CONTENTS

Journal, Indian Academy of Clinical Medicine • Vol. 14, Number 1, January - March, 2013

Contains 100 pages from 1to 100 inclusive of all advertisements

CONTENTS

Journal, Indian Academy of Clinical Medicine • Vol. 14, Number 1, January - March, 2013

Contains 100 pages from 1to 100 inclusive of all advertisements

Journal, Indian Academy of Clinical Medicine

JOURNAL, INDIAN ACADEMY OF CLINICAL MEDICINE

is edited by

Dr. D.G. Jain

for the

Indian Association of Clinical Medicine

Headquarters :

Post-graduate Department of Medicine, Sarojini Naidu Medical College, Agra - 282 002 (U.P.)

Editorial/Mailing Address

Barnala House, 867, Guru Gobind Singh Marg, Karol Bagh, New Delhi - 110 005.
Tel.: (011) 23671305

E-mail: iacmjournal@gmail.com

ISSN 0972-3560

RNI Regn. No. : DELENG/2000/1686

Indexed in IndMED (http://indmed.nic.in)

"Bibliographic details of the journal available in ICMR-NIC's database – IndMED (http://indmed.nic.in). Full-text of articles (from 2000 onwards) available on medIND database (http://medind.nic.in)."

Typesetting by: Initials, Tel.: 2354 7929 E-mail: sanjeev.initials@gmail.com

Published by Dr. D. G. Jain
for and on behalf of the Indian Association of Clinical Medicine
from Barnala House, 867, Guru Gobind Singh Marg, New Delhi - 110 005
and printed by him at Tan Prints, A-47, Mangolpuri Industrial Area, Phase II, Delhi. Editor: Dr. D.G. Jain

Indian Association of Clinical Medicine

Headquarters:
Post-graduate Department of Medicine, Sarojini Naidu Medical College, Agra - 282 002 (U.P.)

GOVERNING BODY

President
G Sidhu (Ludhiana)

President-Elect
BB Rewari (New Delhi)

Immediate Past-President
Ajay Kumar (Patna)

Vice-Presidents
NK Soni (Ghaziabad)
YS Raju (Hyderabad)

Founder-President
(Permanent Invitee)
MC Gupta (Agra)

Hony. General Secretary
Ashok Shiromany (Agra)

Hony. Editor, *JIACM*
DG Jain (New Delhi)

Associate Editor, *JIACM*
Alladi Mohan (Tirupati)

Hony. Treasurer
Tejpal Singh (Agra)

Members
Subhash Chandra (Agra)
Suresh Kushwah (Agra)
Prashant Prakash (Agra)
Sujit Kumar (Biharsharif)
MP Singh (Agra)
Ramakant Yadav (Saifai)
Siddharth Kumar Das (Lucknow)
Dipanjan Bandyopadhyay (Kolkata)

Zonal Members

North Zone
Santokh Singh (Amritsar)

South Zone
MA Kabeer (Chennai)

East Zone
HS Pathak (Naihati)

West Zone
PK Sinha (Kota)

Central Zone
Parbhat K Agrawal (Agra)

Organising Secretary
(IACMCON-2013)
Girish Mathur (Kota)

Organising Secretary
(IACMCON-2012)
MPS Chawla (New Delhi)

Joint Secretaries
Rajesh Mahajan (Ludhiana)
DP Agarwal (Agra)
MPS Chawla (New Delhi)

VIEWPOINT

JIACM 2013; 14(1): 6-7

Medical science – a golem?

*BM Hegde**

"Honesty is for the most part less profitable than dishonesty."

– Plato.

The latest editorial in the *Britich Medical Journal (BMJ)* is an eye opener for the conventional thinkers who believe that medical interventions are all very scientific and are the solution for all human ills from common cold to cancer. The truth, though, is otherwise. People are blinded to see the writing on the wall which I have been indicating for more than four decades now by way of articles, books, and lectures all over the globe. The impact has been rather lukewarm – ranging from derision to contempt. For more than 2500 years our ancestors believed what Galen said: that all ills are due to bad humors which needed to be purged or regurgitated from the stomach; or if the humor has got into the blood, to be bled. They hastened the patients' exit from this world in almost all cases save a few who were providentially saved from the jaws of death. Even President George Washington was not an exception. However, we did not learn our lessons from our ready made controls (for an RCT) – the poor who could not pay the doctors for their services. The latter survived with the help of their immune systems. We ignored those glaring evidences to show that blood letting failed.

Today the USA spends the maximum per capita for medical care, mistakenly called health care. They have what they call the highest technology and best drugs in the world. Notwithstanding all that, Americans live the shortest among the industrialised west and have minimum health. It is in this background that today's editorial makes me happy as it is the ratification of my belief in the area. Steven Woolf, professor of family medicine at Virginia Commonwealth University in Richmond, Virginia, and chairman of the panel, explained as to how we have reached this point and what needs to happen next. (www.bmj.com/multimedia).

Americans are used to hearing about the shortcomings of their health system-fragmented healthcare, a shortage of primary care, a lack of public health services – but what Woolf talks about are things that are far more difficult to change: social, environmental, and cultural factors – intrinsic to the American way of life. "There were some recurring themes that led us to start thinking about political science issues and how we govern in the United States," he says. "How our values and lifestyles may be shaping a lot of these issues. There were common themes behind the fact that Americans are more likely to engage in unhealthy behaviours ... it brought us back to thinking about the value system in the United States and how it might be a factor," writes the *BMJ* editorial.

Change of mode of living alone should bring about a healthy society and not medicines, technology, and hospitals. Even in this new awakening in the western thought Professor Woolf misses the crux of the problem, the all encompassing human mind (consciousness) which science is yet to catch up with. **Tranquility of mind filled with universal compassion is a good vaccine against major killer diseases**. Indian wisdom of yore had the science of *Yoga* which has now gone round the world obviously because of its good effect on human health. Western science seems to agree with its good effects now. In a recent study published in the *Journal of the American College of Cardiology* (2013;0:10:10/jack 2012.11.060) the authors have shown that in paroxysmal atrial fibrillation – a common occurrence in old age, resulting in heart failure – *yoga* does improve symptoms, heart rate, arrhythmia burden, as also the quality of life. We have shown many years ago that *yoga* does help coronary artery disease patients significantly. David Shannanoff Khalsa, a neurobiologist from San Diego, has done and published extensive research to demonstrate *yoga's* effect on many psychiatric and neurological illnesses, including epilepsy.

Quantum physics takes medical care to a higher level of understanding. Mind and body are but the two facets of the same coin. With matter and energy being the two faces of the same thing, the human body becomes immaterial – mental and spiritual. Spirituality is just sharing and caring. If we leave the human mind out of modern medicine as we do today, we only will be further

**** Padma Bhushan; Former Vice-Chancellor, Manipal University; Editor-in-Chief, The Journal of the Science of Healing Outcomes; Chairman, State Health Society's Expert Committee, Govt. of Bihar, Patna; Visiting Professor of Cardiology, The Middlesex Hospital Medical School, University of London, U.K.; Affiliate Professor of Human Health, Northern Colorado University, U.S.A.***

harming the system. As of now, the medical establishment is one of the leading causes of death and disability, (*JAMA* 2000; 284: 483). Our scientific view of this world is distorted. Quantum physics guru Hans Peter Durr feels that this world is just a changing drama – Wirklichkeit – changing and changing all the time non-stop. Our body is but a bundle of energy vibrations. The word *world* has a better root in German *wer-ald* – as seen by man. Man's eyes are designed to give us this distorted view of the world. Look at the TV screen. When you see some one talking you miss to see the hundreds of movements of the lips which are the precursors of what you see as speech. This is a special feature of the eye design, called saccades! Saccade is a jerky, fast movement of the eyes. Initiated cortically by the frontal eye fields and sub-cortically by the superior colliculus, the jerky movements cannot be controlled by us and are not seen by us which give us this *wer-ald* view of the world.

"Old science of man takes reality as a primary substance and matter, space filling, impenetrable, invariant, and ever-lasting, mobile properties of change and so on," feels Hans Peter. We stand tall at six feet and look solid. We seem to have a form – Gestalt – in German. This form is not real. There is an inside form which keeps changing and outside we do not see it as the photon lights that make us see things cannot be observed by the naked eye. Our concept of changing the form with drugs and surgery can only have a temporary placebo effect but not the lasting good effect on the whole person and his inside Gestalt. In this background our medical quick-fixes are a long-term menace to human wellbeing, most of them at least.

In view of the above facts, we need to devise a new system of medical care for the future which incorporates the best of corrective surgery and emergency measures for emergencies from modern medicine to be clubbed with a new holistic system which is needed for the vast majority of the chronically ill. They need a new paradigm shift in our thinking.

The first textbook of medicine written in 1773 in Vienna advised the right method even as far back as the 18th century thus:

a) change of mode of living,

b) tranquility of mind, and

c) drugs – rarely ever, if ever.

The sick people rarely might require treatment from outside in the unlikely event of the body's own internal healer, our immune guard, not helping! The last advice is now well founded in science. Almost all reductionist chemical drugs are treated by the body as poison and sent to the liver for destruction, in the bargain many a time damaging the liver. What comes out of the liver (first pass effect) is then used to treat illnesses. Chemical reductionist drugs should be used very parsimoniously, if ever (*Genetics* 2008; 117: 727). Herbal drugs, on the contrary, are treated by the human system as food and do not go to the liver for destruction.

