td>
<td>Paired difference</td>
</tr>
<tr>
<td>MCV</td>
<td>72.16 ± 0.0157</td>
<td>72.15 ± 0.0157</td>
<td>-0.0157</td>
</tr>
<tr>
<td>MCH</td>
<td>19.38 ± 0.0176</td>
<td>19.39 ± 0.0176</td>
<td>-0.016</td>
</tr>
<tr>
<td>RDW-CV</td>
<td>18.96 ± 1.204</td>
<td>20.16 ± 1.204</td>
<td>1.11</td>
</tr>
<tr>
<td>RET-He</td>
<td>19.18 ± 2.381</td>
<td>22.56 ± 2.381</td>
<td>1.11</td>
</tr>
<tr>
<td>IRF</td>
<td>27.20 ± 5.07</td>
<td>35.70 ± 5.07</td>
<td>3.08</td>
</tr>
</tbody>
</table>

All values are mean ± SD; * Significant

### Table 3: Comparison of mean increase in RET-He and IRF at 48 hours after initiation of intravenous iron therapy between group A and B

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean difference in group A</th>
<th>Mean difference in group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET-He</td>
<td>3.8133 ± 0.3966</td>
<td>1.4947 ± 2.1309</td>
<td>&lt; 0.0001 *</td>
</tr>
<tr>
<td>IRF</td>
<td>8.5169 ± 5.0252</td>
<td>8.4000 ± 5.3905</td>
<td>0.9283</td>
</tr>
</tbody>
</table>

All values are mean ± SD; * Significant
useful marker of response to iron therapy. RET-He had the advantage of being measured on routine haemogram at a little increment of cost and the results can be obtained readily.

All these studies support utility of RET-He as an early indicator of response to iron therapy in IDA. Our previous article also showed utility of RET-He as a marker of bone marrow iron store in iron deficiency anemia.18 On the basis of our observations, we can conclude that RET-He can be used as a marker of bone marrow iron store as well as an earliest indicator of response to therapy in iron deficiency anemia.

**Limitations**

Our study had certain limitations. We included patients only with severe anemia in our study. Whether our findings can be extrapolated to those with mild to moderate degree of anemia or with iron deficiency state is debatable. We studied effect of intravenous iron in IDA so the results may not applicable on oral iron therapy. This study was done at a tertiary care centre, and recruited inpatients only, resulting in a limited sample size, thus the nature of the investigation and the results do not imply a general case, and further studies with a larger sample size are needed.

**Conclusion**

Both RET-He and IRF increase as early as 48 hours after initiation of intravenous iron therapy. However, the mean change in IRF was not significant while mean change in RET-Hb had statistical significance. In essence, RET-Hb, a real time indicator of iron supply (hemoglobinization) to the developing RBC’s, is the earliest marker of response to iron therapy.

**Conflicts of Interests**

None of the authors have conflict of interest.

**References**


Clinical Profile and Treatment Outcome of Drug Resistant Tuberculosis Patients of Western Maharashtra, India

Sachin S Dole¹, VN Waghmare², AM Shaikh³

Abstract
Background: Drug-resistant tuberculosis (DR-TB) imposes formidable burden on national health systems.

Objectives: This study aims to evaluate clinical profile and treatment outcome of drug resistant tuberculosis patients at tertiary care centre using a standardised treatment regimen (STR)

Methods: Retrospective analysis of 146 patients with DR-TB from Solapur district who were treated with STR from period of September 2012 to December 2014 was done. Statistical analysis of treatment outcome data was done to know predictors of treatment success of DR-TB.

Results: Out of total 146 bacteriologically proven cases of DR-TB, 95 were males and 51 females. 41% of patients were residents of Solapur city and the rest from different parts of Solapur district. Out of the 146 patients, 130 (89%) patients achieved sputum culture conversion within three months. Treatment outcome of these patients was as follows: treatment success in 84 (58%), 20(14%) died, 28(19%) defaulted and failure in 14(9%) patients. Three predictors were identified for successful treatment outcome of DR-TB that include urban residence, patients with chest x-ray findings of moderately advanced disease and patients whose DR-TB status diagnosed by genexpert technology.

Conclusion: In resource-poor settings, well-designed STR under national programme provides satisfactory results.

Introduction

Drug-resistant tuberculosis (DR-TB) has become a significant public health problem in number of countries and one of the major obstacles in effective tuberculosis control programme. Multidrug resistant tuberculosis (MDR-TB) is tuberculosis resistant to isoniazid and rifampicin. 3.7% of new cases and 20% of previously treated cases are estimated to have multi-drug resistant tuberculosis worldwide.¹

The global TB epidemic has been complicated by the presence of multidrug-resistant tuberculosis.² In India MDR-TB in new cases has been reported to be nearly 3% and in treated patients has been reported to be 12%.³ Use of second line anti-tubercular drugs which are expensive and associated with adverse drug reactions given for longer duration often results in decreased compliance and success rates.¹,²

Facility for diagnosis and treatment of drug-resistant tuberculosis patients in Solapur district, Maharashtra was started under Revised National Tuberculosis Control Programme (RNTCP) of India in 2012. So, we conducted study at tertiary care centre of Western Maharashtra, India to evaluate clinical profile and treatment outcome of drug-resistant tuberculosis patients who were treated with standardized MDR-TB regimen.

Materials and Methods

After institutional ethical committee approval, a hospital based, descriptive, cross-sectional study was conducted at tertiary care centre of Solapur, Western Maharashtra.

Total 2127 suspected DR-TB cases from Solapur district, attending outpatient department...

¹Assistant Professor, ²Associate Professor, ³Professor and Head of Department, Department of Respiratory Medicine, Dr. Vaishampayan Memorial Govt. Medical College, Solapur, Maharashtra
Received: 29.03.2017, Revised: 10.05.2017, Accepted: 03-06-2017
All confirmed DR-TB cases underwent pretreatment investigations which includes serum electrolytes, renal function tests, urine examination, complete blood count, serum TSH (thyroid-stimulating hormone) levels etc. Those patients with abnormal laboratory values, their DR-TB treatment regimen was modified e.g. in patients with raised TSH level, ethionamide was replaced with PAS (para-amino salicylic acid). Such patients were shifted on modified or individualized regimen, hence not fit for our study, as our study was based on standardized treatment regimen.

Total 146 confirmed DR-TB cases registered for starting standardized MDR-TB regimen were enrolled in this study.

All MDR-TB cases were treated with standardized regimen which consists of 6-9 months of intensive phase with kanamycin, levofloxacin, ethionamide, pyrazinamide, ethambutol and cycloserine and continuation phase of 18 months with ethambutol, levofloxacin, ethionamide and cycloserine on daily basis. All data of MDR-TB cases were collected from pretreatment evaluation records.

Definition of treatment outcome of MDR-TB patients according to WHO 2013 guidelines are-

1. Cured: patient who has completed MDR-TB treatment, is culture-negative in the last month of treatment and has been culture-negative during the preceding 11 months of treatment.
2. Treatment completed: patient who completed MDR-TB treatment but did not meet the definition for cure or failure due to lack of bacteriologic results.
3. Treatment failure: defined as more than one positive culture in the last 12 months of treatment, with a minimum of five cultures performed during the last 12 months, or if patient is persistently culture-positive and a clinical decision has been made to terminate treatment early.
4. Death: defined as patient who dies for any reason during the course of MDR-TB treatment.
5. Treatment default: defined as patient whose MDR-TB treatment was interrupted for two or more consecutive months.

Chest radiographs was obtained for every patient and classified according to the National Tuberculosis Association of USA (1961).6

1. Minimal: Non-cavitatory lesions involving one or both lungs but the volume of involvement regardless of distribution less than or equal to one zone.
2. Moderately advanced: More advanced lesions than minimal but the total involvement not more than the volume of one lung. Cavities, if present, not to exceed a total diameter (of all cavities) of 4 cm.
3. Far advanced(Extensive) (III): Any lesion more advanced than moderate

Culture conversion was defined as three negative consecutive cultures taken at least one month apart after treatment initiation.7

All data from these patients including clinical profile and treatment outcome was entered. Statistical analysis was done by using mean method and results were expressed in terms of percentages. Univariate analysis of treatment outcome data was done to know predictors of treatment success of MDR-TB.

Results

Out of 146 patients included in the study, there were 95 male and 51 female patients with a mean age of 38 years and 35 years and a mean weight of 52 kilograms and 40 kilograms respectively. 41 % patients were residents of Solapur city and rest from various parts of Solapur district. Baseline characteristics of the 146 patients are given in table 1. Out of 146 patients 7% patients had pleural effusion.

At presentation, all had radiographic evidence of pulmonary tuberculosis. 46 patients had moderately advanced disease, 100 patients had extensive disease while none of our patients had minimal advanced radiological disease. Overall, 16 (11%) cases had co-morbid illnesses like diabetes mellitus(DM) and human immunodeficiency virus (HIV) infection.

All of our patients had DR-TB of pulmonary etiology. 11 patients (7%) had findings of pleural effusion in addition to pulmonary TB. As per RNTCP guidelines, patients of pleural effusion with pulmonary TB are considered as pulmonary tuberculosis patients. In our study none of our patients had extrapulmonary TB.

Among patients included in the study 104 were diagnosed with Line Probe Assay(LPA) and 42 were diagnosed with genexpert technology. All patients had received standardized treatment
In our study 1. Urban residence; 2. Patients with chest X-ray findings of moderately advanced disease and 3. Patients whose MDR-TB Status diagnosed by genexpert technology were found to be positive predictors of a successful treatment outcome in MDR TB. Some factors, which did not influence the treatment outcome were age, sex, weight and residence. The demographic profile of MDR-TB patients in our study was similar to other series, with majority of male patients in the economically productive age group (25-54 years). Sputum culture conversion of 74-82 per cent at 6 months have been reported from other studies in India on treatment of MDR-TB cases. Patients in our study appear to have had a more rapid clearance of bacilli from sputum (89 % by three months). This finding indicates that effective management of MDR-TB with an adequate regimen, can make the patient noninfectious rapidly and probably give a better treatment outcome.

A successful outcome was seen in 58% patients in our study which is comparable to the results seen of a successful treatment outcome observed was as follows- 1. Treatment success in 5 patients (55%), 2 patients defaulted (18%), 2 died (18%) and treatment failure was observed in 1 patient (9%). Thirty four (23%) patients had minor side-effects. Loss of taste, nausea and occasional vomiting were seen in 26 (18%) patients. These were effectively managed in hospital by dietary modifications and symptomatic treatment. Mild depression, responding to symptomatic treatment, was noticed in 11 (8%) patients; five (3 %) had mild skin reactions; ten (7%) had minor joint pain. Two patients developed psychotic reaction with suicidal tendency.

### Table 3: Univariate analysis of predictors of successful treatment outcome in MDR-TB patients

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Treatment success (84)</th>
<th>Other outcomes (62)</th>
<th>Total (146)</th>
<th>95% CL</th>
<th>Odds ratio</th>
<th>Probability (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-50</td>
<td>73</td>
<td>51</td>
<td>124</td>
<td>0.57-3.55</td>
<td>1.43</td>
<td>0.59</td>
</tr>
<tr>
<td>&gt;50</td>
<td>11</td>
<td>11</td>
<td>22</td>
<td>0.40-1.62</td>
<td>0.81</td>
<td>0.68</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53</td>
<td>42</td>
<td>95</td>
<td>0.40-1.62</td>
<td>0.81</td>
<td>0.68</td>
</tr>
<tr>
<td>Female</td>
<td>31</td>
<td>20</td>
<td>51</td>
<td>0.40-1.62</td>
<td>0.81</td>
<td>0.68</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26-45 kg</td>
<td>60</td>
<td>40</td>
<td>100</td>
<td>0.68-2.78</td>
<td>1.38</td>
<td>0.48</td>
</tr>
<tr>
<td>45-70 kg</td>
<td>24</td>
<td>22</td>
<td>46</td>
<td>0.68-2.78</td>
<td>1.38</td>
<td>0.48</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>42</td>
<td>18</td>
<td>60</td>
<td>1.22-4.90</td>
<td>2.44</td>
<td>0.018*</td>
</tr>
<tr>
<td>Rural</td>
<td>42</td>
<td>44</td>
<td>86</td>
<td>1.22-4.90</td>
<td>2.44</td>
<td>0.018*</td>
</tr>
<tr>
<td>X-ray findings#</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>35</td>
<td>11</td>
<td>46</td>
<td>1.51-7.24</td>
<td>3.31</td>
<td>0.003*</td>
</tr>
<tr>
<td>Advanced</td>
<td>49</td>
<td>51</td>
<td>100</td>
<td>1.51-7.24</td>
<td>3.31</td>
<td>0.003*</td>
</tr>
<tr>
<td>Test used for Genexpert diagnosis</td>
<td>29</td>
<td>13</td>
<td>42</td>
<td>1.14-5.52</td>
<td>2.51</td>
<td>0.031*</td>
</tr>
</tbody>
</table>

### Table 1: Baseline characteristics of 146 MDR-TB patients

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>18-50 yrs.</td>
<td>124</td>
</tr>
<tr>
<td>&gt;50 yrs.</td>
<td>22</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>95</td>
</tr>
<tr>
<td>Female</td>
<td>51</td>
</tr>
<tr>
<td>Body wt (kg)</td>
<td></td>
</tr>
<tr>
<td>26-45</td>
<td>100</td>
</tr>
<tr>
<td>45-70</td>
<td>46</td>
</tr>
<tr>
<td>Area of residence</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>60</td>
</tr>
<tr>
<td>Rural</td>
<td>86</td>
</tr>
<tr>
<td>HIV positive</td>
<td>6</td>
</tr>
<tr>
<td>Presence of DM</td>
<td>10</td>
</tr>
<tr>
<td>X-ray findings of TB</td>
<td></td>
</tr>
<tr>
<td>Minimally advanced</td>
<td>0</td>
</tr>
<tr>
<td>Moderately advanced</td>
<td>100</td>
</tr>
<tr>
<td>Extensive disease</td>
<td>46</td>
</tr>
<tr>
<td>Presence of effusion</td>
<td>11</td>
</tr>
</tbody>
</table>

### Table 2: Treatment outcome of MDR-TB patients treated with standardized regimen (total patients-146)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of pts. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>39 (27)</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>45 (31)</td>
</tr>
<tr>
<td>Died</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Defaulted</td>
<td>28 (19)</td>
</tr>
<tr>
<td>Failure (Switch to Cat-5)</td>
<td>14 (9)</td>
</tr>
</tbody>
</table>

*X-ray findings of disease involvement; *Denotes significant p value (p value <0.05)
previously in some studies. However, this figure is relatively in comparison to cure rates of about 60% observed in Denver, New York and Netherlands and higher than study done by Dhingra et al and lower than 80% seen in Turkey, Peru and Netherlands. In our study patients those defaulted, most of them had migrated out of area. Holding patients to a defined geographical area for two years was difficult. In failure patients, delayed development of bacteriological resistance was the probable cause. These patients later were shifted on individualized regimen.

Our findings are similar to recently published reports from New Delhi where cure rates of 61 per cent have been reported. These results contrast to the 48 per cent favourable response reported from Peru using a standardized regimen for chronic TB patients with MDR-TB.

Higher treatment success rate was observed in patients of urban area, this may be due to better facility of transportation and more awareness of disease. Similarly better treatment success rate was observed in patients with moderately advanced disease. In our study among tests used for diagnosing DR-TB, patients who were diagnosed with genexpert test has shown fairly high treatment success as result of above test is available within 90 minutes compared to LPA, where diagnosis takes 72 hours. Earlier the results are obtained, patients can be started on treatment earlier, thus increasing the success rate.

Some studies have demonstrated that individualized treatment yields more favourable outcomes than standard regimens, while in other studies appropriate treatment results are achieved using standardized regimens. However, it has been clearly demonstrated that individualised treatment is highly expensive and difficult to implement in the majority of low income countries, which bear the highest burden of MDR-TB. Therefore, the use of standardized treatment regimens for MDR-TB patients, reduces the number of health care facilities need and lowers the overall cost of treatment by five to ten times.

The majority of studies on the treatment of MDR-TB have been performed in referral centres. In our study, the treatment was initiated and continued in peripheral health centres, along with follow-up. Given that a favourable treatment outcome was achieved in our study, it can be assumed that the treatment protocol for MDR-TB can be properly integrated into the national health care system.

Conclusions

From this study, it appears feasible to treat MDR-TB patients effectively in India on the predominantly ambulatory RNTCP standardized regimen. This study has shown that standardized treatment of MDR-TB can provide satisfactory results. The standardized treatment strategy may be a justifiable alternative to the individually tailored regimens. Use of rapid diagnostic tests for MDR-TB like genexpert should be increasingly use to achieve higher treatment success in these patients.

References

4. WHO guidelines for the programmatic management of drug-resistant tuberculosis 2013
APO B/APO AI Ratio with Coronary Artery Disease with Normal Lipid Profile in the Indian Population

Ranjan Modi¹, VA Kothiwale², Suresh Patted¹, PC Halkati¹

Abstract

Background: Abnormal lipids are an important risk factor for development of Coronary Artery Disease, significant patients have normal lipid profile and yet develop CAD. Apolipoproteins B, Apolipoproteins A and their ratio have been shown to be better predictor of risk of developing Coronary artery disease.

Objective: Assess the Apo B / Apo A ratio with coronary artery disease in patients with normal lipid profile.

Methods and Results: In 4232 patients with history of CAD 3724(88 %) had abnormal apo b / apo a ratio. Of 2920 patients with normal LDL levels (<100 mg), 2454 patients had abnormal apob/apoa ratio of which 2200 (91%) had CAD. In 1946 patients on lipid lowering agents 1819 had abnormal apo b/ apo a ratio and all had CAD.

Conclusion: This study ascertains the importance Apo B, Apo A ratio over conventional lipid profile values for predicting CAD and its severity. Apo B/ Apo A ratio and CAD was found to be significant in patients with normal LDL, even in patients with history of dyslipidemia on statins this ratio was significant. Statins have been effective in lowering LDL, but have not shown changes in Apo B levels. Apo B and Apo A should be used to assess the atherogenic potential of lipid disorders.

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in the developed world and is rapidly assuming epidemic proportions in developing countries including India. India has to its discredit the highest number of coronary artery diseases in the world. Premature mortality in terms of years of life lost because of CVD in India increased by 59%, from 23.2 million (1990) to 37 million (2010). Despite wide heterogeneity in the prevalence of cardiovascular risk factors across different regions, CVD has emerged as the leading cause of death in all parts of India, including poorer states and rural areas.¹

Conventionally, serum abnormal lipid profile has been considered to be an important risk factor for development of coronary artery disease. However there are subsets of patients who do not have raised lipid profile and yet develop coronary artery disease.

Extensive research has been done to determine the risk factors unique to this group which may predispose to the elevated risk of this disease. Important amongst them are lipoproteins, homocysteine, lipoprotein (a), pro-inflammatory cytokines. Considerable interest arose in apolipoproteins, mainly apolipoprotein B, the major protein in non–HDL-C atherogenic lipoprotein particles (including low-density lipoprotein [LDL], intermediate density lipoprotein, very low density lipoprotein, and Lip(a)) and apolipoprotein A-I, which is the major apolipoprotein constituent of high-density lipoprotein (HDL).²

Atherosclerotic disease implicates a multitude of risk factors, of which lipid and lipoprotein metabolism assumes central importance. Furthermore, lipoprotein cholesterol (particularly low density lipoprotein cholesterol [LDL-C]) constitutes an established risk factor and a primary treatment target for the prevention of coronary heart disease (CHD). The third Adult treatment Panel of the National Cholesterol Education program (NCEP ATP-III) introduced non–high-density lipoprotein cholesterol (HDL-C) as a better
Table 1: Classification of BMI

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (Kg/m²)</th>
<th>Risk of co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>Low (But increased risk of other clinical problems)</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.5 to 24.99</td>
<td>Average</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥ 25</td>
<td></td>
</tr>
<tr>
<td>Preobese</td>
<td>25.0 to 29.99</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese I</td>
<td>30 to 34.99</td>
<td>Moderate</td>
</tr>
<tr>
<td>Obese II</td>
<td>35 to 39.99</td>
<td>Severe</td>
</tr>
<tr>
<td>Obese III</td>
<td>&gt;40</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

Risk predictor particularly among hypertriglyceridemic individuals. A polipoprotein B, apolipoprotein A-I, and even more so their ratios has been suggested by a number of epidemiological and clinical studies as superior indicators of cardiovascular risk. Numerous studies have been conducted with contrasting results. Various studies reported a similar predictive power for lipids and apolipoproteins. Some argued that apolipoprotein add to prediction of the traditional lipids, whereas others did not find apolipoprotein to have a predictive power beyond that of lipids.

Studies have been undertaken to evaluate the role of the apolipoprotein-B100 (apo-B)/apolipoprotein-AI (apo-AI) ratio as a predictor of CAD risk in the atherosclerosis-prone Indian population, as compared to other conventional lipid ratios. Although most of comparative studies of apolipoproteins A-I and B with lipids were conducted among healthy individuals, only a few studied the association between lipoprotein components and prognosis among CHD patients. In various studies national and international, lower levels of plasma apolipoprotein AI (Apo A-I) and higher levels of ApoB, and the ratio of ApoB to ApoA-I have been proved to be independent risk factors for coronary heart disease.

There are very few studies in this regard in Indian subcontinent. No study has been done exploring the association of Apo B/Apo AI ratio with angiographically proven coronary artery disease with normal lipid profile in the Indian population.

Methodology

The present study was conducted in the Department of Cardiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients during the period of one year. One cross sectional study was done on patients admitted with history suggestive of ischemic heart disease (clinically symptoms of ischemia like chest pain and ECG changes) including MI, Unstable angina and Stable angina were included. Patients with liver disease and renal disease over excluded.

The study was approved by the Institutional Ethics Committee and a written informed consent was obtained. Demographic data like gender and age were collected along with relevant history and recorded on predesigned and pretested proforma. A thorough clinical examination was conducted and the findings were also recorded.

Body Mass Index = Weight (Kg) / Height² (m). Body mass index was classified according to Overweight and obesity by BMI in adults as below (Table 1).

Routine investigations such as haemogram (haemoglobin, total count, differential count, erythrocyte sedimentation rate), mini renal, liver function test, urine routine and microscopy were done. Others tests like fasting blood sugar, electrocardiogram were carried out. Special tests such as cardiac enzymes, fasting lipid profile, apolipoprotein A (by Turbidimetry method), apolipoprotein B (by Turbidimetry method), hsCRP (by PETIA method) and coronary angiography were conducted and recorded.

The results of the angiography were termed as significant depending on the number of diseased vessels and stenosis of >70% of the vessel diameter.

- Normal
- Single vessel disease
- Double vessel disease
- Triple vessel disease

Based on NCEP (National Cholesterol Education Program) guidelines normal values of lipid parameters were;

- Low density lipoprotein < 100 mg/dL
- High density lipoprotein
  - Females > 50 mg/dL
  - Males > 40 mg/dL
- Total Cholesterol < 200 mg/dL.

Inflammatory marker hsCRP was calculated and its association with Apo b and Apo a was noted. Normal values were defined as hsCRP < 3 mg/dL.

Apo B to A Ratio

Although clinical evidence clearly demonstrates that apoB and apoA-I are significantly associated with CAD risk, they have not been generally accepted as therapeutic targets by the various bodies providing lipid-regulating guidelines. The gold standard test for CAD prevails to be Coronary angiography. However, a target apoB level of <90 mg/dl for patients with CAD or at high risk of CAD has been suggested by the Canadian Cardiovascular Society. Based on the known strong positive relationship between non-HDL cholesterol and apoB, a target levels for apoB has been proposed by an updated revision of the NCEP ATPIII guidelines. According to various studies apoB/apoA-I ratios of 0.8 is considered as abnormal.

Statistical Analysis

The data obtained was tabulated and analysed using rates, ratios and percentages. The data was analysed using Fisher exact test, chi-square test with Yate’s correction wherever indicated and Odd’s ratio. A ‘p’ value of less than 0.05 was considered as statistically
Results

In the study, age distribution of most of the patients (40%) were in the in the age group of 51 to 60 years followed by 24% in 41 to 50 years and 16% in 61 to 70 years (Table 2).

Majority of the patients (97%) presented with complaints of chest pain and breathlessness was noted in 31%. However, both complaints were seen in most of the patients.

The major risk factors were dyslipidemia (46%) followed by hypertension and smoking (Table 3). A large proportion of the patients were in the obese I group (72%). However 13% of patients were in obese II group and 11% were at risk. The mean waist circumference was 84.66 ± 8.38 cms. The mean BMI was 27.21 ± 2.41 Kg/m².

In the present study mean pulse rate was 80.20 ± 8.56 beats per minutes. The mean systolic and diastolic blood pressure were 133.20 ± 18.29 and 82.20 ± 9.70 mm Hg respectively.

In this study mean fasting blood sugar levels were 128.70 ± 55.56 mg/dL. The cholesterol, HDL, LDL and hsCRP levels with percentage distribution (Table 2).

Overall mean Apo A1 was 107.3 ± 23.5 mg/dL and Apo B was noted as 72.1 ± 21.14 mg/dL. The mean Apo B to Apo A1 ratio was 1.61 ± 0.56. (Table 4) with abnormal Apo B to Apo A1 ratio in 88% patients.

Table 2: Baseline characteristics and biochemical profile of patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Males (Mean ± SD)</th>
<th>Females (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.23 ± 10.98</td>
<td>56.25 ± 10.15</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.97 ± 2.35</td>
<td>28.47 ± 2.41</td>
</tr>
<tr>
<td>Waist circumference (cms)</td>
<td>83.96 ± 8.13</td>
<td>88.31 ± 8.97</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>171.12 ± 31.42</td>
<td>165.63 ± 38.56</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>132.65 ± 51.94</td>
<td>123.56 ± 51.70</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>43.57 ± 16.10</td>
<td>43.44 ± 8.59</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>90.32 ± 31.83</td>
<td>93.06 ± 38.51</td>
</tr>
<tr>
<td>HDL to Total cholesterol ratio</td>
<td>0.26 ± 0.08</td>
<td>0.28 ± 0.08</td>
</tr>
</tbody>
</table>

Table 3: Risk factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Distribution No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>931 (22)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1693 (40)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1947 (46)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1354 (32)</td>
</tr>
<tr>
<td>Angina</td>
<td>466 (11)</td>
</tr>
<tr>
<td>MI</td>
<td>762 (18)</td>
</tr>
<tr>
<td>CVA</td>
<td>42 (1)</td>
</tr>
</tbody>
</table>

Table 4: Cholesterol, hsCRP and ApoB Apo A1 levels

<table>
<thead>
<tr>
<th>Cholesterol levels (mg/dL)</th>
<th>Normal (&lt; 200)</th>
<th>Abnormal (&gt; 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low density lipoprotein</td>
<td>804 (19)</td>
<td>3428 (81)</td>
</tr>
<tr>
<td>hs-CRP Levels (mg/dL)</td>
<td>Normal (&lt; 3)</td>
<td>Raised (&gt; 3)</td>
</tr>
<tr>
<td>Apo B A1 ratio</td>
<td>Normal (&lt; 100)</td>
<td>Raised (&gt; 100)</td>
</tr>
</tbody>
</table>

Table 5: Comparison of Apo B to Apo A1 ratio with CAD

<table>
<thead>
<tr>
<th>Angiographic findings</th>
<th>Apo B to Apo A1 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>69.23</td>
</tr>
<tr>
<td>Coronary arteries</td>
<td>90.8</td>
</tr>
<tr>
<td>CVA</td>
<td>95% CI</td>
</tr>
</tbody>
</table>

Table 6: Correlation of History of dyslipidemia with Apo B/A1 ratio

<table>
<thead>
<tr>
<th>Abnormal Apo B/A1</th>
<th>Normal Apo B/A1</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/o of dyslipidemia</td>
<td>H/o of dyslipidemia</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>No (n=1904)</td>
<td>No (n=1820)</td>
</tr>
<tr>
<td>Single</td>
<td>Single</td>
</tr>
<tr>
<td>677 (37.21)</td>
<td>1058 (55.56)</td>
</tr>
<tr>
<td>Double</td>
<td>Double</td>
</tr>
<tr>
<td>635 (34.88)</td>
<td>254 (13.33)</td>
</tr>
<tr>
<td>Triple</td>
<td>Triple</td>
</tr>
<tr>
<td>508 (27.91)</td>
<td>211 (11.11)</td>
</tr>
</tbody>
</table>

x²=13.679; p<0.001

Discussion

Lipids have been correlated to severity of coronary atherosclerosis. Various epidemiological and clinical studies in the past have consistently demonstrated that an elevated concentration of LDL-C is associated with an increased risk of CAD. They have been a well-established risk factor for CAD and have been the recommended as the primary target for lipid-lowering therapy for the prevention and treatment of cardiovascular disease.

Apolipoproteins are important components of lipoprotein particles, and there is accumulating evidence that the measurement of various forms of apolipoproteins may improve the prediction of the risk of cardiovascular disease. Apo B is present as a single molecule in non-HDL, while Apo A-I is the major apolipoprotein associated with HDL. There is abundant evidence that the risk of CAD is related to plasma lipid and apolipoprotein levels.

In the study of the 4232 subjects 84% were males and 16% were females indicating male preponderance, overall, the mean age was 52.87 ± 10.89 years.
In various studies, similar findings have been noted. This might be due to the increased prevalence of risk factors of CAD in males. Dyslipidemia was the most common among the risk factors (46%) followed by hypertension, smoking and diabetes (40%, 32% and 22%).

In this study, most of the patients were in the obese I group reiterating the fact that CAD is intimately related to BMI. The mean BMI in the study was 27.21 ± 2.41 Kg/m². In males the mean BMI was 26.97 ± 2.35 and in females it was 28.47 ± 2.41 Kg/m². In males the HDL levels were 43.57 ± 16.10 mg/dL and in females it was 43.44 ± 8.59 mg/dL which was similar to previous studies (Table 2).

Apolipoprotein B/A 1 ratio was found to be significantly higher (>0.8) in 88% of the patients who were found to have CAD on coronary angiography. The significant number of patients in this category reiterated Apolipoprotein B/A1 ratio as a predictor for risk of CAD. These were similar to the findings in this study.

A significant relationship was found between ratio of Apo B / Apo A1 and coronary artery disease. Significantly more number of patients 3343 (90.8%) with Apo B / Apo A1 in the abnormal range (>0.8) were found to have CAD and only 381 had normal coronary arteries (p<0.001). With regard to patients with normal Apo B / Apo A1 ratio only 339 (9.19%) patients had CAD whereas 169 had normal coronaries (Table 5).

In this study many patients had dyslipidemia as a risk factor. These patients had either history of dyslipidemia or were already on lipid lowering agents (atorvastatin and rosuvastatin), on optimal dosage according to ATP 4 guidelines. Of the 3724 patients with abnormal Apo B to A1 ratio, 1820 patients had history of dyslipidemia. Among them 27.91% patients had triple vessel disease, 34.8% had double vessel disease, and 37.21% had single vessel disease whereas in those with no history of dyslipidemia (45 patients) 11.11% had triple vessel disease, 33.33% had double vessel disease and 55.5% had single vessel disease. This difference statistically significant (p<0.001). Thus having established that single vessel disease was still seen (55.5%) with no history of dyslipidemia but abnormal Apo B to Apo A ratio. Previously no other study has observed this correlation which is statistically significant among dyslipidemia Apo B to Apo A1 ratio and severity of CAD. This findings confirmed that Apo B to Apo A1 ratio and dyslipidemia are reliable and important factors for CAD (Table 6).

Among patients with abnormal Apo B to Apo A1 ratio, majority were in obese I category. Among them 41.43% had single, 28.57% had double and 20% had triple vessel disease. Of the obese II patients, 53.85% had single, 7.69 had double and 23.03% had triple CAD. However, all the patients with at risk obesity had normal coronaries. This difference was statistically significant (p<0.001) thus proving that the ratio of the apolipoprotein were correlated to

### Table 7: Correlation of abnormal Apo B/A ratio with BMI and CAD

<table>
<thead>
<tr>
<th>Angiographic findings</th>
<th>Abnormal Apo B/A ratio (n=3724)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Underweight (n=0)</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Single</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Double</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Triple</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

\[ \chi^2=28.250; p<0.001 \]

### Table 8: Correlation of Apo B/A ratio with total cholesterol and CAD

<table>
<thead>
<tr>
<th>Angiographic Findings</th>
<th>Abnormal Apo B/A1 (n=3724)</th>
<th>Normal Apo B/A1 (n=508)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC &lt; 200 (n=3301)</td>
<td>TC &gt; 200 (n=423)</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>212 (6.41)</td>
<td>168 (40)</td>
</tr>
<tr>
<td>Single</td>
<td>1651 (50)</td>
<td>85 (20)</td>
</tr>
<tr>
<td>Double</td>
<td>804 (24.36)</td>
<td>85 (20)</td>
</tr>
<tr>
<td>Triple</td>
<td>635 (19.23)</td>
<td>85 (20)</td>
</tr>
<tr>
<td>Total</td>
<td>3301 (100.00)</td>
<td>423 (100)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 11.564; p=0.009 \]
BMI. The higher the BMI, the more was the risk of CAD indicating importance of Apo B/A ratio as a predictive marker (Table 7).

According to NCEP guidelines total cholesterol is considered a risk factor for CAD with cutoff values of >200 mg/dL. In this study we compared patients having abnormal Apo B / Apo A ratio and their total cholesterol values with CAD. Out of 3724 patients with abnormal Apo B / Apo A, 3301 had total cholesterol < 200 mg/dL. In this group of 3301 patients with total cholesterol <200 mg/dL 3089 had significant cad (p=0.009) (Table 8).

Low density lipoprotein has been established as a risk factor and the primary treatment target for prevention of heart disease. In the study, 2920 patients were found to have normal LDL (<100 mg/dL). Among these patients, 58% patients were found to have abnormal Apo B /Apo A ratio; out of which 52% had proven CAD on angiography. This value was statistically significant (p=0.014) (Table 9). These finding were consistent with AMORIS study9 which postulated that Apo B was more significant than LDL cholesterol in prediction of risk of MI in both men and women but especially in those having normal / low LDL-C levels. Similar study23 examined the levels of LDL-C with severity of CAD and found no differences among the subgroup of the patients. The authors examined whether levels of LDL-C, were related to CAD, but did not find an association with CAD. Study revealed strong relations between Apo A-I and Apo B levels and the presence of CAD as defined by the observation of vessel stenosis. These findings were similar to the present study. This suggests that the traditional thought about risk for CAD being less in patients with normal LDL does not hold weightage.

In the study 69% of the patients with CAD had LDL less than 100 mg/dL. The mean LDL was found to be 91.72 ± 32.93 mg/dL.24 Low density lipoproteins have been the standard marker for determination of the risk of CAD. LDL levels more than 100 mg/dL in patients have been known to be associated with higher risk of CAD. The disparity in the levels of LDL in the present study and other studies can be explained by the fact that most of the patients in this study were on lipid lowering agents like statins. Patients which were admitted in the hospital had either history of dyslipidaemia in the family (35%) or had been already initiated on lipid lowering agents by primary health care physicians (65%) because of deranged lipid parameters. It has been proven beyond doubt that lipid lowering agents decrease the levels of LDL but their effects on Apo B has been controversial as proved by ACCESS study.25 This study has shown that statins have been effective in lowering LDL, but have not shown commensurate changes in Apo B levels. Also, these findings suggest that determination of the risk for CAD may not entirely be associated with the levels of LDL and it may not be the gold standard determinant for the risk of CAD thus, necessitating the need for newer markers to assess risk of CAD (Table 9).The mean Hs-CRP was found to be 5.06 ± 4.58 mg/dL.

Hence, a new marker for determination of CAD in patients with normal lipid profile is required. Apo B / Apo A ratio seems to be the much needed answer. 

**Summary**

Apo B / Apo A 1 ratio has been an established risk factor for CAD. The treatment goals for prevention of CAD have been attributed to LDL levels. Few patients have optimal LDL levels, yet develop CAD.

In this study, of the patients with CAD, 90.8% had abnormal Apo B/Apo A ratio and 9.19% had normal ratio. This difference was statistically significant (p<0.001). We established that single vessel disease was still seen (55.5%) with no history of dyslipidemia but abnormal Apo B to Apo A1 ratio. Previously no other study has observed this correlation which is statistically significant among dyslipidemia Apo B to Apo A 1 ratio and severity of CAD. This findings confirmed that Apo B to Apo A 1 ratio and dyslipidemia are reliable and important factors for CAD.

In patients of normal LDL (<100 mg/dl), 2454 had abnormal Apo B/ Apo A1 ratio of which 89.7% had angiographically proven CAD. In these patients with normal LDL Apo B/Apo A1 ratio was found abnormal with statistically significant correlation to severity of CAD on angiography (p=0.008). This finding reiterated that Apo B, Apo A 1and their ratio are better markers of coronary artery disease than conventional lipid profile.

This study proved that CAD was prevalent in patients with normal LDL levels but abnormal Apo B / Apo A 1 ratio thus establishing Apo B / Apo A 1 ratio as an important diagnostic criteria for prognostication of CAD and to assess atherogenic potential of lipid disorders.

**References**

Submission of API Awards Nomination

1. Recommendations are invited from API Chairman / Secretaries of all State Chapters / City Branches for the following award:

Best State Chapter and Best City Branch Award

The award is based on overall API/ICP/PRF activities by the State Chapter / City Branch from 1st January to 31st December. Selected City Branch and State Chapter will get the award of Silver Memento and a citation from API during Annual General Body meeting to be held on 22nd February 2018.

Chairman / Secretaries of all state Chapters / City Branches are requested to send the report of their activities for the year 2017 by 10th January 2018.

All the above nomination should reach to Hon. General Secretary – API, Dr. Mangesh Tiwaskar of API, Unit No. 6 & 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E. Moses Road, Near Mahalaxmi Station (West), Mumbai – 400 011

Dr. Mangesh Tiwaskar
Hon. General Secretary
A Bidirectional Observational Study of Concomitant Chemo-Radiotherapy in Adenocarcinoma Stomach

Vishesh Gumdal¹, Prashant Kumbhaj¹, Yadlapalli C Deepak¹, Ankur Punia¹, Rakesh Taran², Prakash Chitalkar³

Abstract

**Background:** Although many cancers have seen a significant improvement in survival and reduction in morbidity in the past few decades, the same cannot be said about adenocarcinoma stomach. Upfront surgery in non metastatic stomach cancers definitely improves survival. It is well established that any form of adjuvant therapy adds to the improvement in survival, controversy remains if adjuvant chemoradiotherapy is the standard or not.

**Methodology:** This study is a single arm bidirectional observational study of the stomach cancer patients undergoing adjuvant concurrent chemoradiotherapy with 5 FU (5 Fluorouracil) with an aim to estimate the disease free survival (DFS) and to analyze toxicity patterns. A total of 73 patients with stomach cancer undergoing gastric resection with a curative intent were evaluated.

**Results:** With a median follow up of 16 months, the estimated disease free survival is 31.6 months. Of the 73 patients, recurrences were observed in 33 patients and the most common site was liver metastasis. Except for 2 patients, out of which one expired because of 5 FU induced myocardial infarction and another expired because of neutropenic sepsis during the first cycle of chemotherapy, most of the patients tolerated the regimen well.

**Conclusion:** 5 FU based adjuvant CT-RT can be safely given in the Indian population with acceptable survival rates.

Editorial Viewpoint

- **Not much reduction in mortality in adenocarcinoma of stomach has been noted.**
- **In this study adjuvant 5 FU was given to estimate disease-free survival and found acceptable benefits.**

Introduction

Malignancies in the stomach are one of the first malignancies known to humanity with references in hieroglyphic inscriptions and papyri manuscripts from ancient Egypt dating back to 3000 BC. Up till the 1980’s gastric cancer was one of the most common causes of cancer related mortality before being overtaken by lung cancer. In India crude incidence rates were highest in south and north-eastern parts and least in the north with Chennai reporting the highest rates but overall incidence rates is on the declining trend.¹,²

H. pylori has been associated with development of gastric cancer as evidenced by the results of several cross sectional studies.³ Pickles, salted fish, smoking, alcohol, obesity, poor socioeconomic status, Epstein Barr virus have also been associated with increased incidence of gastric cancer.

Biologically and histologically there are mainly two types of gastric cancer: Intestinal type, and Diffuse type which is associated with a germ line mutation and has a more aggressive course clinically.

Upfront surgical resection with either total or subtotal gastrectomy along with lymphnodal dissection gives the best chance to have long term survival.⁴ The five year OS for patients with completely resected stage I gastric cancer is about 70 percent, but it falls to 35 percent or less for stage II disease and beyond.⁵ Because of these dismal results with surgery alone for stages II and more, there have been efforts to develop some form of adjuvant therapy to improve survival.

¹Senior Resident, ²Associate Professor, ³Professor and HOD, Sri Aurbindo Medical College and PG Institute, Indore, Madhya Pradesh
Received: 04.03.2017; Revised: 28.04.2017; Accepted: 13.07.2017
In many parts of the world including Europe, chemotherapy alone is the preferred treatment strategy. Much of the heed in adjuvant RT comes from the observation that more than 80 percent of patients who die from gastric cancer develop a local recurrence at some stage when RT is not given. A large American Intergroup trial (INT0116) demonstrating a significant survival benefit for chemoradiotherapy after complete resection resulted in the adoption of this strategy in the United States.

This study is a single institution study with an aim to estimate the disease free survival and toxicity profile of gastric cancer patients who undergo adjuvant concomitant chemoradiotherapy after gastric resection with a curative intent.

**Methodology**

The aim of this study is to estimate the disease free survival (DFS) and analyze the toxicity patterns with the regimen mentioned below. All the patients with non metastatic gastric carcinoma who have undergone gastrectomy with a curative intent and who have presented to Sri Aurobindo Institute of Medical Sciences from 2011 to 2016 and who are willing to be a part of this observational study are included in this study. The study design was chosen to be bidirectional as the subjects enrolled in the years 2015 and 2016 were prospectively observed.

All patients underwent a pre operative work up included hemogram, renal and liver function tests, upper GI endoscopy and biopsy, contrast CT scan of chest, abdomen and pelvis, laproscopy and cytology to exclude peritoneal involvement. These patients are explained about the prognosis of the disease, complications and cost related factors regarding this therapy. Informed consent form was obtained from all the patients and Institutional Ethics committee clearance was also obtained prior to data collection.

Demographic parameters, surgical and histological details were collected as per the proforma of the patient. Location of the tumor was defined as Fundus, Body and Pylorus according to the location of the epicenter of the tumor. Close margins were defined by the presence of tumor cells within 5mm of the surgical margin. Positive Margins were defined by the presence of tumor cells on the inked margin. Presence of H.pylori was based on identification of the organism by light microscopy only. AJCC 7th edition, 2010 was used to stage the patients.

Treatment consisted of one cycle of 5-FU (425 mg/m2 per day) and leucovorin calcium (20 mg/m2 per day) daily for five days, followed one month later by RT (45 Gy in daily 1.8 Gy fractions) given with concurrent 5-FU and leucovorin calcium (400 mg/m2 and 20 mg/m2, respectively) on days 1 through 4, and on the last three days of RT. Two more five day cycles of chemotherapy (FU 425 mg/m2 per day and leucovorin calcium 20 mg/m2 per day) were given at monthly intervals beginning one month after completion of chemoradiotherapy.

Prior to all the chemotherapy cycles, blood counts, renal parameters and electrolytes were done and chemotherapy was administered only if they were within acceptable limits (Hb >10gm%, TLC >3500/mm3, ANC > 1500/mm3, Platelets >1.5 lakhs/mm3 and Urea < 40mg/dl, Creatinine <1.2 mg/dl, Na >130mg/dl, K+ >3.6mg/dl and <5mg/dl, Calcium >9mg/dl and <10.3 mg/dl). Chemotherapy was given with adequate anti emetic measures including dexamethasone, pheniramine, ranitidine, ondansetron, metaclopamide. The toxicities associated with this chemotherapy such as diarrhoea, anaemia, neutropenia, thrombocytopenia were monitored. Blood counts were monitored weekly during radiotherapy and also monitored during chemotherapy cycles and then grading is done. Only maximal toxicity experienced was recorded weekly during radiotherapy and at 3 weeks post chemotherapy during chemotherapy part of the regimen. Corrective measures including delaying treatment were done if any toxicity grade becomes Grade 3 or above and treatment was restarted if the grade falls down to grade 1 or 0.

All the toxicities were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Thermoplastic mould was used for immobilization with patient in supine position and hands overhead. After a fast of 3 to 4 hours, radiotherapy planning CT scan images were taken at 5mm thickness from mid thorax to the bottom of L4 vertebra. Intravenous contrast was used to help contour the lymph nodal groups. Target volumes were contoured as per the institutional protocol.

3D Conformal Radiotherapy was used to treat all the patients. Treatment was delivered on ELEKTA Precise Linear Accelerator with 1.8 Gy per fraction, one fraction per day, 5 days per week. The Clinical target volume was treated till 45Gy/25#/5weeks. All patients were treated using 6MV/15MV photons with antero-posterior parallel opposed and opposed laterals, mono isocentric technique. The 45 Gy of radiation was delivered in 25 fractions, five days per week, to the tumor bed, to the regional nodes, and 2 cm beyond the proximal and distal margins of resection. The tumor bed was defined by preoperative computed tomographic (CT) imaging, and in some instances, surgical clips. Japanese Research Society for Gastric Cancer guidelines were used for the delineation of the lymph nodal areas. Perigastric, celiac, local paraaortic, splenic, hepatoduodenal or hepatic-portal, and pancreaticoduodenal lymph nodes were included in
the radiation fields. When it was necessary to spare the left kidney in patients with antral lesions, splenic nodes were not included. Radiation was delivered with at least 6-MV photons. The dose constraints to organs at risk were defined as per the institutional protocol.

Follow up of the patients were done every month. Follow up visit consisted of a physical exam and further investigations like endoscopy or CT scan as clinically indicated. During the follow up visits if the patient is found to have a clinical/radiological/histological recurrence, he is deemed to have relapsed. Disease free survival is calculated from the date of diagnosis till the date of relapse or last follow up whichever the case may be.

SPSS v16 was used for all statistical analyses. Kaplan meir curves were used to estimate the disease free survival and Log rank test was used to test for significance for disease free survival among sub groups.

Results

A total of 73 patients who were diagnosed to have non metastatic gastric adenocarcinoma were enrolled in this study after gastrectomy with a curative intent. Out of these 73 patients, 1 of the patient expired after the first cycle of chemotherapy because of severe neutropenic sepsis, another patient expired after the first cycle of chemotherapy because of 5-FU induced myocardial infarction. One patient discontinued the treatment in the middle of chemoradiotherapy in view of personal reasons. All the patients were taken for toxicity grading and DFS calculations. The year wise distribution of patients enrolled is shown in Table 1.

Of the 73 patients, 53 were males and 20 were females. Median age of the entire cohort was 54 years with a range of 26 to 71 years. A+ and O+ were the most common blood groups with O+ comprising 33 patients and A+ comprising 24 patients. Pylorus was the most common site of origin with 50 patients falling under this group. All degrees of differentiation were seen but diffusely infiltrating type when seen was slightly more common among females.

54 patients underwent subtotal gastrectomy and 19 underwent total gastrectomy. Except for 2 patients who underwent D0 nodal dissection, remaining underwent either D1/D2 dissections with 65 patients undergoing D1 nodal dissection and 6 patients underwent D2 nodal dissection. Surgery was associated with negative margins in 57 patients whereas 16 patients had positive margins. Lymph vascular invasion was seen in 16 patients whereas perineural invasion was seen in 6 patients. H. pylori organism was identified on light microscopy in 16 patients. 21 patients had T4 disease, 36 patients had T3 disease and 16 patients had T2 disease. When nodal staging was done, 6 patients had N3 disease, 16 patients had N2 disease, 29 patients had N1 disease and 22 patients had N0 disease. AJCC Stage III was seen in 25 patients and Stage II was seen in 42 patients and Stage I was seen in 6 patients.

Maximal incidence of Anemia was 16 patients developing Grade 2 (10 gm % to 8 gm %) toxicity during week 5 of chemoradiotherapy (Graph 1). Maximal incidence of Neutropenia was 25 patients developing Grade 1 (ANC up to 1,500/mm3) toxicity during week 5 of chemoradiotherapy, although 1 patient developed severe neutropenic sepsis and expired as a consequence (Grade 5 Neutropenia) (Graph 2). Maximal incidence of thrombocytopenia was 8 patients developing Grade 2 (50,000 to 75,000/mm3) toxicity during week 5 of chemoradiotherapy (Graph 3). Maximal incidence of diarrhea was 14 patients developing Grade 3 (>7 episodes of loose stools per day, requiring IV fluids) toxicity during week 5 of chemoradiotherapy, although the same patient who had Grade 5 Neutropenia also had Grade 5 Diarrhoea (Graph 4).
Of the 73 patients, 33 patients developed recurrence. All the recurred patients developed systemic metastasis and only one of the 33 patients had a local recurrence also. Liver was the most common site of systemic metastasis with 30 patients developing liver metastasis. The next common site was the lung. Other sites include Brain, Ovary, Left Supraclavicular Lymph node, Bone in decreasing order of occurrence.

Of the 25 patients with stage III disease, 21 developed recurrences with around 50% recurring within 1 year of diagnosis. Only 12 patients of the 42 patients with stage II disease developed recurrences with most of them recurring after 1 year of diagnosis, while none of the patients with stage I disease developed recurrence.

With a Median follow up of 16 months following the diagnosis, the estimated median disease free survival for the entire cohort was 31.6 months (95% CI: 22.24 to 40.96) with a standard error of 4.77 as depicted in Figure 1.

The Estimated median disease free survival for patients with stage III is 15.7 months (95% CI: 11.58 to 19.82) with a standard error of 2.1. The Estimated median disease free survival for patients with stage II is 45.5 months (95% CI: 30.87 to 60.12) with a standard error of 7.46. The same could not be calculated for stage I patients as none of them developed recurrence. Difference in survival was significant for different stages (p<0.0001). Stage wise Kaplan meir survival curves are depicted in Figure 2.

Discussion

This bidirectional observational study included eligible gastric cancer patients enrolled during the study period mentioned above. The results are discussed as below.

When compared to the INT 0116 trial7, where around 53% patients developed grade 3 or higher hematological toxicity and 33% patients had grade 3 or higher diarrhea, only 19% developed grade 3 or higher diarrhea in this study with negligible hematological toxicity. Although the reasons are not clear as to why there is such a difference in toxicity, lesser incidence of Dihydropyrimidine dehydrogenase (DPD) deficiency in our populace8 might be one of the several contributing factors. Epidemiological studies are required to investigate other possible causes. One patient who developed Grade 5 Neutropenia along with Grade 5 diarrhoea immediately after the first cycle of 5 FU-LV probably had severe DPD deficiency. Routine testing for DPD deficiency prior to giving 5 FU is not a standard recommendation and we do not routinely test all the patients prior to prescribing 5 FU in our institute.

When compared to the patients in the INT 0116 trial7 where around 8.2% and in the ARTIST trial9 where around 4.8% had local recurrences, only one patient (0.01%) had local recurrence in this study. Although our study has significantly less number of subjects compared to INT 0116 trial, we feel one possible reason might be because of the possible delays the patients might have had in the INT 0116 and ARTIST trials because of the higher toxicity. Another possible reason could be that, in our study upper GI endoscopy was advised only when the patient had symptoms suggestive of local recurrence.

Around 45% of the patients developed systemic recurrences which is similar to 49% as reported in the updated INT 0116 results.10 Systemic recurrences continue to be a major cause of disease relapse in gastric cancers. Systemic recurrences can be reduced by intensifying chemotherapy as noted in the ARTIST trial9 where around 20.4% had systemic recurrences. Further studies are required which have a longer follow up for estimating a benefit in the overall survival.

MAGIC trial4 of UK is another seminal trial where perioperative chemotherapy was studied. In this study tumors arising from
the distal esophagus were also included. There was a significant OS benefit with a Hazard ratio of 0.75 with relatively lower systemic recurrences of 24% but with relatively higher local recurrences of 14% as compared to INT 0116, ARTIST trials or this study.

INT 0116 trial reported a median disease free survival of 30 months as against an estimated median disease free survival of 31.6 months in this study. The most important limitation of the study is poor follow up. Most of our patients were lost to follow up shortly following the diagnosis of recurrence consequently resulting in a paucity of data regarding deaths. Efforts to collect overall survival data via telephone, postal mail were in vain because of which overall survival could not be calculated. Moreover, symptom based evaluation for recurrences could have potentially underestimated the number of recurrences. The numbers of patients included into the study are also relatively small preventing us from obtaining statistically significant correlations.

D2 dissection rates were low in our study. Although D2 dissection is considered standard now, our surgical team has recently embraced this recommendation. Hence this study which has patients from 2011 onwards has predominantly D1 dissection with most of the 6 patients who underwent D2 dissection were of 2016.

**Conclusion**

Adjuvant concurrent chemoradiotherapy in this study was tolerated well with relatively few side effects. The estimated median survival is 31.6 months.

**References**

In frequent urination, delay of urination, weak stream & terminal dribbling associated with BPH

Veltam Tablets
Tamsulosin MR 0.2 mg & 0.4 mg
The first tablet formulation of Tamsulosin in India

In patients with fast progression of LUTS in BPH

Veltam Plus
Tamsulosin MR 0.4 mg + Dutasteride 0.5 mg Tablets
The smallest size tablet to combat BPH

In patients with slow progression of LUTS in BPH

Veltam F
Tamsulosin MR 0.4 mg + Finasteride 5 mg Tablets
Trust your experience

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

INTAS PHARMACEUTICALS LTD.
Gujarat Centre, O.T. Mahru Bridge, Aslania Road, Ahmedabad 380 052, INDIA

ALERON
Association between QTd, Tp-e/QT Ratio and In-hospital Prognosis in Thrombolysed Acute ST-elevation Myocardial Elevation (STEMI) Patients

G Ravi Kiran¹, K Ramesh², V Chandrashekar³

Abstract

Background: Both QTd and Tp-e/QT ratio have been linked to increased risk for arrhythmia and mortality. But Significance of QTd in STEMI Patients is not documented in all studies and Tp-e/QT ratio is a novel index which is understudied in these patients. Therefore, the present study is aimed to determine the short term, in-hospital prognostic value of QTd and Tp-e/QT ratio in thrombolysed STEMI patients.

Methods: This is a prospective, observational study that includes 321 patients. Relevant clinical data is collected. QTd and Tp-e/QT ratio (tangent method) is calculated from “at admission ECG” just before thrombolysis. Multivariate logistic regression analysis was done to determine the predictors of in-hospital outcomes. A p-value of <0.05 is considered statistically significant.

Results: The mean age of study population was 56.72 ± 11.36 with males:females ratio of 2.73:1. Mean value of QTd and Tp-e/QT ratio were 80.29 ±10.2 ms and 0.28 ± 0.05 respectively. The QTd and Tp-e/QT ratio are found to be independent predictors of in MACE, in addition to absence of beta-blocker therapy at admission, AWMI. Tp-e/QT ratio is independent predictor of in-hospital mortality in addition to reduced LVEF and AWMI. Analysis of the ROC curve demonstrated that the optimal cut-off value for in-hospital outcomes was a Tp-e/QT ratio of ≥0.30.

Conclusion: Both QTd and Tp-e/QT ratio may serve as a prognostic predictors of in hospital MACE independently but only Tp-e/QT ratio predicts patients with in-hospital all cause mortality in thrombolysed STEMI patients.

Editorial Viewpoint

• QTd and Tp-e/QT ratio have been linked to increased risk for arrhythmia and mortality.
• This study finds that Tp-e/QT ratio predicts in hospital all cause mortality in thrombolysed STEMI patients.

Introduction

Acute Myocardial infarction (AMI) represents one of the catastrophic events in the natural history of coronary artery disease (CAD). Despite remarkable advances in the treatment of AMI the occurrence of AMI is associated with substantial early and late mortality. In majority of cases both early (out and in-hospital) and late mortality is attributed to two main sequel of acute coronary occlusion namely pump failure and arrhythmogenesis. Predominant arrhythmic events, attributing to this burden are ventricular arrhythmias namely ventricular tachycardia (VT) and ventricular fibrillation (VF).

Investigators have focused on the electrophysiological characterization of arrhythmogenic substrates in the myocardium of AMI patients, such as QT interval and T wave. These studies have shown clinical promise for predicting malignant arrhythmias and sudden cardiac death (SCD).¹⁻³

Previously many of the contemporary studies gave importance to QT dispersion (QTd) for quantifying the arrhythmogenesis substrate than QT interval because QT interval shows certain degree of inter-lead spatial variability and thus serves as an index of the spatial dispersion of the ventricular recovery times.⁴ Consequently,
QT dispersion is regarded almost a direct measure of the heterogeneity of myocardial repolarization. This QTd is used clinically in many situations. However, not all studies demonstrated this clinical usefulness of QT dispersion, causing it to call as ‘the greatest fallacy in electrocardiography in the 1990s” by few researchers.

Recently, the Interval from the peak to the end of the T wave (Tp-e interval) was used in predicting arrhythmias and sudden cardiac death (SCD) in some cardiac channelopathies. Studies shown that the Tp-e interval may serve as an index of total dispersion of repolarization (transmural, apico-basal, and global). As body weight and heart rate (HR) increases, there is a linear increase in the QT interval and is accompanied by a parallel increase in the Tp-e interval. Hence the Tp-e/QT ratio remains shows consistency within the narrow range of 0.15 to 0.25. A higher Tp-e/QT ratio has been associated with arrhythmic events associated with many clinical conditions.

However, little is known about this index in patients with STEMI undergoing thrombolysis. Therefore, the present study is aimed to evaluate the QTd and Tp-e/QT ratio immediately before thrombolysis in patients with STEMI and to determine their short term prognostic value.

**Methods**

This is a Prospective observational study, that included patients who had been diagnosed with acute STEMI and were treated at Mahatma Gandhi Memorial hospital (MGMH). This is a busy government run tertiary care institution with non-selective intake of acute or emergency patients and is referral centre for more than 1.2 crore population and hence patients with STEMI are redirected to this hospital. This study is carried over a period of 10 months (from January 2016 to October 2016).

**Study population**

This study did not alter the standard care given to the patients in the hospital and the study was approved by the institutional ethics review committee, MGM hospital prior to onset (KIEC/KMC/ MGMH/NCT/2015/10/002). All patients provided written informed consent prior to collection of data, which were obtained interviews conducted by the authors and from hospital records.

**Inclusion Criteria**

(1) History of chest pain at rest or other symptoms suggestive of an ACS with the most recent episode occurring within 24 hours of admission and (2) Electrocardiographic (ECG) changes fulfilling current ECG criteria in the diagnosis of acute STEMI and positive cardiac biomarkers.

**Exclusion Criteria**

(1) ECG was unsuitable for analysis i.e. if at admission ECG shows atrial fibrillation or flutter or had left or right bundle branch block and admission ECG exhibited technical limitations for analysis of QTd or Tp-e interval (<8 evaluable leads, T wave amplitude <2mm, biphasic T wave iso-electric T wave). (2) Active renal or hepatic diseases. (3) Suffering from any chronic infectious/inflammatory diseases. (4) On anti-arrhythmic drugs. (5) Known coronary artery disease (CAD). (6) Known case of valvular heart disease or heart failure. (7) Family history of SCD, HCM. (8) Known case of heart failure. (9) If patients are not thrombolysed and electrolyte imbalances (in particular, potassium and calcium).

**Data acquisition**

Assessment with history, physical examination, anthropometric measurements, biochemical investigations, ECG and 2D echocardiography was performed for every patient included in the study. All the patients were evaluated serially throughout their hospital course to identify complications like need of inotropic support and / or ventilator support, death and
ventricular arrhythmias.

**ECG Recordings and Measurements**

A copy of all the “at admission - Suitable” 12-lead standard ECG recorded at 25 mm/s was obtained and it is digitalized, then this digitalized ECG is uploaded into a computer and were analyzed by a computer based program. (adobe reader DC®, measuring tool) (Figure 1). Observers responsible for data recording were trained prior to the study.

The Tp-e was evaluated only in Leads exhibiting ST-segment elevation at the J point. The QT interval was measured from the onset of the QRS complex to end of T wave (Te) (defined as the point at which the tangent of the maximal down-slope of the descending limb of the T wave crossed the iso-electric baseline). T peak (Tp) is defined as maximal deflection of the T wave.\(^{17-19}\) The Tp-e was calculated from Tp to Te (Figure 1). All measured intervals are expressed as the average of measurements made from 2 or 3 consecutive complexes. 30 randomized ECGs were measured by a second physician to determine inter- and intra-observer variability. QT dispersion (QTd) is calculated as difference between longest and shortest QT interval.

**2.4 Primary endpoints**

The primary end points were the incidence of In-hospital Major adverse Cardiac events (MACE) [includes Heart failure, Cardiogenic Shock, Ventricular tachyarrhythmias namely malignant sustained and non-sustained Ventricular tachycardia (VT) fibrillation (VF)] and death from all causes.

**Statistical Analysis**

Statistical analyses was performed using Medcalc statistical software\(^\text{®}\) (V.16.8.4) and MS Excel 2007 for Windows and Macintosh. Categorical and numerical variables were expressed in percentage and mean (± standard deviation, SD) respectively. Numerical variables were tested with independent samples t-test, and categorical variables were tested using chi-square test. Multivariate logistic regression analysis\(^\text{20}\) was performed to determine the predictors of in-hospital outcomes. This analysis included variables with statistical significance in the univariate logistic regression analysis, and those with a known clinical impact. The statistical significance was considered for a p-value <0.05. Receiver operator characteristic (ROC) curves\(^\text{21}\) were computed for the Repolarization indice (s) to assess the optimal cut-off value to predict in-hospital outcomes. The optimal cut-off value was defined as the value yielding the maximal Youden index (Youden index=b[ sensitivity]+[specificity]−1).\(^\text{22}\)

**Results**

**Demographic and Baseline Characteristics**

539 patients were admitted with diagnosis of STEMI and treated in our hospital during this study period, of which 392 patients underwent thrombolysis with Tenecteplase and after considering inclusion and exclusion criteria 321 patients were included in the study and 71 patients were excluded (41 patients - unsuitable at admission ECG, 8 - Known case of organic valvular lesions, 6 - renal/hepatic disease, 8 - hypo-kalemia, 4 - Hypocalcemia, 3 - Known case of heart failure, 2 - Hyper-kalemia, 1 - on anti-arrhythmic drugs).

The age of patients range from 24 to 81 with a mean of 56.72 ± 11.36 years. The majority of patients, 196 (61.1%) belonged to the age group of 50–69 years, and a further 13.7 % were from the >70 year group, notably 9.6% (31) of patients are <40years. Among the study population males form the predominant subgroup (235, 73.2%) with males : females (M/F) ratio of 2.73:1.

About 39.2% and 34.5% of patients were hypertensive and diabetic respectively. It was found that 99 (30.8%) patients had a habit of alcohol intake and 122 (38%) patients had history of smoking among which 88 patients were current smokers and remaining were past smokers (Table 1).

**Biochemical, Echo-cardiographic and Basic ECG features**

Chest pain was chief complaint in 297 patients (92.5%) and remaining patients have presenting symptom other than chest pain. 231 (71.9%) patients had anterior wall STEMI (Majority have Antero-septal involvement 46.7%) Posterior wall STEMI is seen in only 11 patients (2.8%) and remaining patients have inferior wall STEMI.

Mean ejection fraction (LVEF) of the study population during the index admission was 45.2% . About 68.5% of patients have dyslipidemia. The mean CK-MB at index admission was 111.44 IU/L and quantitative Troponin T was not performed at our unit.

**Medical therapy**

During hospitalization almost all the Thrombolysed patients received dual anti - platelet therapy and a statin. 64.2% patients received nitrates and oral beta blockers were prescribed to 72% of patients during their in-hospital course (Table 2).

**In-Hospital Major adverse events (MACE)**

During hospitalization about 66 (20.5%) patients experienced MACE of which 33 patients had Ventricular tachyarrythmias (sustained and non-sustained) and 58 patients had heart failure. The in-hospital all cause mortality was 5% (Table 2).

**QTd and Tp-e/QT**

The inter-observer and intra-observer coefficients of variation (COV) in calculating these repolarization indices were 2.1% (95% CI: 2.0%-2.3%) and 1.3% (95% CI: 1.2%-1.4%) respectively. Mean value of QTd is 80.29 ± 10.2 ms (ranges from 41.2ms to 196.3ms) and of Tp-e/QT was 0.28 ± 0.05 (ranges from 0.19 to 0.37),
subgroup analysis show that both
these indices were significantly
higher in patients having AWMI,
in patients experiencing MACE and
in patients who died in hospital (p
= <0.01).

In multivariate regression
analysis there is significant
association between absence of
beta-blocker therapy, Increased
QTd, Increased Tp-e/QT ratio,
and MACE (Table 3). Similarly
multivariate regression analysis
show that Anterior wall location of
STEMI, reduced LVEF, and Tp-e/QT
ratio were independent risk factors
for in-hospital all cause mortality
(Table 4). It is notable that though
QTd associated with increased
risk of mortality, in univariate
analysis this is not documented
in multivariate analysis. Hence
Tp-e/QT ratio is associated with
increased risk for both all cause
in-hospital mortality (area under
ROC curve: 0.942, 95% CI: 0.93 - 0.95,
P < 0.001) and MACE (area under
ROC curve: 0.961, 95% CI: 0.98 - 0.95,
P < 0.001) and Tp-e/QT ratio
of 0.30 found to be of optimal
cut-off (Sensitivity = 96.6% and
specificity = 88.6%). The sensitivity
and specificity of a Tp-e/QT ratio
>0.30 for death were 94% and
82.9%, respectively; the sensitivity
and specificity of a Tp-e/QT ratio
>0.30 for MACE were 89.2% and
96.9% respectively (Figure 2).

Discussion
The mean age of study
population was 56.72 ± 11.36 years
this is consistent with mean age of
ACS in Indian population (56.3
years). 23 39.6% and 34% of patients
were hypertensive and diabetic
respectively. Similar proportion
of prevalence of hypertension
(30%-40%) and diabetes (30%-40%)
in STEMI is reported in other recent
Indian studies. 24-26

Majority have AWMI (65.2%).
All patients received aspirin,
clopidogrel, and a statin. Our use
of aspirin and clopidogrel seems
to be more than satisfactory and
compares well with other studies of
the developing world in general. 27

Table 1: Demographic, clinical and
biochemical data

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>235 (73.2%)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>31 (9.6%)</td>
</tr>
<tr>
<td>40-49 years</td>
<td>50 (15.6%)</td>
</tr>
<tr>
<td>50-69 years</td>
<td>196 (61.1%)</td>
</tr>
<tr>
<td>≥70 years</td>
<td>44 (13.7%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>111 (34.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>126 (39.2%)</td>
</tr>
<tr>
<td>Alcohol habit</td>
<td>99 (30.8%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>122 (38%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>88 (27.4%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>220 (68.5%)</td>
</tr>
</tbody>
</table>

Table 2: Electrocardiographic,
echocardiographic data and
in-hospital management and
outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT dispersion (QTd)</td>
<td>80.29 ± 10.2 ms</td>
</tr>
<tr>
<td>Tp-e/QT ratio</td>
<td>0.28 ± 0.05</td>
</tr>
<tr>
<td>LVEF</td>
<td>45.2 ± 10.3 %</td>
</tr>
<tr>
<td>In-Hospital stay</td>
<td>7.4 ± 2.1 days</td>
</tr>
<tr>
<td>MACE*</td>
<td>66 (20.5%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>58 (18.1%)</td>
</tr>
<tr>
<td>VT/VF</td>
<td>33 (10.3%)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>27 (8.4%)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>16 (5%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>319 (99.4%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>314 (97.8%)</td>
</tr>
<tr>
<td>Statin</td>
<td>321 (100%)</td>
</tr>
<tr>
<td>Oral β-blockers</td>
<td>231 (72%)</td>
</tr>
<tr>
<td>ACEI</td>
<td>241 (75.1%)</td>
</tr>
</tbody>
</table>

*NR: Not received

Table 3: Multivariate regression
analysis for in-hospital MACE

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI (AWMI = 1)</td>
<td>2.015 (1.059-8.314)</td>
<td>0.002</td>
</tr>
<tr>
<td>β-blocker therapy (NR= 1)</td>
<td>1.949 (0.097-6.260)</td>
<td>0.017</td>
</tr>
<tr>
<td>QTd</td>
<td>2.332 (1.103-5.608)</td>
<td>0.005</td>
</tr>
<tr>
<td>Tp-e/QT</td>
<td>4.938 (2.862-13.553)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.704 (0.593-0.903)</td>
<td>0.059</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.881 (1.041-3.001)</td>
<td>0.073</td>
</tr>
</tbody>
</table>

Table 4: Multivariate regression
analysis for in-hospital death

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI (AWMI = 1)</td>
<td>3.015 (2.059-13.314)</td>
<td>0.024</td>
</tr>
<tr>
<td>β-blocker therapy (NR= 1)</td>
<td>1.141 (0.492-2.160)</td>
<td>0.055</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.981 (0.504-2.001)</td>
<td>0.066</td>
</tr>
<tr>
<td>QTd</td>
<td>1.010 (0.932-1.094)</td>
<td>0.8019</td>
</tr>
<tr>
<td>Tp-e/QT</td>
<td>2.818 (1.081-6.508)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.804 (0.693-0.933)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*1 patient may experience > 1 MACE VT/
VF: Ventricular tachycardia/fibrillation

Fig. 2: Receiver operating characteristic (ROC) curves of the Tp-e/QT ratio
An ACE inhibitor was administered to over 75% of patients, ACCESS investigators who studied over 11,000 patients with ACS in the developing world reported the use of ACEIs to be 68%. 72% of patients received beta blockers, compared with 78% in other developing countries.