Writing in his blog, Mike Adams has this to say: "Think you might someday get breast cancer? There's a quick fix for that: Chop 'em off! It's called a "preventive double mastectomy" and surgeons are right now successfully convincing women who don't even have breast cancer to have both their breasts surgically removed. Is your government drowning in debt? There's a quick fix for that: Print more money! Don't worry about currency debasement and the long-term blowout collapse of the US dollar that will bankrupt the nation. We need another hit of that bailout money!" For complete healing and long-term benefit this new paradigm of western medicine should be complimented by *yoga* and other ancient methods to keep the mind tranquil. This is all the more important in our western style monetary economy where distress is the rule than exception. Hope the world of medical science listens to this sagely advice.

"Regardless of the moral issue, dishonesty in advertising has proved very unprofitable."

– Leo Burnett .

ORIGINAL ARTICLE

JIACM 2013; 14(1): 8-12

Clinical profile of dengue fever and use of platelets in four tertiary level hospitals of Delhi in the year 2009

KN Tewari, NR Tuli**, SC Devgun****

Abstract

This is a retrospective study based on the record of 230 patients admitted in 2009 in four tertiary level hospitals situated at different locations in Delhi. 163 cases (70.8%) had dengue fever and 25 cases (15%) had evidence of haemorrhagic manifestations. The predominant presenting symptoms of dengue syndrome fever cases were that of vomiting (36%), pain abdomen (34%), headache (27%), myalgia (24%), and nausea (19%). Major bleeding manifestations were epistaxis, haematemesis and melaena. Hepatomegaly with pleural effusion and ascitis was the commonest finding (70.5%) in cases of DHF (N67). Only 3 cases (4.4%) were in DHF grade-III. Severe thrombocytopenia as low as 2,000 was observed in cases of DF and another of DHF – without any bleeding manifestations in DF and minor bleeding manifestations in DHF. Fresh blood has been given to one patient of DF and of DHF. Blood and platelet both have been given to one patient of DF and two patients of DHF. Platelet transfusion was given to 48.7% (80) cases of DF cases and 73.5% (50) cases of DHF. Minimum unit transfused is one and maximum was 16 units with an average of 4.23 units. There is significant difference in the value of p in the average number of days of stay in hospital for those who were given platelet transfusion. Two deaths have been reported in cases of DF – one due to atypical presentation, and the other due to gastro-intestinal tract bleeding.

Key words: Dengue fever (DF), dengue haemorrhagic fever (DHF), platelet transfusion.

Introduction

DF/DHF is one of the important emerging diseases globally expanding in newer areas with greater morbidity. Dengue is endemic in 112 countries of the world and affects almost 50 to 100 million people every year with over 500,000 reported cases of DHF/DSS[1]. Dengue virus infection may be asymptomatic or may cause undifferentiated febrile illness (viral syndrome), dengue fever, dengue haemorrhagic fever including dengue shock syndrome. DF is commonly benign, is defined as acute febrile illness with two or more manifestations among headache, retro-orbital pain, myalgia, arthralgia. Haemorrhagic manifestation i.e., skin haemorrhage with tourniquet test, and petechiae, are not uncommon. There have been reports of epistaxis, gingival bleeding, gastrointestinal bleeding, haematuria, and hyper-menorrhagia[4,6]. DF complicated by unusual haemorrhage and thrombocytopenia must be differentiated from DHF. Haemorrhage in DHF is defined as 2 to 7 days acute febrile illness with bleeding, thrombocytopenia, an evidence of plasma leakage and rise in haematocrit to or greater than 20% above the average.

This study was conducted to know the predominant symptoms of admitted cases of dengue syndrome in Delhi.

Background

DF/DHF has been notified as a dangerous disease. In Delhi, all health institutions are obliged to notify all cases of DF/DHF to the Municipal Corporation of Delhi (MCD)[2]. DF outbreaks have been reported from Delhi since 1967. The outbreak in 1996 was the most serious one resulting in 10,252 cases with 423 deaths. Since then there have been regular and frequent dengue outbreaks in Delhi. It is endemic in Delhi and all 4 serotypes of DENV have been reported in the community[3].

2009 was a non-epidemic year and DENV-I was predominant (source: NCDC).

Methodology

- **Study design**

  It is a retrospective, and observational study in which data has been collected by observing the formats and records of the selected hospitals notified by Municipal Corporation of Delhi and serologically confirmed by NCDC.

- **Study area**

  Three private super-speciality hospitals and one hospital of Municipal Corporation of Delhi (having 650, 600, 250, and 980 beds) situated at different locations of Delhi were selected. The 230 cases out of 426 patients of DF/DHF admitted from July to December 2009, were randomly selected from the hospital records to study the clinical features.

**** Public Health Consultant and former Municipal Health Officer, Municipal Corporation of Delhi, ** Deputy Health Officer, Municipal Corporation of Delhi, *** Former Head of the Department of Medicine, Hindu Rao Hospital, Delhi.***

- **Inclusion criteria**

  Cases of fever serologically positive for DF/DHF by NCDC.

- **Exclusion criteria**

  Cases where records were not complete and not tested positive by NCDC, and institutions not willing or had not given consent, were excluded from the study.

- **Limitations**

  Institutional data limited to admitted cases only.

Results

In 2009, the first case was admitted on 7th July and the last case on 25th December. 230 cases were admitted in these four hospitals. Two deaths were reported in DF, one with hypertension with cardiac arrest (as per record, the patient had severe haematemesis and melaena) and the other due to encephalopathy with acute renal shutdown.

- **Age group**

  The minimum age of the patient in study group was 6 years and maximum age of a patient was 82 years. Average age in years for males was 30.4 and for females 39.0 and total were 31.9.

- **Co-existing diseases**

  The DHF cases have been found to be associated with malaria, aplastic anaemia, thalassaemia major, hypertension, diabetes mellitus, and cancer breast.

- **Duration of stay**

  The range has been from 2 to 9 days. Average stay of patients in the hospital was 4.9 days for those who were given transfusion and 5.3 for those who were not given transfusion. The value of p = 0.0416 is greater than 0.025.

- **Clinical features**

  The fever was always the first to start, followed by other symptoms after 2 - 4 days i.e., vomiting, headache, pain abdomen, and myalgia. The generalised associated symptoms observed in less than 2% of cases as shown in Table I, were dry cough, burning micturation, loss of appetite, scrotal swelling, breathing difficulty, constipation, palpitation, sore throat, altered behaviour, oral ulcers, icterus, sub-conjunctival haemorrhage, etc. Retro-orbital pain was not a predominant symptom. Fever with arthralgia and retro-orbital pain is less than 3% in admitted cases.

Table I: Clinical features of cases (N = 230).

Clinical feature	Total patients	Total %
Fever	230	100
Vomiting	75	32.6
Headache	63	27.39
Pain abdomen	59	25.65
Myalgia	50	21.73
Nausea	36	15.65
Rash	24	10.43
Weakness	17	7.39
Itching	13	5.5
Petechiae	10	4.34
Loose stools	10	4.34
Arthralgia	14	3.04
Retro-orbital pain	5	2.18
Restlessness	5	2.17
Breathlessness	5	2.17
Icterus	4	1.73

Enlargement of liver (N=15) and spleen (N=17) was observed in nearly 1% of cases of DF.

The most common clinical observation in cases of DHF was enlargement of liver (70.5%) followed by pleural effusion (55.8%) and ascites (55.8%). Detail is given in Table II. The findings were from minimal detected by ultrasound/ radiology to physical findings depending on amount of plasma leak. The patients had shown multiple combinations of above features with varying degree of severity.

Table II: The clinical and radiological findings of plasma leak (N = 67).

Findings	Total cases*	Total %
Hepatomegaly	48	70.5%
Pleural effusion	38	55.8%
Ascites	38	55.8%
Thickening of gall bladder wall with or without oedema	4	5.8%

**Patients had more than one finding.*

All cases have been classified as per WHO Guidelines[4] given in Table 3. 163 cases (70.5%) had dengue fever. 141 cases (82.6%) of DF had count less than 1,00,000. 25 cases (15%) of DF had evidence of haemorrhagic manifestations[4]. Three cases (12%) had platelet count more than 100,000. Minimum count observed was 2,000 followed by 3,000 in cases of DF without any signs of bleeding. Platelet transfusion was given to 80 (48.7%) cases of DF.

Table III: Cases of dengue fever (N = 163) given platelet transfusion (N = 80).

S. No.	Category	No. of cases and percentage	No. of cases given platelet transfusion and percentage	Criteria
1	DF (classical dengue)	137 (59.56)	58 (42.33)	Cases without evidence of plasma leak
1.1	Abnormal presentation (acute renal shutdown)	1 (1.5)	0	Clinical and laboratory
1.3	DF with haemorrhagic manifestations	25 (19.23)	22 (88)	All cases of bleeding without any evidence of plasma leak

The cases of DHF (N=67) have been further categorised. Nearly 76% of cases are of category 1; no case was in category IV. Detailed distribution of cases are shown in Table III(a).

Table III(a): Cases of DHF (N = 67) given platelet transfusion (N = 50).

S. No.	Category	No. of cases and percentage	No. of cases given platelet transfusion and percentage	Criteria
2	DHF Category I	51 (76.11)	40 (78.43)	Positive tourniquet test without obvious evidence of clinical haemorrhage with plasma leak
2.1	DHF Category II	13 (19.40)	8 (61.53)	In addition to category I, with spontaneous haemorrhagic manifestations
2.2	DHF Category III	3 (4.47)	2 (66.6)	Cases with profound shock in addition to symptoms mentioned in category II.
2.3	DHF Category IV (DSS)	0	0	Cases with profound shock.

50 (73.5%) of DHF cases were given transfusion. Cases of DHF (N=67) have been further classified into minor and major bleeding manifestations. Minor bleeding manifestations include petechiae, purpura, rash, haemoptysis, bleeding gums and mucosa, sub-conjuctival haemorrhage, haematoma, etc. Major bleeding manifestations were epistaxis, haemetamesis, melaena, and haematuria as shown in Table IV.

Table IV: Cases of DF/DHF having major bleeding.

Major categories of bleeding	DF	DHF	Total
Epistaxis	11	2	13
Haematemesis	10	3	12
Melaena	10	1	11
Haematuria	2	2	4
Bleeding per vaginum	1	1	2
	34	9	43

Few cases had more than one bleeding manifestation. It was observed that platelet count dipped after the first bout of bleeding manifestation without further bleeding. The severe bleeding manifestation had started at platelet count more then 30,000. Minimum count observed was 2,000 in one case of DHF without any signs of major bleeding. Raised liver enzymes are directly related to severity of disease.

The total units of platelets transfused are 524 units, with an average of 4.23 per patient. The minimum unit transfused is one unit whereas maximum units transfused to one patient was 16 units. Fresh blood was given to two patients only, and another three patients were given both blood and platelets; and 125 cases have been given platelet transfusion including two patients who were also given FFP.

The platelet count in all cases, irrespective of transfusion of blood or blood product, reached more than 100,000 within 24 to 48 hours.

Table V: Distribution of cases of dengue infection (N = 230) with range of platelet count given transfusion (N=130).

Range of platelets	Total no. of cases of dengue infection (N = 230)	No. of DF cases in the range (N = 162)	No. and % of DF cases given platelet transfusion (N = 80)	No. of DHF cases in the range (N = 67)	No. and % of DHF cases given transfusion (N = 50)
Less than 10,000	14	8	8 (100)	6	6 (100)
10,000 to 20,000	65	38	36 (94.7)	27	26 (96.2)
20,000 to 50,000	85	63	32 (53.9) #1+2*	22	15 (77.2)#1+*1
50,000 to 100,000	45	38	0	7	1#
>100,000	21	15	0	6	0

** Denotes cases given platelets and blood; # denotes cases given blood only.*

Discussion

Minor and major bleeding manifestations mostly in the GI tract have been observed in DF cases. Major bleeding cases in DF (20.85%) was more than in DHF (13.43%). Most of dengue infection cases (94.8%) have platelet count less than 100,000. The classical DF also had severe thrombocytopenia.

In cases of DF and DHF, platelet count was observed to be even less than 10,000 without severe bleeding manifestations. It is inferred that bleeding has no relation with platelet count[5]. Most of the cases were admitted with history of bleeding. There was no further bleeding even though the count dropped during hospitalisation. The most common site of haemorrhage was gastrointestinal tract (32.2%); this finding is in accordance with that of other studies[5,10,11]. Statistical analysis of our data showed no association between haemorrhagic manifestations and the degree of thrombocytopenia. In addition, the mean platelet count of patients with and without haemorrhagic manifestations was not significantly different indicating that platelet count has no predictive value for bleeding.

Platelet count has been done more frequently than serial haematocrit. The serial haematocrit has been done only in 27 (11.73%) cases. Haematocrit value should have been used for prognosis and effective management of cases rather than platelet count.

As per guidelines, platelets may be given to adults with underlying hypertension and very severe thrombocytopenia (less than 10,000 cells/cumm)[12,13,14]. In case of systemic massive bleeding, platelet transfusion may be needed in addition to red cell transfusion. However, none of the cases studied by us had either hypertension or platelet count < 10,000/cumm.

The guideline does not support the use of blood components such as platelet concentrates, fresh frozen plasma (FFP), or cryoprecipitate. In management of DF/DHF[6], the immediate replacement of plasma loss is by rapid volume expanders (which include, physiological saline, Ringer's lactate or Ringer's acetate, 5% glucose solution diluted 1:2 or 1:1 in physiological saline, plasma), and by plasma substitutes.

In the present study, FFP has been used only for two patients. Platelet transfusion which has been given to 125 cases of dengue syndrome is suggestive of overemphasis and dependency on platelet transfusion in management of cases[6,16]. It seems platelet transfusion has been given as prophylaxis in cases of thrombocytopenia. It may be due to pressure from relatives and fear of uncertainty about the outcome of the disease[7] rather than on merit.

There is a significant difference in the value of p (= 0.0416 is greater than 0.025) in the average number of days of stay in the hospital for those who were given platelet transfusion (4.9 days) with those who were not given platelet transfusion (5.3 days).

The notable features observed in this study are:-

1. Lack of appropriate categorisation of patients.
2. Haemorrhagic manifestations have no association with thrombocytopenia.
3. Guidelines by WHO have not been followed in management of cases.

Conclusion

Use of platelet transfusion is not in accordance with guidelines and has been used as prophylaxis. Bleeding is not related to platelet count. Further study is needed to know the relationship between platelet transfusion and stay in hospital vis-à-vis cost effectiveness and risk of transfusion of blood products.

Acknowledgment

I am grateful to Dr JP Narain, CDS, WHO, SEARO for his

support, motivation and encouragement. I am thankful to Dr Rajesh Bhatia, RA, for his advice to incorporate platelet transfusion in the study, and Dr NR Dass, Dy. MHO/ Malaria, Dr Om Prakash Gahlot, DHOMCD, and the medical record officers of the concerned hospitals for providing the records and related important inputs.

References

1. Dengue Fever - Overview http://www.medindia.net/patients/patientinfo/dengue.htm#ixzz0yqwiocuc
   Dengue/Dengue Hemorrhagic Fever / Dengue Shock Syndrome
2. The Delhi Municipal Corporation Act 1957, under provision 2.(9) (b).
3. Guidelines for Prevention and Control of Dengue.
   Zoonosis Division, National Institute of Communicable Diseases (Directorate General of Health Services), 22, Sham Nath Marg, Delhi-110 054. Copyright © World Health Organization (2006).
4. Monograph on Dengue/Dengue Haemorhagic Fever Regional publication, SEARO No. 22, page 5.
5. Chairulfatah A, Setiabudi D, Agoes R, Colebunders R. Thrombocytopenia and Platelet Transfusions in Dengue Haemorrhagic Fever and Dengue Shock Syndrome, *Dengue Bulletin* 2003; 27: 138.
6. Dengue Haemorrohagic fever - diagnosis, treatment, prevention and control. 2nd Edition, WHO, Geneva, 1997.
7. Makroo RN , Raina V, Kumar P, Kanth RK. Role of platelet transfusion in the management of dengue patients in a tertiary care hospital. *Asian Journal of Transfusion Science* 2007; 1: 4.
8. Chhina DK, Goyal O, Goyal P *et al*. Haemorrhagic manifestations of dengue fever & their management in a tertiary care hospital in north India. *Indian J Med Res* 2009; 129: 718-20.
9. Clinical Management of Dengue Fever (DF) and Dengue Haemorrhagic Fever (DHF). B. Management of DHF Average Grade (Febrile Phase). www.nvbdcp.gov.in/Doc/Dengue Clinical Management.pdf
10. Sharma S, Sharma SK. Clinical profile of DHF in adults during 1996 outbreak in Delhi, India. *Dengue Bull* 1998; 22 : 20-7.
11. Daniel R, Rajamohanan, Philip AZ. A study of clinical profile of dengue fever in Kollam, Kerala, India. *Dengue Bulletin,* 2005; 29: 197-202.
12. Suchitra Nimmannitya CLinical Manifestation of DF/DHF. WHO Regional Publication No. 22 - monograph of Dengue/DHF - pp 48 n-n 54, WHO/SEARO, New Delhi.
13. Suchitra Nimmannitya. Management of DF/DHF. WHO Regional Publication No. 22 - monograph of Dengue/DHF - pp 55-61, WHO/ SEARO, New Delhi.
14. Regional Guidelines for Prevention and Control of Dengue/DHF, WHO/SEARO, New Delhi, 1998.

ORIGINAL ARTICLE

JIACM 2013; 14(1): 13-9

Surgical site abdominal wound infections: Experience at a north Indian tertiary care hospital

Barnali Kakati, Ashish Kumar**, Pratima Gupta***, PK Sachan****, Bhaskar Thakuria**

Abstract

Background: SSIs are the foremost cause of post-operative morbidity. The present prospective study was undertaken to identify the risk factors, the causative bacteria and their antibiotic susceptibility patterns at a tertiary care teaching hospital in north India.

Methods: 685 patients undergoing various abdominal surgical procedures admitted in Unit I of the dept. of general surgery over a 20 months period at HIMS, Dehradun, Uttarakhand, were included in the study group. Infected wounds were studied bacteriologically. Samples such as pus swabs from the infected wound site, aspirates, surgical drain tips or blood were collected as indicated. Direct staining, aerobic bacterial cultures and identification followed by antibiotic sensitivity testing were performed and the results analysed.

Results: The overall infection rate of 7.44% was observed among 685 patients included in the study. A higher SSI rate was observed in cases of emergency surgeries and with increasing degree of wound contamination. Prolonged duration of surgery and drain usage contributed significantly to the incidence of SSI. The most common isolate was E. coli followed by S. aureus. A predominance of Gram-negative bacteria in causing infection was observed. The isolates were commonly resistant to antibiotics used for surgical prophylaxis.

Conclusions: A high incidence of SSI, especially in clean interventions (3.77%), emphasises the importance of implementing active SSI surveillance in surgical wards so as to obtain standardised incidence ratios targeting modifiable risk factors. Emergency surgeries, duration of surgery, and drain usage were a few identified risk factors. E. coli was the commonest isolate (41.17%). A rising trend of MRSA strains in our hospital is an existing problem. Drug regimens using amoxicillin-clavulanate and gentamycin for prophylactic coverage before surgery need to be carefully and urgently revised for controlling SSIs in our hospital, considering the high level of resistance observed.