Although studies of the Tp-e/QT ratio have been performed in the context of specific channelopathies and some organic heart diseases, the current study is novel in its investigation of its association with short term prognosis in STEMI patients. There were many studies directly evaluating the prognostic role of QTd in this population however there were no studies to our knowledge which directly compared QTd and Tp-e/QT ratio and evaluated their prognostic role in patients with STEMI undergoing thrombolysis.

Mean value of QTd in our study population is 80.29±10.23 ms, Even QTd is significantly higher in AWMI patients, in patients experiencing MACE and who died in hospital (Figure 3) similar to other studies. There is a wide variation in studies on mean value of QTd because of methods employed in calculation of end of T wave and also on because of variations in proportion of site of AMI (anterior vs. inferior). However all studies demonstrate that QTd is significantly increased in patients with acute myocardial infarction (STEMI).

The Tp-e/QT ratio is a relatively new index of ventricular repolarization that remains constant despite dynamic changes in heart rate, thus allowing comparison of patient data. Studies have described the utility of the Tp-e/QT ratio as an arrhythmogenic index in a variety of cardiac conditions.

Shu.et.al evaluated 120 patients with STEMI and reported that the Tp-e/QT ratio was significantly elevated in those who suffered malignant ventricular arrhythmias as compared with those who did not experience these events (0.32 ± 0.07 vs 0.26 ± 0.05, P < 0.001). However no information was provided neither on type of reperfusion strategy used in the study (PCI or thrombolytic therapy) nor on the onset period for these malignant ventricular arrhythmia after diagnosis of STEMI was made, even association with mortality and optimal cut-off of Tp-e/QT was not eluded.

Mean value of Tp-e/QT in our study population is 0.28±0.05. Even this ratio is significantly higher in AWMI patients, in patients experiencing MACE and who died in hospital (p<0.01). In study done by Xio.WT et. al found that Tp-e/QT ratio>0.25 before thrombolysis independently predicts patients suffering MACE within 30 days but its association with in-hospital events in not evaluated.

In recently conducted investigation by Mugnai G et. al the Tp-e/QT ratio of >0.31 was found to be an independent predictor of both in-hospital malignant VA and mortality, this study, however included patients presenting with anterior wall STEMI only and used PCI as reperfusion strategy. In contrast, the current study included patients with all types of STEMI undergoing thrombolysis and established precise observational end points during hospitalization. In addition independent prognostic role of Tp-e/QT is demonstrated and compared directly with QTd.

This study clearly demonstrates the applicability of the Tp-e/QT ratio as a important clinical index of in-hospital MACE and mortality in thrombolysed STEMI patients. Its similar applicability in variety of other cardiac conditions, such as heart failure and chronic MI, remains to be examined.

**Study Limitations**

The current study was a single-centre study, that necessitate confirmation in larger multicenter trials. Furthermore, the indexes in patients with STEMI were only calculated and no measurement in healthy subjects was made. Thus, no information for comparison between these groups exists, which may be useful in future studies.

**Conclusion**

In Thrombolysed STEMI patients, QTd serves as independent risk
factor for in-hospital MACE but not death, whereas Tp-e/QT ratio serve as a useful tool in predicting the patients at high risk of suffering both in- hospital mortality and MACE. More extensive studies should be carried out, to fully standardize its prognostic value for general clinical application.

Acknowledgments

We acknowledge the contributions of the staff of department of cardiology, MGM hospital and also study participants for their co-operation in data collection and analysis.

References


17. Galen S, Wagner MD, David G. Strauss MD PhD, Marriott's practical electrophysiology 12th Ed.


Pulmonary and Ear, Nose and Throat (ENT) Involvement in ANCA-Associated Vasculitis at Diagnosis—Experience from a Tertiary Care Centre in North India

Aman Sharma¹, Arjun Lakshman², Ram V Nampoothiri², Roshan Verma¹, Manish Rathi¹, Godasi SRSNK Naidu², Benzeeta Pinto², Kusum Sharma³, Varun Dhir⁴, Ritambhra Nada³, Ranjana Minz³, Naresh Panda³, Sanjay Jain³

Abstract

Background and Aims: There is paucity of data on pulmonary and ENT involvement in ANCA-associated vasculitis from India. We aimed to review the pattern of lung and upper respiratory tract involvement in patients with AAV diagnosed at our centre.

Methods: A retrospective review of all AAV patients between January 2007 and June 2014 was done. A complete clinical evaluation for Pulmonary and ENT involvement was done. Advanced investigations including computed tomography (CT) bronchoscopy and nasal endoscopy were done when indicated. Proportion of involvement was noted and different variables among patient groups were compared.

Results: 92 patients (median age 42 years; 60% female) of AAV were included. Clinical and/or radiological evidence of lung involvement was seen in 70 (76.1%) patients. Diffuse alveolar haemorrhage was present in 6 (60%) patients with MPA and 7 (10.1%) patients with GPA (p=0.002). ENT involvement was present in 55 (59.8%) patients and was more in GPA (p=0.000). Absence of renal involvement [p=0.047] and absence of GI involvement [p=0.012] were associated with ENT involvement in GPA.

Conclusions: Pulmonary involvement was common in GPA, MPA and CSS, ENT involvement was almost characteristic of GPA. DAH was common in MPA. Population based and multicentre studies are needed to assess the true burden of organ involvement in AAV in the Indian population.

Introduction

ANCA associated vasculitis (AAV) is an umbrella term which encompasses the three primary systemic vasculitides viz. granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA), united by their predilection to involve small-sized blood vessels of the body and presence in blood of anti-neutrophil cytoplasmic antibodies (ANCAs). However, they differ markedly with respect to their epidemiology, possibly pathogenesis and genetic predisposition, and involvement of major organ systems. Microvascular inflammation, the uniting pathological hallmark

Editorial Viewpoint

• This is a large study of a relatively uncommon ANCA-associated vasculitis (AAV) which has myriad manifestations.
• Pulmonary manifestations are most common in all the forms of AAV.
• ENT involvement was characteristic of granulomatosis with polyangiitis (GPA).

causes tissue infarction and resultant dysfunction, leading to morbidity and mortality. AAV is a group of rare diseases with estimated incidence of up to 20 cases per million population per year from European studies. In Europe, GPA is more common while in Japan and Kuwait, the incidence of MPA is very high. Absence of proper epidemiological studies or a vasculitis registry, rarity of AAV and the difficulty in making a diagnosis renders the true morbidity and mortality burden of AAV in India unknown.
blood vessels make the pulmonary parenchyma and the upper respiratory mucosa common anatomical areas involved in AAV. While pulmonary manifestations can range from asymptomatic radiographic abnormalities to life threatening manifestations like diffuse alveolar haemorrhage (DAH), ear, nose and throat (ENT) involvement can be debilitating and sometimes disfiguring.\(^4,5\) Pulmonary involvement in AAV at diagnosis is associated with increased disease activity on follow-up, despite improved overall survival due to use of systemic immunosuppressive therapy.\(^6\) We have previously published the outcomes of patients with AAV seen at our center.\(^7-11\) Apart from a few series on lung involvement in GPA, data from India on pulmonary and ENT involvement in AAV is lacking.\(^12,13\) We aimed to retrospectively review the pattern of lung and upper respiratory tract involvement in patients with AAV diagnosed at our centre, a tertiary care teaching hospital in North India.

**Methods**

We conducted a retrospective review of all patients diagnosed with AAV between January 2007 and June 2014 in the Rheumatology and Clinical Immunology wing, department of Internal Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. At diagnosis, all patients underwent comprehensive evaluation with clinical history, physical examination, complete blood count, biochemical investigations and testing for hepatitis B and hepatitis C. A plain chest film and x-ray of paranasal sinuses were done in all patients. Advanced investigations including computed tomography (CT) scan of chest, abdomen and paranasal sinuses, bronchoscopy and nasal endoscopy were done when clinically indicated. A complete clinical evaluation of ENT was done at diagnosis in all patients. A biopsy was obtained from feasible lesion to establish a tissue diagnosis whenever possible. Classification into each type of vasculitis in each patient was made according to Chapel Hill consensus classification criteria.\(^14\) One patient who was classified as EGPA did not have bronchial asthma at diagnosis, though she had cough, eosinophilia, histological proof for eosinophilic vasculitis and MPO ANCA positivity. She was treated as EGPA. Disease activity at diagnosis was calculated using the Birmingham Vasculitis activity Score (BVAS) version 3. Diffuse alveolar haemorrhage (DAH) was diagnosed in patients presenting with hemoptyis, hemoglobin drop and characteristic shadows on CT scan of chest and was confirmed whenever possible by bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy.

At our centre, testing for anti-neutrophil cytoplasmic antibodies (ANCA) were done by indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA) methods. ELISA assay was done for proteinase 3 (PR3) and myeloperoxidase (MPO) using commercially available kits (EURO DIAGNOSTICA).

All quantitative variables were summarised as medians and qualitative variables were summarised as proportions. Difference in quantitative variables and qualitative variables among patient groups were tested using appropriate statistical tests. Variables with a significance level of 0.25 or less in univariate analysis were included as independent variables in logistic regression models. A two-sided p-value <0.05 was considered significant for all tests. Statistical analysis was done using IBM SPSS Statistic version 22.0 (Chicago, IL). The study was cleared by the ethics committee of the institute.

**Results**

A total of 92 patients were included in the study. Baseline clinical and laboratory characteristics and organ system involvement and distribution of patients according to different types of vasculitis is shown in Table 1. Median age at diagnosis was 42 years. Median age at diagnosis for MPA was high (55 years) when compared to other forms of vasculitis. Overall, 60% of patients were women. CSS (75.0%) showed a clear female predilection though the difference between groups was not statistically significant. The median BVAS at diagnosis was 18 (range, 4-41) and was similar in the three subgroups. Testing for ANCA by IIF and ELISA were available in 89 and 58 patients respectively. c-ANCA was commonly positive in patients with GPA (80.6%) while p-ANCA were common in patients with CSS and MPA (75% and 85.7% respectively) and the difference was statistically significant (p=0.000). Similarly, PR3 positivity was seen in 88.9% patients with GPA while, 100% patients with CSS and 91.7% patients with MPA had anti-MPO positivity (p=0.000).

A histopathological examination of tissue sample was performed in 60 (64.5%) of patients. More than one anatomical site was biopsied in 13 (14.1%) patients. Renal biopsy was obtained in 16 (17.4%) patients. Skin, lung and, nose and PNS biopsies was obtained in 19 (20.7%), 14 (15.2) and 13 (14.1) patients respectively including 3 (3.3%) patients who underwent an open lung biopsy. Seven (7.6%) patients had nerve biopsy. One patient each had biopsy samples from tongue, pleura, prostate mass and orbital mass. Two patients had histological examination on surgical resection specimens- one of small bowel and the other of pituitary mass lesion. One patient with GPA who died underwent post-mortem examination.

Renal involvement was most
### Table 1: Clinical and laboratory characteristics of the study population and organ involvement at diagnosis according to the type of vasculitis (n=92)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=92)</th>
<th>Granulomatosis with polyangiitis (n=69, 75.7%)</th>
<th>Eosinophilic granulomatosis with polyangiitis (n=8, 8.7%)</th>
<th>Microscopic polyangiitis (n=15, 16.3%)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>42 (16-70)</td>
<td>40 (16-68)</td>
<td>40 (25-70)</td>
<td>55 (38-70)</td>
<td>0.005</td>
</tr>
<tr>
<td>BVAS, median (range)</td>
<td>18 (4-41)</td>
<td>17 (4-41)</td>
<td>18.5 (4-29)</td>
<td>19 (12-29)</td>
<td>0.767</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>55 (59.8)</td>
<td>39 (56.5)</td>
<td>6 (75.0)</td>
<td>10 (66.7)</td>
<td>0.584</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (16.3)</td>
<td>10 (14.5)</td>
<td>0 (0)</td>
<td>5 (33.3)</td>
<td>0.089</td>
</tr>
<tr>
<td>T2DM</td>
<td>8 (8.7)</td>
<td>5 (7.2)</td>
<td>0 (0)</td>
<td>3 (20.0)</td>
<td>0.247</td>
</tr>
<tr>
<td>Cardiac comorbidity</td>
<td>1 (1.1)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coexisting CTD</td>
<td>1 (1.1)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>7 (7.6)</td>
<td>0 (0)</td>
<td>7 (87.5)</td>
<td>0 (0)</td>
<td>0.000</td>
</tr>
<tr>
<td>HBsAg positive (n=60)</td>
<td>1 (1.7)</td>
<td>1 (2.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>ANCA by IIF (n=89)</td>
<td>54 (60.7)</td>
<td>54 (80.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.000</td>
</tr>
<tr>
<td>C-ANCA</td>
<td>4 (18.2)</td>
<td>4 (23.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.674</td>
</tr>
<tr>
<td>PR3</td>
<td>39 (67.2)</td>
<td>40 (88.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.000</td>
</tr>
<tr>
<td>MPO</td>
<td>17 (29.3)</td>
<td>4 (9.1)</td>
<td>2 (100.0)</td>
<td>11 (91.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>Negative</td>
<td>2 (3.4)</td>
<td>1 (2.3)</td>
<td>0 (0)</td>
<td>1 (8.3)</td>
<td>0.674</td>
</tr>
<tr>
<td>ANA positive (n=74)</td>
<td>4 (5.4)</td>
<td>1 (1.4)</td>
<td>1 (20.0)</td>
<td>2 (14.3)</td>
<td>0.061</td>
</tr>
<tr>
<td>Positive CRP (n=10)</td>
<td>9 (90.0)</td>
<td>8 (88.9)</td>
<td>0 (0)</td>
<td>1 (100.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Renal involvement at presentation</td>
<td>46 (50)</td>
<td>31 (44.9)</td>
<td>3 (37.5)</td>
<td>12 (80.0)</td>
<td>0.030</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>70 (76.1)</td>
<td>52 (75.3)</td>
<td>8 (100.0)</td>
<td>10 (66.7)</td>
<td>0.227</td>
</tr>
<tr>
<td>ENT involvement</td>
<td>55 (59.8)</td>
<td>52 (75.3)</td>
<td>1 (12.5)</td>
<td>2 (13.3)</td>
<td>0.000</td>
</tr>
<tr>
<td>MSK involvement</td>
<td>41 (44.6)</td>
<td>31 (44.9)</td>
<td>1 (12.5)</td>
<td>9 (60.0)</td>
<td>0.094</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (2.2)</td>
<td>2 (2.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>32 (34.8)</td>
<td>24 (34.8)</td>
<td>1 (12.5)</td>
<td>7 (46.7)</td>
<td>0.291</td>
</tr>
<tr>
<td>Arthritis</td>
<td>8 (8.7)</td>
<td>6 (8.7)</td>
<td>0 (0)</td>
<td>2 (13.3)</td>
<td>0.669</td>
</tr>
<tr>
<td>Cutaneous involvement</td>
<td>38 (41.3)</td>
<td>29 (42)</td>
<td>6 (75.0)</td>
<td>3 (20)</td>
<td>0.045</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>52 (56.5)</td>
<td>41 (59.4)</td>
<td>0 (0)</td>
<td>11 (73.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fever</td>
<td>49 (53.3)</td>
<td>38 (55.1)</td>
<td>0 (0)</td>
<td>11 (73.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>8 (8.7)</td>
<td>6 (8.7)</td>
<td>0 (0)</td>
<td>2 (13.3)</td>
<td>0.669</td>
</tr>
<tr>
<td>Loss of weight</td>
<td>15 (16.3)</td>
<td>12 (17.4)</td>
<td>0 (0)</td>
<td>3 (20)</td>
<td>0.502</td>
</tr>
<tr>
<td>Gastrointestinal involvement</td>
<td>11 (11.8)</td>
<td>10 (14.5)</td>
<td>0 (0)</td>
<td>1 (6.7)</td>
<td>0.630</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>5 (5.4)</td>
<td>4 (5.8)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
<td>0.502</td>
</tr>
<tr>
<td>Digital gangrene</td>
<td>1 (1.1)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>VTE</td>
<td>5 (5.4)</td>
<td>3 (4.3)</td>
<td>0 (0)</td>
<td>2 (13.3)</td>
<td>0.235</td>
</tr>
<tr>
<td>Genitourinary involvement</td>
<td>2 (2.2)</td>
<td>2 (2.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Testicular involvement</td>
<td>1 (1.1)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Prostatic mass</td>
<td>1 (1.1)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td>25 (27.2)</td>
<td>24 (34.8)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>36 (39.1)</td>
<td>24 (34.8)</td>
<td>7 (87.5)</td>
<td>5 (33.3)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

*p-value for Kruskall Wallis test for age and vasculitis index, and Fischer’s exact test for all other parameters. ANA- anti-nuclear antibody, ANCA- anti-neutrophil cytoplasmic antibody, BVAS- Birmingham Vasculitis Activity Score, CRP- c-reactive protein, CTD- connective tissue disease, EGPA- eosinophilic granulomatosis with polyangiitis, GPA- granulomatosis with polyangiitis, HBsAg- hepatitis B surface antigen, MPA- microscopic polyangiitis, MPO-myeloperoxidase, MSK- musculoskeletal, PRE- proteinase-3, T2DM- type 2 diabetes mellitus, VTE- venous thromboembolism.

Overall, clinical and/or radiological evidence of lung involvement was seen in 70 (76.1%) patients of AAV. Lung involvement was present in all patients with CSS and 75.4% and 66.7% patients with GPA and MPA respectively, though this difference was not statistically significant (p=0.227). The clinico-radiological pattern of involvement in patients is shown in Table 2. Pulmonary symptoms were present in 57 (62%) patients overall. Common pulmonary symptoms were shortness of breath, cough and hemoptysis occurring in 36 (39.1%), 29 (31.5%) and 27 (29.3%) patients respectively. Shortness of breath was most common among patients with MPA occurring in 9 out of 10 (90%) patients (p=0.025). Wheezing was exclusive to patients with CSS, occurring in 37.5% patients (p=0.001). Symptom complex suggestive of bronchial asthma were encountered in 7 (87.5%) patients with CSS (p=0.000). Clinico-radiological findings suggestive of diffuse alveolar haemorrhage were present in 6 (60%) patients with MPA and 7 (10.1%) patients with GPA (p=0.002). One patient with GPA had bronchial stenosis at diagnosis.

Overall, a CT scan of chest was available at diagnosis in 69 patients. The radiological abnormalities identified are shown in Table 3. 50 (98.0%), 8 (80%) and 3 (37.5%) patients with GPA, MPA and CSS respectively had an abnormal CT scan (p=0.000). The most common findings on CT scan were pulmonary...
The occurrence of pulmonary, ENT or renal involvement did not differ between GPA patients with c-ANCA or p-ANCA positivity as shown in Table 5. We analysed the association between clinical and laboratory characteristics and pulmonary and ENT involvement in patients with GPA. The details of the analysis are shown in Table 5. On univariate analysis, presence of constitutional symptoms (p=0.002) was the only factor which showed significant association with pulmonary involvement at diagnosis. Binary logistic

Simultaneous upper and lower respiratory tract affection was found in 39 (42.4%) patients overall. These included 38 (55%), 0 (0%) and 1 (12.5%) patients with GPA, MPA and CSS respectively (p=0.000). Fourteen (20.3%) patients each with GPA had either ENT or pulmonary involvement alone without the other. Coexistent pulmonary and renal involvement at presentation was identified in 34 (37%) patients overall. This was most common in MPA seen in 9 (60%) patients and in 22 (31.9%) and 3 (37.5%) patients with GPA and CSS respectively (p=0.123). Renal involvement and DAH was present in a total of 10 (10.9%) patients which included 5 patients each with GPA (7.2%) and MPA (33.3%). No patient with EGPA had this presentation. Coexistent ENT and renal involvement was seen in 19 (20.6%) patients. Eighteen (26.1%) patients with GPA, 1 patient (6.7%) with MPA and no patient with CSS had simultaneous renal and ENT involvement (p=0.072).

The occurrence of pulmonary, ENT or renal involvement did not differ between GPA patients with c-ANCA or p-ANCA positivity as shown in Table 5. We analysed the association between clinical and laboratory characteristics and pulmonary and ENT involvement in patients with GPA. The details of the analysis are shown in Table 5. On univariate analysis, presence of constitutional symptoms (p=0.002) was the only factor which showed significant association with pulmonary involvement at diagnosis. Binary logistic
Table 4: Ear, nose and throat (ENT) involvement in patients with ANCA-associated vasculitis (n=92)

<table>
<thead>
<tr>
<th>Upper respiratory tract involvement</th>
<th>Total (n=92)</th>
<th>Granulomatosis with polyangitis (n=69)</th>
<th>Eosinophilic granulomatosis with polyangitis (n=8)</th>
<th>Microscopic polyangitis (n=15)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose and PNS involvement</td>
<td>48 (52.2)</td>
<td>45 (65.2)</td>
<td>1 (12.5)</td>
<td>2 (13.3)</td>
<td>0.000</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>28 (30.4)</td>
<td>27 (39.1)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>25 (27.2)</td>
<td>25 (36.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>20 (21.7)</td>
<td>18 (26.1)</td>
<td>1 (12.5)</td>
<td>1 (6.7)</td>
<td>0.256</td>
</tr>
<tr>
<td>Nasal crusting</td>
<td>9 (9.8)</td>
<td>9 (13.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.379</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>8 (8.7)</td>
<td>7 (10.1)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
<td>0.434</td>
</tr>
<tr>
<td>Saddle nose</td>
<td>4 (4.3)</td>
<td>4 (5.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Nasal polyps</td>
<td>3 (3.3)</td>
<td>2 (2.9)</td>
<td>0 (0)</td>
<td>1 (6.7)</td>
<td>0.578</td>
</tr>
<tr>
<td>Nasal ulcers</td>
<td>2 (2.2)</td>
<td>2 (2.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ear involvement</td>
<td>17 (18.5)</td>
<td>17 (24.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.024</td>
</tr>
<tr>
<td>Suppurative otitis media</td>
<td>13 (14.1)</td>
<td>13 (18.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.061</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>14 (15.2)</td>
<td>14 (20.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.061</td>
</tr>
<tr>
<td>Conductive</td>
<td>4 (4.3)</td>
<td>4 (5.8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sensorineural</td>
<td>3 (3.3)</td>
<td>3 (4.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mixed</td>
<td>7 (7.6)</td>
<td>7 (10.1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subglottic stenosis</td>
<td>1 (1.1)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*p-value for Fisher’s exact test.

Table 5: Comparison of pulmonary, ear, nose and throat (ENT), and renal involvement at diagnosis in patients with granulomatosis with polyangitis (GPA) according to ANCA type

<table>
<thead>
<tr>
<th></th>
<th>c-ANCA (n=54)</th>
<th>p-ANCA (n=5)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary involvement</td>
<td>40 (74.1)</td>
<td>4 (80.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Abnormal CT scan of chest (n=49)</td>
<td>38 (97.4)</td>
<td>4 (100.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>ENT involvement</td>
<td>39 (72.2)</td>
<td>5 (100.0)</td>
<td>0.318</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>25 (46.3)</td>
<td>4 (80.0)</td>
<td>0.188</td>
</tr>
</tbody>
</table>

*p-value for Fisher’s exact test

A regression analysis was done with presence of constitutional symptoms and female gender (p=0.172) as independent variables and pulmonary involvement as dependant variable. The model was significant with chi-square= 11.56 (p=0.003) and Nagelkerke R-square= 0.224. Presence of constitutional symptoms was associated with pulmonary involvement [p=0.004, OR 5.91 (95%CI= 1.77-19.74)] while female gender did not show significant association [p=0.304; OR= 0.519 (95% CI=0.15-1.81)]. Similarly, absence of renal involvement at presentation (p=0.032) and absence gastrointestinal involvement (p=0.015) showed significant association with ENT involvement in GPA at diagnosis. With the above variables, and absence of musculoskeletal involvement (p=0.108), absence of ocular involvement (p=0.085), absence of genitourinary involvement (0.063) and neurological involvement (p=0.085) as independent variables and ENT involvement as dependant variable, we performed binary logistic regression analysis. The model was significant with chi-square= 22.67 (p=0.004) and Nagelkerke R-square= 0.407.

Absence of renal involvement at diagnosis [p=0.047 and OR=4.22 (95%CI= 1.02-17.50)] and absence of GI involvement [p=0.012 and OR= 9.30 (95%CI= 1.64-52.71)] were associated with ENT involvement in GPA (Table 6).

Univariate analysis for patient characteristics associated with pulmonary involvement in MPA and CSS (n=23) revealed significant association with higher vasculitis index at presentation (p=0.009). The results of the analysis are shown in Table 7. We did not attempt a regression analysis on this subset as the sample size was small. Also, we did not analyse the characteristics associated with ENT involvement in MPA and CSS as only 2 out of 23 patients had ENT involvement.

**Discussion**

GPA, MPA and EGPA have pulmonary and upper respiratory tract manifestations which have been well characterised. We present the results of a single centre retrospective review from a tertiary care centre in North-west India. Out of 92 patients in our series, 69 had GPA and only 8 and 15 patients had CSS and MPA respectively. Overall, 75.1% of all patients with AAV had pulmonary involvement in our series. These included 75.4% patients with GPA, 100% patients with EGPA and 66.7% patients with MPA. DAH was most common in MPA. An abnormal CT scan of chest was more likely to be encountered in GPA and MPA compared to CSS. ENT involvement was more likely in GPA than the other two AAV subgroups.

In a large series of patients with GPA which included 158 patients, 45% patients had pulmonary involvement at presentation. Cough (19%), hemoptysis (12%) and pleurisy (10%) were the most common symptoms at diagnosis. In two small series published before from India, pulmonary involvement was present in 84-94% patients. In our series, 74% patients had pulmonary involvement at diagnosis. Symptoms pertaining to pulmonary involvement were present in about 58% patients at diagnosis. Shortness of breath and cough occurring in a little over 30% patients were the most common symptoms. Hemoptysis was present in about 28% patients.
Table 6: Association between pulmonary and upper respiratory tract involvement and patient characteristics and other organ involvement in patients with granulomatosis with polyangiitis (GPA) (n=69)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pulmo (+) (n=52)</th>
<th>Pulmo (-) (n=17)</th>
<th>p-value*</th>
<th>ENT (+) (n=51)</th>
<th>ENT (-) (n=18)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40 (17-68)</td>
<td>46 (16-67)</td>
<td>1.000</td>
<td>38 (16-68)</td>
<td>41 (20-67)</td>
<td>0.330</td>
</tr>
<tr>
<td>Vasculitis index</td>
<td>17.5 (6-41)</td>
<td>16 (4-34)</td>
<td>0.472</td>
<td>18 (4-38)</td>
<td>17 (6-41)</td>
<td>0.893</td>
</tr>
<tr>
<td>Female gender</td>
<td>27 (51.9)</td>
<td>12 (70.6)</td>
<td>0.172</td>
<td>31 (60.8)</td>
<td>8 (44.4)</td>
<td>0.272</td>
</tr>
<tr>
<td>ANCA type (n=68)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-ANCA</td>
<td>40 (80.0)</td>
<td>14 (82.3)</td>
<td>1.000</td>
<td>39 (78)</td>
<td>15 (88.2)</td>
<td>0.500</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>4 (8)</td>
<td>1 (5.9)</td>
<td>0.787</td>
<td>5 (10)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>6 (12.0)</td>
<td>2 (11.8)</td>
<td>0.784</td>
<td>6 (12)</td>
<td>2 (11.8)</td>
<td>0.108</td>
</tr>
<tr>
<td>ANCA by ELISA (n=45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1 (3.1)</td>
<td>0 (0)</td>
<td>1.000</td>
<td>1 (3.2)</td>
<td>0 (0)</td>
<td>0.504</td>
</tr>
<tr>
<td>PR3</td>
<td>28 (87.5)</td>
<td>11 (91.6)</td>
<td>0.002</td>
<td>26 (83.8)</td>
<td>13 (100)</td>
<td></td>
</tr>
<tr>
<td>MPO</td>
<td>3 (9.4)</td>
<td>1 (8.3)</td>
<td>1.000</td>
<td>4 (12.9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>ANA positivity (n=56)</td>
<td>1 (2.5)</td>
<td>0 (0)</td>
<td>0.002</td>
<td>1 (2.6)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Renal involvement at presentation</td>
<td>22 (42.3)</td>
<td>9 (52.9)</td>
<td>0.594</td>
<td>19 (37.2)</td>
<td>12 (66.7)</td>
<td>0.032</td>
</tr>
<tr>
<td>MSK involvement</td>
<td>24 (46.2)</td>
<td>7 (41.2)</td>
<td>0.784</td>
<td>20 (39.2)</td>
<td>11 (61.1)</td>
<td>0.108</td>
</tr>
<tr>
<td>Cutaneous involvement</td>
<td>21 (40.4)</td>
<td>8 (47.1)</td>
<td>0.787</td>
<td>20 (39.2)</td>
<td>9 (50.0)</td>
<td>0.418</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>37 (71.2)</td>
<td>4 (23.5)</td>
<td>0.002</td>
<td>30 (58.8)</td>
<td>11 (61.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Fever</td>
<td>34 (65.4)</td>
<td>4 (23.5)</td>
<td>0.012</td>
<td>28 (54.9)</td>
<td>10 (55.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Gastrointestinal involvement</td>
<td>7 (13.5)</td>
<td>3 (17.6)</td>
<td>0.710</td>
<td>4 (7.8)</td>
<td>6 (33.3)</td>
<td>0.015</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>3 (5.8)</td>
<td>1 (5.9)</td>
<td>1.000</td>
<td>2 (3.9)</td>
<td>2 (11.1)</td>
<td>0.271</td>
</tr>
<tr>
<td>Digital gangrene</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>1.000</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>VTE</td>
<td>2 (3.8)</td>
<td>1 (5.8)</td>
<td>1.000</td>
<td>2 (3.8)</td>
<td>1 (5.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td>17 (32.7)</td>
<td>7 (41.2)</td>
<td>0.403</td>
<td>21 (41.17)</td>
<td>3 (16.7)</td>
<td>0.085</td>
</tr>
<tr>
<td>Genitourinary involvement</td>
<td>2 (3.8)</td>
<td>0 (0)</td>
<td>1.000</td>
<td>0 (0)</td>
<td>2 (11.1)</td>
<td>0.063</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>17 (32.7)</td>
<td>7 (41.2)</td>
<td>0.403</td>
<td>21 (41.12)</td>
<td>3 (16.7)</td>
<td>0.085</td>
</tr>
</tbody>
</table>

*p-value for Mann-Whitney U-test for age and vasculitis index, and Fisher's exact test for all other variables. ANA- anti-nuclear antibody, ANCA- anti-neutrophil cytoplasmic antibody, ELISA- enzyme linked immunosorbent assay, ENT (+/-): ENT involvement present/absent, MSK- musculoskeletal, MPO- myeloperoxidase, PR3- proteinase-3, Pulmo(+/-): pulmonary involvement present/absent and VTE- venous thromboembolism.

and chest pain in only 4.3% patients. Presence of symptoms and pulmonary involvement in slightly higher percentage of patients in our series compared to Western series may represent an advanced stage of disease at presentation due to delay in diagnosis.

Most common abnormalities noted on CT scan of chest in GPA were parenchymal nodules followed by consolidation and ground glass opacities. Previous series from India, though included only chest x-ray have noted similar findings.12,13 Many series show similar findings with multiple nodules being the most common findings in CT scan of chest. These nodules were predominantly subpleural and diffuse.16–20 Multiple cavitating nodules were also common, while large cavities were rare.18 In our series, 7.8% patients had large cavities with air-fluid level identified on chest CT scan. Bronchiectasis and bronchial wall thickening which have been documented previously in GPA were not seen in our patients.17,19 Occurrence of pleural effusion was slightly lower than the reported prevalence of 13-15%.17,19

Constitutional symptoms such as fever and weight loss are reported to occur in 23% and 15% patients of GPA respectively at diagnosis.15 In our series, fever, loss of weight and loss of appetite were present approximately in 55%, 17% and 9% patients with GPA. Also 73% patients with MPA in our series had fever at diagnosis. Only presence of constitutional symptoms showed significant association with pulmonary involvement in GPA on multivariate analysis. In developing countries like India, pulmonary disease with constitutional symptoms would initially invariably be investigated and mostly treated for a chronic infection like tuberculosis. A previous report from our centre described how clinical suspicion combined with a policy of aggressive investigation with tissue diagnosis in so-called “resistant tuberculosis cases” led to timely institution of immunosuppressive therapy and saved lives at a time when vasculitis was rarely recognised in India.13 Presence of granuloma on histology in GPA and ANCA- positivity which has been identified in upto 30% patients with tuberculosis, make the distinction between the two difficult.21 While awareness about AAV and presence of other organ involvement are important, lack of response to anti-tubercular therapy in a suspected tuberculosis patient should prompt physicians to obtain appropriate tissue samples and timely expert opinion.