Introduction

The term surgical site infections (SSIs) includes all post-operative infections occurring at surgical site(s). Inspite of advances in infection control, SSI remains a major limiter of surgical horizons[1]. These are the third most frequently reported nosocomial infections (NI), accounting for nearly 14 - 16% among hospital inpatients[2]. SSIs are a major cause of post-operative illness resulting in increased morbidity, mortality, and do have a major impact on the cost of health care[3].

A surgical wound may get infected by the exogenous bacterial flora which may be present in the environmental air of an operation theatre (OT) or by the endogenous flora[4]. A spectrum of microorganisms with varied antimicrobial susceptibility patterns have been identified as causative agents of SSIs, which vary with time, hospital location, and with the type of surgical procedure performed[5,6].

A summation of several factors contribute to the development of SSIs such as the inoculum of bacteria introduced into the wound during the procedure, the virulence of the contaminants, the microenvironment of each wound. and the integrity of the patient's host defense mechanisms[7,8]. In 1964, the National Academy of Sciences and the National Research Council USA, published a classification scheme for surgical wounds that has been widely adopted[9] which includes clean, clean contaminated, contaminated, and dirty wounds. Infection of a surgical wound is also related to the class of the wound as described by many authors[5,6].

The aim of this clinico-microbiological investigative work was to conduct a study of SSIs to assess their incidence, identify risk factors, the causative aerobic bacteria and their *in vitro* antibiotic susceptibility patterns.

Materials and methods

The present study was carried out in the Department of Microbiology and Unit I of General Surgery at Himalayan Institute of Medical Sciences (HIMS), Dehradun, India, over a period of 20 months.

**** Assistant Professor, ** Associate Professor, *** Professor and Head, Department of Microbiology, **** Professor, Department of Surgery, Himalayan Institute of Medical Sciences (HIMS), Doiwala, Jolly Grant, Dehradun - 248 140, Uttarakhand.***

All patients of either sex who were admitted to the General surgical wards of the hospital through the Unit I of General Surgery, in the above-mentioned period and underwent emergency or elective procedures (except those excluded as per the under-mentioned criteria) were included in the study group. Wound infection was suspected if there was a serous, non-purulent discharge with or without signs of inflammation (oedema, redness, raised local temperature, tenderness, induration, fever >38°C) at the wound site(s), pus discharge or visible wound dehiscence.

Patients who were admitted to the other surgical sub-speciality units and wards such as paediatric surgery, urosurgery, neurosurgery, orthopaedic surgery, cardiothoracic and vascular surgery, plastic surgery and burns department were not included in the study. Patients developing stitch abscesses were also excluded from the study[10].

For clean wounds, standard procedure for skin preparation was followed using application of 3 coats of povidone iodine to the skin, followed by a compulsory waiting period of 20 minutes until the skin dried up preceding surgical incision.

For wounds other than clean wounds povidone iodine scrub was applied as 3 coats to the skin, followed by 3 coats of spirit and 3 repeat coats of povidone iodine again. An intervening drying period of 15 - 20 minutes was uniformly followed after application of antiseptics to the skin preceding incision.

All patients uniformly received prophylactic antibiotic dosage before incision. Standard antibiotics used for peri-operative SSI prevention in our hospital was amoxicillin-clavulanic acid preoperatively, and a combination of flouroquinolones (e.g., ciprofloxacin), aminoglycosides (e.g., gentamicin) and metronidazole post-operatively. Standard time of prophylactic administration of antibiotic was just before anaesthetic induction pre-operatively in the operation theatre and post-operatively within 20 minutes of wound closure.

Surgical wound was inspected by the investigators during biweekly rounds performed at the time of opening of the dressing for the first time and subsequently at the time of next dressing. In case of suspicion of wound infection other than on these rounds, information was obtained from the surgical team performing the routine dressings and followed up until complete wound healing occurred or the patient was discharged from the hospital. The signs of SSI were observed by the surgeons and approved by the investigators.

A standardised proforma was filled-in for each patient included in the study group describing relevant clinical history, pre-operative hospitalisation stay, duration and type of surgery, drain usage and class of surgical wound. Swabs from the infected wound site, aspirates in sterile syringes, surgical drain tip or blood were collected as indicated.

Sample processing

Samples, except blood, collected from infected wounds were processed for Gram's and Ziehl-Neelsen staining. Aerobic cultures were performed using blood agar, MacConkey's agar, chocolate agar and brain heart infusion broth (BHI) with subsequent overnight incubation at 37°C in 5 - 10% CO_2. For blood cultures, the samples were aseptically inoculated in standard blood culture bottles and incubated at 37° C overnight. These were analysed for presence of turbidity and checked by Gram's staining every subsequent day for 7 days.

Final identification of the bacteria was done on the basis of primary Gram's stain appearance, colony morphology, production of haemolysis or pigment, and interpretation of biochemical tests. Antimicrobial susceptibility testing was performed as per standardised Clinical Laboratory Standards Institution(CLSI) guidelines using Kirby Bauer disc diffusion technique[11]. The size of zones of inhibition for test strains were compared with those mentioned in the standard interpretative charts provided by the antibiotic disc manufacturer (Himedia Laboratories). The results were interpreted as sensitive (S), intermediate sensitive (I) or resistant (R) for each isolate identified. Methicillin resistance in *S. aureus*, was determined following standard CLSI guidelines[11].

Statistical analysis

The collected data were analysed and the significance of the results obtained was statistically evaluated using appropriate tests.

Results

The study group comprised of 685 patients of which 353 (51.53%) were men and 332 (48.46%) were women. The mean age was 40.13 years for men (CI ± 2.39) while for women it was 41.82 years (CI ± 2.59). Overall mean age was 40.97 years. Various surgical procedures on spleen, hepatobiliary system and appendix were performed in the surgical unit 1. Exploratory laparotomy was associated with the highest incidence (60.4%) of SSI amongst all the surgical procedures.

Out of these 685 patients, 51 patients (7.44%) developed SSI of which 34 (66.66%) were men and 17 (33.34%) were women. The SSI rate was found to be 3.77% in clean surgeries, 4.45% in clean contaminated surgeries, 11.02%

in contaminated surgeries and 16.82% in dirty-infected surgeries. (p value= 0.002). The correlation of pre-operative stay with incidence of SSI was not found to be statistically significant in the study. The infection rate was found to be higher with emergency surgeries (15.2%) than with planned elective surgeries (4.86%) and the data was found to be highly significant (p value = 0.0001). It was observed that the duration of surgery had a direct influence on the development of SSI. Numbers of SSI were found to rise with an increase in the duration of surgery. Obtained data was found to be statistically significant (p value = 0.016). Out of 685 patients, surgical drain was post-operatively used in 272 patients, out of which 43 (15.75%) patients developed SSI as compared to only 1.93% in those without surgical drains (p value <0.000001) (Table I).

Thirty-nine samples of pus, 12 drain tips, 2 serous aspirates and 6 blood samples from 51 suspected SSI patients were collected.

Gram-negative bacilli were found in 37 (72.54%) samples and gram-positive cocci were found in 14 (27.45%) samples. None of the samples were positive for ZN staining. Only pus and drain tip samples showed bacterial growth. None of the blood and aspirate samples collected were culture positive (Table II).

Out of the 59 samples received, 51 were culture positive and *E. coli* was the commonest bacteria isolated (41.17%). *Staphylococcus epidermidis* was the predominant organism isolated from class I, followed by *E. coli* from class II and IV. A mixed picture was seen in class III wounds (Table 3). Two out of seven (28.57%) isolates of *S. aureus* were determined to be methicillin resistant (MRSA).

Table II: Correlation between Gram's stain and culture results of samples obtained from patients with SSI (n = 51).

Samples	Gram's stain results		Culture results		Total no. of samples
	Positive	Negative	Positive	Negative	
Pus	39	0	39	0	39
Drain tip	12	0	12	0	12
Aspirate	0	2	0	2	2
Blood	–	–	0	6	6
Total	**51**	**2**	**51**	**8**	**59**

Table III: Bacterial isolates obtained from samples of SSI (n=51).

Bacteria	Number	Percentage
*Staphylococcus aureus**	7	13.72 %
Staphylococcus epidermidis	3	5.88 %
Enterococcus faecalis	4	7.84 %
Escherichia coli	21	41.17 %
Klebsiella pneumoniae	5	9.80 %
Citrobacter koseri	3	5.88 %
Citrobacter freundii	1	1.96 %
Proteus mirabilis	1	1.96 %
Enterobacter aerogenes	1	1.96 %
Pseudomonas aeruginosa	4	7.84 %
Acinetobacter saccharolytic	1	1.96 %
Total	**51**	**100 %**

Table I: Distribution of SSIs in the study.

	No. of SSIs	No infection	Total no.	Statistical analysis
Class of Wound				
I	6 (3.77%)	153 (96.22%)	159 (23.21%)	p value = 0.002
II	13 (4.45%)	279 (95.54%)	292 (42.62%)	
III	14 (11.02)	113 (88.97%)	127 (18.54%)	
IV	18 (16.82%)	89 (83.17%)	107 (15.62%)	
Type of procedure				
Elective	25 (4.86%)	489 (95.13%)	514 (75.01%)	χ^2 test:
Emergency	26 (15.20%)	145 (84.79%)	171 (24.96%)	p value = 0.00011
Duration of surgery				
< 1 hr	2 (6.666%)	38 (95%)	40 (5.83%)	Correlation = 0.93,
1-2 hr	27 (6.23%)	406 (93.76%)	433 (63.21%)	χ^2 test = 0.016
> 2 hr	22 (10.37%)	190 (89.62%)	212 (30.94%)	
Drain usage				
Yes	43 (15.75%)	229 (83.88%)	272 (39.70%)	χ^2 test:
No	8 (1.93%)	405 (98.06%)	413 (60.29%)	$5.8796E^{-07}$
Total	**51 (7.44%)**	**634 (92.55%)**	**685 (100%)**	

All Gram-positive bacteria were sensitive to vancomycin, linezolid, rifampicin. However, all isolates showed resistance to ampicillin but a few were sensitive to a combination of amoxycillin-clavulanic acid (21.42%). Gram-positive isolates showed a high level of resistance to cephalosporins (50-62%). Most of the isolates showed relatively good sensitivity (60%) to quinolones, 50% were sensitive to amikacin, but only 21.42% were sensitive to gentamicin (Table IV).