The most common symptoms in EGPA patients at presentation were shortness of breath (92%), cough (65%), chest pain (16%) and hemoptysis (7%), and bronchial asthma was present in all patients.22 In two other series, 40-55% patients with EGPA had lung involvement other than asthma with lung nodules being the most common manifestation.23,24 In our series, shortness of breath and cough were the most common symptoms and wheezing was the symptom that separated EGPA from other vasculitides, most likely related to bronchial asthma. Only three of our 8 patients had any abnormality on CT scan of chest with pulmonary nodules being present in 2 (25%) patients. In a large series consisting of 136 patients, 39% had GGOs while 28% had consolidation and 24% had small pulmonary nodules. Pleural effusion was identified in
Table 7: Association between pulmonary and upper respiratory tract involvement and patient characteristics and other organ involvement in patients with microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (n=23)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pulmo (+) (n=18)</th>
<th>Pulmo (-) (n=5)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50 (25-70)</td>
<td>56 (38-66)</td>
<td>0.745</td>
</tr>
<tr>
<td>Vasculitis index</td>
<td>20 (4-29)</td>
<td>14 (12-18)</td>
<td>0.009</td>
</tr>
<tr>
<td>Female gender</td>
<td>14 (77.8)</td>
<td>2 (40.0)</td>
<td>0.142</td>
</tr>
<tr>
<td>ANCA type (n=22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-ANCA</td>
<td>14 (77.8)</td>
<td>4 (100)</td>
<td>0.554</td>
</tr>
<tr>
<td>Negative</td>
<td>4 (22.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>ANCA ELISA (n=14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1 (9.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>MPO</td>
<td>10 (90.9)</td>
<td>3 (100.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>ANA positivity (n=19)</td>
<td>3 (20.0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Renal involvement at presentation</td>
<td>12 (66.7)</td>
<td>3 (60.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>MSK involvement</td>
<td>7 (38.9)</td>
<td>3 (60.0)</td>
<td>0.618</td>
</tr>
<tr>
<td>Cutaneous involvement</td>
<td>9 (50.0)</td>
<td>0 (0)</td>
<td>0.116</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>7 (38.9)</td>
<td>4 (80.0)</td>
<td>0.155</td>
</tr>
<tr>
<td>Gastrointestinal involvement</td>
<td>1 (5.6)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>1 (5.6)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Digital gangrene</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>2 (11.1)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td>1 (5.6)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Genitourinary involvement</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>8 (44.4)</td>
<td>4 (80.0)</td>
<td>0.317</td>
</tr>
</tbody>
</table>

*p-value for Mann-Whitney U-test for age and vasculitis index, and Fisher’s exact test for all other variables. ANA- anti-nuclear antibody, ANCA- anti-neutrophil cytoplasmic antibody, ELISA- enzyme linked immunosorbent assay, MSK- musculoskeletal, MPO- myeloperoxidase, PR3- proteinase-3, Pulmo (+/-) - pulmonary involvement present/absent and VTE- venous thromboembolism.

12% patients. Only 1 patient in our series with EGPA had pleural effusion.

Pulmonary involvement in MPA has been noted to occur in about 69% patients. In our series, 67% patients had pulmonary involvement. The most common radiographic manifestation of MPA are pulmonary parenchymal including GGOs and reticular pattern (41%) each and consolidation (23%). Airway abnormalities were seen in 66% and pleural effusion in 53%. Eight of 10 patients who underwent CT scan had GGOs and 3 each had consolidation and pleural effusion in our series. Patients with MPA have high incidence of pulmonary fibrosis. However, we did not notice radiological evidence of pulmonary fibrosis in any of our patients.

Diffuse alveolar haemorrhage is a life-threatening pulmonary manifestation of AAV. In a series of patients with DAH and vasculitis, about 60% had GPA, 25% had MPA and 10% had EGPA. However, the DAH was more common among MPA patients. Among thirteen patients in our series who had DAH, 7 had GPA and 6 had MPA. In presence of DAH in MPA at diagnosis in our series of 40% is much higher than 7% reported in large series. This could be partly due to referral bias. Three to four percent patients with EGPA at presentation are reported to have DAH. However, no patient of EGPA in our series had DAH.

The primary limitation of our study was its retrospective design. A chest CT scan was not available at diagnosis in all patients. Referral bias and lack of geographical delimitation of the population we cater limits us from estimating the incidence of AAV in North India.

In conclusion, while pulmonary involvement was common in GPA, MPA and CSS, ENT involvement was almost characteristic of GPA. Fulminant presentation with DAH was most common in MPA. The strong association of constitutional symptoms in GPA with pulmonary involvement makes it an important clinical challenge in India to distinguish GPA from chronic infections including tuberculosis. Physicians should be careful to keep systemic vasculitis in the rubric of differential diagnoses in patients with ENT problems which are unresponsive to usual therapy. Awareness among physicians and early referral to centres with
infrastructure and expertise for diagnosis and treatment of these rare disorders is crucial. Population based and multicentre studies are needed to assess the true burden of AAV in Indian population.

References

Insulin Myths and Impact of Round-Tree Group Education Programme on Acceptance of Insulin in Persons with Diabetes: A Study from the Himalayas

Jatinter Mokta¹, Kiran Mokta², Parmod Sinha³, Asha Ranjan⁴, Deepika⁵, Rahul Gupta⁵

Abstract

Background: Insulin is the natural treatment of diabetes mellitus. It is the oldest, most potent and natural therapy of diabetes mellitus; if used timely and in appropriate doses. Most diabetic patients either do not receive it or do not receive it timely. This study was conducted to assess the myths about insulin therapy among type 2 diabetes patients and the impact of open-air discussion on its acceptance in the rural areas of Himachal Pradesh.

Methodology: Study was conducted in 21 rural areas of the state. 909 non-pregnant diabetic adults were surveyed through 32 diabetes camps organized between April 2008 to August 2013. The date and place of camp decided one month in advance. Group education programmes, including ‘lectures’ and “round tree” discussions conducted.

Results: The mean age was 53.94 ± 6.87 years (27-84 years). 49.91 % (279) were eligible for insulin therapy (59.49% male) based on A1C >9 %, and/or >7% despite maximum doses of oral hypoglycemic drugs. Only 7.88% (13males and 9 females) agreed to take insulin at first suggestion. Economic status and educational standard inversely related to the acceptance of insulin. After this educational activity, 34.76% (67 males and 30 females) more patients agreed for insulin therapy, increasing total number to 42.65%.

Conclusion: This study reveals the myths regarding insulin and suggests that community-based group education programs help increase in acceptance of insulin. Sensitization of local health care providers is necessary to ensure persistence with insulin therapy.

Editorial Viewpoint

• Initiation of insulin therapy meets a lot of psychological resistance from the patients.
• This community based study has demonstrated increased acceptance of insulin through community-based group education programmes.

Introduction

Diabetes has emerged as a major public health concern worldwide associated with serious long-term consequences with ever-rising incidence and prevalence.¹ According to recent estimation from International Diabetic Federation (IDF), approximately 382 million people world-over had diabetes in 2013 and expected to increase to approximately 592 million by 2035.² This pandemic; knows no geographical boundaries and lofty Himalayas are no exception. Himachal Pradesh is a remote Himalayan state of India located at an elevation of 350 meters (1,148 feet) to 6900 meters (22,966 feet) above level; where diabetes is emerging as a major public health concern like other parts of India. Primary care providers (PCPs) are the main source of health care for most diabetic patients in this Himalayan state. Lack of access to updated treatment protocols, clinical inertia, lack of time spent with diabetic patients due to the overburden

¹Professor, Department of Medicine, ²Asst. Professor, Department of Microbiology, IGMC, Shimla, Himachal Pradesh; ³Senior Consultant Physician, Haribar Hospital, Himachal Pradesh; ⁴Senior Resident, ⁵Junior Resident III, Department of Medicine, IGMC, Shimla, Himachal Pradesh
Received: 10.11.2015; Accepted: 31.05.2017
of communicable diseases in conjunction with peculiar socio-geographical conditions poses formidable challenges in the management of diabetic patients in this region of the country.

Beta cell dysfunction and insulin resistance are the main physiological defects responsible for the development of hyperglycemia in type 2 diabetes. The defects in beta cell dysfunction seems to be progressive; as newly diagnosed diabetic patients had 50% loss of beta cell function and they had further 25% loss of beta cell function over next 6 years. Consequently, up to 60% of patients will require insulin therapy within 6-10 years of initial diagnosis for good glycemic control.

Insulin is the natural treatment of diabetes mellitus. It is the oldest, most potent and natural therapy of diabetes mellitus; if used timely and in appropriate doses. Unfortunately, it is one of the most underused medical therapies of humankind and is not used early enough or aggressively enough to achieve glycemic goals that have been proven to reduce morbidity and mortality. Most diabetic patients either do not receive it or do not receive it timely. Most primary care providers prefer to delay initiation of insulin therapy until necessary and there is reluctance on the part of patient to take insulin therapy until the last resort. Beliefs and perceptions about diabetes and its treatment and consequences of insulin therapy are the factors responsible for this resistance among diabetic patients. This study was conducted to assess the myths about insulin therapy among type 2 diabetic patients and the impact of open-air discussion on its acceptance in the rural areas of Himachal Pradesh.

**Material and Methods**

This mixed method study was conducted in 21 rural areas of the state, located 50 to 400 kilometers from the capital, at 2200 to 10,000 feet altitude (Figure 1). An arduous 12-15 hours journey navigated to reach 10,000 feet destination in tribal area for organizing a camp. Nine hundred and nine (909 total patients) diabetes camps were surveyed through 32 diabetes camps organized between April 2008 to August, 2013. The date and place of camp decided one month in advance, and people informed through newspapers, pamphlets, banners, social workers, public representatives and health providers. Detailed history, weight, height, waist circumference, body mass index were recorded. Fasting and/or random blood glucose, glycated hemoglobin, lipid profile and blood pressure measured.

**Results**

Glycated hemoglobin (A1C) was measured in 559 patients (60.64% male). The mean age was 53.94 ± 6.87 years (27-84 years) with a mean of 55.43 ± 1.39 years in males and 51.74 ± 2.56 years in females. The mean fasting blood glucose was 164.50 ± 31.16 mg/dl (165.71 ± 32.09 in males; 163.82 ± 32.16 in females). The average A1C was 8.71 ± 2.034 (8.74 ± 2.34 % for male and an average of 8.61 ± 2.04 % for female). The mean duration of disease was 3.83 ± 1.06 years, ranging from to 9 month-24 years. Only 21.64% had A1C <7% and 42.75% had severely uncontrolled blood glucose with an A1C of >9%. 49.91% (279) were eligible for insulin therapy (59.49% male) based on A1C >9 %, and/or >7% despite maximum doses of oral hypoglycemic drugs. Only 7.88% (13 males and 9 females) agreed to take insulin at first suggestion. 92.11% (153 males and 104 females) disagreed for insulin injection at first suggestion; citing the following reasons: They have heard from others that:

- Insulin leads to “Addiction” (“Habit” - in local language) meaning by: insulin injection started once has to continue lifelong for control of sugar (83%).
- Insulin injection is the “last resort” in the treatment of diabetes and usually given in the last stage of disease and it is too early to begin insulin: they believe (64%).
- Injection fear and lack of self-confidence in injecting insulin are also reasons for not accepting insulin injection in 24% and 17% respectively.
- Hypoglycemia and weight gain were not reasons for not accepting insulin.

Economic status and educational standard “inversely” related to the acceptance of insulin (only 5% above 10 standards and 6% high socio- economic status patients accepted insulin) and found big hindrance for initiation of insulin. Group education programmes, including ‘lectures’ and “round tree” discussions conducted, in open air, in the village square, involving patients, their family, and community members. The benefits of early and timely initiation of insulin in glycemic control and the time immemorial myths inebriated in the minds of diabetic patients and their family members were discussed in the “round tree” open education programme. To build up the confidence in self-injection of insulin “a live- demo” was conducted in groups among diabetic patients and confidence of self-injection was also demonstrated. Most common comment after live demonstration and self injection of insulin was “How is it so easy
Hyperglycemia and poses characterized by progressive is a chronic metabolic disorder. Discussion

Initiating insulin. Should be initiated are barriers in when and what dose of insulin that they are not prescribing insulin initial 9.88 ± 1.86%. Increased to 10.38 ± 2.26% from initial 9.88 ± 2.03%. 41.87% patients who insulin despite well-controlled 13 patients refused to discontinue from 11.14 ± 2.06% to 8.41 ± 1.91%. In this “treat to failure” approach many years or even decade is lapsed without having target A1C goals achieved and substantial glycemic burden is carried for years; before insulin is initiated.

The more recent professional diabetes standard-of-care guidelines advocate insulin as the first line therapy in patients with initial A1C >9% and as the second step after failure on metformin monotherapy to achieve an A1C <7% in patients who are symptomatic or have A1C >8.5%. In treated patients whose A1C remains >7.0% despite life style modifications and non-insulin therapies; insulin therapy should be initiated. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial observed that in a real-world setting for glycemic control; 32% of diabetic patients need insulin therapy in next 5-years after the diagnosis and; the need for insulin therapy doubled over 5-years. However, despite these observations, the proportion of people with diabetes (T1DM or T2DM) in US taking insulin or insulin with oral hypoglycemic agents is 12% and 14%, respectively. As was observed in our study, a major reason for this is attributed to resistance to take insulin among patients and resistance to prescribing insulin among health care providers; based on variety of beliefs and perceptions about diabetes and its treatment. Regardless of reason insulin therapy is often resumed as a last resort. The findings of our study does not support the previously proposed common misconceptions among diabetic patients about insulin therapy that included: the perception that initiating insulin represents a personal failure and disease has worsened, fear of hypoglycemia and weight gain, the complexity of insulin regimen that interferes in their lifestyle and fear of pain and needle phobia. One important observation noted in this study was that fear of hypoglycemia and weight gain, the complications most commonly highlighted in medical literature about insulin therapy and also observed in other studies were found missing in our study. The discordance between our study and previous studies suggests that attitude about diabetes and insulin therapy differ as a function of cultural and regional beliefs and perceptions. The findings of the Diabetes Attitude, Wishes and Needs (DAWN) study found that health care providers in general and primary care providers in particular prefer to delay initiation of insulin therapy until necessary and Indian physicians are among the most resistance of all nations to initiate insulin. How to initiate insulin and fear of hypoglycemia are the physician concerns that delay initiation of insulin therapy and similar concerns were observed.

Discussion

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by progressive hyperglycemia and poses challenge in maintaining optimal glycemic control. Much of the burden of diabetes is due to its chronic micro and macro vascular complications. Early diagnosis followed by prompt aggressive treatment to achieve optimal glycemia control is associated with a lower incidence of micro and macro vascular complications. Different International diabetes organizations such as American Diabetes Association (ADA), the American Association of clinical Endocrinology (AACE), and the European Association for the study of diabetes (EASD) all have set aggressive goals in their guidelines for glycemia control. Despite, strong recommendations for aggressive glycemia control to reduce micro and macro-vascular complications; 2 out of 3 and 1 out of 2 fail to meet the AACE and ADA target hemoglobin (A1C) goal of 6.5% and 7.0% respectively, in US. In real-world setting, the traditional stepwise approach is followed in diabetic management i.e. the sequence of lifestyle modification, monotherapy, combination of non-insulin therapies, and finally treatment with insulin.
in our study. However, delay in prescribing oral anti-diabetic agents had the strongest relationship with delay in prescribing insulin and this orientation reflect a lack of awareness about need to keep glycemic target at goal. Moreover, the propensity to use medications is an important determinant of prescribing behavior. Therefore it is important that for timely prescription of insulin, more general reluctance to prescribe diabetes medication need to be changed first among primary health care providers through educational program as they assume a greater role in managing diabetes.

Motivational or educational interactions are a patient oriented rapport-building process to explore the patient’s belief about insulin therapy and then overcome these barriers gently in a systematic approach. In this study, the initial rapport-building interactions with the patients was able to identify patient’s barriers about insulin therapy and through open round tree discussion with the patients and their family members, we were able to overcome the barriers and were found to be effective. Through group discussion, it was possible to make them understand that insulin does not cause habituation and insulin does not act as a last resort, rather it prevent going into the last stage of complications. Through discussion, we were able to make them understand that need for insulin is a consequence of natural progression of the disease and is just another option like non-insulin therapies. Delivery of the message regarding the value of insulin therapy, in addition to providing encouragement and education in our study was able to overcome any reticence about insulin therapy; increasing the percentage of accepting insulin from 7% at first contact to 34% at the end of group discussion.

A Building-up patient confidence by demonstrating how to inject insulin followed by self administration of insulin injection in presence of health providers help not only in removing needle anxiety but also dependency for injection on health care providers; a big barrier insulin therapy. In our experience most often, the patient’s response is “Oh that’s it?”. “It did not hurt me even little!”. Patient’s concern about insulin storage (insulin needs refrigerator for storage) and need to carry insulins vials, needles, and syringes are also the major barriers in insulin initiation and needs appropriate intervention. In addition, motivate patient for healthy life style changes such meal planning (in particular in between snacks to avoid hypoglycemia) and physical activities and importantly educate patient about hypoglycemia. Lastly, a simple patient driven insulin initiation algorithm that is flexible, simple, convenient and suits best to the patient lifestyle is preferred and can increase the rate of insulin acceptance. An eminent endocrinologist from Mumbai, Professor Shashank R Joshi’s quote is so true about Insulin in type 2 diabetes: “it is time to change and use insulin not just as a replacement hormone in Type 1 Diabetes, Gestational Diabetes or Secondary diabetes but in the garden variety type 2 diabetes”. He further said: “The real crux is early and optimal use of insulin beyond emergency hospital and replacement in office type 2 diabetes”. In accordance with it, our findings suggest that health care providers should try to identify specific beliefs about patient’s resistance to insulin therapy and address the beliefs through educational interventions to making insulin therapy easier in type 2 diabetes.

**Conclusion**

Insulin is not a universally accepted paradigm of diabetes management; though various international guidelines universally recommend timely initiation of insulin for glycemic control. No one kind of treatment paradigm benefits everyone. The most effective treatment paradigm is rarely superimposed but instead evolves and implemented with the participation from its recipients. The disconnection between patient’s perception of insulin therapy (Habit formation and used as last treatment option) as against the scientific evidence (hypoglycemia and weight gain) is evident in this study and needs public measures. This study reveals the myths regarding insulin, and suggests that community-based group education programmes help increase acceptance of insulin. Sensitization of local health care providers is necessary to ensure persistence with insulin therapy.


---

**Obituary**

“An astute clinician-scientist, dexterous gastroenterologist, humane doctor, last word in Liver diseases in India, a gem as an individual -teacher-researcher & brilliance personified,” are impossible words to describe, was Dr. Deepak Narayan Amarapurkar. Who passed away in an unfortunate freak accident on 29th August 2017 in Mumbai. He had an extraordinary career in academics, from Dr. V.M. Medical College Solapur, 1977 batch, topper at MBBS, MD Medicine with a Distinction, best student of the year loved by one & all VMCitites till date. After MD (Medicine) from Solapur, he persuaded his DM in Nair Hospital, Mumbai, received, Bombay University Merit scholarship during DM, Best resident award and consecutive 3 years best research paper award, Young Investigator award at 10th World Congress of Gastroenterology 1994, Asian pacific Congress 1996, Asian pacific congress at 1998. Best paper award at INASL meeting 1998, 1999, 2000. Delivered Netaji Oration at APICON 2010, Late Dr. Salaskar Memorial Oration in Goa and Late JN Berry Oration in Nagpur.

Very few doctors have a real star personality on facets of being a good academician, having huge patient load, humane behaviour, astute clinical acumen, masterly skills over the procedures, adored by both teachers & students, cutting edge in teaching, research & publication-presentation. He was one of the darling speakers at both National & International level. As a member of many Indian and international professional societies and is a Fellow of American college of Gastroenterology, contributed to the academics. A Pubmed list of 202 articles, 400 Publications & Google scholar entries of 723 publications, contributing more than 20 chapters in various textbooks is the testimony. Featured as a member in several consensus panels dealing with the management of Hepatitis B & C, NASH, hepatocellular carcinoma, EHPVO and minimal hepatic encephalopathy formed by all liver societies. Was on a reviewer board on various national and international journals & judged as best reviewer in APICON Patna 2006. Served on the editorial board of Journal of Gastroenterology & Hepatology, World Journal of Gastroenterology, Hepatology, Euroasian Journal of Gastroenterology, International Journal of Hepatology & Bombay Hospital Journal.

A guest editor of special issues on Hepatology & Therapeutic Endoscopy, Emergencies in Gastroenterology of Indian Society of Gastroenterology & Improving Survival in Patients with Liver Cirrhosis. Investigator for many trials on different aspects of liver disease. His untimely demise is a great loss for his family, friends, patients as well the academic medical world.

---

*Shriram V. Kulkarni*  
*Khopoli, Raigad*
ADD PLUS
in Micro- & Macro-vascular Complications of Diabetes

DIAVIT™ PLUS

Protect The Vital Organs

Provide Vitamins, Minerals & Anti-Oxidants

Alpha Lipoic Acid 200 mg
Beta Carotene 3 mg
Methylcobalamin 1500 mcg
Zinc 20 mg
Selenium 70 mcg
Chromium 50 mcg
Magnesium 40 mg
Manganese 2 mg
Copper 0.5 mg
Dibasic Calcium Phosphate 316.23 mg
In **Type 2 Diabetes**

**with High PPHG**

Choose the **No. 1 brand**

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

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

↓

Uptitrate to

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

**Glycomet® Trio 2 mg/0.3 mg**
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 1 mg**
Metformin HCl 1000 mg SR + Glimperide 1 mg + Voglibose 0.2 mg

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

Ref.: # - MAT AIOCD : Dev 2016
In Hypertension get your patients to BP goal with newer age ARB

Ideally suited for

 пациентs uncontrolled on other ARBs

**USV**

Azilday*  
On BP goal... All Day  
Azilsartan 80 mg

Ideally suited as

An add-on to ongoing CCB/Diuretic therapy

**USV**

Azilday*  
On BP goal... All Day  
Azilsartan 40 mg

USV LIMITED
**NovoMix™ 30 FlexPen®**

**(biphasic insulin aspart)**

*The ‘Start Insulin’ for type 2 diabetes*[^1]

---

**Superior efficacy**[^2][^3]

**Improved safety**[^2]

**Better quality of life**[^2]

**Simplicity**[^4]

---

**Say YES to...**

---

**References:**

**Abridged Prescribing Information: NovoMix™ 30 (biphasic insulin aspart)**

NovoMix™ 30 FlexPen® contains biphasic insulin aspart 100 units/ml. **Indication:** Treatment of diabetes mellitus. **Dosage:** individualised by subcutaneous injection. NovoMix™ 30 has a faster onset of action than biphasic human insulin and should generally be given immediately before a meal. When necessary, NovoMix™ 30 can be given soon after a meal. No studies in children and adolescents under the age of 18 years. **Contraindications:** hypoglycaemia, hypersensitivity. **Warnings and precautions for use:** Inadequate dosing or discontinuation of treatment may lead to hyperglycaemia and diabetic ketoacidosis, which are potentially lethal. Change in usual warning symptoms of hypoglycaemia may be seen upon tightening control. The fast onset of action may be considered in patients where a delayed absorption of food might be expected. Transferring to a new type of insulin to the patient under strict medical conditions may cause a need of change in dose. Compared with biphasic human insulin, NovoMix™ 30 significantly lowers postprandial glycaemia up to 6 hours after injection. This may need to be compensated for through adjustment of dose and/or food intake. Hyperglycaemia may constitute a risk when driving or operating machinery. **Pregnancy and lactation:** Limited clinical experience in pregnancy. No restrictions on use during lactation. **Unsolicited effects:** Hypoglycaemia, oedema and refractoriness on insulin therapy, local hypersensitivity reactions; generalised hypersensitivity reactions are rare but potentially life-threatening; lipoatrophy.

For the use of a registered medical practitioner or a hospital, or in a laboratory only: NovoMix™ 30 FlexPen®, PenFill®, Changing Diabetes® and the Apio bull logo are registered trademarks owned by Novo Nordisk A/S and registered in Denmark.
Efficacy, Safety and Immunogenecity study of Intravenous Infusion of Rituximab (Hetero) and Reference Medicinal Product (Rituximab, Roche) in Indian Patients of Follicular Lymphoma Preliminary report (HERILY)

Suresh Advani¹, Shubhadeep Sinha², Pankaj Thakur³, Neetu Naidu³, Sreenivas Chary³, Ghanshyam Biswas⁴, Vamsi Krishna Bandi⁵

Abstract

Objective To compare the antitumor efficacy, safety, and pharmacodynamics (PD) characteristics of Hetero-Rituximab (test) with Reference Medicinal Product (Rituximab, Roche) in Non-Hodgkin's Lymphoma (NHL)

Patients and Methods: Total 40 Follicular Lymphoma (FL) patients were randomized to receive intravenous infusion of either test or reference product. Efficacy (best overall response [BOR] rate [primary end point]), safety, PD (CD19), and immunological assessments (secondary end points) were done at the end of cycle 3 and cycle 6.

Results: Out of 40 patients randomized, 17 were in test arm while 23 were in reference arm.

At the end of 6 cycles, BOR (complete response [CR] and partial response [PR]) rate was 64.71% (n=11) in Hetero Rituximab compared to the 43.48% (n=10) in reference arm.

The difference between test and reference proportions of best overall response rate at cycle 6, lies within the pre-specified limit for non-inferiority. Anti-Rituximab antibodies were found to be negative at cycle 3 and cycle 6 for all FL patients. The FL patients who were treated with Hetero Rituximab, showed significant depletion in CD19+ cell which was comparable with Reference drug. Safety and Immunogenic potential of the test drug was comparable to the reference drug in the patients of FL.

Conclusion: Best overall response rate at Cycle 3, Cycle 6 and end of the study lies within the pre-specified limit for non-inferiority which concludes that test product is therapeutically non-inferior to reference medicinal product.

Introduction

Non-Hodgkin’s lymphoma (NHL) are classified as a heterogeneous group of malignancies arising from lymphoid tissue that are highly responsive to initial therapy but relapse with less responsive disease, accounting for ∼5.1% of all cancer cases and 2.7% of all cancer deaths.¹ Its incidence has been increasing over the past several decades globally in North America, Western Europe at an annual rate of 4%.² In India as well, reported incidence was on the upsurge at 5.1 per 100,000.³

NHL treatment has dramatically changed with the introduction of rituximab (Rituxan, Genetech, San Francisco, CA). Its greatest impact has been in follicular lymphoma (FL), which constitutes approximately 70% of indolent lymphomas and up to 25% of all cases of NHL. Although there are

¹Investigator, Department of Medical Oncology, Jaslok Hospital and Research Centre, Mumbai, Maharashtra; ²Vice President, AGM, Hetero Labs Limited, Hyderabad, Telangana; ³Investigator, Sparsh Hospitals and Critical Care Pvt. Ltd., Bhubaneswar, Orissa; ⁴Director, Hetero Labs Limited, Hyderabad, Telangana

Received: 23.03.2017; Revised: 02.05.2016; Accepted: 16-06-2017
no defined first line therapies for NHL, rituximab has become a standard component in treatment of FL.

Rituximab is the first genetically engineered chimeric (murine-human) monoclonal antibody (mAb) against the CD20 antigen for the treatment of cancer recommended at dosage of 375 mg/m²/infusion, weekly for 4 weeks. Because of its human component, rituximab has low immunogenicity. For approval by the US Food and Drug Administration, multiple studies were conducted internationally. In phase-II Study, low-grade or follicular B-cell non-Hodgkin’s lymphoma patients treated with Rituximab (375 mg/m² per dose) along with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy shown overall response rate of 95%. Most frequent events to rituximab were fever and chills, observed primarily with the first infusion, which conclude additive therapeutic benefit for the combination with no added toxicity.

In phase III study, patients with advanced-stage follicular lymphoma (n=428) were randomly assigned to either CHOP alone arm (n = 205) or CHOP combined with rituximab (R-CHOP) (n = 223). The objective response rate (ORR) was found to be higher (96%) in the group received CHOP plus Rituximab vs 90% in the group received CHOP alone.

Rituximab was approved by the Food and Drug Administration on November 26, 1997 (and by the European Union on June 2, 1998), for the indication of follicular non-Hodgkin’s lymphoma. In 2014, a subcutaneous formulation of Rituxan was further approved by European Commission (EC) for the treatment of both FL and Diffuse Large B-Cell Lymphoma (DLBCL).

Since, rituximab binds to CD20 antigen, its presence in blood samples can interfere with assay of CD20 cells. Hence, rituximab administration can confound CD20 assay measurements. Moreover, CD19 expression mirrors CD20 expression and can therefore serve as a surrogate marker in patients with circulating rituximab.

In India, safety of biosimilar rituximab is already established in Indian patients with two Biosimilar products readily available in market. As per the Guidelines of Central Drugs Standard Control Organization, comparative clinical trials are critical to demonstrate the similarity in efficacy and safety profiles between the similar biologic and reference biologic. Hence, phase 3, randomized non-inferiority trial was conducted in FL patients to compare the efficacy, safety and immunogenicity of intravenous infusion of test and reference medicinal product.

### Material and Methods

This was a phase 3, randomized, multiple-dose, multicentre, comparative, parallel study to evaluate the efficacy, safety of intravenous infusion of rituximab, test and reference medicinal product in previously untreated Indian patients with non-hodgkin’s lymphoma (stage III-IV follicular lymphoma subtype). The study was carried out from Sep 2013 to Aug 2015 at 36 oncology sites of India. The study protocol was approved by office of Drug Controller General of India and Ethics Committees. Independent ethics committees or institutional review boards at participating sites approved the protocol. The study was registered to clinical trial registry-India (CTRI) prior to initiation of the study (CTRI Registration No: CTRI/2013/08/003921). The study was conducted in accordance with the Declaration of Helsinki (2000) and the International Conference on Harmonisation Guidelines for Good Clinical Practice. Written informed consent was obtained from patients or their legally authorised representatives before initiation of any trial procedures.

Key inclusion criteria were male or female ≥18 years and ≤65 years of age (both inclusive), histologically confirmed CD20-positive, previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy, patients who are eligible for rituximab and CHOP, patients with at least one measurable lesion as per International Working Group Response (IWGR) criteria for malignant lymphoma, adequate liver, renal, cardiac and haematological function, subjects with a performance status of 0 to 2 according to the Eastern Cooperative Oncology Group (ECOG), life expectancy more than six months.

### Study Treatments

Hetero-Rituximab (Test drug) or reference medicinal product (Reference drug manufactured by Roche) 375 mg/m² was administered on Day 1 of each chemotherapy cycle in combination with CHOP for 6 cycles. Premedication consisting of an anti-pyretic and an antihistaminic, e.g., paracetamol and diphenhydramine or prednisolone or as per institutional standard was administered before each infusion of IMP. Since, this was a parallel open label study, thus no blinding was done.

### Endpoints Assessment

Primary efficacy end point of the study was calculated on best overall response rate at the end of cycle 3 and cycle 6. BOR was defined as patients with response of complete response (CR) and partial response (PR). The secondary evaluation was based on evaluation of safety, immunogenicity and clinical pharmacodynamics (PD). Safety was measured by adverse events by monitoring of significant clinical signs and symptoms and laboratory abnormalities during treatment. Immunogenicity was evaluated by assessing blood serum for the presence of anti-rituximab antibodies in all patients at the end.
of cycle 3 and at the end of cycle 6. Clinical Pharmacodynamics was evaluated by circulating B-cell measurements using CD19+ as a surrogate marker for B-cells expressing CD20 at the end of cycle 3 and at the end of cycle 6.

Statistical Analyses

A total of 40 patients were randomized to receive intravenous infusion of either Hetero-Rituximab or reference medicinal product (Rituximab, Roche). During the study, as per randomization schedule, 17 patients received test product and 23 patients received reference medicinal product.

Randomization schedule was generated using SAS version 9.3 before the commencement of the study. Block randomization of size two in ratio of 1:1 (Test: Reference) was generated and balanced treatment allocation within block was ensured at the time of randomization generation. To evaluate safety, a set was made for all patients who received at least one dose of study drug. All statistical analysis was performed using SAS® Version 9.3 (SAS Institute Inc., USA).

Results

Pharmacodynamics and Immunogenicity

Immunogenicity was evaluated by assessing serum for the presence of anti-rituximab antibodies in all patients at baseline, at the end of 3rd cycle and at the end of cycle 6. Anti Rituximab Antibodies were found to be negative at cycle 3 and cycle 6 for all patients. For CD19+ parameter, the Geometric Mean Titer (GMT) was comparable at baseline [FL: Test = 5.08 micro liter (i.e. 2.31%) and Reference = 5.46 micro liter (i.e. 2.45%)] and got reduced over the study period with [FL: Test = 3.36 micro liter (i.e. 1.12%) and Reference = 2.59 micro liter (i.e. 0.96%)] at the end of cycle 6.

Efficacy

A total of 40 FL patients were included for efficacy analysis. As part of the primary efficacy analysis, data was evaluated at the end of cycle 6. At the end of the cycle 6, 17 patients in test arm and 23 patients in Reference arm were evaluable. The result of the study indicates that proportion of patients with best overall response rate (CR + PR) is 64.71% (n=11) in Hetero Rituximab compared to the 43.48% (n=10) in reference Rituximab at the end of the cycle 6. These results shows that the lower limit of 97.06% CI (-12.60%, 55.05%) (Table 1) for the difference between test and reference proportions of best overall response rate at cycle 6, lies within the pre-specified limit for non-inferiority i.e. lower limit > -20% (Table 2).

Additionally, the CR rate was 17.65% (n=03) in patients receiving Hetero Rituximab compared to 13.04% (n=03) patients received reference Rituximab while PR rates were 47.06% (n=08) and 30.43% (n=07) for FL patients who were exposed to test and reference formulations, respectively (refer to Table 14.2.1.1-FL).

Safety Results

A total of 277 adverse events (AEs) were reported by 34 patients during the conduct of study. Of the 277 adverse events, 113 AEs were mild, 134 AEs were moderate and 30 AEs were severe in nature as per common terminology criteria for adverse events (CTCAE) gradation.

The relationship was judged as unlikely for one hundred and two (102) AEs, as possible for one hundred and two (102) AEs, as probable/likely for fifty five (55) AEs and as certain for eighteen (18) AEs.

One hundred sixty nine (169) treatment emergent adverse events (TEAEs) were reported after receipt of Reference Medicinal Product and one hundred and eight (108) TEAEs were reported after receipt of Test Product. One Hundred and Eight TEAEs were reported by 76.47% (n=13) of 17 patients under Test Product, 169 TEAEs were reported by 91.30% (n=21) of 23 patients under Reference Medicinal Product. The outcomes of the TEAEs were 247 AEs – complete recovery, 16 AEs – Ongoing, 10 AEs - Recovered with sequelae, 02 AEs – Unknown, 01 AE – Death and 01 AE - Event worsened.

One (01) death and nine (09) other serious adverse events were reported during the conduct of study. The causality assessment

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Endpoint</th>
<th>Test product</th>
<th>Reference product</th>
<th>Difference between proportions (Test-reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 3 (Test (10): Reference (9))</td>
<td>ORR</td>
<td>100%</td>
<td>88.89%</td>
<td>11.11%</td>
</tr>
<tr>
<td>Cycle 6 (Test (17): Reference (23))</td>
<td>ORR</td>
<td>64.71%</td>
<td>43.48%</td>
<td>21.23%</td>
</tr>
<tr>
<td>End of study (Test (17): Reference (23))</td>
<td>BOR</td>
<td>88.24%</td>
<td>82.61%</td>
<td>5.63%</td>
</tr>
</tbody>
</table>

| Table 1: Point estimate and confidence interval for difference in percentage of patients with best overall response rate (ITT, FL group) |
|---|---|---|---|---|
| Cycle | Difference between proportions (%) | 97.06% confidence interval | Acceptance range (%) | Conclusion |
| Cycle 3 | 11.11% | (-11.71%, 33.93%) | Lower Limit Non-Inferior Limit > -20% |
| Cycle 6 | 21.23% | (-12.60%, 55.05%) |
| End of study | 5.63% | (-18.58%, 29.83%) |
The rate of response was found to be higher ORR (96%) in the group that received CHOP plus Rituximab vs 90% in the group who received CHOP alone. These beneficial effects even translated to superior overall survival (OS) \( (P = .016) \), with 6 deaths in the R-CHOP group compared with 17 deaths in the CHOP group within the first 3 years. The predominant treatment-related adverse effect was myelosuppression. Severe granulocytopenia was more frequently observed after R-CHOP (63% vs 53%; \( P = .01 \)).

In another phase-II study with 40 patients- low-grade or follicular B-cell non-Hodgkin’s lymphoma were treated with 6 infusions of Rituximab (375 mg/m² per dose) along with CHOP chemotherapy. Overall response rate was observed 95% (38 / 40): 22 pts.- complete response (55%), 16 pts- partial response (40%), and 2 patients, who received no treatment, classified as non-responders. Most frequent events to rituximab were fever and chills, observed primarily with the first infusion.

The efficacy results of our study in patients with FL are consistent with those reported in literature. Several pivotal clinical trials have demonstrated the benefit of adding rituximab to the chemotherapy regimen vs. chemotherapy alone. There were no clinically relevant changes in vital signs or biochemical parameters throughout the study. No significant differences were observed between the test and reference groups.

In this study, none of the analyzed samples, either in the Test or Reference group were found to be positive for anti-rituximab antibodies, i.e., immunogenicity was not observed with the study drugs.

Rituximab treatment leads to decrease in the CD19 count in FL patients. This was observed in both the test as well as reference arms. Hence, the data suggests that FL patients treated with test, had significant depletion in CD19+ cell which was comparable with reference and also with the values previously reported for reference rituximab.

Conclusion
Since difference between test and reference proportions of best overall response rate at Cycle 3, Cycle 6 and end study lies within the pre-specified limit for non-inferiority, it could be concluded that test product, a biosimilar of rituximab is also therapeutically similar to reference medicinal product FL patients.

References
8. Mabthera 100 mg and 500 mg concentrate for solution for infusion, Mabthera® Summary of Product Characteristic.


Award Sessions

1. Dr. D. P. Basu Young Award in Cardiology
2. E. Merck Award
3. Dr. J. N. Berry Memorial Award
4. Dr. M. J. Shah Memorial Award in Tropical Medicine

There will be three award sessions at the 2018 Annual Conference of API at Bengaluru. The rules and regulations of these awards are as under:

1. Papers those are accepted for the Award Session have to be presented at the Annual Conference APICON 2018. The papers will be divided subject-wise into four groups.

Group I : Cardiology Dr. D.P. Basu Young Award
Group II : Chest Diseases E. Merck Award
Group III : Other Specialties Dr. J.N. Berry Award
Group IV : Tropical Medicine Dr. M.J. Shah Award

Dr. J.N. Berry Memorial Award and E. Merck Award are given alternate yearly for Group II and III papers. At the 2018 Annual Conference, Dr. J. N. Berry Award for other specialties will be awarded. Dr. D.P. Basu Young Award will be for Cardiology paper and Dr. M.J. Shah Memorial Award will be given for Tropical Medicine paper.

The competitor must be the first author of the paper submitted for presentation at the API sessions of the Annual Conference. A testimonial must be submitted from the Head of the Institution stating that the major work has been done by the competitor. Papers which are previously presented or published will not be considered. The competitor should also give a written pledge stating that the work has not been presented or published before. He / she should be a member of API.

Dr. D. P. Basu Awards are of Rs. 1,000/- each, Dr. J. N. Berry award fetches Rs. 2,000/- and Dr. M. J. Shah Memorial Award is of Rs. 2,500/-. Suggestions should be accompanied with eight copies of a brief bio-data of the suggested name, so as to reach not later than 30th November, 2017 the Hon. General Secretary – API, Dr. Mangesh Tiwaskar of API, Unit No. 6 & 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E. Moses Road, Near Mahalaxmi Station West Mumbai – 400 011

The upper age limit of the competitor is 40 years for all the awards.

Dr. Mangesh Tiwaskar
Hon. General Secretary
A Pan-India Study to Assess the Quality of Life, Symptom Profile and Management Trends in Patients with Migraine: A Cross-Sectional Study

Sumit Singh¹, Kushal Sarda², Rashmi Hegde²

Abstract

Objectives: Migraine, a common primary headache disorder which can be severely disabling, associated with poor health-related quality of life (HRQoL) amongst affected patients. The present study was performed to provide adequate clinical data on migraine and the management practices in India.

Material and Methods: A cross-sectional study was designed to assess disease burden, HRQoL, symptom profile, management trends and comorbidities associated with migraine patients across ten centres in India.

This study assessed HRQoL using Migraine Specific Quality of life (MSQ) and Migraine Disability Assessment Scores (MIDAS) questionnaire. Categorical variables were summarized as frequency, and percentage and continuous variables as mean and standard deviation respectively.

Results: A total of 705 patients were enrolled with a mean age of 35.2 years. Hypertension (7.0%) was the highest co-morbid illness associated with migraine. A higher MSQ score was observed in females as compared to males (39.3±12.4 and 37.4±11.6) while MIDAS showed a comparable score (27.7±47.6 and 27.2±35.4). Majority of migraine patients were unemployed (61.6%) and in profession, females had poor HRQoL than males by MIDAS and MSQ. Majority of patients had pulsating, bilateral attacks for the duration of 4h to 72 h. Paracetamol (47.1%) and propranolol (50.9%) was most commonly prescribed drugs for acute attack and prophylaxis, respectively.

Conclusions: The quality of life was superior in males as compared to females amongst migraine patients in India. Hypertension was the commonest comorbidity associated with migraine.

Key Messages: Migraine is associated with substantial disability with higher prevalence in females and older people (age <40 years). NSAIDs and propanol was widely prescribed drug in acute attacks and prophylaxis of migraine respectively. Cardiovascular diseases, diabetes mellitus and anxiety were common comorbidities associated with migraine.

Introduction

Migraine, essentially an episodic primary headache syndrome, is ranked as the third most common disease in the world. Migraine, with moderate to severe intensity, can induce functional disability enforcing a substantial burden in terms of impairments of lifestyle and routine activities in a large number of patients. Despite the high occurrence, disease severity and relevance of health-related problems associated with migraine, there is a lack of adequate clinical data and its management practices in Indian population. Present study was planned to understand the symptom profile and management trends and Quality of life in patients with migraine in India.

Subjects and Methods

Study design and participants

This multicentre, observational cross-sectional study was conducted across ten centres to assess several variables associated with the disease burden, health related quality of life (HRQoL), symptom profile, management trends (treatment of acute attack,
Table 1: Baseline features

<table>
<thead>
<tr>
<th>Parameters/Statistics</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 134</td>
<td>n = 571</td>
<td>n = 705</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5 (underweight)</td>
<td>5 (0.71)</td>
<td>33 (4.68)</td>
<td>38 (5.39)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>18.5 to 23 (normal)</td>
<td>38 (5.39)</td>
<td>179 (25.39)</td>
<td>217 (30.78)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>23 to 27.5 (overweight)</td>
<td>59 (8.37)</td>
<td>207 (29.36)</td>
<td>266 (37.73)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>&gt;27.5 (obesity)</td>
<td>32 (4.54)</td>
<td>152 (21.56)</td>
<td>184 (26.10)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Personal habits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>22 (3.12)</td>
<td>6 (0.85)</td>
<td>28 (3.97)</td>
<td>0.4731</td>
</tr>
<tr>
<td>Smoking</td>
<td>11 (1.56)</td>
<td>1 (0.14)</td>
<td>12 (1.70)</td>
<td>0.9344</td>
</tr>
<tr>
<td>Tobacco chewing</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profession</td>
<td>52 (7.38)</td>
<td>79 (11.21)</td>
<td>131 (18.58)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Semi-Profession</td>
<td>14 (1.99)</td>
<td>19 (2.70)</td>
<td>33 (4.68)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Clerical, shop-owner</td>
<td>20 (2.84)</td>
<td>11 (1.56)</td>
<td>31 (4.40)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Skilled Worker</td>
<td>16 (2.27)</td>
<td>14 (1.99)</td>
<td>30 (4.26)</td>
<td>0.3403</td>
</tr>
<tr>
<td>Semi-Skilled Worker</td>
<td>8 (1.13)</td>
<td>6 (0.85)</td>
<td>14 (1.99)</td>
<td>0.0066</td>
</tr>
<tr>
<td>Unskilled Worker</td>
<td>3 (0.43)</td>
<td>29 (4.11)</td>
<td>32 (4.54)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Unemployed</td>
<td>21 (2.98)</td>
<td>413 (58.58)</td>
<td>434 (61.56)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Monthly family income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥36017</td>
<td>54 (7.66)</td>
<td>156 (22.13)</td>
<td>210 (29.79)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>18000-36016</td>
<td>64 (9.08)</td>
<td>336 (47.66)</td>
<td>400 (56.74)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>13495-17999</td>
<td>6 (0.85)</td>
<td>52 (7.38)</td>
<td>58 (8.23)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>8989-13494</td>
<td>7 (0.99)</td>
<td>20 (2.84)</td>
<td>27 (3.83)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>5387-8988</td>
<td>3 (0.43)</td>
<td>1 (0.14)</td>
<td>4 (0.57)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>1803-5386</td>
<td>0</td>
<td>5 (0.71)</td>
<td>5 (0.71)</td>
<td></td>
</tr>
<tr>
<td>≤1802</td>
<td>0</td>
<td>1 (0.14)</td>
<td>1 (0.14)</td>
<td></td>
</tr>
</tbody>
</table>

Health-related quality of life assessment

Migraine specific quality of life (MSQ) questionnaire (v.2.1) is a 14-item, self-administered disease-specific HRQoL instrument developed to assess patient perception in migraine.\(^4\)

Migraine disability assessment (MIDAS) questionnaire is designed to quantify headache-related disability over a three-month period, has been utilized to record acute disability from headache.\(^5\)

Collection of other variables

A questionnaire was designed to collect data on demography (age, gender, body mass index [BMI]), personal details, marital status, family history and habitual risks (alcohol, smoking, and tobacco chewing). Socioeconomic status was determined by modified Kuppuswamy scale. In addition, history of migraine with its onset age, type of headache (pulsating/non-pulsating, unilateral/bilateral), and characteristics of acute attack such as duration less than 30 minutes, 30 minutes to 45 minutes, 45 minutes to 60 minutes, one hour to four hours, more than four hours), and frequency of attacks per month (one to ten attacks, 11 to 20 attacks, 21 to 30 attacks) were also recorded. Associated comorbidities, medications used for management of acute attack as well as for migraine prophylaxis were also documented. The research worker/co-investigator/investigator was trained and carefully entered the data from the source documents into the case report form.

Statistical analysis

All data were statistically analysed by SAS (version 9.4). Categorical variables were summarized as frequency and percentage of patients and compared using Chi square test. Continuous variables were summarized as mean and standard deviation (SD). Total MSQ scores and MIDAS scores were summarized as mean and SD for various sub-categories (Table 1). Stratification of data for MSQ and MIDAS scores was done on the basis of age groups and gender. A two-tailed p-value <0.005 was considered as significant.

Results

Patients characteristics

A total of 705 participants with a mean ±SD age of 35.2 ± 11.1 (range-18-76) years were enrolled form a period of Apr-2016 to Dec-2016. Out of total patients, there were significantly higher number of females (81.0%) than males (19.0%) in our study. After stratifying patients as per BMI, we observed significantly higher proportion of females as compared to males in each BMI category. There were higher percentage of male patients who were indulged in alcohol (3.1%) and smoking habit (1.6%). More than half of patients were unemployed by occupation (61.6%). Significantly greater percentage of females had shown higher family

and prophylaxis in migraine) and comorbidities linked with migraine patients in India. Consecutive patients attending the outpatient department of the study site/clinics with history and symptoms suggestive of migraine or confirmed diagnosis of migraine were considered for this study. Patients were enrolled after obtaining written informed consent. This study was approved by independent ethics committee or institutional review board of respective sites and registered in clinical trial registry India (Reg. No. REF/2016/03/011040).

Patient selection

Patients aged ≥18 years with confirmed diagnosis of migraine based on clinical presentation and/or International Classification of Headache disorders (ICHD) criteria were recruited. Considering the observational nature of this study, no formal sample size calculation was performed.
income as compared to male in each income category. The baseline characteristics of patients were mentioned in Table 1.

**Co-morbidities and symptoms of migraine**

Hypertension was the most prevalent comorbid condition associated with migraine, which was followed by diabetes mellitus, anxiety, asthma, epilepsy and others (Figure 1). While assessing the symptoms associated with migraine, majority of patients had headache for the duration of 4-72 hours (44.4%) followed by one-four hours (20.3%). Approximately two third (69.5%) patients were noted with one-ten headache attacks per month and more than three fourth (76.2%) patients had pulsatile nature of headache (Table 2).

**Management of migraine**

The most common drug for acute attacks of migraine was paracetamol (47.1%) followed by naproxen (12.9%) and sumatriptan (12.2%). Among fixed dose, domperidone plus naproxen (29.2%) were the mostly prescribed combination. Beta blockers (51.3%) were the most widely prescribed class which was followed by calcium channel blockers (40.1%), anticonvulsant (33.5%) and antidepressant (30.5%) (Table 3). In prophylaxis, propranolol was prescribed in approximately half (50.9%) of patients. This was followed by flunarizine (39.9%), amitriptyline (19.2%), topiramate (17.3%) and divalproex sodium (15.3%).

**Health-related quality of life assessment**

**MIDAS scores**

MIDAS questionnaire classified significant proportion of patients into moderate disability (46.2%) followed by severe disability (37.3%), mild disability (8.4%) and little or no disability (7.7%) classes. Overall, mean MIDAS scores were comparable between males and females. However, a higher score has been observed in females with BMI < 18.5 kg/m² in comparison to males. Interestingly, alcoholic males demonstrated higher score than females. Additionally, females with smoking habits had numerically higher score than males, females with a professional background had numerically higher score than males, females with smoking habits had higher score than male workers had higher score than female. The scores were comparable between males and females when the data were categorized by monthly family income and BMI. The patients indulged in smoking habits had higher score than females. Additionally, females with a professional background had higher score than males, females with a professional background had numerically higher score than males, females with smoking habits had higher score than males. The scores were comparable between males and females when the data were categorized by monthly family income. However, females with monthly family income between INR 5387-8988 shown higher score than males (Table 4).

**Type of headache**

Pulsating
Non-pulsating
Unilateral
Bilateral

**Table 2: Symptoms of migraine**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Total (n = 705)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of headache attacks</td>
<td></td>
</tr>
<tr>
<td>Less than 30 minutes</td>
<td>66 (9.36)</td>
</tr>
<tr>
<td>30 minutes to 45 minutes</td>
<td>76 (10.78)</td>
</tr>
<tr>
<td>45 minutes to 60 minutes</td>
<td>107 (15.18)</td>
</tr>
<tr>
<td>1 hr to 4 hrs</td>
<td>143 (20.28)</td>
</tr>
<tr>
<td>4 hrs. to 72 hrs</td>
<td>313 (44.40)</td>
</tr>
<tr>
<td>Frequency of attacks per month</td>
<td></td>
</tr>
<tr>
<td>1 to 10 attacks</td>
<td>490 (69.50)</td>
</tr>
<tr>
<td>11 to 20 attacks</td>
<td>145 (20.57)</td>
</tr>
<tr>
<td>21 to 30 attacks</td>
<td>70 (9.93)</td>
</tr>
<tr>
<td>Type of headache</td>
<td></td>
</tr>
<tr>
<td>Pulsating</td>
<td>537 (76.17)</td>
</tr>
<tr>
<td>Non-pulsating</td>
<td>124 (17.59)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>321 (45.53)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>344 (48.79)</td>
</tr>
</tbody>
</table>

Although the mean total MSQ scores were comparable between males and female, majority of patients (39.29%) had trouble in concentrating on work or daily activities. High MSQ scores were reported in male patients with BMI < 18.5 kg/m² as compared to female patients (Table 4). Male patients had high MSQ scores in comparison to females indulged in consumption of alcohol and smoking.

The MSQ scores were comparable between males and females when the data was categorized by occupation. The MSQ scores were higher in female patients as compared to male patients in all category except clerical - shop owner and unskilled worker category (Table 4). Data categorized by monthly family income revealed high MSQ scores for females as compared to males in all categories of income slabs except INR 13495-17999 and INR 8989-13494. The MSQ scores were found to be higher in patients of age group 41-60 years having BMI < 18.5 and age > 61 years having BMI 23 – 27.5 kg/m² respectively.

The patients indulged in consumption of alcohol in age group 41-60 had higher MSQ than in age group 18-40. However, patients indulged in smoking in age group 18-40 had higher MSQ.
Migraine is reported as the leading cause of disability among neurological disorders, accounting for over half of all Years lived with disability (YLDs). It has been ranked as the third most common disease in the world in both males and females. With an estimated lifetime prevalence of 7-17%, approximately 12% of the adult population suffer from migraine in United States and Western Europe. In a recent study, migraine reported as highly prevalent ailment with age-standardized prevalence of one-year was 25.2% in Karnataka state in India. Furthermore, migraine is associated with substantial disability, especially among women and those living in rural populations. This assertion was supported in the current study in which approximately 81.0% patients were females and only 19.0% were males. Another study from India has reported 78.0% of female patients within the study cohort. It is also notable that migraine is found in 15–18% of population of the United States and Western Europe respectively. Literature has reported a wide range of age (5 to 28 years) of onset of migraine with an average at midteens. We noted mean onset age of 25.6 and 25.5 years in male and female respectively.

In our study, comparable proportion of patients reported unilateral and bilateral headache. Additionally, more than 3/4th patients demonstrated pulsatile headache than non-pulsatile headache. However a recent study found 59.8% of migraineurs develop unilateral headache, while in 40.2% cases pain was bilateral. While analysing the frequency of attacks, our study observed 1-10 attacks per month in most of our patients. This indicates a wide variability in the headache frequency and also that most of our patients had episodic and not chronic migraine. Bhatia and Gupta (2012) observed 3.5-times higher proportion of migraine in females as compared to males. Migraine is more commonly reported in patients between 20-45 years of age group. In the current study also, the mean age of patient with migraine was 35.16 years. This result is in agreement with another report in which majority of patients were in the age group of 31-40 years followed by 21-30 years. Jette et al (2012) reported migraine to be most common in patients between aged 18-40 years, 41-60 years, and > 61 years. The total mean MSQ score was numerically higher in patients with age 41-60 (73.0) years with monthly family income of INR 1803-5386 as compared to patients with age 18 – 40 years (Table 5).

### Discussion

Migraine is associated with various other disorders as comorbidities which complicate the its diagnosis and clinical manifestation. Clinical and
Table 4: Total MIDAS and MSQ scores as per gender

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MIDAS score</th>
<th>MSQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male n = 134</td>
<td>Female n = 571</td>
</tr>
<tr>
<td>Overall score</td>
<td>27.72±47.61</td>
<td>27.18±35.35</td>
</tr>
<tr>
<td>BMI‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>7.60±10.26</td>
<td>33.30±45.41</td>
</tr>
<tr>
<td>18.5 to 23</td>
<td>31.76±48.43</td>
<td>30.14±49.15</td>
</tr>
<tr>
<td>23 to 27.5</td>
<td>31.56±59.29</td>
<td>25.60±26.93</td>
</tr>
<tr>
<td>&gt;27.5</td>
<td>18.97±11.99</td>
<td>24.52±20.30</td>
</tr>
<tr>
<td>Personal habits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>33.86±61.31</td>
<td>18.17±6.52</td>
</tr>
<tr>
<td>Smoking</td>
<td>22.36±11.37</td>
<td>30.00±0.00</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profession</td>
<td>37.79±12.20</td>
<td>43.97±16.26</td>
</tr>
<tr>
<td>Semi-profession</td>
<td>39.79±12.43</td>
<td>43.32±11.73</td>
</tr>
<tr>
<td>Clerical, shop-owner</td>
<td>34.25±9.96</td>
<td>31.73±6.87</td>
</tr>
<tr>
<td>Semi-Skilled worker</td>
<td>43.38±9.80</td>
<td>46.50±8.04</td>
</tr>
<tr>
<td>Unemployed</td>
<td>34.67±12.05</td>
<td>38.18±11.54</td>
</tr>
<tr>
<td>Monthly family income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18000-36016</td>
<td>27.39±40.20</td>
<td>23.67±25.13</td>
</tr>
<tr>
<td>13495-17999</td>
<td>49.00±76.86</td>
<td>46.42±66.76</td>
</tr>
<tr>
<td>8989-13494</td>
<td>16.00±9.78</td>
<td>23.95±35.95</td>
</tr>
<tr>
<td>5387-8988</td>
<td>9.33±8.33</td>
<td>35.00±0.00</td>
</tr>
<tr>
<td>1803-5386</td>
<td>0</td>
<td>45.00±40.75</td>
</tr>
<tr>
<td>≤1802</td>
<td>0</td>
<td>350±0.00</td>
</tr>
</tbody>
</table>

†MIDAS: Migraine disability assessment; ‡MSQ: Migraine Specific Quality of life; †BMI: Body mass index

‡ Patients were asked to provide their response to each question using a standard 6-point Likert-type scale (0: none of the time; 1: a little bit of the time; 2: some of the time; 3: a good bit of the time; 4: most of the time; 6: all the time)

Community-based studies have demonstrated that psychiatric disorders, mood (major depression, unipolar and bipolar depression) and anxiety disorders (panic disorder and bipolar disorders) are frequently encountered among patients with migraine. In addition, the association of migraine and hypertension is also coincidental. In consistent with these evidences, the current study also observed highest occurrence of hypertension, followed by diabetes, asthma, anxiety. Notably, all these comorbidities were higher in females than males. This finding could be because in our study females outnumbered the males by a significant percentage. In patients with migraine and established comorbidities, a careful consideration of the different therapeutic option is imperative.

For acute attack, NSAIDs alone were prescribed in 74.5% (n=525) of cases in our study. NSAIDs are a usual first-line therapy for mild to moderate migraine. A 2007 meta-analysis reported that 200 mg and 400 mg doses of ibuprofen were effective in short-term pain relief in moderate to severe migraine. American Academy of Neurology recommends sumatriptan, ergotamine and its derivatives to be more effective than NSAIDs for acute attack. Sumatriptan was the most widely prescribed triptans (12.2%) in our study. Sumatriptan was prescribed in 11.1% cases for acute attack in a recently published study in India. In fixed dose combination therapy, we noted that more than one-fourth patients (29.2%) were on domperidone + naproxen followed by sumatriptan + naproxen (3.3%) in acute attack. The study clearly indicates that triptans still remain an underutilized modality for the abortive medications for migraine attacks. In the current study, approximately half of the patients (50.9%) were prescribed with propranolol, followed by flunarizine (39.9%), amitriptyline (19.2%), topiramate (17.3%) and divalproex (15.3%). Propranolol + flunarizine (3.7%) fixed dose combination was prescribed infrequently. The guidelines provided by the American Family Physician recommends the use of propranolol, timolol, amitriptyline, divalproex, sodium valproate and topiramate as the first-line medication in prophylaxis of migraine.
revealed that patients with migraine experienced some form of functional impairment in approximately 91% of cases. Moreover, severe headaches in 53% of these patients reported substantial impairment in daily activities which led to an ultimately bed rest. In our study, the analysis of mean values from MSQ questionnaires indicate a trend of worse HRQoL in females as compared to males. In MSQ questionnaires, females have poor HRQoL scores in different BMI groups, except those of underweight (<18.5 kg/m²) patients. However, analysis of MIDAS demonstrated worse HRQoL in females across the all BMI ranges. After stratifying patients as per the occupation and monthly family income, this study further found that mean HRQoL scores were comparatively poor in female than male in MSQ questionnaire. This trend may stem from the fact that the women may have more social and domestic responsibilities, with additional burden of taking care of their young children, apart from household and domestic responsibilities. The urban women could be in the process of their career advancement which in turn compromises their domestic and social atmosphere causing a poor HRQoL. However, in MIDAS questionnaire, the scores were relatively poor in males in occupation (semi-profession, clerical, shop-owner, semi-skilled worker and unskilled worker) and monthly income category (≥36017, 18000-36016 and 13495-17999). An Italian study concluded that deterioration in quality of life has substantial economic consequences; causes poor patient satisfaction, which in turn cause lapses from care and may increase the risk of self-medication which, eventually leads to medication overuse.

In conclusion, the evidence from present study suggests that migraine is associated with substantial disability, especially in women. The disease burden was observed to a lesser extent in 18-40 years of age group. NSAIDs was widely prescribed drug in acute attacks whereas propranolol was the most commonly used drug in migraine prophylaxis. The majority of patients were unemployed with moderate and severe disability. Many disorders were found to be comorbid with migraine, in particular cardiovascular diseases, diabetes mellitus and anxiety.

**Acknowledgement**

The authors would like to thank to all doctors at sites involved, Dr. Pankaj Aneja (Delhi), Dr. Ajay Kumar Vyas (Mumbai), Dr. Joseph Sebastian (Kottayam), Dr. M V Francis (Alappuzha), Dr. Tapas Banerjee (Kolkata), Dr. Yogesh Patidar (Mumbai), Dr. Manoj Rajani (Mumbai), Dr. Ashish Malhotra, (Kolkata), Dr. Suresh Kumar Somani (Kolkata), Dr. K K Jindal (New Delhi), Dr. Manish

---

**Table 5: Total MIDAS and MSQ scores as per age groups**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MIDAS score</th>
<th>MSQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18-40 yrs n = 510</td>
<td>41-60 yrs n = 174</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>27.29±36.90</td>
<td>25.45±38.41</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5 (underweight)</td>
<td>32.25±46.46</td>
<td>17.50±15.93</td>
</tr>
<tr>
<td>18.5 to 23 (normal)</td>
<td>29.52±44.24</td>
<td>33.21±33.67</td>
</tr>
<tr>
<td>23 to 27.5 (overweight)</td>
<td>26.79±36.51</td>
<td>22.71±25.78</td>
</tr>
<tr>
<td>&gt;27.5 (obesity)</td>
<td>23.67±19.45</td>
<td>22.97±19.25</td>
</tr>
<tr>
<td><strong>Personal habits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>33.90±62.69</td>
<td>20.29±11.16</td>
</tr>
<tr>
<td>Smoking</td>
<td>21.44±11.04</td>
<td>27.67±11.93</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>27.29±36.90</td>
<td>25.45±38.41</td>
</tr>
<tr>
<td>Profession</td>
<td>38.70±61.57</td>
<td>37.70±63.49</td>
</tr>
<tr>
<td>Semi-Profession</td>
<td>24.05±29.40</td>
<td>30.60±33.45</td>
</tr>
<tr>
<td>Clerical, shop-owner</td>
<td>22.59±14.98</td>
<td>19.38±11.31</td>
</tr>
<tr>
<td>Skilled worker</td>
<td>21.11±13.61</td>
<td>17.00±14.53</td>
</tr>
<tr>
<td>Semi-Skilled worker</td>
<td>57.56±93.23</td>
<td>18.80±4.97</td>
</tr>
<tr>
<td>Unskilled worker</td>
<td>20.04±8.93</td>
<td>22.43±12.08</td>
</tr>
<tr>
<td>Unemployed</td>
<td>24.18±24.20</td>
<td>23.23±34.23</td>
</tr>
<tr>
<td><strong>Monthly family income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥36017</td>
<td>26.82±38.74</td>
<td>22.39±25.62</td>
</tr>
<tr>
<td>18000-36016</td>
<td>24.97±26.70</td>
<td>22.10±32.83</td>
</tr>
<tr>
<td>13495-17999</td>
<td>39.20±56.61</td>
<td>55.06±80.52</td>
</tr>
<tr>
<td>8989-13494</td>
<td>22.33±35.80</td>
<td>23.63±21.24</td>
</tr>
<tr>
<td>5387-8988</td>
<td>17.50±24.74</td>
<td>14.00±2.83</td>
</tr>
<tr>
<td>1803-5386</td>
<td>48.00±46.41</td>
<td>33.00±0.00</td>
</tr>
<tr>
<td>≤1802</td>
<td>350±0.00</td>
<td>0</td>
</tr>
</tbody>
</table>

MIDAS: Migraine disability assessment; MSQ: Migraine specific quality of life; BMI: Body mass index
Sinha (New Delhi) and patients who participated in this study. The authors would also like to acknowledge site management and medical writing team (JSS India) for their efforts.

Study Support
This study was funded by Abbott India Limited.

Conflict of Interest
Dr. Singh has received research funding from Abbott as a consultant. Dr. Sarda and Dr. Hegde are employees of Abbott India Ltd.

References
Indian College of Physicians Position Statement: Addictive Disorders Among Persons with Diabetes Mellitus

Yatan Pal Singh Balhara1, Sanjay Kalra2, Pooja Patnaik Kuppili3, V Kalaiselvan4, AG Unnikrishnan5, Mangesh Tiwaskar6, Pramod Kumar Sharma7, Manisha Sahay8, Rakesh Sahay8, Banshi Saboo9, Milind Y Nadkar10, A Muruganathan11, Deepak Khandelwal12, Tarun Jeloka13, Sujoy Ghosh14, Bharati Dhorepatil15, Puneet Dhamija16, AK Das17, Ganapathi Bantwal18, Rajesh Badani13

Abstract
India is witnessing a steady increase in prevalence of Diabetes Mellitus (DM). A substantial proportion of persons with DM (around 17%) have been found to report co-occurring use of psychoactive substances. The addictive disorders involve pathological use of one or more of these psychoactive substances. Addictive disorders due to psychoactive substance use have a multi-faceted interaction with DM. Addictive disorders have important bearings on the treatment, course and outcome of DM. Addictive disorders co-occurring with DM are an important issue of clinical and public health concern. It is important for clinicians engaged in treatment and care of persons with DM and/ or addictive disorders to have clear understanding of the clinical issues relevant to co-occurring addictive disorders and DM. With this background, the Indian College of Physicians has developed a position statement, based on evidence-based recommendations, which addresses addictive disorders co-occurring with DM. The statement includes recommendations targeted at the clinicians engaged in treatment and care of persons with DM.

Background
India is witnessing a steady increase in prevalence of Diabetes Mellitus (DM). The number of persons with DM in the country are expected to rise to 57 million by the year 2025.1 A substantial proportion of persons with DM (around 17%) have been found to report co-occurring use of psychoactive substances, with tobacco and alcohol being the two of the most commonly used psychoactive substances.2 3 Opioids, cannabis, stimulants, benzodiazepines, inhalants are the other psychoactive substance that are abused in India, and are likely to be encountered among persons with DM. The addictive disorders involve pathological use of one or more of these psychoactive substances (also commonly known as alcohol, tobacco and other drugs- ATOD).

Addictive disorders due to psychoactive substance (ATOD) use have a multi-faceted interaction with DM. These two disorders have complex aetio-pathological association with each other, with a causal association suggested between DM and use of certain psychoactive substances. Evidence exists regarding diabetogenic potential of nicotine, alcohol (in heavy quantity), opioids and cannabis, as these have a tendency to cause hyperglycemia and insulin resistance.4-8 Addictive disorders also have important bearings on the treatment, course and outcome of DM. These disorders are known to worsen prognosis of DM by impairing glycemic control and hastening development of both microvascular as well as macrovascular complications.9-13 Persons with both addictive

1All India Institute of Medical Sciences, New Delhi; 2Bharti Hospital and B.R.I.D.E., Karnal, Haryana; 3JIPMER, Puducherry; 4Indian Pharmacopeia Commission, Ghaziabad, Uttar Pradesh; 5Chellaram Diabetes Institute, Pune, Maharashtra; 6Asian Heart Institute & Research Centre, Mumbai, Maharashtra; 7All India Institute of Medical Sciences, Jodhpur, Rajasthan; 8Osmania Medical College, Hyderabad, Telangana; 9Dia Care - Diabetes Care and Hormone Clinic, Ambawadi, Ahmedabad, Gujarat; 10Seth G.S. Medical College & KEM Hospital, Mumbai, Maharashtra; 11Coimbatore, Tamil Nadu; 12Maharaja Agrasen Hospital, Punjab Bagh, Delhi; 13Aditya Birla Memorial Hospital, Pune, Maharashtra; 14IGPGMER, Kolkata, West Bengal; 15Shree Hospital, Pune, Maharashtra; 16All India Institute of Medical Sciences, Rishikesh, Uttarakhand; 17Pondicherry Institute of Medical Sciences, Puducherry; 18St. John's Medical College & Hospital, Bengaluru, Karnataka

Received: 01.03.2017; Accepted: 15.03.2017

Received: 01.03.2017; Accepted: 15.03.2017
disorders and DM have a high risk for developing medical comorbidities and hospital readmissions. Psychoactive substance use has been found to adversely affect diabetic self care behaviours. Moreover, complex relationship exists between cessation of substance use and improvement of glycemic status.

Addictive disorders co-occurring with DM are an important issue of clinical and public health concern. Further, management of DM co-occurring with substance use (addictive) disorders is even more challenging in India, which faces a high patient burden, but has relatively limited infrastructure and trained human resources to address the issue. It is important for clinicians engaged in treatment and care of persons with DM and/or addictive disorders to have clear understanding of the clinical issues relevant to co-occurring addictive disorders and DM. Currently, there are no recommendations or guidelines addressing co-occurring addictive disorders among persons with DM.

With this background, the Indian College of Physicians has developed a position statement, based on evidence-based recommendations, which addresses addictive disorders co-occurring with DM. The statement includes recommendations targeted at the clinicians engaged in treatment and care of persons with DM.

### Scope and Purpose

The objective of this position statement is to offer clinical recommendations for screening, diagnosis and management of co-occurring addictive disorders among persons with DM. The document aims to provide education to clinicians engaged in care and management of persons with co-occurring addictive disorders and DM, and improve access to treatment for co-occurring addictive disorders among persons with DM.