All Gram-negative isolates were found to be sensitive to imipenem (100%) and mostly to polymyxin B (97.29%). The newer antibiotic aztreonam was found to be effective against 51.35% isolates. All the Gram-negative isolates showed resistance to ampicillin and amoxycillin-clavulanic acid. Most of the isolates showed resistance to all generation of cephalosporins (>64.86%) and to quinolones (>75%). Nearly 27% - 59.45% of the Gram-negative isolates were sensitive to aminoglycoside drugs such as tobramycin (59.45%), kanamycin (54.05%), amikacin (43.24%), netilmicin (43.24%) and least to gentamicin (27.02%) (Table IV).

All the *Pseudomonas aeruginosa* isolates were sensitive to imipenem and polymyxin B (100%), while all isolates were found to be resistant to aminoglycosides (100%) except one that was sensitive to netilmicin. High resistance was seen with cephalosporins (66%). The *Pseudomonas* isolates were relatively resistant to anti-pseudomonal drugs such as piperacillin and ticarcillin. However, the susceptibility marginally increased when the same antibiotic was fortified with tazobactam or clavulanic acid.

Discussion

The overall SSI rate determined in this study was 7.44%. Data from other studies performed at various periods of time, report an overall infection rate ranging from 6.1% to 25%[5,6,12-14] (Table V).

Paucity of available data in Indian medical literature hinders the comparative analysis of emerging spectrum and resistance patterns among the class III and IV wounds.

It was evident that SSI increases with an increase in the degree of contamination of the wounds operated upon. The infection rate was found to be almost 3-times higher following emergency procedures than planned elective procedures (4.86%). In a comparative study conducted by Cruse and Foord, the infection rate encountered in emergency surgeries was double the rate of elective surgeries[15]. Several other studies also corroborate the evidence that emergency surgeries are more prone to wound infections[3,18-20].

In the present study the numbers of SSIs were found to be influenced by the duration of surgery.

Two patients (6.66%) developed SSI in surgeries of duration less than 1 hour, 6.23% between 1 - 2 hours, and 10.37% patients developed SSI in surgeries lasting for more than 2 hours. Similar trends were found in an Indian study which reported 2.6% SSI in surgeries of duration less than 1 hour, 4.8% SSI in surgeries between 1 - 2 hours and 5.4% SSI in surgeries that lasted for more than 2 hours[5]. These findings are in concordance with a Peruvian hospital report[17] and a Brazilian report[7].

In our study, wounds in which drains were used showed a higher incidence of SSI (15.75%) as compared to those without usage of drains (1.93%). Other scientific reports exploring such a correlation have also emphasised that drain usage potentiated the development of SSI[9,17,18].

On culture, the most common bacteria isolated was *E. coli* (41.17%) followed by *S.aureus* (13.72%). Gram-negative bacilli as causative bacteria of SSI have been frequently reported by infection surveillance workers[5,16,21,22] and this is in agreement with our study as we found predominance of Gram-negative bacilli as the aetiological agents for SSI.

Resistance of isolated micro-organisms from surgical patients is an emerging problem worldwide[5,14]. Isolation of 28.57 % MRSA strains from wounds of admitted patients with a rising trend over the past few years is a cause for concern not only for the control of NIs but also for the treating physicians and surgeons in our hospital. All the Gram-positive isolates in our study were resistant to ampicillin (100%) and a combination of amoxycillin-clavulanate (71.42%) substantiating the ineffectiveness of penicillin against Gram-positive isolates and such findings have been demonstrated in other studies also[5,6,14]. The pre-operative prophylactic therapy using amoxycillin-clavulanate therefore needs to be revised in our hospital keeping in view the large number or resistant isolates. In our study, 50% of the Gram-positive isolates were sensitive to amikacin, whereas only 21.42% of the isolates exhibited sensitivity to gentamicin. An even lower susceptibility of only 1.1% has been reported in India by Anvikar *et al*[5]. Resistance in Gram-positive isolates was further augmented with a high level of resistance against cephalosporins (40-60%).

None of the Gram-positive isolates were found to be vancomycin resistant in our study. This is consistent with some studies from India and neighboring Asian countries that have reported a near 100% sensitivity to vancomycin[6,23,24,25].

Table IV: Overall sensitivity pattern of Gram-positive and Gram-negative isolates (n = 51).

Antibiotics tested	Gram-positive isolates (No. = 14)			Gram-negative isolates (No. = 37)		
	S	I	R	S	I	R
Amikacin	7 (50%)	0	7 (50%)	16 (43.24%)	2 (5.40%)	19 (51.35%)
Amoxy-clav	3 (21.42%)	1 (7.14%)	10 (71.42%)	0	0	37 (100%)
Ampicillin	0	0	14 (100%)	0	0	37 (100%)
Aztreonam	–	–	–	19 (51.35%)	0	18 (48.64%)
Cefaclor	–	–	–	6 (16.21%)	1 (2.7%)	30 (81.08%)
Cefexime	–	–	–	3 (8.10%)	3 (8.10%)	31 (83.78%)
Cefoperazone-sulbactam	6 (42.85%)	4 (28.57%)	4 (28.57%)	16 (43.24%)	5 (13.51%)	16 (43.24%)
Cefpirome	–	–	–	9 (24.32%)	4 (10.81%)	24 (64.86%)
Ceftazidime	–	–	–	6 (16.21%)	2 (5.40%)	29 (78.37%)
Ceftriaxone	4 (28.57%)	3 (21.42%)	7 (50%)	10 (27.02%)	2 (5.40%)	25 (67.56%)
Cefuroxime	2 (14.28%)	3 (21.42%)	9 (64.28%)	0	0	37 (100%)
Cephalexin	4 (28.57%)	3 (21.42%)	7 (50%)	0	0	37 (100%)
Chloramphenicol	9 (64.28%)	0	5 (35.71%)	22 (59.49%)	0	15 (40.54%)
Ciprofloxacin	9 (64.28%)	0	5 (35.71%)	6 (16.21%)	3 (8.10%)	28 (75.67%)
Clindamycin	10 (71.42%)	0	4 (28.57%)	–	–	–
Cloxacillin	4 (28.57%)	1 (7.14%)	9 (64.28%)	–	–	–
Cotrimoxazole	0	0	14 (100%)	1 (2.7%)	0	36 (97.29%)
Erythromycin	4 (28.57%)	1 (7.14%)	9 (64.28%)	–	–	–
Gentamicin	3 (21.42%)	0	11 (78.57%)	10 (27.02%)	3 (8.10%)	24 (64.86%)
Imipenem	–	–	–	37 (100%)	0	0
Kanamycin	–	–	–	20 (54.05%)	0	17 (45.94%)
Linezolid	14 (100%)	0	0	–	–	–
Netilmicin	–	–	–	16 (43.24%)	1 (2.70%)	20 (54.05%)
Penicillin	0 (0%)	0	14 (100%)	–	–	–
Piperacillin	–	–	–	4 (10.81%)	0	33 (89.18%)
Piperacillin-Tazobactam	–	–	–	7 (18.91%)	3 (8.10%)	27 (72.97%)
Polymyxin B	–	–	–	36 (97.29%)	0	1 (2.70%)
Rifampicin	14 (100%)	0	0	–	–	–
Sparfloxacin	–	–	–	4 (10.81%)	2 (5.40%)	31 (83.78%)
Tetracycline	5 (35.71%)	0	9 (64.28%)	3 (8.10%)	4 (10.81%)	30 (81.08%)
Ticarcillin	–	–	–	4 (10.81%)	0	33 (89.18%)
Ticarcillin clavulanate	–	–	–	6 (16.21%)	3 (8.10%)	28 (75.67%)
Tobramycin	–	–	–	22 (59.45%)	0	15 (40.54%)
Vancomycin	14 (100%)	0	0	–	–	–

(S = Sensitive; I = Intermediate sensitive; R = Resistant; grey area denotes - testing not done)

Table V: Global SSI rates in relation to the class of wounds.

Class of wound	Our study	Canada[15]	Japan[16]	Peru[17]	Brazil[7]	India[5]	India[6]
Clean	3.77	1.5	1.2	13.9	3.1	4.04	3.03
Clean contaminated	4.45	7.7	7.4	15.9	5.2	10.60	22.41
Contaminated	11.02	15.2	35.7	13.5	11.2	-	-
Dirty	16.82	40.0	66.7	47.2	20.7	-	-

In the present study, all the Gram-negative isolates were found to be resistant to ampicillin and amoxycillin-clavulanate (100%) which holds in agreement to the findings of Anvikar *et al* from India[5].

Most of the Gram-negative isolates in our study showed resistance to cephalosporins (>70%); however, 43.24% of them were sensitive to cefoperazone-sulbactam combination. This was comparable to a study performed in Vietnam, that reports 88% resistance to a third-generation cephalosporin[19]. Similarly, a high resistance to quinolones (75.67%) compares with similar data from Asian countries where a still higher resistance of nearly 100% to ciprofloxacin has been observed[19].