### Intended Audience

The position statement is targeted the clinicians engaged in care at and management of persons with DM. Policy makers, program planners, and community medicine specialists may find this position statement useful. While Indian in origin, this document is global in its coverage and reach.

### Limitations

The position statement is based on comprehensive coverage of best available evidence. There is limited literature that has explored the management of co-occurring addictive disorders among persons with DM. Moreover, most of this evidence is from a few countries. The position statement is not a substitute to the clinical practice guidelines and, in fact, is best used in combination with existing guidelines on management of DM and addictive disorders.

### Grading of Evidence

The current recommendations are graded based on the available evidence. The available evidence for individual recommendation is categorized in different levels as strong, intermediate, weak and no evidence. The strength of the recommendations are based on the level of evidence for the specific recommendation. The categories of the level of evidence and strength of recommendation are listed in Tables 1 and 2, respectively. The American Association of Clinical Endocrinologists has used such an approach previously for various recommendations pertaining to DM. Majority of the recommendations are extrapolated from literature available on substance use disorder, as limited literature exists about DM co-occurring with substance use disorders.

### Clinically Relevant Issues Related to use of Psychoactive Substances (ATOD) by Persons with DM

#### Adverse impact of psychoactive substance (ATOD) use on DM

- Alcohol, tobacco and other drugs (ATOD) are not recommended in patients with DM as they are known to impair glycemic control and accelerate development of complications. (1A)
- Persons with psychiatric illness co-occurring with DM have a greater prevalence of alcohol, tobacco and other drugs (ATOD) use and greater risk of relapse after quitting. (3B)
Table 3: Interaction between alcohol and medication metabolised by Cytochrome P

<table>
<thead>
<tr>
<th>Duration of alcohol use</th>
<th>Current state</th>
<th>CYP activity</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular moderate drinkers</td>
<td>Moderate alcohol consumption</td>
<td>Competition between alcohol and medication</td>
<td>Decreased metabolism</td>
</tr>
<tr>
<td>Chronic heavy drinkers</td>
<td>Sober</td>
<td>Increased</td>
<td>Decreased excretion</td>
</tr>
<tr>
<td>Chronic heavy drinkers</td>
<td>Intoxicated</td>
<td>Activated</td>
<td>Higher medication level</td>
</tr>
</tbody>
</table>

- **Binge drinking is not recommended in patients with DM as it is known to precipitate diabetic ketoacidosis as well as accelerate development of retinopathy and peripheral neuropathy.** \(3B\)\(^{32}\)

**Socio-Culturally acceptable substance use**

- **Persons with DM must be advised not to use any form of substance of addictive potential, including hookah, areca nut (supari), betel quid (paan), gul (tobacco), even if socioculturally accepted.** \(3B\)\(^{33}\)

**Alcohol – Drug interactions in persons with DM**

Pharmacokinetic interactions between alcohol and medications metabolized by Cytochrome P (CYP) given below are relevant to the context, as many oral glucose lowering drugs (OAD) are metabolized by CYP.\(3B\)\(^{(Table 3)}\).\(^{34}\)

**Pharmacodynamic interactions**

- Disulfiram like reaction can be caused by conventional sulfonylureas like chlorpropamide, glyburide, tolazamide and tolbutamide after alcohol consumption. \(3B\)\(^{34}\)
- The levels of lactic acid may be increased in patients taking metformin after alcohol consumption. \(3B\)\(^{34}\)
- Patients on OAD are at greater risk of hypoglycemia on consumption of alcohol. \(3B\)\(^{34}\)
- The effects of benzodiazepines on CNS such as sedation, drowsiness are increased by alcohol. This needs to be taken into account by clinicians treating patients with DM with alcohol dependence. \(3B\)\(^{34}\)
- Histamine 2 receptor blockers like ranitidine which are commonly prescribed for relieving dyspepsia in patients with alcohol use disorders block alcohol dehydrogenase. Thereby blood alcohol level may be higher than what is expected for the given dose of alcohol. \(3B\)\(^{34}\)

**Screening for addictive disorders among persons with DM**

**General recommendations**

- Every person with DM must be asked about psychoactive substance (ATOD) use \(3B\)\(^{38}\)
- Screening for psychoactive substance (ATOD) use is highly recommended in the following clinical situations \(4D\):
  - Difficulty in controlling the use with increasing pattern of substance use
  - Difficulty in functioning in social and occupational domain secondary to increasing time and amount of substance used
  - Patients presenting with symptoms of withdrawal such as restlessness, nausea, vomiting, body aches, tremor, seizure, confusional state
  - Patients presenting with symptoms of intoxication such as slurring of speech, gait disturbance, red eyes
  - Medical complications of substance use
  - Worsening glycemic profile with increasing trend of substance use
  - Frequent episodes of hypoglycemia
- Young persons with DM must be specifically asked about illicit drug use such as cannabis, cocaine, heroin, and ecstasy, as these are commonly
used in this age group and can accelerate development of complications.\(^{2B}\)\(^{36,37}\)

- History about psychoactive substance (ATOD) use must be obtained systematically and should include details on duration, quantity, frequency, last dose and the usual dose. (4D)

**Screening tools**

- Screening tools recommended for assessing psychoactive substance (ATOD) include ASSIST (Alcohol Smoking Substance Involvement Screening Test), AUDIT (Alcohol Use Disorders Identification Test), CAGE (1B) and Fagerström Test for Nicotine Dependence (FTND). (1B)\(^{38-43}\)

- ASSIST is a clinician rated questionnaire which consists of 8 questions screening for various substances of abuse namely alcohol, tobacco, cannabis, amphetamines, cocaine, inhalants, sedatives, hallucinogens, opioids. It assesses the substance use pattern and gives the cut off values for brief intervention and intensive intervention. (1B)\(^{38}\)

- AUDIT is a 10 item screening instrument assessing domains of alcohol consumption, drinking behavior, and alcohol-related problems. The cut-off value of 8 points is used for harmful or hazardous drinking. (1B) (Table 4)\(^{39}\)

- CAGE questionnaire\(^{42}\) consists of four simple questions and answering yes to two questions is a strong indication towards alcohol dependence (1B). The questions are as follows:
  - Have you ever felt you needed to cut down on your drinking?
  - Have people annoyed you by criticizing your drinking?
  - Have you ever felt guilty about drinking?
  - Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover?

- FTND\(^{43}\) is a 6 item questionnaire assessing nicotine use and gives score for various severity of dependence

**Diagnosis of addictive disorders co-occurring with DM**

- Persons who screen positive for psychoactive substance (ATOD) are recommended to be further evaluated for dependence or harmful use. Diagnosis for dependence or harmful use can be established through the following criteria as laid by International Statistical Classification of Diseases and Related Health Conditions (ICD)-10.\(^{44}\)
  - A diagnosis of harmful use refers to a pattern of psychoactive substance use that is causing damage to health i.e. either physical or mental harm
  - A diagnosis of dependence can be made if three or more of the following criteria have been present over the previous 12 months:
    - Strong desire or sense of compulsion to take the substance
    - Difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use
    - A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms
    - Evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses
    - Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects
    - Persisting with substance use despite clear evidence of overtly harmful consequences

**Treatment of addictive disorder co-occurring with DM**

- Integrated management of co-occurring addictive disorder and DM is recommended.

- A comprehensive management plan including pharmacological and non pharmacological interventions is recommended.

**Non-pharmacological treatment**

- Anti-craving measures in form of reducing exposure to stimulus (stimulus control), coping imagery, “urge surfing” incorporating 5 ‘D’ approach may be recommended to the persons with co-occurring addictive disorders. (3B)\(^{46}\) The 5 ‘D’ include:
  - Delay the urge
  - Distract yourself
  - Drink water
  - Deep breathing
  - Discuss with someone

- Nicotine cessation counseling in form of 5 ’A’ approach is recommended for tobacco users
who are willing to quit. (3B). The 5 ‘A’ approach includes
- Ask about tobacco use at each visit
- Advise to quit
- Assess willingness to quit
- Assist in quitting
- Arrange for follow up
  • Nicotine cessation counselling in form of 5 ‘R’ approach is recommended for tobacco users who are not willing to quit. (3B). The 5 ‘R’ approach includes
    - Relevance of quitting tobacco to the patient
    - Risks of tobacco use
    - Rewards of tobacco cessation
    - Roadblocks to quit
    - Repetition of the message to quit

  • Evidence based psychosocial interventions include Cognitive-behavioral therapy (CBT) including relapse prevention (RP), motivational enhancement/motivational interviewing (MI), Contingency management (CM), and brief interventions (BI). Brief intervention (BI) is recommended for persons with DM with harmful use of. (1A) Components of BI strategy can be summarized using the acronym FRAMES and it stands for:
    - F- Feedback
    - R- Responsibility

  • Principles of CBT include evaluating and challenging cognitive distortions (dysfunctional thoughts) about substance and assessing factors such as “Apparently Irrelevant Decisions” leading to relapse. Relapse prevention is an important component of treatment. It may not be feasible to apply all the strategies of Relapse Prevention by a busy clinician. Thereby the physician may adopt one of the relapse prevention strategies which are relevant and feasible, individualized and tailor made for every patient. It is recommended to offer RP under guidance of mental health professional.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Score/ risk level</th>
<th>Recommended intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSIST</td>
<td>Lower risk</td>
<td>General health advice</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Brief intervention</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Brief intervention</td>
</tr>
<tr>
<td></td>
<td>Moderate &amp; high risk</td>
<td>Referral to specialist assessment &amp; treatment</td>
</tr>
<tr>
<td></td>
<td>- injected drugs in last 3 months</td>
<td>Referral for testing for blood borne infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUDIT</td>
<td>8-15</td>
<td>Simple advice focused on reduction of hazardous drinking</td>
</tr>
<tr>
<td></td>
<td>16-19</td>
<td>Brief counselling</td>
</tr>
<tr>
<td></td>
<td>20 or above</td>
<td>Assess for dependence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Referral to mental health professional</td>
</tr>
</tbody>
</table>

  • Principles of CBT include evaluating and challenging cognitive distortions (dysfunctional thoughts) about substance and assessing factors such as “Apparently Irrelevant Decisions” leading to relapse. Relapse prevention is an important component of treatment. It may not be feasible to apply all the strategies of Relapse Prevention by a busy clinician. Thereby the physician may adopt one of the relapse prevention strategies which are relevant and feasible, individualized and tailor made for every patient. It is recommended to offer RP under guidance of mental health professional.

  • A- Advice
  • M- Menu of options
  • E- Express Empathy
  • S- Support self efficacy

  • Brief intervention (BI) is recommended for persons with DM with harmful use of. (1A) Components of BI strategy can be summarized using the acronym FRAMES and it stands for:
    - F- Feedback
    - R- Responsibility

  • Evidence based psychosocial interventions include Cognitive-behavioral therapy (CBT) including relapse prevention (RP), motivational enhancement/motivational interviewing (MI), Contingency management (CM), and brief interventions (BI). Brief intervention (BI) is recommended for persons with DM with harmful use of. (1A) Components of BI strategy can be summarized using the acronym FRAMES and it stands for:
    - F- Feedback
    - R- Responsibility

  • Principles of CBT include evaluating and challenging cognitive distortions (dysfunctional thoughts) about substance and assessing factors such as “Apparently Irrelevant Decisions” leading to relapse. Relapse prevention is an important component of treatment. It may not be feasible to apply all the strategies of Relapse Prevention by a busy clinician. Thereby the physician may adopt one of the relapse prevention strategies which are relevant and feasible, individualized and tailor made for every patient. It is recommended to offer RP under guidance of mental health professional.

  • A- Advice
  • M- Menu of options
  • E- Express Empathy
  • S- Support self efficacy

Role of Diabetic Counselor
• In the background of scarcity of trained personnel, the concept of task shifting is well established. Diabetic counselors can be trained to offer psychoeducation as well as deliver psychosocial interventions such as Brief intervention, and Motivational interviewing. (4B)

Pharmacological management of nicotine dependence
• Low quality evidence exists regarding the role of electronic cigarette in smoking cessation. (1A)
• NRT is recommended for increasing the rate of quitting, as it shows 50 to 70% efficacy in any setting. (1A)
• Limited evidence exists for the role of varenicline, bupropion and cystine in the management of nicotine dependence and further research is needed before recommending the use of the above mentioned agents in long term management of nicotine dependence. (1A)
Pharmacological management of alcohol dependence

- **Patients with alcohol dependence with no history of withdrawal seizures or delirium tremens can be managed in an out-patient setting.** *(4A)*

- **Management of alcohol dependence includes two phase. Phase one (short-term management) (detoxification phase), involves use of benzodiazepines to manage withdrawal symptoms which may be managed by the physician. Phase two (maintenance phase) involves use of anti-craving agents and/or deterrent agent which should be supervised by the mental health professional.** *(58)*

  **Short-term management of alcohol dependence**

  - For detoxification, patient is given benzodiazepines for 7-10 days such as diazepam (20-60 mg/day), lorazepam (4-12 mg/day), clordiazepoxide (50-120 mg/day). *(1A)* The exact dose is decided by a host of factors including the age, subjective and objective withdrawals, level of subjective comfort, general physical condition, etc. *(4A)*

  - Lorazepam is preferable to diazepam or clordiazepoxide in cases of deranged hepatic laboratory profile. *(4A)*

  - **Benzodiazepines are recommended to be gradually tapered and stopped due to risk of seizures.** *(4A)*

  - Parenteral thiamine 100 mg/day is recommended for 5-7 days followed by oral thiamine for a minimum of three months. *(4A)*

  - **Correction of nutritional deficiencies and symptomatic management of gastrointestinal symptoms are recommended.** *(4A)*

  - **Disulfiram has been found to be cost effective in the Indian setting. However it needs to be prescribed considering the level of motivation and side effect profile. It should be used with extreme caution among persons with DM, especially if the glycemic control is poor, and the risk of hypoglycemic episodes and ketoacidosis is perceived to be high.** *(4A)*

  - Acamprosate is recommended as an anti-craving agent in patients with compromised liver function and where complete abstinence is required. *(1B)*

  - Naltrexone in recommended as anti-craving agent in patients with intense craving and controlled drinking and with comorbid opioid dependence. *(1B)*

  - **Pharmacological management of opioid dependence**

  - **Short-term management of opioid dependence**

    - Long-term maintenance agents include anti-craving agents such as acamprosate, naltrexone, buprenorphine, topiramate and deterrent agent like disulfiram. However, the evidence base in terms of efficacy of these medicines is modest. Recent evidence supports the use of acamprosate, naltrexone and disulfiram. *(1A)*

    - The choice of anti-craving agent or deterrent agent should be guide by multiple factors including the availability, accessibility, side effect profile, past response, personal preference and drug interactions. *(4A)*

    - **Long-term maintenance of opioid dependence**

      - The treatment of choice for long term management needs to be finalized through shared and informed decision making by patient and mental health professional, considering the role of patient related factors such as motivation and availability. *(4A)*

      - **Agonist maintenance termed as “Opioid Substitution Therapy” is recommended with methadone being found superior to buprenorphine in retaining patients.** *(2B)*

        However the accessibility, availability, need for supervised administration and risk of diversion are some of the factors limiting its use.

      - **Buprenorphine is recommended in patients above 21 years of age, with at least 5 years of opioid use, with at least two unsuccessful abstinence attempts from recognized treatment centers.** *(4B)*

      - **In patients with good motivation, shorter duration of opioid dependence (3 years or less), good social support, good occupational functioning, who had earlier been on agonist maintenance for several months, opting for abstinence and antagonist medication, naltrexone is recommended.** Combining naltrexone therapy with behavioural therapy is recommended to improve treatment retention. *(2B)*

  - **Management of Cannabis dependence**

    - The cannabis withdrawals can be managed symptomatically using long acting benzodiazepines such as diazepam. *(4C)*

    - **Management of cannabis**
dependence is mainly through non-pharmacological means i.e. psychosocial interventions. No robust evidence exists regarding role of pharmacotherapy. (4B) 68

• A combination of Motivation Enhancement Therapy with Cognitive Behavioural Therapy (CBT) is recommended as psychosocial intervention for cannabis dependence. (1C) 69

Management of Co-occurring Mental Disorders

• Patients must be actively screened for presence of co-occurring mental disorders at every follow-up. (4A)

• Appropriate assessment and management should be imitated at the earliest for those diagnosed with co-occurring mental disorders. (4A)

Active Monitoring and Follow Up

• Serial monitoring of liver function is recommended in patients with DM with alcohol use disorder. (4A) 70

• Patients with co-occurring addictive disorders and DM must be monitored for drug interactions, effects of OHA mimicking alcohol intoxication and benzodiazepines for episodes of hypoglycemia. (4A) 71

• Patients must be actively asked for substance use in the follow-up. (4A) 71

• Patients who are unable to abstain despite the intervention measures may have co-occurring psychiatric disorder and should be referred to psychiatrist for detailed assessment. (4A) 71

Referrals of Persons with Addictive Disorders Co-Occurring with DM

• Referral must include the details of the patient, treatment given both for DM as well as addictive disorders and the reason for referral. (4D) 71

• Patients with complicated alcohol withdrawal (withdrawal seizures / delirium tremens) or severe withdrawal may be referred to an in-patient setting. (4D)

• Patients who are unable to abstain on outpatient basis following psychosocial interventions administered by clinician / counselor should be referred to mental health professional. (4D) 71

• Suspicion of presence of co-occurring psychiatric comorbidity warrants referral to mental health professional. (4D)

• Patients with suicidal ideation or past history of suicide attempts should be referred to mental health professional. (4D)

• Patients who need specialized psychosocial intervention such as Motivation Enhancement Therapy / Cognitive Behavioural Therapy should be referred to mental health professional. (4D)

• Patients belonging to special groups such as child and adolescents, pregnant women and geriatric age groups should be referred to mental health professional. (4D)

• Patients suffering with other physical comorbidity like HIV/ Hepatitis/ TB should be referred to mental health professional. (4D)

Summary

This ICP document summarizes evidence based recommendations related to the management of addictive disorders in persons with DM. It is hoped that this will improve the quality of care, and encourage further research on this important aspect of medicine.

References


17. Ahmed AT, Karter AJ, Warton EM, et al. The...


47. World Health Organization, 2014. Toolkit for delivering the 5A’s and SR’s brief tobacco interventions to TB patients in primary care.


An Introduction to Meta-Analysis

NJ Gogtay, UM Thatte

Introduction

Whether it is conducting a general literature search or finding an answer to a specific research question, clinicians, researchers and policy makers alike are faced with a huge volume of information that does not necessarily give them an answer to what they are seeking to find. For instance, if they are looking to answer the question is Drug A a better anti-hypertensive than Drug B, they are likely to find studies of three types – 1) Where the answer is equivocal, or 2) favors A or 3) favors B. Thus, results of a search often do not direct them to a clear, coherent or cogent result. While researchers are usually able to deal with ambiguity, practicing clinicians and policy makers can easily get befuddled with it. Thus, a single paper that summarizes and synthesizes all relevant papers to answer a specific research question with the help of statistics would be of great value. A meta-analysis is that single paper.

Definitions and Historical Perspective

The first definition of meta-analysis was given by Gene Glass [1976] as “the statistical analysis of a large collection of results from individual studies for the purpose of integrating the findings”. Glass also called meta analysis as “an analysis of analyses”. The Greek word “meta” refers to “after” or beyond and therefore meta-analysis go beyond individual studies. Huque [1988] defined the term as “A statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be combinable”. Historically, it was social scientists and statisticians in America who began to actively develop methods that would deal with large volumes of data and quantitatively synthesize them.

Why a Meta-Analysis is Needed

There are several reasons why it is commonplace to find results of studies that are asking similar research questions to be at variance with each other. This diversity that inherently exists amongst studies is called heterogeneity [see later].

These include-
1. Use of different case definitions for the disease under investigation [for instance, bleeding due to warfarin in one study may include mild bleeds only while another study may include hospitalizations and deaths due to bleeding which are severe events].
2. The study population may come from different parts of the same country or even from different countries [this would be important in infectious diseases like malaria where resistance patterns vary from country to country and within the same country].
3. The inclusion and exclusion criteria may vary and methodology to arrive at conclusions may be different [for example, peripheral smear diagnosis of malaria in one study to PCR based diagnosis in another].

One way of combining all studies on a particular topic is the traditional narrative review. This review typically combines several studies in a chronological discourse by an expert in that field. While the research question itself for the review may be well thought through, these reviews tend to be largely subjective and prone to bias as they are dependent upon the expert evaluating the studies, quality of the search and number of studies identified therein. They are also easier to carry out when the number of studies is not too many. Additional disadvantages include different researchers coming to different conclusions and lack of critical and in-depth analysis of each study included in the review. Meta-analyses, on the other hand, offer the advantage of applying objective statistical criteria, including addressing the variability between studies (heterogeneity) and thus can easily be done with the ready to use software [combined with training] regardless of the number of studies that need to be synthesized.

The Distinction between a Systematic Review and a Meta-Analysis

A term that is often used alongside a meta-analysis is “systematic review”. The two terms are also erroneously used as synonyms. A systematic review is
a type of review which answers a focused research question, and within which “meta-analyses” may or may not be a part.5 Systematic reviews typically have a specifically formulated research question, a clear search strategy, a pre-decided protocol that includes methods to identify which studies are to be included [or excluded based on selection criteria], quality assessment of studies and methods to analyze the ones included. When systematic reviews contain a statistical synthesis of the included studies to generate a single number this becomes a meta-analysis. Thus, systematic reviews can be standalone [without a meta-analysis] or include a meta-analytic component. In summary, a Meta-analysis refers to that portion of the systematic review that involves the statistical analysis. Since there is a fair amount of overlap between the two, one or both may be alluded to as appropriate within individual sections of this paper.

Steps in a Meta Analysis

A total of seven steps need to be followed while conducting a systematic review and/or meta-analysis. These include-

1. Formulating a research question
2. Writing the protocol and registering it in public domain
3. Identification of the studies using a clear and comprehensive search strategy
4. Selecting the right studies to be included [based on the protocol]
5. Data abstraction
6. Quality Assessment of included studies
7. Statistical analysis [including generating the Forest plot]

Each of these steps is now described in detail.

Step 1- Formulating the Research Question

Perhaps the most important step of clinical research in general and meta-analysis in particular, is to formulate the research question well. This is the uncertainty or lacuna that the researcher is attempting to answer. Asking the right question will lead to the right study design, an appropriate literature search strategy and statistical analysis that will generate the right research evidence that is needed to drive practice decisions. Thus, it ensures that the question will be answered in all likelihood. There are several choices available for formulating a research question and these are given below given by acronyms or mnemonics.

I. PICOT

A widely accepted and used acronym or mnemonic for formulating a research question is PICO or PICO[T].6 It stands for

P- Patient or Problem or Population
I- Intervention
C- Control
O- Outcome
T- Time

It essentially involves breaking down the research question into five components that ensures that the researcher and the reader are able to identify its’ individual elements.

Let us understand this with a classical meta-analysis from published literature. Lau J and colleagues [1992] performed a meta-analysis of n = 33 trials done between 1959 and 1988 that evaluated the impact of streptokinase on mortality after an acute coronary syndrome. The meta analysis showed a 21% reduction in death following the use of streptokinase.

The PICOT for this study would be framed as follows

P- In patients with acute myocardial infarction
I - Does treatment with intravenous streptokinase
C- Compared to placebo
O- Impact mortality?

II. ECLIPSE7

This stands for Expectation [what does the search requester want the information for], Client Group [for whom is the service intended], Location [where is the service physically situated], Impact [what constitutes success and how is this measured?] Professionals [who provide or improve this service], Service [Its nature- outpatient/inpatients/day care only and so on]. The mnemonic helps formulate research questions in the area of health policy management. For example, the Director of a major hospital may be interested in reducing the waiting time for out-patients who visit his hospital. The ECLIPSE for this study would be as follows

E- Reduce patient waiting time
C- All out-patients visiting the hospital
L- Hospital located at south end of the city
I- Impact- Reduction [by at least 15 minutes] in waiting time measured in minutes
P- All doctors or department/s who evaluate these out-patients
S- Outpatients who attend the hospital

However, not all questions are well served by the PICOT or the ECLIPSE mnemonics. Hence, other authors have proposed other models that can be used and the acronyms are listed below. These include

S P I D E R "- Sample, Phenomenon, Design, Evaluation and Research type [largely for qualitative research and/or mixed research methods


8
Table 1: Elements that should be included in a protocol for a meta-analysis

<table>
<thead>
<tr>
<th>Elements that should be included in a protocol for a meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong> Describes the key contextual and conceptual factors relevant to the review question and provide the justification for the review.</td>
</tr>
<tr>
<td><strong>The research question using the PICOT format</strong> Clear search strategy including databases that will be searched for identifying the research evidence.</td>
</tr>
<tr>
<td><strong>Describe inclusion and exclusion criteria</strong> Describe how studies will be shortlisted for final inclusion.</td>
</tr>
<tr>
<td><strong>Describe process of Data extraction</strong> Describe how studies will be shortlisted for final inclusion.</td>
</tr>
<tr>
<td><strong>Pre-specify the tool/s to be used for assessment of quality of the included studies</strong> Describe how results will be synthesized.</td>
</tr>
</tbody>
</table>

The choice of model (random effects/fixed)

[that involve a combination of quantitative and qualitative research], SPICE - This stands for Setting [where?], Perspective [for whom?], Intervention [what is being tested?], Comparison [versus what?] and Evaluation [with what result?]. This mnemonic is believed to work well in the context of social sciences research and COPES - Client Oriented Practical Evidence Search (COPES) which addresses problems seen in day to day practice.

**Step 2- Writing and registering the study protocol**

The protocol for a systematic review and/or meta-analysis should clearly state the rationale, objectives, search strategy, methods, end points and quality checks that would be used. The PRISMA [Preferred Reporting Items Systematic Reviews and Meta-Analyses] guidelines recommend registration of the protocol à priori. Registration ensures that the protocol and the systematic review [with or without a meta-analytic component] are available from the Cochrane Database of Systematic Reviews [CDSR]. In 2007, the Indian Council of Medical Research [ICMR] became the first low income country to purchase national access for Indians with internet to the Cochrane Library through an agreement with the publishing partner of The Cochrane Collaboration, John Wiley and Sons Limited. This access continues with a recent renewal of the agreement with John Wiley and sons.

One feature that is unique to the Cochrane reviews is that they are dynamic and updated as and when new evidence emerges. Non-Cochrane systematic reviews and meta-analysis can be registered with PROSPERO [International Prospective Register of Systematic Reviews - http://www.crd.york.ac.uk/Prospero/] an international database that has been set up by the University of York and is free. From October 2013, PROSPERO also docks Cochrane protocols [these automatically get added to the PROSPERO database].

All elements that should necessarily be present in a protocol for a meta-analysis are outlined in Table 1. The Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA-P 2015) is a 17-item checklist that helps authors in preparing a robust protocol. This can also be used by peer reviewers and editors to assess the quality of systematic reviews and/or meta-analysis protocols submitted.

**Step 3 - Identification of the studies using a clear and comprehensive search strategy**

The search strategy should be all encompassing and ensure that all relevant articles are retrieved. Serious bias and erroneous conclusions may be drawn if the search strategy is poor. As many databases as possible should be included with the search being tailored for each individual database. Sensitivity of a strategy refers to identification of as many potentially relevant articles as possible. Specificity refers to picking up the definitely relevant articles. All search strategies should aim at maximizing sensitivity so as not to miss articles that are likely to be relevant.

Commonly searched databases include National Library of Medicine [Medline], Experta Medica Database [EMBASE], Biosciences Information Service [BIOSIS], Cumulative Index to Nursing and Allied Health Literature [CINAHL], Health Services Technology, Administration and Research [HEALTHSTAR], and Cochrane’s central register of controlled trials. Boolean operators [AND, OR, NOT] should be used along with search terms to narrow or broaden the search. All databases have filters [for example type of article, language of publication, dates of publication, age of participants and so on] and these should be used to narrow down the results to those articles likely to be relevant to the research question. In addition, the search should also include evaluating the cross-references from the articles retrieved. Use of controlled vocabulary [subject headings only] may result in a sub optimal yield. Therefore, uncontrolled vocabulary for example, variations such as abbreviations, generic name, terms used internationally, differential spellings used in another country and so on should also be used in the search.

Given that negative results are often not published, the search strategy should also include [to the extent possible] unpublished data, thesis/project reports that may be available on Institutional or University websites, conference proceedings and abstracts and telephonic/email contact with trialists and experts in that field. Developing a search strategy is an iterative process- that is a
process of continual assessment and refinement

Citation managers- Once the results from the search are available, it is useful to export them into a citation manager. The advantage of these is that as they are electronic, preclude manual errors, eliminate duplicates, save time and also back up search results. Zotero and Mendeley are two citation managers that available free for use. EndNote and RefWorks are paid software. Citation managers also incorporate an array of reference styles and in the event that the paper is rejected by one journal, it is easy to change the formatting and style of referencing for another journal.

Step 4- Selecting the right studies to be included - narrowing the results of a search strategy to a final number

The next step is to read the title and abstract of each reference obtained and eliminate those that are not relevant. Subsequently, we obtain full texts of potentially relevant articles [those likely to pass the selection criteria]. The focus while reading the full text should remain on the methods and results section rather than the Introduction.

Step 5- Data Extraction

Once the final list is ready, from each article, depending upon the protocol, we extract the relevant information-case/disease definitions used, key variables, study design, outcome measures, nature of participants; therapeutic area, year of publication; results; setting and so on. These will now need to be fed into the software for analysis [Revman, see later].

Step 6- Quality assessment of included studies

Once the number of studies to be included is firmed, it is important to assess their quality. This is because a flawed study is in fact worse than no study at all. Several methods are available to assess quality of studies, each with its own merits and demerits. These include among others, the Jadad score,20 the CONSORT statement,21 and the Cochrane Back Review Group criteria.22 We describe the Jadad score here as an illustrative example. It is a 5 point score where one point each is allocated to randomization, description of the method used for generating the random sequence, whether or not blinded, description of the method used for blinding/masking and clear cut information on drop outs and withdrawals. One point each is deducted if randomization is described but the method therein is inappropriate and if blinding is described but again the method for binding is inappropriate [flawed]. Its strength lies in brevity and thereby ease of use. For example, Boussagen [2013] conducted a meta-analysis of RCTs that evaluated all cause mortality and deaths from cardiovascular events related to intensive glucose lowering treatment in people with type 2 diabetes. Quality of the RCTs was assessed using the Jadad score. Studies with a score of more than 3 were indicative of high quality. The overall meta-analysis using all studies irrespective of the quality (as assessed by their Jadad score) showed limited benefits of intensive glucose lowering treatment. This was confirmed by evaluating only studies with a Jadad score of more than 3 which also showed that intensive treatment was NOT associated with any benefit.23

Step 7 - Statistical analysis of included studies

Understanding what Effect Size is

One term that is frequently used in meta-analysis [and subsequently used in this paper] is “effect size” which represents the basic unit of a meta-analysis. We have seen this earlier in the article on sample size calculation.24 When we compare two interventions [say A and B], we are seeking to find the difference between them. Meta – analysis is also about A vs. B comparisons. Simply put, the effect size is the difference between A and B and the “size” or “magnitude” of this difference. This is a standardized metric that expresses the difference between two groups- usually an experimental and a control group.25 The effect size can be expressed as any one of these metrics- odds ratio, risk ratio, standardized mean difference, person time data and so on.

Statistical synthesis of data-Once data from all the shortlisted studies is ready, it is fed into Revman (see later). The two commonly used methods for analysis are Mantel-Haenszel [Fixed effects model, see below] and DerSimonian-Lard [Random effects model, see below].26 Both methods essentially provide a single number or summary statistic along with 95% Confidence Intervals, which is the goal of any meta-analysis.

Allocating weights to the different studies –As the ultimate goal of any meta-analysis is to estimate one overall effect after pooling all the studies; one way of doing it is to simply add all effect sizes and compute their mean. However, each study in a meta- analysis is actually different from the other. Hence, we allocate a “weight” to each study- in other words, we give more weight to some studies and less to the others and compute a “weighted mean”. How do we decide how much weight each study should get? This is driven by two key factors- the sample size of the study [bigger the better] and the outcomes in each study [the more the better].

Fixed and random effects models-In the fixed effects model, we assume that the effect size in all included studies is identical and any difference between them is a result of differing sample sizes and associated variability, and hence the term “fixed effects”. Thus, when we allocate weights to the studies [see below], the studies with smaller sample sizes get a lower weight and the larger studies a higher weight. In the
random effects model on the other hand, we assume that each study is unique and therefore will have its own effect size. Here, unlike the fixed-effects model, the studies with smaller sample sizes are not discounted by giving them lower weights as each study is special and is believed to make an equally important contribution to the overall analysis. The random effects model is based on the assumption that if a large number of studies for the same research question using the pre-set selection criteria, the true effect sizes for all these studies would be distributed about “a” mean. The studies included in the meta-analysis are believed to represent a “random” sample from this larger number. Hence the term “random effects”. Thus, the weights allocated in the random effects model are more balanced [relative to the fixed effects model].

In the former, the only source of uncertainty lies within the study itself, whereas in the latter model, we also take the between study variance into account. Thus, the fixed-effects model will have narrower confidence intervals and the random effects model wider confidence intervals. Conventionally, the choice of the model must be decided before beginning the analysis and described in the protocol. However, Revman [see later] can give the summary effect and the 95% CI with both models at the same time and thus both are often presented in published
Testing for Heterogeneity—An important issue in meta-analysis apart from looking at the significance of treatment effects is to look at the extent to which studies included are similar to [or dissimilar] to each other. In other words, we need to assess consistency [or inconsistency!] across studies and the method to do this is called the test for heterogeneity.\(^\text{27}\) The extent of heterogeneity will significantly impact the conclusions of the meta-analysis.

Two statistics are used to assess this—the Cochran’s \(Q\) [or the Q-test] and the \(I^2\) [I square]. The former is a less used metric as it has poor power [ability to detect a difference] when the number of studies is few. The \(I^2\) statistic describes heterogeneity as a percentage. For example, if the \(I^2\) value is 50%, it means that 50% of the variation across studies is a result of heterogeneity and not chance. It is not dependent upon the number of studies and its ease of use makes comprehension easier for clinicians.\(^\text{27}\) When testing for heterogeneity the null hypothesis would state that there is no difference in effect size between the included studies. The alternative hypothesis is that there is a difference in effect size across the studies. If the \(p\) value obtained after testing for heterogeneity is significant, [the \(p\) value is conservatively set at \(< 0.1\)], it may not be appropriate to combine the studies and the researcher should reassess the studies he/she has included.

The Forest Plot

The output from Revman at the end of the meta-analysis is the Forest plot. This generally consists of between 6 and 10 columns. A Forest plot from published literature is given below and explained in Figure 1. This was a study by Headon H and colleagues who evaluated the improvement in survival with post mastectomy radiotherapy in patients with 1-3 positive axillary lymph nodes relative to those not given post mastectomy radiotherapy [post mastectomy radiotherapy or PMRT is given only if the number of axillary lymph nodes is 4 or more]. The study showed that PMRT significantly reduced the risk of locoregional recurrence and was associated with a minor overall survival benefit.

The elements of a Forest plot are

Column 1—This is the column on the far left that identifies the study by the first author’s name and year of publication.

Column 2—This describes the experimental intervention. The sub columns here describe number of events for the desired outcome of interest and the total number of patients [n and N respectively].

Column 3—This describes the control group. The sub columns here, similar to Column 2, describe number of events for the desired outcome of interest and the total number of patients [n and N respectively].

Column 4—This gives the weight allocated to individual studies and is described as a percentage

Column 5—The summary measure [risk ratio in this case] is described for each individual study along with the 95% confidence intervals [CIs]. The model used [Mantel Hanzel (MH) random effects in this case] is also mentioned here.

Column 6—This is the graphical depiction of the summary effect along with 95% CI around a central line.

Let us now understand other parts of the Forest plot.

- The central vertical line—This indicates the line of no effect [when the two interventions being studied are not different from each other].
- The squares and the horizontal lines that cut the “squares” pertain to the summary statistics of individual studies [risk ratio in this example] and the horizontal lines that run through them indicate the 95% CI of the risk ratio

- The “diamond”—This is located at the bottom of all studies. This could fall on either side of the central line or fall in the middle and “cut” it. It represents the summation of all studies and the horizontal edges of the diamond indicate the 95% CI of the summation. If the diamond falls on the line it indicates no difference between the two groups. If it falls on the left it favors the experimental intervention and if it falls on the right it favors the control group.

- The lower left corner of the Forest plot—This gives the \(F\) statistic, the measure of heterogeneity along with its \(p\) value. In this case the \(p=0.24\) indicating a lack of significant variance between the studies. This is followed by a second \(p\) value for the effect size of this meta-analysis (in this case it is \(p<0.00001\) which indicates there is a significant difference between the two interventions studied. Note—the second \(p\) value relates to the diamond that can fall on the central line or to its left or to its right.

Revman

The software that is used for both statistical analysis and maintaining systematic reviews that are done by the Cochrane group is called Revman [Version 5 with latest major version being 5.3].\(^\text{29}\) It is freely downloadable for use for academic meta-analysis. Once the data is entered, Revman generates a Forest Plot.

Criticisms of Meta-Analyses

Several critics have pointed out that meta-analyses may be flawed. These criticisms have been summarized and eloquently answered by Borenstein.\(^\text{30}\) These are outlined in Table 3.
Table 3: Criticisms of Meta-analysis and responses

<table>
<thead>
<tr>
<th>Criticism</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>A single number cannot summarize an entire area of research as each study is different from the other</td>
<td>The very idea of a meta-analysis is to generate a single summary statistic after combining the studies. Between study variation are assessed by calculating measures of heterogeneity that are accurately reported and interpreted.</td>
</tr>
<tr>
<td>Publication bias- the file drawer syndrome. Negative studies are less likely to be published</td>
<td>While this is a valid argument, in itself this should not preclude a meta-analysis. Methods to address publication bias [such as the funnel plot] - must be stated clearly. This problem would also be true for a narrative review.</td>
</tr>
<tr>
<td>When studies are combined, it is like mixing apples and oranges [as every study fundamentally differs from another]</td>
<td>Studies put together in a meta-analysis will no doubt differ from each other. Which studies to include will be a judgment call and can be clearly delineated in the protocol. Both apples and oranges can also be viewed as “fruit”. It must be remembered that meta-analysis always answers a much broader question than individual studies. In addition, we assess and address the variance between the studies using the statistics for heterogeneity.</td>
</tr>
<tr>
<td>Garbage in, Garbage out or GIGO i.e., [the quality of what we put into a meta-analysis will determine its finding]</td>
<td>Rather than the GIGO approach, a meta-analysis can be viewed as a process of waste management. Quality assessment of included studies is a key component of meta-analysis and is always outlined in the protocol. A sub group analysis of good quality studies versus those of low quality can be done to see if the effect size changes in anyway.</td>
</tr>
<tr>
<td>Key studies may be ignored.</td>
<td>All systematic reviews and meta-analysis have explicit selection criteria listed in a protocol available in the public domain. Studies that are pooled are thus sufficiently similar to yield results that can be believed.</td>
</tr>
<tr>
<td>A meta-analysis may show a completely different result that a large Randomized Controlled Trial [RCT]</td>
<td>Two possibilities exist here- that there is indeed a difference or simply that two looked at different aspects of the same research question. Also, two RCTS on the same topic may lead to disparate conclusions. A true difference, should one actually exist can be assessed by evaluating the any differences in methodology, patient population and other parameters between the meta – analysis and the RCT to uncover the source of the difference.</td>
</tr>
<tr>
<td>The researcher may perform the meta-analysis poorly</td>
<td>A valid argument. However, this is a problem related to the use of the method incorrectly rather than the method itself.</td>
</tr>
</tbody>
</table>

Reporting a Meta-analysis

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) is an evidence based tool that gives the minimum number of items [n = 27 items] that need to be present while reporting a Systematic Review and/or Meta-analysis. Authors are expected to use this while preparing their manuscripts for publication and journal editors and peer reviewers for evaluating submitted publications.

Conclusions

Meta-analyses are extremely important in today’s world of Evidence Based Medicine as they have the ability to use powerful statistical tools and software to combine studies with identical research questions [those that have similar designs, selection criteria and patient populations]. Their utility lies in the fact that individually, these studies may be small and underpowered to pick up treatment differences, but when combined in a meta-analysis; answer a well-formulated question to guide Evidence based clinical practice. There are some key challenges though in any meta-analysis. The first is the adequacy of the literature search and the subsequent data abstraction. The second is how similar [or dissimilar] are the studies that have been put together and thus looking at heterogeneity [the I² value] and the choice of the model used [fixed and random effects] is important. The others are the quality of the studies and the presence [or lack thereof] of publication bias. Both researchers carrying out the meta-analysis and readers who evaluate and use them should bear all of the above in mind as decision making in clinical practice is influenced by them.

References


THE ASSOCIATION OF PHYSICIANS OF INDIA
INDIAN COLLEGE OF PHYSICIANS

Dr. Vithalrao Nadgouda All India Best Annual Thesis Award

The award is open to the physicians from various medical institutions / hospitals from India within one year of passing the MD / DNB examination in Medicine / General Medicine / Internal Medicine as on the last date for submission of the application by 30th November 2017.

Full format for the application is available on API and JAPI websites: www.apiindia.org / www.japi.org

Dr. Mangesh Tiwaskar
Hon. General Secretary

Dr. A. M. Bhagwati
Joint Secretary
Frank’s Sign

VA Arun¹, Shrutiraj²

Fig. 1: Frank’s sign grade 2a on right ear

Fig. 2: Frank’s sign grade 3 on left ear

A 66 year old female with underlying hypertension and type 2 diabetes mellitus presented with sudden onset recurrent focal seizures involving left upper limb, left upper limb paresis and facial asymmetry with facial deviation towards right of 3 days duration. Examination revealed spastic left upper limb paresis and upper motor neuron type left facial palsy. MRI brain revealed lacunar infarct in left middle cerebral artery territory. The patient was noted to have bilateral Frank’s sign, which is a diagonal crease in the earlobe that runs backward from the tragus at a 45-degree angle across the lobule to the rear edge of the auricle (Figures 1 and 2). Her baseline ECG revealed left ventricular hypertrophy with no strain pattern. 2D Echo revealed left ventricular hypertrophy with grade 2 diastolic dysfunction and preserved ejection fraction and no regional wall motion abnormalities.

The eponymous sign is named after Dr Sanders T. Frank, who in 1973 first observed it in cohort of patients with angina.¹ It has been hypothesized to be a peripheral marker of likely underlying coronary artery disease and thus being a possible predictor of an unforeseen major cardiac event in otherwise asymptomatic individuals. Frank’s sign is thought to indicate premature aging and loss of dermal and vascular elastic fibers. Although it has limited sensitivity, the sign is more useful diagnostically in persons younger than 60 years of age than in older persons. Although many studies have found it to be a sensitive (75%) sign, its specificity falls way behind (57%).² It has also been found to be a marker of underlying subclinical atherosclerotic vasculopathy in patients who are otherwise found to have absence of any underlying overt cardiovascular disease. Association have also been related with carotid intima-medial thickness and may identify the cohort of patients who are likely to be prone to early ageing and premature development of coronary artery disease.³ However in population with low prevalence of coronary artery disease it appears to be of limited value. Its absence does not exclude presence of an underlying coronary artery disease, rather the presence it can help identify and evaluate subset of patients likely prone to early ageing and to the early development of coronary artery disease, whose might benefit with early preventive measures.

There has also been further description about the various grades of severity of this sign and likelihood of its predicting the underlying vascular pathology. One such classification grades it as 1-3 viz. Grade1-small wrinkling < 50% of total diagonal distance between tragus and the free end of earlobe, Grade 2a- superficial crease with visible floor of the crease, Grade 2b- crease > 50% of diagonal distance, Grade 3- deep crease traversing from tragus to the free end of earlobe with floor of crease not visible⁴. However, no association with increased cardiovascular event has been linked to the different grades of severity in the latter.

References

¹Assistant Professor, ²Resident, Dept. of Internal Medicine, Armed Forces Medical College, Pune, Maharashtra
Received: 08.04.2017; Accepted: 08.05.2017
Fascinating World of Windpipe: A Case with Variation and Implications

Kranti Garg\textsuperscript{1}, Varinder Saini\textsuperscript{2}

\textbf{Fig. 1: Scout view of the patient on radiology showing a left sided hydropneumothorax (black arrow) with intercostal chest tube drain (white arrow) in situ}

\textbf{Fig. 2: Fibre-optic video bronchoscopy showing the carina (black arrow), and the opening of an aberrant bronchus (tracheal bronchus) arising from trachea superior to carina (white arrow)}

\textbf{Fig. 3: Negotiation of tracheal bronchus with a pediatric bronchoscope revealing two openings (black arrows)}

\textbf{Fig. 4: Coronal MinIP (minimal intensity projection) of the lung showing tracheal bronchus (white arrow) with left sided hydropneumothorax with passive collapse of the left lung (black arrow)}

\textbf{Fig. 5: HRCT (High Resolution Computed Tomography) Chest showing Right upper lobe bronchus dividing into anterior (white arrow) and posterior (black arrow) segmental bronchi, with left sided hydropneumothorax (curved arrow)}

5-yr-old male presented to the Department of Pulmonary Medicine, Government Medical College and Hospital, Chandigarh with fever and dyspnoea since 2 months. Chest radiograph revealed left sided hydropneumothorax, subsequently diagnosed as tubercular. Patient was managed with intercostal chest tube drainage (Figure 1) and anti-tubercular therapy. However, due to non expanding lung and as a part of routine work-up as per surgical advise, Fibre-optic bronchoscopy (FOB) was done. It revealed an aberrant bronchus (tracheal bronchus) arising from lateral tracheal wall superior to carina (Figure 2). Negotiation of tracheal bronchus with pediatric bronchoscope revealed two openings (Figure 3). Rest of the bronchial tree was normal, except that right upper lobe bronchus was dividing and supplying only two segments. CT (Computed Tomography) reconstruction confirmed the findings (Figures 4 and 5) and showed that aberrant tracheal bronchus was supplying apical segment of right upper lobe. Patient meanwhile subsequently responded, and drain was removed.

Tracheal bronchus is an aberrant bronchus originating from the lateral tracheal wall, superior to carina\textsuperscript{1}. Found within 2 cm of carina, it supplies the right upper lobe.\textsuperscript{2} Detailed assessment of tracheobronchial tree, keeping in mind the presence of aberrant bronchi/segments, is needed for the following reasons. Firstly, besides the basic indications, complete assessment of airways to look for anatomical variation is in itself a valid reason for such an invasive FOB procedure. Secondly, if patient is taken up for surgery, gross one lung ventilation with an endotracheal tube placed too distally (overlooking tracheal bronchus) may cause complications and endanger life.\textsuperscript{3} Thirdly, modifiable risk factors like Quitting smoking are of paramount importance because of reported increased incidence of malignancies in patients with tracheal bronchus.\textsuperscript{4}

**Acknowledgements**

Authors acknowledge Dr. Rekha Gupta, Assistant Professor, Department of Radiodiagnosis, for her substantial contribution.

**References**


\textsuperscript{1}Assistant Professor, \textsuperscript{2}Professor, Department of Pulmonary Medicine, Government Medical College and Hospital, Chandigarh

Received: 08.06.2016; Accepted: 02.02.2017
Dyskeratosis Congenita with Acute Myeloid Leukemia, Cryptogenic Liver Fibrosis and Portal Hypertension

Prasan Kumar Panda¹, Rita Sood¹, Kewal Kanabar¹, Ranveer Jadon¹, Arundhati Sharma², Sweta Birla³, Pravas Mishra⁴, Tarun Kumar⁵

Abstract

Dyskeratosis Congenita (DC), a 100-year-old known rare hereditary entity, has recently changed its definition as per the pathogenetic model in the last decade. Now it is well known as one of the telomeropathies, pathognomonically characterized by a triad of reticulate pigmentation of the skin, nail dystrophy, and mucosal leukoplakia. It is a progressive systemic disorder which usually presents with involvement of several family members. Malignancies are increasingly reported. Clinical diagnosis is simple once there is a suspicion, but nowadays genetic diagnosis is advocated. Treatment is symptomatic and organ-oriented. We hereby report an adolescent male who presented with the classical mucocutaneous triad of DC with pancytopenia for four months. Bone marrow examination later revealed evolution of acute myeloid leukemia (AML). Liver function tests, imaging, and liver biopsy showed cryptogenic fibrosis with portal hypertension. Chemotherapy was started since hematopoietic stem cell transplantation was not feasible; however, he died very early due to repeated infections before completion of the treatment. AML and liver disease are increasingly reported independently in DC; however, coexistence of both complications in a single patient at first presentation has never been reported earlier. Early age onset of AML is noticeable too.

Introduction

Dyskeratosis congenita (DC), a multisystem disorder, initially known as inherited bone marrow failure (BMF) syndrome, was first described by Zinsser in 1906, but recognized as a clinical entity by Engman (1926) and Cole (1930). Since then it is also known as ‘Zinsser–Cole–Engman syndrome’. Recently, it emerged as a new entity of ‘telomere biology disorder (TBD)’ or ‘telomeropathy’ which is characterized by a very short telomere (<99th percentile).¹ Till date 11 genes DKC1, TINF2, TERT, TERC, WRAP53 (TCAB1), NOP10, NPH2, RTEL1, CTC1, ACD, and PARN have been found to be associated with DC and exhibiting a complex genotype–phenotype relationship.²,³

It is seen mostly in men with a reported annual incidence of less than one per one million populations. Usually it manifests as abnormal mucocutaneous-nail changes by 10 years of age, BMF by 20 years, and malignancy by 30 years.⁴ After the recognition of its pathogenetic mechanism as telomere dysfunction in the last decade, every system of the body is known to be affected with a greater involvement of high proliferative tissues like skin, bone marrow, immune cells, and intestinal epithelium. The degree of telomere dysfunction is the major determinant of the disease onset and manifestations.⁵ Clinical diagnosis is not difficult once suspicion is high in patients with pancytopenia and pathognomonic muco-cutaneous triad. Nowadays, genetic testing is being considered for confirming the diagnosis with or without use of a screening test i.e. telomere length analysis, which could be false positive. The management requires a multidisciplinary approach with symptomatic organ based treatment.

Hereby, we report this case to share its uncommon and rare associations as well as to review this emerging disorder, especially the pathogenetic model of telomeropathy.

Case Report

A 15-year boy, non-smoker, from the state of Bihar in India, presented with a history of easy fatigability and dyspnea on exertion...
for one month and dry cough with high grade fever including chills and rigors for 15 days. He had no history of jaundice, bleeding from any site, abdominal pain, or chest pain. He had a similar history of fatigue with dyspnea four months prior to this event when he was evaluated outside and found to have pancytopenia with a hypercellular bone marrow. Since then, he had received eight packs of RBC transfusions following which his symptoms improved. He had no history of exposure to toxins. Two other family members were reported to be suffering from similar blood problem and one of whom was transfusion dependent. There were also other diseases present among other family members (Figure 1).

On examination, he was pale and febrile. His weight was 45 kg with BMI of 16.7 kg/m². He had reticulate pigmentation of the skin over the neck along with diffusely distributed depigmented macules over the chest, abdomen, back, palms, and soles. He had oral mucosal leukoplakia along with pigmented macules and dystrophy of nails and toes (Figure 2). Similar skin lesions were also present in many of his family members as shown in the pedigree. This triad of skin, mucosa, and nail changes is classical of DC. The pattern of transmission was autosomal dominant. He had a firm, non-tender spleen palpable 5-cm below the left costal margin. On complete dental evaluation, there was dental caries, losses, and stains.

His hemogram revealed pancytopenia with Hb, 49 g/L; WBC, 1.51 ×10⁹/L with ANC of 0.5 ×10⁹/L; and platelet counts, 80 ×10⁹/L. Peripheral smear revealed a leftward granulocyte shift with few macrocytes. His liver function test (LFT) revealed total bilirubin, 13.68 µmol/L (normal range, 5.0-21.0); albumin, 28 g/L (32-56); globulin, 40 g/L (2.3-3.5); ALT, 0.94 µkat/L (0-50); AST, 0.89 µkat/L (0-50); alkaline phosphatase, 15.68 µkat/L (240-840); and PT, 19s (control PT, 11.8s). These LFT abnormalities were persistent for more than three months suggesting a possibility of chronic liver disease (CLD). His CLD workup for chronic viral hepatitis, Wilson disease, hemochromatosis, and autoimmune hepatitis was negative. Serum B₁₂ and folate were in the normal range. Iron study was suggestive of an iron overload state with transferrin saturation, 98%; ferritin, 2471.70 pmol/L (33-450); and TIBC, 38.66 µmol/L (44.8-80.6). RK-39 for Kala azar was negative. Contrast-Enhanced Computed Tomography of chest and abdomen revealed left side pneumonia and CLD with portal hypertension. This was also supported by an ultrasound doppler study of hepato-portal vein axis. Upper gastro-intestinal endoscopy revealed low grade oesophageal varices. Transient liver elastography (fibroscan) suggested an early portal fibrosis (Score of 8.8 kPa). Bone marrow (BM) aspirate and biopsy showed a hypercellular marrow with granulocyte prominence without any evidence of infection or LD bodies (Figure 3).

The patient received multiple RBC and single donor platelet transfusions. However, his haematological parameters did not improve. Considering hypersplenism as an aetiology of persistent pancytopenia he was subjected to splenectomy and multiple peri-operative liver biopsies were obtained. Intraoperative findings were splenomegaly and a firm nodular liver. Histopathology of the liver revealed maintained lobular
architecture, mild portal triaditis, focal interface hepatitis, extensive iron deposition in hepatocytes and Kupffer cells, and mild fibrous expansion of few portal tracts which is suggestive of an early hepatic fibrosis with probable secondary hemochromatosis (Figure 4).

Spleen histopathology showed fibro-congestive features. The patient’s haematological profile improved transiently after the splenectomy. However, he became pancytopenic once more after about three weeks. Therefore, he underwent a repeat BM evaluation in view of high suspicion of BMF. Surprisingly it revealed blast cells (20%) with a positivity for CD34 on flow cytometry and positivity for myeloperoxidase (MPO), suggesting acute myeloid leukaemia (AML) (Figure 3). Hence, the patient was diagnosed as a case of Dyskeratosis congenita with early cryptogenic liver fibrosis, secondary hemochromatosis, portal hypertension, AML, and superadded infection as pneumonia.

**Genetic testing**

Detailed pedigree information and peripheral blood samples were collected for molecular investigations after taking an informed consent from the patient and available family members (Figure 1). Karyotype was normal. Genomic DNA was isolated using standard salting out protocol and subjected to PCR amplification of the TERC, TERT, and DKC1 using 100ng DNA, 2.5mM MgCl2, 0.30 mM of each of the dNTPs (Invitrogen, Carlsbad, CA, USA), 20pM of each primer, and 0.5 units of Taq Polymerase (Invitrogen, Carlsbad, CA, USA) in a 25 µL volume mixture using thermocycler ABI 9700 (Applied Biosystems, Foster City, CA). All the amplified products were purified using Qiagen kits (Qiagen, GmbH, Hilden, Germany), sequenced using BigDye Terminator Mix version 3.1 (Applied Biosystems [ABI], Foster City, CA), and analyzed on an ABI-3100 Genetic Analyzer (ABI). Nucleotide sequences were compared with the reference cDNA sequences of TERC (GenBank accession number ENSG00000270141), TERT (GenBank accession number ENSG00000164362), and DKC1 (GenBank accession number ENSG00000130826) gene. No pathogenic mutation was identified in these three genes. Hence, other family members were not studied further. However, single nucleotide polymorphisms (SNP) rs2728532 in DKC1 and rs13167280, rs2075786, rs2853690, rs79662648, and rs2736098 in TERT were identified.

During the hospital course, he received two cycles of chemotherapy (Cytarabine, 100 mg/m²/day×24hr infusion×7days and Daunorubicin, 60 mg/ m²/day×3days) for AML. However, there was no significant
Our case had classic triad with liver disease, teeth abnormality, and malignancy as systemic features. For a case definition, individuals with characteristic clinical findings having very short telomeres and/or a mutation in one of the DC-associated genes should be considered. Telomere length testing is usually done by flow-FISH which is considered the best having sensitivity of 97%, specificity of 91%, and positive predictive value of 85%. Yet, there is false negativity as seen in Swachman–Diamond syndrome and Fanconi anaemia. Therefore, genetic analysis should be performed in such cases. Cancer is more common in DC caused by TERT and TERC, intermediate by DKC1, and least common by TINF2 gene mutation. Therefore, in the present case study genetic screening for TERT, TERC, and DKC1 was undertaken but no pathogenic lesions were identified in these genes. Only six SNPs were identified in TERT and DKC1. TINF2 molecular screening is ongoing. Pediatric patients of sporadic AML have not shown any positivity to TERT/TERC mutations in contrast to adults. Hitherto, gene mutations are more of a risk factor than etiologic factors for the disease and till date, mutations have been identified in about 60-70% of DC cases. Variable expression is seen in families wherein some members have typical skin lesions and some have isolated BMF syndromes or malignancies without skin features; while others do not present with similar features exhibiting variable penetrance. Children often have multisystem involvement, but adults show much variability and may present with a single major feature. In pre-molecular diagnostic era, patients were classified based on inheritance patterns into X-linked, autosomal dominant, or autosomal recessive; however, availability of clinical genetic testing has shown that the inheritance of DC may be more complex. Since telomere length is heritable and exhibits anticipation, subsequent generations show increased severity and an early age of onset of manifestation as seen in our pedigree. Prenatal testing for pregnancies at increased risk is possible if a specific mutation is known.

Our case had pancytopenia, splenomegaly, and mucocutaneous involvement, therefore we thought of two inherited BMF syndromes. One is DC which has greater emphasis in the ectodermal picture while skeletal and renal anomalies are more prominent in Fanconi’s anaemia; besides, splenomegaly is not a feature of later one. Bone marrow picture in DC ranges from hypercellular to normocellular to hypocellular. In our case within very short time span i.e. one month, BM picture changed from hypercellular to leukemic changes without going to end stage BMF which is one of the uniqueness of this case. Allogenic-HSCT is the only curative treatment available for BMF or leukemia, but there is associated high toxicity including risk of malignancies, even after reduced-intensity conditioning regimens.

Malignancies are being increasingly reported in about 10 to 15% cases of DC. Telomeropathy was initially thought to be protective for cancer development due to decreased telomerase activity, later on proved to be having increased risk due to the genotoxic stress by persistent DNA damage signals at the telomeres, telomere fusions, and genomic rearrangements driven by telomere repair-mediated recombination. The DC Registry of United Kingdom (1995 onward) and the National Cancer Initiative’s DC cohort (2002 onward) are two large disease databases providing information on most of the cancers. These data and other case reports have showed head and neck cancer being most common type with only few registered cases of AML but with an approximately 200-fold odd ratio. Their average age of presentation of AML was 30 years but our case was only 15 years of age. This is possibly due to the genetic anticipation of an autosomal dominant transmission.

### Table 1: Multisystem clinical features of Dyskeratosis congenital

<table>
<thead>
<tr>
<th>Major clinical features</th>
<th>Other recognized somatic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous triad</td>
<td>Epiphora</td>
</tr>
<tr>
<td>1. Abnormal skin pigmentation</td>
<td>Learning difficulties/developmental delay/</td>
</tr>
<tr>
<td>2. Nail dystrophy</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>3. Leukoplakia</td>
<td>Pulmonary disease</td>
</tr>
<tr>
<td>Bone marrow failure</td>
<td>Short stature</td>
</tr>
<tr>
<td>Extensive dental caries/loss</td>
<td>premature hair loss/graying/sparse eyelashes</td>
</tr>
<tr>
<td>Esophageal stricture</td>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>Liver disease/peptic ulceration/enteropathy</td>
<td></td>
</tr>
<tr>
<td>Ataxia/cerebellar hypoplasia</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Hypogonadism/undescended testes</td>
<td>Intrauterine growth retardation</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>Liver disease/peptic ulceration/enteropathy</td>
</tr>
<tr>
<td>Urethral stricture/phimosis</td>
<td>Ataxia/cerebellar hypoplasia</td>
</tr>
<tr>
<td>Osteoporosis/aseptic necrosis/scoliosis</td>
<td></td>
</tr>
<tr>
<td>Deafness</td>
<td></td>
</tr>
</tbody>
</table>
as shown in the pedigree. To the best of our knowledge, this is the first case report from India with DC having three malignancies in one family. AML is not reported in DC from India, but single case of acute lymphoblastic leukemia (ALL) has been reported. In our case, we had started chemotherapy and HSCT was not possible due to lack of the non-carrier sibling. Post-transplant (with low intensity Fludarabine based protocol) survival has been documented to be 10 to 72 months in BMF cases; however, no survival has been reported in AML cases.\textsuperscript{1,3}

Liver diseases in DC are not common but detection rate has increased among the family members. Its spectrum may range from asymptomatic LFT abnormality as in our case to cirrhosis of the liver. Early screening may help in detection of more cases. Histologically, there is also a spectrum of manifestations in form of steatosis, hepatitis, early fibrosis to cirrhosis, and hemosiderosis (more often due to frequent use of iron tablets and blood transfusions).\textsuperscript{15} Our single case is having a similar picture with steatosis, inflammation, necrosis, fibrosis, and iron accumulation though not cirrhosis. From India, one case of DC with CLD (image proven) & portal hypertension without any malignancy has been reported.\textsuperscript{16}

There are usually repeated infections due to the telomere dysfunction causing an aberrant immune system. Our case was having recurrent pneumonia and enterocolitis. Infective pneumonia should be differentiated from idiopathic pulmonary fibrosis (IPF), which is the most common and serious lung involvement in DC and usually seen after HSCT.\textsuperscript{2} Lung transplant is the only available treatment in IPF.

Until now, the recommended treatment is only supportive and organ-oriented with the care of all family members including genetic counseling and avoiding toxic agents like smoking, alcohol, or non-leucodepleted or non-irradiated blood products. Future possibilities of telomerase therapeutics (gene therapy) and vaccines are there in genetic variant syndromes. There is a society group with a website named, www.dcoutreach.org, which maintains accounts on Twitter, Pinterest, and Facebook for DC outreach group facilitating an interaction among different family members and professionals.\textsuperscript{3}

**Conclusion**

In summary, we describe a case of pathognomonic mucocutaneous triad of DC who presented with AML and CLD, refractory to the existing medical treatment. This is the first report of co-existence of both complications in DC. Simultaneously, we learn the genetic approach to a telomeropathy, although the mutations were not detected in any of the tested genes. This case also give us the opportunity to learn more about the telomeropathy as a family diagnosis and DC as an individual diagnosis.

**Authors’ contributions**

PKP had given the concept, searched literatures, analyzed and drafted the work, RS had analyzed and critically revised the work, KK had collected data and drafted the work, and RJ had interpreted and drafted the work. AS and SB had done genetic analysis, given their data, and drafted the work. PM had interpreted, especially hematological data and critically revised the work. TK had collected pathological data and drafted the work. PKP, RS, RJ, KK, and PM were the physicians involved in the patient management. All authors read and approved the final manuscript.

**Acknowledgements**

Special thanks to Dr. Ramam (Department of Dermatology, AIIMS) for academic input regarding the skin findings of the patient, photographic section of CMET Department, AIIMS for taking patients’ photo, and late Mr. X (the patient) and his family members for giving us valuable learning points.

**References**

Scleroderma-like Initial Presentation of Multiple Myeloma

Ayan Basu1, Santanu Kundu2, Mehebubar Rahman3, Yogiraj Ray4, Rama Prosad Goswami5

Abstract
Systemic sclerosis (SSc) is a multisystem connective tissue disease affecting skin and internal organs. Certain drugs, environmental toxins and some viruses have been implicated in SSc-like illnesses. Scleroderma may be associated with some connective tissue disorders or autoimmune diseases but coexistence of scleroderma with multiple myeloma (MM) is an unusual finding. We here report a case of a 59 years old female patient with 5 months history of progressive thickening of skin all over the body. Multiple myeloma was diagnosed by osteolytic lesion in skull X-ray, increase in clonal plasma cells by bone marrow biopsy, very high Kappa light chain in serum light chain assay and detection of M band by serum protein electrophoresis.

Introduction
Systemic sclerosis (SSc) is a chronic multisystem complex connective tissue disease of unknown etiology affecting the skin and internal organs, occurs more commonly in women. Hallmark of SSc is induration and thickening of the skin (scleroderma).1 Scleroderma is reported to be associated with Sjogren syndrome, rheumatoid arthritis and systemic lupus erythematosus. It is also associated with solid tumours such as lung, breast, stomach and rectum but association with multiple myeloma (MM) has seldom been reported. To the best of our knowledge, only 13 cases of scleroderma associated with MM have been reported in the literature.2 Inflammation and deregulation of immune system in SSc may cause clonal expansions of plasma cells but such aberrations still remain under investigation. Most scleroderma patients present with positive ANA and anti Scl 70/antitopoisomerase (diffuse) and/or antitcentromere (localized variety) and follow a chronic course.3 Some paraneoplastic syndromes like MM or solid organ tumours may mimic clinical features of scleroderma but with rapid progressive course and negative autoantibody.

Case Report
59 years female patient, known cased diabetes and hypertension presented with features of generalized thickening and tightening of skin (Figure 1) for 5 months and mild difficulty in deglutition for last 3 months. Oral ulcer, photosensitivity, fever, alopecia or joint pain were absent. Patient gave history of dry eye and dry mouth for last 3 months. She also gave history of digital colour changes on exposure to cold water or cold environment (Raynaud’s phenomenon). On examination, pallor and bilateral pitting type of pedal oedema were found. On musculoskeletal examination, fixed flexon deformity of both wrist, elbow, small joints of hand (Figure 2) and proximal muscle weakness were found. Investigation showed, Hb-9.8 gm/dL, total leucocyte count-8700/µL, Platelet count- 286000/µL, ESR-122 mm/1 hr. Liver function test, urea, creatinine and uric acid were within normal limit. Anti Nuclear Antibody (ANA) with ANA profile were negative. HBsAg, Anti-HCV and HIV were non reactive. Chest X-ray, ultrasonography of abdomen did not reveal any abnormality.

Initially we thought it was a case of systemic sclerosis. But due to very rapid progression (within 5 months) of this disease and negative ANA with ANA profile, we considered a paraneoplastic syndrome to be the etiology of this scleroderma like clinical scenario (ie Pseudoscleroderma). For this we searched for multiple myeloma and other solid organ tumours. We found serum calcium level was 12.1 mg/dL, Serum IgG 2240 mg/dL (reference range: 700-1700), IgM 77 mg/dL(50-300), IgA 199 mg/dL (70-350). Serum light chain assay showed: Kappa light chain-766 mg/L(3.3-19.4) and Lambda light chain-2.59 mg/L(5.71-26.3). Kappa Lambda ratio was 295.8(0.26-1.65) and serum ß2 microglobulin was 3781 ng/ml (609-2366). Xray of skull showed multiple osteolytic lesions (Figures 3 and 4). M band were detected by serum protein electrophoresis (Figure 5) but Bence Jonce protein was not detected by urine analysis. Bone marrow aspiration and biopsy showed 12% plasma cell (Figure 6). Even after extensive search...
we did not find any solid organ tumour. Then she was started on injection Bortezomib 1.3 mg/m² subcutaneous once daily on Day 1, 4, 8, 11 followed by a 10 day rest period (days 12-21) for six cycles and tablet Cyclophosphamide 300 mg/m²/day on day 1, 8, 15 and 22 for 4 cycles. We also gave tablet dexamethasone 40 mg once daily from day 1 to 4 and day 9 to 12. Tablet Acyclovir was given as anti-viral prophylaxis. Patient is doing well with improvement in skin lesions after one year of post treatment follow up.

Discussion

SSc is a chronic autoimmune connective tissue disease that occurs when the immune system damages normal body tissue. It involves the skin, blood vessels, muscles and internal organs such as gastro intestinal tract, heart, lungs and kidneys.²

Patients with scleroderma can have specific serum auto antibodies like antinuclear antibody, anticientromere or antitopoisomerase (anti Scl 70) antibody. It is characterised by formation of scar tissue (fibrosis) in the skin and organs of the body leading to thickening of involved areas.² Scleroderma may be associated with diabetes, monoclonal gammopathy of undetermined significance, MM, primary hyperparathyroidism, rheumatoid arthritis, Sjogren syndrome and systemic lupus erythematosus.³

In world literature association of scleroderma with monoclonal gammopathy of undetermined significance had been reported but scleroderma like initial presentation of MM is very rare.³,⁴ Scleroderma like intial presentation of MM may be due to inflammation and molecular deregulation that precedes clonal proliferation of plasma cells. The duration of development of multiple myeloma from appearance of skin lesions of scleroderma is variable.³,⁴ In our case, the patient was diagnosed as MM after a period of 5 months from the onset of the skin lesion.