In the present study, it was determined that 42 - 57% of the isolates were sensitive to aminoglycoside group of drugs. Of all the aminoglycoside drugs, maximum resistance was found against gentamicin (64.86%), a drug that is routinely used for post-operative prophylaxis in our hospital corresponding to a reported gentamicin resistance ranging from 60 - 89% in other Indian hospitals[5].

All the isolates were found to be sensitive to imipenem (100%), and 97.29% were found to be sensitive to polymyxin B comparable to similar effectiveness of imipenem against Gram-negative isolates as reported by Giacometti *et al* from Italy (90.5-93.9%)[23].

Variations in drug resistance patterns in different studies are due to variations in the local pattern of drug prescriptions, cost and availability of drugs. Overall resistance in our study was more common for commonly prescribed drugs such as penicillin, ampicillin, cotrimoxazole, cephalosporins, etc., whereas good susceptibility pattern was seen against newer, lesser used drugs like vancomycin, linezolid, rifampicin, imipenem, and fourth generation cephalosporins and also to drug combinations like amoxycillin-clavulanate, ticarcillin-clavulanate and cefoperazone-sulbactam.

Conclusions

An overall high incidence of SSIs (7.44%), especially for clean interventions (3.77%) emphasises the importance of implementing active SSI surveillance in our surgical wards to obtain standardised incidence ratios targeting modifiable risk factors. Emergency surgeries, duration of surgery, and drain usage were a few identified risk factors for SSI causation**.**

Though the exact increase in the cost of patient care could not be calculated for our hospital, a rise in SSI incidence should be a cause of financial concern too.

The spectrum of bacteria most frequently involved in surgical infections has changed over a period of time. Streptococcus being the most frequent and feared pathogen nearly a century ago was replaced by Staphylococcus about eight decades later, and Gram-negative isolates as principal offenders in recent years. *E. coli* was the commonest bacteria (41.17%) isolated from SSIs in this study. Isolation of MRSA strains is an existing problem with a rising trend in Indian hospitals.

Drug regimens using amoxicillin-clavulanate for pre-operative prophylaxis and gentamicin for post-operative prophylactic coverage need to be carefully but urgently revised for controlling the existing status of SSIs in our hospital considering the high level of resistance observed.

Ongoing surveillance on a long-term follow-up basis and a higher degree of collaboration or co-operation between surgeons and microbiologists is necessary for formulating newer definitions and adapting control measures.

Conflict of interest: None between the authors

References

1. Dellinger EP. Surgical Infections and Choice of Antibiotics. In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL, editors. Sabiston Textbook of Surgery. 16th ed. Philadelphia, Pennsylvania: Saunders; 2002.p.171-2.
2. Emori TG, Gaynes RP. An overview of nosocomial infections, including the role of the microbiology laboratory. *Clin Microbiol Rev* 1993; 6: 428-42.
3. Cruse PJE. Surgical wound infection. In: Gorbach SL, Bartlett GC, Blacklow NR, editors. Infectious diseases. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: W.B. Saunders Company, Harcourt Brace Jovanovich Inc; 1992, P.738-64.
4. Culbertson WR, Altemeier WA, Gonzalez LL, Hill EO. Studies on the epidemiology of post-operative infection of clean operative wounds. *Ann Surg* 1961; 154: 599-603.

5. Anvikar AR, Deshmukh AB, Karyakarte RP, *et al*. A one year prospective study of 3,280 surgical wounds. *Indian J Med Microbiol* 1999; 17: 129-32.
6. Lilani SP, Jangale N, Chowdhary A, Daver GB. Surgical infection in clean and clean contaminated cases. *Indian J Med Microbiol* 2005; 23(4): 249-52.
7. Medeiros AC, Tertuliano AN, Azevedo GD, *et al*. Surgical site infection in a university hospital in north east Brazil. *Brazilian J Infect Dis* 2005; 9(3): 310-4.
8. Buggy D. Can anaesthetic management influence surgical-wound healing? *Lancet* 2000; 356(9227): 355-7.
9. Bernard F, Gandon J. Post-operative wound infections: the influence of ultraviolet irradiation of the operating room and of various other factors. *Ann Surg* 1964; 160: 1-192.
10. Horan TC, Gaynes RP, Martone WJ, *et al*. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol* 1992; 13(10): 606-8.
11. Clinical and Laboratory Standard Institute. Performance standards for antimicrobial susceptibility testing: Sixteenth informational supplement. CLSI document CLSI, Wayne, Pa. 2006; M100-S16.
12. Lul Raka, Avdyl Krasniqi, Faton Hoxha, *et al*. Surgical site infections in an abdominal surgical ward at Kosovo Teaching Hospital. *J Infect Developing countries* 2007; 1(3): 337-41.
13. Razavi SM, Ibrahimpoor M, Sabouri KA. Abdominal surgical site infections: incidence and risk factors at an Iranian teaching hospital. *BMC Surg* 2005; 5: 2. *http://www.biomedcentral.com/1471-2482/5/2*
14. Rao AS, Harsha M. Post-operative wound infections. *J Indian Med Assoc* 1975; 64: 90-3.
15. Cruse Peter JE, Foord R. The epidemiology of wound infection. A 10-year prospective study of 62,939 wounds. *Surg Clin North Am* 1980; 60: 27-40.
16. Saito T, Aoki Y, Ebara K, *et al*. Surgical site infection surveillance at a small-scale community hospital. *J Infect Chemother* 2005; 11(4): 204-6.
17. Hernandez K, Ramos E, Seas C, *et al*. Incidence of and risk factors for surgical-site infections in a Peruvian hospital. *Infect Control Hosp Epidemiol* 2005; 26(5): 473-7.
18. Cruse PJE, Foord R. A five year prospective study of 23,649 surgical wounds. *Arch Surg* 1973; 107: 206-9.
19. Sohn AH, Pervez FM, Vu T, *et al*. Prevalence of Surgical–site infections and patterns of antimicrobial use in a large tertiary care hospital in Ho chi Minh city, Vietnam. *Infect Control Hosp Epidemiol* 2002; 23: 382-7.
20. Michalopoulos A, Sparos L. Post-operative wound infections. *Nurs Stand* 2003; 17(44): 53-6, 58, 60.
21. Mofikoya Bo, Neimogha Mi, Ogunsola Ft, Atoyebi Oa. Bacterial agents of abdominal surgical site infections in Lagos Nigeria. *Euro J Sci Res* 2009; 38(3): 509-13.
22. Santos KR, Fonseca LS, Bravo Neto GP, Gontijo Filho PP. Surgical site infection: rates, etiology and resistance patterns to antimicrobials among strains isolated at Rio de Janeiro University Hospital. *Infection* 1997; 25: 217-20.
23. Giacometti A, Cirioni O, Schimizzi AM, *et al*. Epidemiology and Microbiology of surgical wound infections. *J Clin Microbiol* 2000; 38: 918-22.
24. Kasatpibal N, Norgaard M, Sorensen HT, *et al*. Risk of surgical site infection and efficacy of antibiotic prophylaxis: a cohort study of appendectomy patients in Thailand. *BMC Infectious Diseases* 2006; 6: 111.
25. Hedrick TL, Turrentine FE, Smith RL, *et al*. *Surgical infections* Aug 2007; 8(4): 425-36.

ACKNOWLEDGEMENT

LIST OF *JIACM* REVIEWERS (2012)

- Ajay Ajmani (New Delhi)
- Anil Chaturvedi (New Delhi)
- Annil Mahajan (Jammu)
- Anita Sharma (Dehradun)
- B.B. Rewari (New Delhi)
- Bhawani Singh (New Delhi)
- Bindu Kulshreshtra (New Delhi)
- B.M. Hegde (Mangalore)
- Desh Deepak (New Delhi)
- Gautam Alhuwalia (Ludhiana)
- Geeta Khawaja (New Delhi)
- H.K. Kar (New Delhi)
- Harpreet Singh (Rohtak)
- Harsh Mahajan (New Delhi)
- Himansu Sekhar Mahapatra (New Delhi)
- J.R. Sankaran (Chennai)
- K.S. Anand (New Delhi)
- Madhuchanda Kar (Kolkata)
- M. Bhardwaj (New Delhi)
- M.P. Sharma (New Delhi)
- M.P.S. Chawla (New Delhi)
- M.U. Rabbani (Aligarh)
- Meenu Walia (Noida, U.P.)
- Nakul Varshney (California, U.S.A.)
- Naveen Garg (Lucknow)
- Neeraj Pandit (New Delhi)
- Nihal Thomas (Vellore)
- N.P. Singh (New Delhi)
- O.P. Kalra (New Delhi)
- Praveen Aggarwal (New Delhi)
- Pushpa Yadav (New Delhi)
- Rajesh Khadgawat (New Delhi)
- Rajesh Rajput (Rohtak)
- Rajesh Upadhyay (New Delhi)
- Rakesh Sahay (Hyderabad)
- Rohini Handa (New Delhi)
- R.K. Garg (Lucknow)
- R.P. Pai (Mangalore)
- R.S.K. Sinha (New Delhi)
- S. Anuradha (New Delhi)
- S.C. Sharma (New Delhi)
- S. Dwivedi (New Delhi)
- S.K. Agarwal (New Delhi)
- S.K. Guha (Kolkata)
- S.K. Mishra (Rourkela)
- S.K. Sharma (New Delhi)
- S.K. Verma (Dehradun)
- S.N. Gosavi (Pune)
- Shalini Rajaram (New Delhi)
- S.S. Chauhan (Patiala)
- Sushil Modi (New Delhi)
- Tushar Roy (New Delhi)
- Vijay Achari (Patna)
- Vineet Talwar (New Delhi)

ORIGINAL ARTICLE

JIACM 2013; 14(1): 20-2

Comparison of aspiration versus non-aspiration technique of cytodiagnosis in thyroid lesions

Nisha P Malik, Medha Jain*, Col. VK Sharma**, Nidhi Verma*, Ashutosh Singh***, Ganesh Singh****, Sanjul Kumar****

Abstract

Fine needle aspiration cytology (FNAC) and fine needle non-aspiration cytology (FNNAC) technique were studied in 144 patients of thyroid lesions. The study was single blind and prevented observation bias. The smears were assessed for cellularity, cellular dilution with blood or clot and retention of appropriate architecture. They were then further categorised as unsuitable, adequate, and diagnostically superior for cytological evaluation. After evaluation of FNAC and FNNAC on the basis of these scores, FNAC yielded more cellular material than FNNAC (p < 0.001). In a similar manner FNAC has higher average score for background blood (p < 0.001) than FNNAC. However there was no statistical difference in average architecture score. Both the techniques yielded equal diagnostically unsuitable smears (H" 12%). Diagnostically superior samples were more by FNAC; FNNAC yielded more diagnostically adequate smears.