Multiple myeloma is a plasma cell dyscrasia. MM can be diagnosed by bone marrow clonal plasma cell>10%, M protein in serum and/or urine and myeloma related organ or tissue impairment (end organ damage including bone lesion).⁷ In our case, bone marrow plasma cell was 12% with high monoclonal Kappa light chain in serum light chain assay, M band was found in serum protein electrophoresis and multiple osteolytic lesions were found in x-ray of skull. Serum calcium and serum ß2 microglobulin levels were also high. MM is ideally treated by combination of lenalidomide, bortezomib, and dexamethasone which achieves close to a 100% response. Other similar three-drug combinations (bortezomib, thalidomide, and dexamethasone or bortezomib, cyclophosphamide, and dexamethasone) also achieve >90% response rate.⁷ We used bortezomib, cyclophosphamide, and dexamethasone as these drugs are freely available in our hospital. Patient is doing well after one year of follow up.

Conclusion

The main purpose of this case report is to raise awareness among the medical students and clinicians that MM can present initially like SSc. So whenever we get a patient with SSc like clinical presentation but with negative autoantibody profile specific for SSc, we must exclude other paraneoplastic syndromes, specifically MM. Early detection of MM with this type of unusual initial presentation would help us to initiate early treatment and modify disease course.
Parathyroid Cancer Causing Acute Severe Pancreatitis

Anil Pal¹, Amey Sonavane¹, Ritesh Agrawal², Pravin Rathi³

Abstract
Parathyroid carcinoma is a rare disease and accounts for less than 1% of all cases of primary hyperparathyroidism. Many times, parathyroid carcinoma is detected only after surgery. Parathyroid carcinoma as a cause of acute pancreatitis is uncommon. We report this case of acute severe pancreatitis associated with parathyroid carcinoma. Hypercalcemia was found during workup for acute pancreatitis which was due to primary hyperparathyroidism. During surgery, there was a suspicion of parathyroid carcinoma and en bloc resection was done followed by adjuvant radiation therapy. It is important to treat the precipitating factor for acute pancreatitis. Surgery is the mainstay of treatment for parathyroid carcinoma.

Introduction
Parathyroid carcinomas account for less than 4% of parathyroid diseases. They principally present with elevated serum calcium and PTH levels. Initial presentation very often is with a “hypercalcemic crisis”.

We report this case of acute severe pancreatitis associated with parathyroid carcinoma. Hypercalcemia was found during workup for acute pancreatitis which was due to primary hyperparathyroidism. During surgery, there was a suspicion of parathyroid carcinoma and en bloc resection was done followed by adjuvant radiation therapy.

Case Report
A 43-years-old gentleman, textile-mill worker, presented in emergency with severe epigastric pain. Generalized weakness, reduced appetite and recurrent vomiting were present for the past 45 days. He also complained of severe, dull continuous pain in the epigastrium radiating to the back for one week which was aggravated on consuming food and was partially relieved on bending forward, associated with dyspepsia, constipation and weight loss. His urine output was reduced.

On examination, he was dehydrated with persistent vomiting, afebrile and tachycardia with normotension. Abdominal examination demonstrated distension with epigastric tenderness. Blood investigations revealed leukocytosis (12,000/cu mm) with polymorphonuclear leucocytosis, elevated pancreatic enzymes- serum lipase (8605 U/L) and serum amylase (2435 U/L), hypercalcemia (14.7 mg/
Parathyroid carcinomas account for less than 4% of parathyroid diseases. They principally present with elevated serum calcium and PTH levels. Initial presentation very often is with a “hypercalcemic crisis”. Metastatic invasion of regional lymph nodes or distant sites can confirm the diagnosis preoperatively. A diagnosis can also be suggested intraoperatively on the basis of tumor invasion into surrounding structures. An intraoperative diagnosis of carcinoma based on frozen section findings is rather controversial because of the overall difficulty of rendering the diagnosis. Histopathologic features include a high mitotic rate and a capsular, vascular or perineural invasion. Other findings include cellular pleomorphism, atypia and atypical mitoses. The abnormal mitotic figures are distinctive, though not pathognomonic. Postoperative recurrence rates are high with significant 2-year mortality rate between 46% and 65%. As the condition is rare, leading authorities including the American Joint Committee on Cancer (AJCC) have not published any staging recommendations.

Acute pancreatitis secondary to primary hyperparathyroidism (PHPT) is infrequent. It was first described by Cope et al. Work-up for PHPT should be routinely performed to detect the etiology of non-gallstone pancreatitis secondary to hypercalcemia. The prevalence of PHPT is estimated to be between 1.5% and 7%. Based on the available epidemiological data, a direct causal relationship between PHPT and acute pancreatitis appears to be doubtful. It is a known fact that hypercalcemia of any etiology can potentially, albeit rarely lead to acute pancreatitis. Other rare causes of hypercalcemia leading to pancreatitis include total parenteral nutrition, metastatic bone disease, vitamin D toxicity, sarcoidosis and infusion of intravenous calcium in high doses perioperatively during cardiopulmonary bypass.

The suggested pathophysiological mechanisms that cause pancreatitis in hypercalcemia include 1) Deposition of calcium in the pancreatic duct causing pancreatic duct obstruction;
II) Activation of trypsinogen within the pancreatic parenchyma due to hypercalcemia leading to autodigestion of the pancreas; and III) Genetic variants in SPINK1 (serine protease inhibitor Kazal type 1) and CFTR (cystic fibrosis transmembrane conductance regulator) genes along with hypercalcemia that increase the risk of acute pancreatitis in patients with PHPT.

Acute pancreatitis is usually associated with a decrease in serum level of calcium and this is mainly related to decreased serum albumin levels. Based on the Ranson grading, low serum calcium levels has prognostic significance and is a marker of severity because it is carried bound to albumin-rich intravascular fluid of the pancreatic parenchyma due to decreased serum albumin level of calcium and this is mainly associated with a decrease in serum calcium levels. Based on the Ranson grading, low serum calcium levels has prognostic significance and is a marker of severity because it is carried bound to albumin-rich intravascular fluid that extravasates to the peritoneum. Hence, it is not common to observe hypercalcemia in a patient with severe acute pancreatitis. Presence of hypercalcemia in pancreatitis should always alert treating physicians about presence of underlying hyperparathyroidism or malignancy. Parathyroid hormone levels should be tested and if hormone is elevated and imaging of the parathyroid glands should be conducted.

In our case, the diagnosis of a parathyroid mass was made by USG neck followed by 99mTc-Sestamibi scintigraphy. Surgical resection of the mass is definitive treatment as parathyroidectomy protects from recurrence of pancreatitis. Post-operative hypocalcemia is common and warrants calcium supplementation.

**Conclusion**

A multi-speciality coordinated approach between gastroenterologists, radiologists and surgeons is imperative in treating this rare phenomenon of acute pancreatitis caused by hypercalcemia secondary to a parathyroid carcinoma.

**References**


---

**Lemierre’s Syndrome in Pregnancy Secondary to Retropharyngeal Abscess**

**Joe James**, **NK Thulaseedharan**, **NV Jayachandran**, **P Geetha**

**Abstract**

Lemierre’s syndrome (LS) refers to suppurrative thrombophlebitis of internal jugular vein (IJV) secondary to oropharyngeal infection. It is caused by the anaerobic bacteria *Fusobacterium necrophorum*. Here we report a case of LS secondary to retropharyngeal abscess in a pregnant lady with possible underlying connective tissue disorder. A 19-year old primigravida at 6-weeks of gestation, presented with fever, cough, dyspnea, right sided neck pain and swelling. Imaging showed right lower lobe pneumonia with bilateral pulmonary infiltrates and pleural effusion. Ultrasound of the neck showed right IJV thrombosis. Magnetic resonance imaging of the neck revealed a retropharyngeal abscess extending from C1 to C4 vertebral level. She had positive ANA, SS-A and Ro-52 titres. She was treated with piperacillin-tazobactam, metronidazole, enoxaparin and short course steroids. Even though she improved initially, fever recurred and she had a massive hemoptyis with hemothorax and expired.

**Introduction**

Lemierre’s syndrome (LS) refers to suppurrative thrombophlebitis of internal jugular vein (IJV) secondary to oropharyngeal infection. It is caused by the anaerobic bacteria *Fusobacterium necrophorum*. Here we report a case of LS secondary to retropharyngeal abscess in a pregnant lady with possible underlying connective tissue disorder.

**Case Report**

A 19-year old primigravida with 6-weeks of gestation presented with high grade fever, headache and dry cough. Physical examination revealed right sided neck pain and swelling. Imaging showed right lower lobe pneumonia with bilateral pulmonary infiltrates and pleural effusion. The investigations at admission were:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Admission</th>
<th>After 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>11.8 g/dL</td>
<td>9.7</td>
</tr>
<tr>
<td>WBC</td>
<td>10200/mm³</td>
<td>11,500</td>
</tr>
<tr>
<td>Differential</td>
<td>P₅₀, Mₐ, P₅₀, Mₐ</td>
<td>4.29</td>
</tr>
<tr>
<td>Platelet</td>
<td>1.69×10⁹/mm³</td>
<td>4.29</td>
</tr>
<tr>
<td>ESR</td>
<td>60 mm in 1 hr</td>
<td>112</td>
</tr>
<tr>
<td>CRP</td>
<td>61.8 mg/L</td>
<td>39</td>
</tr>
<tr>
<td>Blood urea</td>
<td>10 mg/dL</td>
<td>12</td>
</tr>
<tr>
<td>S. creatinine</td>
<td>0.7 mg/dL</td>
<td>0.8</td>
</tr>
<tr>
<td>Urine microscopy</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>S. sodium</td>
<td>130 meq/L</td>
<td>132</td>
</tr>
<tr>
<td>S. potassium</td>
<td>3.9 meq/L</td>
<td>2.9</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.7 mg/dL</td>
<td>0.4</td>
</tr>
<tr>
<td>Total protein</td>
<td>6.7 g/dL</td>
<td>6.4</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.3 g/dL</td>
<td>3.4</td>
</tr>
<tr>
<td>A/G ratio</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>AST</td>
<td>33 IU</td>
<td>36</td>
</tr>
<tr>
<td>ALT</td>
<td>21 IU</td>
<td>23</td>
</tr>
</tbody>
</table>

Table 1: Investigations at admission and after 2 weeks when fever recurred

---

1. Resident, Department of Internal Medicine, Government Medical College, Kozhikode, Kerala
2. Professor and Head of the Department, Department of Internal Medicine, Government Medical College, Kozhikode, Kerala
3. Professor, Department of Internal Medicine, Government Medical College, Kozhikode, Kerala

Received: 04.12.2016; Accepted: 07.07.2017
Cough of 9-days duration. Three days before admission, she started to expectorate moderate amount of whitish sputum and also developed sore throat and progressive dyspnea. She had conceived naturally and had not used oral contraceptives previously. On examination she was febrile with a temperature of 101°F, pulse rate of 126 beats/minute, blood pressure of 110/80 mm Hg, respiratory rate of 38/minute, with oxygen saturation of 70% which increased to 99% after supplementing oxygen. She had reduced chest expansion on right side, bronchial breathing in right infra-axillary and interscapular areas, fine end-inspiratory crepitations in the same areas and stony dullness in right infrascapular area. These findings were suggestive of right lower lobe consolidation with suppurative effusion. Other systems were normal. Investigations were remarkable for high ESR and CRP, but WBC count was normal (Table 1). Arterial blood gas showed respiratory alkalosis. As the patient complained of right sided neck pain. Edema and tenderness was also noticed over right side of neck and right supravacuicular fossa. A doppler ultrasound of the neck showed thrombosis along the entire length of right internal jugular vein (IJV). Magnetic resonance venogram of the brain ruled out any extension from cerebral venous thrombosis. Laboratory workup for thrombophilias including antiphospholipid antibodies were negative. Magnetic resonance imaging (MRI) of the neck showed a thin retropharyngeal fluid collection of 8 mm thickness from C1 to C4 vertebral level and right sided cervical inflammation extending to superior mediastinum (Figure 1). MRI of the thorax showed consolidation of the entire right lower lobe with moderate right pleural effusion and few ill defined patchy infiltrates in both lungs (Figure 2). Magnetic resonance venogram of the neck vessels confirmed right IJV thrombosis (Figure 3). A diagnosis of Lemierre’s syndrome secondary to retropharyngeal abscess with septic lung emboli was made. An otorhinolaryngology consultation excluded any peritonsillar or oropharyngeal pathology. A transthoracic echocardiogram study ruled out infective endocarditis and ultrasound of the abdomen ruled out any other foci of septic abscesses and confirmed good fetal cardiac activity. Aerobic and anaerobic blood cultures, sputum and pleural fluid cultures were sterile. She was started on piperacillin-tazobactam 4.5 g IV sixth hourly, metronidazole 500 mg IV eight hourly, enoxaparin 40 mg subcutaneously twice daily and folic acid. Her fever subsided the next day, headache and edema of neck decreased and dyspnea gradually subsided. A repeat thoracic ultrasound showed bilateral pleural effusion. Meanwhile, her ANA result came out positive and ANA profile showed positivity for SS-A and Ro-52 antibodies. She was started on prednisolone at 20 mg per day and antibiotics were continued.

She remained afebrile and clinically stable for two weeks, after which fever recurred with high spiking temperatures up to 104°F. Repeat investigations showed mild polymorphonuclear leukocytosis (Table 1). A repeat blood, urine and pleural fluid cultures were sterile. Steroids were stopped which she received only for four days and vancomycin was empirically added. Her fever did not respond and 4-days later she started to have cough with streaky hemoptysis and became progressively dyspneic and her clinical condition worsened. Heparin was stopped and she was urged for a medical termination of pregnancy for further radiological imaging including computed tomography of neck and thorax, which she consented. Her hemoptysis subsided, but 2-days later she developed a left sided hemothorax with massive hemoptysis with hemodynamic collapse. She was intubated and supported with blood transfusions and mechanical ventilation, but she succumbed to her illness shortly thereafter.

**Discussion**

Lemierre’s syndrome refers to supplicative thrombophlebitis of internal jugular vein secondary to oropharyngeal infection. It is caused by the anaerobe *Fusobacterium necrophorum*. Other organisms like *Eikenella corrodens*, *Peptostreptococcus*, *Bacteroides*, *Streptococcus*, *Staphylococcus*...
and Klebsiella among many others have also been reported to cause this syndrome.\(^1\) It occurs in teenagers and young adult with a median age of 20 years. It is usually preceded by tonsillitis or pharyngitis and rarely dental infections, parotitis, otitis media or mastoiditis with secondary infection of the parapharyngeal space, which contains the deep vessels of the neck. Fusobacterium possess a lipopolysaccharide endotoxin similar to gram negative bacteria and the organism can also aggregate platelets which leads to intravascular coagulation, creating an anaerobic environment for the bacteria to proliferate within abscesses. The infection spreads through the tonsillar veins into the IJV causing septic thrombophlebitis.

A tonsillar or peritonsillar infection within the past week precedes the illness in most cases. Our case was exceptional in that there was no such preceding infection and the primary focus was in the retropharyngeal space, which has been very rarely described.\(^2\) Many patients with LS have neck pain or edema over the sternocleidomastoid muscle, which in our case was the first clue which lead to the diagnosis. Headache may be caused due to raised intracranial tension secondary to venous obstruction and was a prominent symptom in our patient. The endovascular infection seeds septic emboli most commonly to the lung.\(^3\) Our patient had massive hemothorax, but in addition also had hemothorax. The hemothysis might have been caused by a massive pulmonary emboli and pulmonary infarction. Often, the infection is confused with lobar pneumonia, aspiration pneumonia or infective endocarditis with septic lung emboli, as in our patient who presented with typical features of bilateral pneumonia. But the association of IJV thrombosis and pneumonia should always alert the clinician to consider LS. Less commonly metastatic abscess cause osteomyelitis, septic arthritis, hepatic abscesses with hepatic vein thrombosis, splenic abscess, pyomyositis or thyroid abscess. Thrombosis may extend into the cerebral veins causing sigmoid sinus, or cavernous sinus thrombosis.

Another peculiarity of our case was its occurrence in pregnancy. There has only been two previous reports of LS in association with pregnancy. One of the cases in a 23-year old primigravida with cardiac tamponade and cardiac arrest had a near fatal outcome and resulted in preterm delivery.\(^4\) The other case in a 21-year old multipara in the second trimester presented with septic shock and required ventilatory support, but had a favorable outcome with term delivery.\(^5\) The hypercoagulable state in pregnancy may be involved in the pathogenesis of IJV thrombosis. Considering the three cases, the course of LS in pregnancy is seen to be more fulminant with risk of preterm delivery. There has been three reports of LS in association with systemic lupus erythematosus.\(^6\) Our patient had a positive ANA, SS-A and Ro-52 titres, but did not have features of any connective tissue disorder. We are uncertain of the significance of these findings, and speculate that she might have been in an evolving state of a systemic rheumatic disease. Probably pregnancy, the retropharyngeal abscess with cervical inflammation and an underlying systemic rheumatic disease might have all contributed to IJV thrombosis. Antibiotics form the mainstay of treatment of LS. β-lactamase-resistant antibiotics with anaerobic activity like piperacillin-tazobactam, ampicillin-sulbactam, ticarcillin-clavulanate or carbapenems are recommended. Treatment should be continued for at least 4 weeks, with a minimum of 2 weeks of intravenous therapy to ensure penetration into fibrin clots. Role of anticoagulation is controversial, since antibiotics alone are sufficient in most cases. Some recommend anticoagulation only if there is extension of thrombus into the cerebral veins. Any focus of abscess should be drained surgically and in exceptional cases ligation and excision of IJV may be necessary to control the septicemia.

**Conclusion**

The prognosis of LS is good even with septicemia, with mortality of approximately 5% to 18%, if treated with appropriate antibiotics.\(^7\) Even though the literature considers the prognosis of LS good and mortality occurring only with delay in initiation of antibiotics or multiple metastatic abscesses, we advise caution to this generalization and especially during pregnancy as the predictors of fulminant course in this rare disease are yet unknown.

**References**

1st time in India

Volibo M
(Voglibose 0.2/0.3 mg + Metformin 500 mg)

Boost
PPHG Control

Preserve
β-cell function

Control
65% β-cell

T2DM
48% β-cell
Human influenza is a highly contagious, acute respiratory disease caused by influenza virus. According to glycoprotein, hemagglutinin they are described as H1N1; H1N2 etc. Influenza viruses are unique among respiratory viruses; they undergo antigenic variation, resulting in frequent epidemics and periodic pandemics. On an average, annually, around 0.5-1.0 million die and 6-12 million people become infected due to influenza epidemics worldwide. In 1918, pandemic of A (H1N1) also called as Spanish Flu, infected 500 million people across the world, including remote Pacific islands and the Arctic, and resulted in the deaths of 50 to 100 million (three to five percent of the world’s population), making it one of the deadliest natural disasters in human history.

The first large-scale epidemic of the 21st century began in March 2003, when severe acute respiratory syndrome (SARS) shocked the world by its high virulence and efficient transmissibility. Soon causative corona virus (HCoV-HKU) was identified. SARS involved more than 8,000 patients worldwide, and resulted in 774 deaths.

In 2009, influenza epidemic became pandemic, due to a new strain of swine origin H1N1. This novel H1N1 virus which began in Mexico spread to cause 17,000 deaths by the start of 2010. Clinical features were abrupt onset of fever with chills, running nose, sore throat, cough, headache, body ache, weakness, bronchitis, pneumonia & acute respiratory distress. WHO signaled that a global pandemic of novel influenza A (H1N1) was underway by raising worldwide pandemic alert level to phase-6. Pandemic started in India in Aug, 2009. Worldwide flu activity returned to its normal seasonal pattern and by August 2010, H1N1 pandemic was declared over by WHO. But there was a spurt of cases again at the end of 2014. In 2015, an outbreak became widespread throughout India. India’s ministry of health estimated, there to be 29,938 cases of swine flu across India, during 2015-16 resulting in 1,731 deaths. These figures surpass the country’s H1N1 numbers from the 2009 pandemic, when 27,236 cases and 981 deaths were reported.

In 2017, swine flu epidemic claimed 262 lives in Maharashtra and 1700 affected cases so far (June-30-2017), with highest number of swine flu deaths (55) being registered in Pune.

According to researchers at Massachusetts Institute of Technology (MIT), samples of the H1N1 swine flu strain currently ravaging India indicate that the strain may have mutated to become more infectious and dangerous. Contrary to MIT report, researchers at the National Institute of Virology (NIV) in Pune isolated a new strain called the Michigan strain as part of the on-going H1N1 surveillance. They say it is not really a mutation but a new strain that has been isolated from samples in Maharashtra. So far, since the 2009 pandemic, the California strain has been doing the rounds in India and this is the first time a new strain has been identified here. There has been a slight variation in the symptoms of H1N1 infection, in that a sizeable number of recent cases have GI complaints like abdominal pain and loose motions. The epidemic is notoriously seen to affect younger population in 15-40 years age group. Antiviral agents, commonly osilamivir is made available in Government and Municipal hospitals.
Extent of Implementation of Screening Tuberculosis Patients for Diabetes Component of the Tuberculosis Control Programme in an Urban Setting in South India

Banurekha Velayutham¹, Tarun Bhatnagar², Swaminathan Savithri³, Natarajan Dinesh Kumar³, Boopathi Kangusamy⁴, Sanjay Mehendale⁵

¹ICMR, National Institute for Research in TB, Chennai, Tamil Nadu; ²ICMR, National Institute of Epidemiology, Chennai, Tamil Nadu; ³District Tuberculosis Unit, Tiruchhrappalli, Tamil Nadu

Sir,

In 2012, a policy decision was taken by the Revised National Tuberculosis (TB) Control Programme (RNTCP) of India to screen all TB patients for diabetes in 100 districts of India where National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) is being implemented.¹ However, the extent of implementation of this screening program has not been reviewed. We did a cross-sectional study among adult (age ≥ 18 years) TB patients initiated on anti-TB treatment between 1 November, 2015 and 15 February, 2016 at the District Tuberculosis Unit (TU), an urban setting in Tiruchirapalli District, Tamil Nadu to estimate the proportion of TB patients treated under RNTCP screened for diabetes, to identify the reasons for lack of screening and to describe the management practices for diabetes.

The patients were interviewed and laboratory, clinical and treatment data were extracted from their treatment cards and relevant reports. Diabetics were defined as known or newly identified diabetic with fasting blood sugar (FBS) ≥126 mg/dl and or post prandial blood sugar (PPBS) ≥200 mg/dl and or random blood sugar (RBS) > 200 mg/dl [with symptoms of diabetes].² A total of 206 (94%) of 219 TB patients underwent screening for diabetes. Of the 219 screened TB patients, 39 (17.8%) were known diabetics on diabetic medications. RBS or FBS or PPBS was available for 171 (95%) of the remaining 180 patients who were eligible for blood sugar investigations. Overall, of the 219 TB patients, 60 (27.4%) were identified as diabetics [39 known and 21 newly detected] and 146 (66.6%) were Non-diabetics. The reasons for not undergoing diabetic screening in the remaining 13 (6%) patients included lack of time/interest, and busy with work. Awareness regarding diabetes screening was low (n=13/219, 6%). Private health facility and pharmacy were approached by 32 (53%) and 34 (57%) of the 60 diabetic patients, respectively.

Majority of the adult TB patients treated under the TB Control Programme were screened for diabetes and nearly one-third identified as diabetics based on the screening strategy implemented in the study TU. This indicates that it is feasible to identify diabetes in TB patients by employing appropriate screening strategies. The high coverage for diabetes screening could be attributed to excluding known diabetics on diabetic medications to actively undergo blood sugar investigations, considering previous blood sugar reports during the period of investigating for TB, accepting blood sugar values from private laboratories and recommending FBS/PPBS blood sugar only if RBS > 140 mg/dl. An earlier study done across 8 TUs in India had reported that it is feasible to screen TB patients for diabetes in peripheral health institutions with 98% coverage.³ We observed that about half of the diabetic patients attended private health facility for consultation despite free diabetic treatment available in the government facility. The reasons for not attending public health facility for diabetic management have to be explored, the few barriers in diabetic screening have to be addressed and awareness among TB patients regarding diabetes screening has to be improved.

References


Acute Respiratory Failure and ICU Acquired Weakness in an Adult Patient with Dengue Infection-
Successful Weaning from Mechanical Ventilation after 67 Days

Arun Agarwal¹, Mudit Agarwal²

¹Senior Consultant and HOD, Department of Internal Medicine, Narayana Multispeciality Hospital, Jaipur, Rajasthan; ²Medical Student, AIIMS, New Delhi

Sir,

Dengue infection is the most important mosquito-borne arboviral disease in the world. Pulmonary manifestation are uncommon except for pleural effusions which may develop as a part of capillary leak syndrome. Acute respiratory distress syndrome (ARDS) in dengue is rarely reported and has good outcome with early initiation of mechanical ventilation and supportive therapy. We report a case of primary severe dengue fever who developed ARDS and was successfully managed with mechanical ventilation for 67 days along with supportive care. Her hospital stay was complicated with secondary lung infection, severe sepsis-shock and intensive care unit acquired weakness (ICUAW) - critical illness polyneuropathy (CIN).

Ms LD, 30 years was admitted at a local hospital in Alwar (Rajasthan) on 25.10.2015 with history of fever with chills, body aches, headache, and difficulty in breathing of 4-5 days duration. Capillary leak features and moderate thrombocytopenia were present. She was diagnosed as dengue hemorrhagic fever (DHF) and later developed dengue shock syndrome (DSS) with ARDS and had to be mechanically ventilated on 28.10.2015 due to worsening hypoxemia and respiratory distress. Tracheostomy was done on 11.11.2015. However, she could not be weaned off from mechanical ventilation.
ventilator and was later referred to higher centre for further management. She was admitted in our institution on 28.11.2015 through triage. On examination, she was conscious, well oriented, and saturation was 100% on SIMV-PC mode with FIO2 of 35%. She was afebrile at presentation with a heart rate of 146 per minute, BP was 130/80 mmHg and she had profuse sweating. Examination of the respiratory system revealed scattered coarse crackles bilaterally. CNS examination revealed symmetrical and flaccid weakness (motor power 2-3/5) of all limbs (tetra paresis) with absent deep tendon reflexes and bilateral plantars flexor response. Facial and ocular muscles were spared. Sensory system and other system examination were normal.

Examination of the respiratory system revealed scattered coarse crackles bilaterally. CNS examination revealed symmetrical and flaccid weakness (motor power 2-3/5) of all limbs (tetra paresis) with absent deep tendon reflexes and bilateral plantars flexor response. Facial and ocular muscles were spared. Sensory system and other system examination were normal.

Figure 1 images show her X-rays, Figure 2 computed tomography (CT) chest and Figure 3 bronchoscopy images. She was diagnosed as dengue fever with acute respiratory failure with ARDS. Tracheostomy tube (TT) secretions and urine culture grew significant Klebsiella pneumoniae species which were colistin only sensitive (COS) from TT and colistin and carbapenem sensitive in urine culture. She was managed with colistin and high dose meropenem. She had worsening of her lung condition on 05.12.2015 with hypotension, bilateral coarse crepitations, anuria, leukocytosis and mild fever. Bronchoscopy and broncho alveolar lavage (BAL) were also done on 23.12.2015. Nerve conduction study of all limbs showed features suggestive of Axonal neuropathy in bilateral median, bilateral common peroneal and left posterior tibial nerves.

During her stay she had frequent episodes of tachycardia, bradycardia, tachypnea, hypotension and sweating which were attributed to autonomic dysfunction and managed with supportive treatment. The clinical picture of difficulty in weaning from the mechanical ventilator, tetra paresis, muscle wasting of the limbs, loss of tendon reflexes and neurophysiologic examination confirmed this to be CIN with autonomic dysregulation. CIN, severe hypoalbuminemia, chronic resolving fibro proliferative phase of ARDS was managed with physiotherapy, high protein diet, low dose steroids, trace elements, vitamins and other supportive treatment. She was kept on weaning protocol with intermittent CPAP during day, pressure support during night and frequent T piece trials. She had waxing and waning of her pulmonary status and could be
Tropical infections are one of the common causes for ARDS in tropical countries. Of late there are increasing number of cases of ARDS being reported in dengue patients. Devarajan et al reported two cases of ARDS in dengue from Chennai, India. The patient recovered after mechanical ventilation and supportive treatment. Devarajan et al reported two cases of ARDS in dengue from Chennai, India. The exact pathophysiology of ARDS in dengue is still unknown despite large scale research. Wang et al reported from their study that sepsis and upper gastrointestinal bleeding are the main cause for these patients to progress into ARDS. Our patient also developed features of DHF and later progressed to ARDS due to severe sepsis and ventilator associated pneumonia secondary to Klebsiella Pneumoniae. This was managed with antibiotics, mechanical ventilation, and other supportive treatment.

Our patient’s hospital stay was further complicated by ICUAW secondary to CIN and took 67 days in weaning from the mechanical ventilation. ICUAW may affect peripheral as well as respiratory muscles. This contributes to delay in weaning from mechanical ventilation, which is often the clinical problem with which these patients present. About 70% of patients of severe sepsis and septic shock develop CIN secondary to axonal damage in large myelinated nerve fibers; with frequency increasing up to 100% in patients with multiorgan failure. Our patient developed tetraparesis with respiratory muscle weakness secondary to axonal neuropathy and took long time of 67 days in weaning from the respirator.

Autonomic dysfunction, involving the peripheral and central sympathetic and parasympathetic systems, frequently occurs in critically ill patients. Axonal degeneration of the sympathetic chain and vagal nerve has been documented on autopsy of patients with CIN. Our patient also had frequent episodes of tachycardia, bradycardia, Tachypnea, hypotension and sweating which were attributed to autonomic dysfunction.

There is no specific therapy for ICUAW. Aggressive treatment of sepsis, normalization of glycemia, reducing the duration of immobilization, early physical therapy, daily sedation interruption, early mobilization of the diaphragm, electrical muscle stimulation (EMS), and avoidance of malnutrition are some of the strategies for the prevention and therapy of ICUAW.

Take home message:
1. Dengue infection rarely gets complicated with severe sepsis, ARDS and ICUAW.
2. There is no specific treatment and clinician should be aware of such complications in critical patients.
3. Therapy of ICUAW is largely preventive and supportive.
4. The mortality is low and the patients usually recover after mechanical ventilation and supportive treatment.

References

Sensory Ataxia as First Manifestation of Sjögren’s Syndrome

Rathindranath Sarkar1, Rudrajit Paul2, Rajesh Pandey2, Debaditya Roy2, Tanmay Jyoti Sau4, Avinash Mani3, Aditya Vikram Ruia3, Ayandip Nandi5

1Professor and HOD, 2Assistant Professor, 3Resident, 4Professor, Dept. of Medicine, 5RMG, Dept. of Pathology, Medical College, Kolkata, West Bengal

Sir,

Sjögren’s syndrome is a multisystemic autoimmune disorder with various components like xerostomia, xerophthalmia, myalgia, arthralgia and Raynaud’s phenomenon. It can occur as primary Sjögren’s syndrome (PSS) or it may be secondary to other autoimmune disorders1. Neurological and other systemic manifestations are comparatively rare. However, sometimes, the disease may present with atypical features and this can baffle clinicians for a long time. We here present such a rare initial neurological presentation of Sjögren’s syndrome.

There was no sensory complaint. Bladder and bowel were normal. There was no complaint pertaining to cranial nerves. On examination, tone and power were normal in all four limbs. Pain and temperature sensations were normal. However, joint position sense was absent in the lower limbs along with vibration sense. Romberg’s sign was positive. In the upper limbs, vibration and joint position senses were impaired. There were no signs of cerebellar involvement. There was no pain in the limbs or postural drop of blood pressure.

The patient had no joint pain, rash or dryness of eyes or mouth. There was no photosensitivity or skin tightening. Past or family history did not reveal anything significant. She was on no drugs.

Initial laboratory tests revealed hemoglobin of 9.6 gm/dl, total leukocyte count 6400/µL (N: 68; L: 30) and platelet count of 1.9 lakhs/µL. Erythrocyte sedimentation rate was 80 mm in the 1st hour. CRP was 8 mg/L (N<6). Urea and creatinine were 36 and 0.7 mg/dL respectively. Blood electrolyte study revealed sodium of 133 mEq/L, potassium 3.9 mEq/L and calcium 9 mg/dL. Blood sugar was normal. Serum vitamin B12 and folate levels were also normal. MRI scan (with contrast) of the entire neuraxis was normal. In view
of the neurological findings, a nerve conduction velocity study was done. It showed (Figure 1) axonal type of sensory polyneuropathy with normal motor responses.

Now, in view of the NCV findings and predominant large fibre involvement, an autoimmune profile was tested. Serum anti-nuclear factor was positive at 1:100 dilution. Anti-Ro antibody was positive. Finally, a punch biopsy from buccal mucosa was taken which revealed (Figure 2) lymphocytic and plasma cell infiltration of minor salivary glands. Focus score, as estimated by our laboratory was, 1.6. Everything considered together, the patient was finally diagnosed as Sjogren’s syndrome with axonal large fibre neuropathy. Later, a nerve biopsy was also done from the sural nerve which revealed presence of vasculitis.

In view of the rapidly progressing neuropathy, even before the biopsy results were available, IVIg was given, followed by oral steroids. The improvement in ataxia was only mild. However, on follow up, the progression of the symptoms was halted.

Although the patient did not have any dry eyes or dry mouth to start with, later on follow up, she developed dryness of eyes. Schirmer’s test was 7 mm after 5 minutes. She also had an episode of uveitis of both eyes during follow up.

PSS may involve both and central and peripheral nervous systems. Peripheral nervous system involvement is more common. In many cases, the neuropathy may be subclinical and only diagnosed by electrophysiology. The predominant variety of neuropathy is sensory, axonal. It may be painful in some cases; but in our patient, the neuropathy was painless.

IV Ig has been studied in Sjogren’s syndrome associated neuropathy. The response to the therapy has been variable and ataxic variety did not respond well. In our case also, the improvement in symptoms after IVIg was modest. Cyclophosphamide is also used for vasculitic neuropathy. But our patient refused cyclophosphamide for fear of side effects.

Neuropathy may be the initial symptom in PSS. But it usually presents along with other commoner systemic features like xerostomia. But in our case, except for the ataxia, no other symptoms or signs were present initially. Hence the diagnosis was delayed to some extent.

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
Candesartan Cilexetil 5/10/20 mg Tablets
The Nex... for Cardio Renal Protection

Etizola
Etizolam 0.25 / 0.5 / 1 mg
Shorter action... Lesser side effects
Z PROTECTION at 50% reduced price

Start 'EARLY' in Hypertension

ZILARTA 80

24 POTENT & EFFECTIVE BP CONTROL