Key words: FNAC, thyroid, non-aspiration.

Introduction

Fine needle aspiration cytology (FNAC) of the thyroid gland is now a well established, first-line diagnostic test for the evaluation of diffuse thyroid lesions as well as of thyroid nodules with the main purpose of confirming benign lesions and thereby reducing unnecessary surgery. However, in thyroid lesions, an unsatisfactory specimen, especially mixed with blood, is an obstacle in proper interpretation of the slide. In an attempt to overcome the problem of vascularity of the thyroid gland, an alternative sampling method, i.e., fine needle non-aspiration cytology (FNNAC) was introduced in certain centres in France[1] (Zajdela *et al*). FNNAC avoids aspiration, utilises only the needle and relies on negative pressure to suck the cells inside the needle bore. For thyroid lesions, this technique was first introduced by Santos and Leiman *et al*[2]. Non-aspiration was also used in superficial lesions by Mair *et al*[3]. Studies have also been conducted on deep-seated lesions, that is, transthoracic and intra-abdominal lesions (Dey and Ray *et al*[4]). Till now little has been published regarding the efficacy of FNNAC technique. This study was undertaken to compare the efficacy and quality of FNNAC with that of FNAC of thyroid lesion.

Material and methods

The study population consisted of 144 patients who presented with thyroid swelling and attended cytology clinic at LLRM Medical College, Meerut (study period from July 2008 to June 2009). All these patients were subjected to aspiration & non-aspiration techniques, 23 gauge needles and 20 ml disposable plastic syringe were used for suction. Every slide was assessed without the prior knowledge of techniques utilised. Dry smears were stained with Giemsa stain, and wet smears by Papanicolaou stain. The study was thus single blind and also prevented the observer bias. The smears were assessed for cellularity, cellular dilution with blood or clot, and retention of appropriate architecture by means of a point scoring system employed by Mair *et al*[3]. (Table I). Frequency of various thyroid lesions are given in Table II.

Table I: Table for point allocation.

	Characteristics – Description	Points
1.	Amount of cellular material	
	(a) Abundant; diagnosis simple	02
	(b) Sufficient for cytodiagnosis	01
	(c) Minimal to absent; diagnosis not possible	0
2.	Background	
	(a) Minimal; diagnosis easy; specimen of textbook quality	02
	(b) Moderate amount; diagnosis possible	01
	(c) Large amount; great compromise to diagnosis	0
3.	Retention of appropriate architecture	
	(a) Excellent architectural display closely reflecting histology; diagnosis obvious	02
	(b) Moderate; some preservation e.g., follicles, papillae, acini, flat sheets, syncytia or single cell pattern	01
	(c) Minimal to absent; non-diagnostic	0

**** Lecturer, Department of Pathology, ** Specialist Graded, *** Junior Resident, Department of Pathology, **** Lecturer, Department of Obstetrics & Gynaecology, LLRM Medical College, Meerut, Uttar Pradesh.***

Table II: Frequency of various thyroid lesions.

Type of lesion	No. of cases	Percentage
Colloid goitre	58	40.27%
Hyperplasia	02	1.3%
Thyroiditis	40	27.77%
Follicular neoplasm	32	22.22%
Papillary carcinoma	08	5.5%
Medullary carcinoma	02	1.3%
Anaplastic carcinoma	02	1.3%
Total	**144**	**100%**

A cumulative score between 0 and 6 points was obtained for each specimen which was then further categorised as:-

1. **Unsuitable for cytological diagnosis:** Smears show mainly blood; and cellular material was scanty for determination of benign or malignant change.
2. **Adequate for cytological diagnosis:** It was possible to render an opinion on the nature of the lesion sampled. However, the cellular material present was sub-optimal due to poor cellularity, sample dilution, degenerative changes, or specimen entrapment in blood clot.
3. **Diagnostically superior:** If cells or cell aggregates were concentrated. They are well preserved, unobscured by background blood, and excellently retain architectural features, that is, textbook quality.

Statistical analysis

On the basis of sample observation in hand, the statistical inference has been drawn by using the statistical tool-student t-test for independent sample as well as paired. The difference in the score for the individual parameter was assessed by SPSS software.

Results

In the present study, the aspiration technique yielded more cellular material than non-aspiration technique. On statistical comparision, average scoring for FNAC was greater than FNNAC. The score differences between the two techniques were highly statistically significant ($p < 0.001$). In a similar manner one can infer that average scoring for background blood in FNAC is higher than FNNAC, which is also statistically highly significant ($p < 0.001$) but in the case of architecture, average scoring in FNAC is higher than FNNAC mathematically, however not statistically ($p = 0.052$).

On comparing both the techniques regarding result/performance, the aspiration (FNAC) technique yielded more diagnostically superior results (80/20). The non-aspiration (FNNAC) technique yielded more diagnostically adequate results (108/46). However, the unsuitable cases by both the techniques were nearly the same (Table III).

Table III: The performance/result of FNAC and FNNAC technique.

S. no.	Results/performance	Technique	
		FNAC	FNNAC
1.	Diagnostically superior	80 (55.5)	20 (13.9)
2.	Diagnostically adequate	46 (32)	108 (75)
3.	Unsuitable	18 (12.5)	16 (11.1)
	Total	**144**	**144**

Discussion

FNAC, since its introduction in 1847, has passed through two phases of initial skepticism and interim enthusiasm and has successfully reached the final stage of acceptance as identified by Orell[5]. FNAC is widely accepted as the primary method for diagnosis of thyroid lesions. The cytologists faced the common problem in interpreting the haemorrhagic material from thyroid or other vascular organs obtained by FNAC. To overcome this inherent problem, an alternative technique FNNAC also called cytopuncture or fine-needle capillary (FNC) sampling was used first in France for breast tumour and later for orbital and periorbital tumours. It has been suggested that FNNAC sampling, by eliminating the negative suction pressure employed in FNAC, decreases the dilution of cells by blood. In FNNAC, due to spontaneous capillary action, cells collect in the needle bore[2]. The important advantage of FNNAC sampling is ease of operation and absolute control over operating hand, especially for neck, breast, cutaneous or subcutaneous swellings.

In the present study, the results (when compared for the cellularity on smears) supported the aspiration technique and were highly statistically significant ($p < 0.001$). It is inferred that negative pressure generated during the procedure encourages aspiration of cells from the lesion. These results were similar to those of Jayaram *et al*[6] as opposed to other workers, who observed higher cellularity on FNNAC smear than FNAC smear. In the current study, the results of FNAC and FNNAC were compared in different thyroid lesions. The amount of cellularity was higher on FNAC in all diagnostic categories. These results were at variance with those of Santos *et al*[2] (1988) who inferred that FNNAC was superior. It may be due to the fact that in the present study aspiration was done by a trained cytopathologist. However, in the Santos *et al*[2] study it was done by a surgeon.

Results in the present study (when compared for

background blood contamination), supported the non aspiration technique, p value being < 0.001. The amount of blood was more in thyroid aspirated smears than non-aspirated smears. Santos & Leiman[2] observed that although blood cannot be entirely prevented in thyroid cytology, still FNNAC smears were less obscured by blood than FNA smears.

In the present study, the overall mean score per case for cell architecture preservation was higher for FNAC than FNNAC. However, this difference was not statistically significant (p = 0.052). The results were similar to Mair *et al*[3]. They studied cell preservation under three separate headings, i.e., degree of degeneration, cellular trauma and maintenance of cell arrangement. In their study, there was an overall trend towards higher score on FNAC (1.26) than FNNAC (0.59). However, there was no statistically significant difference between the efficacies of the two sampling technique for any of the parameters studied.

In the present study, FNAC yielded more diagnostically superior cases (55.5%) and FNNAC yielded more diagnostically adequate cases (75%). It was in variance to Santose *et al*[2], Kamal *et al*[7], and Mair *et al*[3]. In their study diagnostically superior specimens were more by FNNAC than FNAC. FNNAC and FNAC was compared on breast mass by Baksh *et al*[8]. They observed that FNNAC yielded more diagnostically superior samples; however, FNAC yielded more number of diagnostically adequate smears. They also observed that FNNAC technique yielded more unsuitable smears. It can be attributed to the breast tissue consistency and composition.

However, in the present study, both the techniques yielded nearly equal diagnostically inadequate samples (i.e., ≈ 12%). Thus both the techniques were able to give nearly equal diagnostic smears. In effect, both the techniques were able to give nearly equal diagnosis in pre-operative patients. This is in variance to Maurya *et al*[9]. In their study FNNAC yielded more unsuitable smears.

Overall, FNAC and FNNAC both are useful and cost effective techniques for pre-operative assessment of patients with thyroid lesions, as Romitelli *et al*[10] concluded. Kamal *et al*[7] found FNNAC sampling was diagnostic in a greater number of cases than FNAC. However, this was not statistically significant. They concluded that incorporating FNNAC as the second puncture will definitely improve the quality and quantity of material at the patient's first visit to the cytoclinic. Rizui *et al*[11] also concluded that non-aspiration technique combined with FNAC technique can result in obtaining good quality cellular material. Nezhad *et al*[12] studied 200 patients with thyroid lesions. They concluded that FNNAC is not superior to FNAC in the cytopathologic studies of thyroid nodules. In their study 43 cases were inadequate and in remaining 157 patients, no statistically significant difference was observed between FNNAC and FNAC average score in each parameters. Tublin *et al*[13] observed that ultrasound guided FNAC and FNNAC sampling results were comparable and equivalent diagnostic yields were obtained. The technical ease of capillary sampling may prompt adoption of FNNAC sampling of organs with higher vascularity. A meta-analysis was done by Pothier *et al*[14] on results of four cross-over trials. They concluded that there is no evidence that one method is superior to the other. Similarly, in our study, both the techniques yielded nearly equal diagnostic and inadequate samples.

Conclusion

The overall fine needle biopsy of thyroid nodules has proved to be sensitive, specific, and well-accepted by patients because of minimal discomfort and complications. However, taking into consideration all available evidence, it seems that FNNAC may be easier to perform and produce results equivalent to FNAC. It is felt that the technique of fine needle sampling employed for cytodiagnosis may be left to the personal preference of the operator.

References

1. Zajdela A, Zillhardt, Voillemet N. Cytological diagnosis by fine needle sampling without aspiration. *Cancer* 1987; 59: 1201-5.
2. Santos JEC, Leiman G. Non aspiration fine needle cytology. Application of a new technique to nodular thyroid diseases. *Acta cytol* 1988; 32: 353-56.
3. Mair S, Dunbar F, Becker PJ, Du Plessis W. Fine needle cytology : Is aspiration section. A study of 100 masses in various sites. *Acta cytology* 1989; 33: 809-13.
4. Dey P, Shashirekha, Ray R. Fine needle sampling without suction in intraabdominal lesion. *Acta cyto* 1994; 38(3), 495-97.
5. Orell SR, Sterrett GF, Walters MNH, Whitaker D. Manual of fine needle aspiration cytology, 2nd Edn. Churchill livingstone. 66 & 96-100, (1992).
6. Jayaram G, Gupta B. Non-aspiration fine needle cytology in diffuse and nodular thyroid lesion : A study of 220 cases. *Acta Cytology* 1991; 35(6): 789-90.
7. Kamal MM, Arjune DG, Kulkarni HR. Comparative study of fine needle aspiration and fine needle capillary sampling of thyroid lesions. *Acta cytol* 2002; 46(1): 30-4.
8. Baksh S, Masih K, Singhs, Das S. Diagnostic utility of fine needle non-aspiration cytology versus fine-needle aspiration cytology in breast masses. *Indian J. Pathol microbiol.* 2004; 47(3): 319-21.
9. Maurya AK, Mehta A, Mani NS, *et al*. Comparison of aspiration vs non aspiration technique in fine needle cytology of thyroid lesions. *Journal of Cytology.* 2010; 27: 51-4.
10. Romitelli F, Di Stasio E, Santoro C, *et al*. A Comparative study of fine needle aspiration and fine needle non aspiration biopsy on suspected thyroid nodules. *Endocr Pathol* 2009; 20: 108-13.
11. Rizvi SA, Husain M, Khan S, Mohsin M. A Comparative study of Fine-needle aspiration cytology versus non-aspiration technique in thyroid lesions. *Surgeon* 2005; 3(4): 273-6.
12. Haddadi-Nezhad S, Larijani B, Tavangar SM, Nouraei SM. Comparison of fine-needle non aspiration with fine needle aspiration technique in the cytological studies of thyroid nodules. *Endocr pathol.* 2003; 14(4): 369-73.
13. Tublin ME, Martin JA, Rollin LJ, *et al*. Ultrasound-guided fine-needle aspiration versus fine-needle capillary sampling biopsy of thyroid nodules: does technique matters ? *J Ultrasound Med.* 2007; 26(12): 1697-701.
14. Pothier DD, Narula AA. Should we apply suction during fine needle cytology of thyroid lesions ? A systematic review and meta-analysis. *Ann R Coll Surg. Engl.* 2006; 88(7): 643-5.

ORIGINAL ARTICLE

JIACM 2013; 14(1): 23-7

Diagnostic application of conventional and newer bone marrow examination techniques in fever of unknown origin

Amit K Dutta, Rita Sood**, Urvashi B Singh***, Arti Kapil****, JC Samantaray*****

Abstract

***Introduction:** Bone marrow examination (BME) including bone marrow cultures (BMC) and polymerase chain reaction (PCR) are often used as diagnostic procedures for the evaluation of fever of unknown origin (FUO). However, objective data are limited about their utility in FUO.*

***Methodology:** Fifty-two patients with FUO were included in the study. After initial evaluation, BME was performed. Bone marrow aspirate was subjected to pathological examination; bacterial, fungal, and mycobacterial cultures; smear examination for AFB/LD bodies/malarial parasite, and PCR for M. tuberculosis. Bone marrow (BM) trephine was subjected to histopathological examination. The diagnostic yield of BME and the number of patients in whom it was the only diagnostic modality were determined.*

***Results:** A definitive diagnosis could be achieved in 43(82.7%) patients. Thirty-two patients had infectious aetiology with extrapulmonary tuberculosis being the commonest cause of FUO. The diagnostic yield of BME was 38.6% and it was the only diagnostic modality in 25.6% of patients. The yield of BM aspirate smear examination was 15.4%. PCR for M. tuberculosis and fungal cultures were diagnostic in one patient each. Bacterial and mycobacterial cultures were sterile in all patients. A correlation of haematological parameters with BME showed that patients with Hb < 7.7 g% or TLC< 4,450/mm^3 had a significantly higher yield on bone marrow examination.*

***Conclusion:** Conventional BME showed a good diagnostic yield in evaluation of FUO. Newer techniques had very low diagnostic yield.*

***Key words:** Bone marrow examination, FUO, newer techniques.*

Introduction

Fever of unknown origin (FUO) is an intriguing problem in clinical medicine. Even with the advances in imaging technology and availability of special diagnostic techniques, persistent pyrexia continues to be a challenging problem in some patients. The current study was planned to study the usefulness of bone marrow examination in diagnosing FUO with emphasis on the role of radiometric aerobic bacterial cultures and molecular technique for rapid detection of *M. tuberculosis* (PCR). As infection accounts for a major proportion of patients with FUO, the yield of bone marrow cultures may be higher in a developing country like India. Also, with the availability of newer modalities like PCR and radiometric cultures, which are more sensitive and quicker than conventional methods, utility of these tests performed on bone marrow tissue in diagnosing FUO may be higher.

Methodology

The study was designed to prospectively assess the diagnostic usefulness of microbiological and pathological evaluation of bone marrow samples in patients with FUO. Patients presenting with fever of prolonged duration to the Medicine out-patient department and wards at the All India Institute of Medical Sciences, New Delhi, were screened. Those satisfying the revised Petersdorf criteria were recruited[1]. This includes (1) temperatures >38.3°C (101°F) on several occasions; (2) a duration of fever of >3 weeks; and (3) failure to reach a diagnosis despite one week of relevant and intelligent investigation as in-patient or out-patient. For HIV positive patients, Durack and Street's criteria were used[2]. This includes (1) fever of > 101°F on several occasions over a period of more than 4 weeks for out-patients, or greater than 3 days duration in the hospital in a patient with HIV infection; (2) diagnosis remaining obscure after 3 days of appropriate investigation including 2 days of incubation of cultures. Patients with neutropenic and nosocomial FUO were not included in this study. The study was approved during the postgraduate research meeting in the department of Medicine, AIIMS.

After detailed history and clinical examination, all patients were subjected to certain minimum investigations, which included complete haemogram (Hb, TLC, DLC, ESR, peripheral smear), serum biochemistry, peripheral smear

**** Associate Professor, Department of GI Sciences, Christian Medical College (CMC), Vellore - 632 002, Tamil Nadu; ** Professor, Department of Medicine, *** Associate Professor, **** Professor, Department of Microbiology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029.***

for malarial parasite, blood and urine cultures, relevant serological investigations, chest X-ray, ultrasonography and/or computed tomography (CT) of abdomen and chest and serology for HIV.

All patients were subjected to bone marrow aspiration and biopsy. Biopsy specimen was sent for histopathological examination. Tests done on bone marrow aspirate in all patients included pathological examination of smear, PCR for *M. tuberculosis*, aerobic radiometric bacterial culture, culture for *M. tuberculosis* and fungal culture. Bone marrow aspirate for *M. tuberculosis* PCR was collected in a sterile vial to which 10 units of heparin was added for each ml of aspirate. MPB 64 gene was amplified using the PCR. Primer used was:-

Primer 1 (460-479) 5′ – TCCGCTGCCAGTCGTCTTCC – 3′

Primer 2 (700-681) 5′ – GTCCTCGCGAGTCTAGGCCA – 3′

This primer has been validated to have a good yield in India[3]. One ml of aspirate was used for aerobic radiometric bacterial culture, which was incubated for 5 days. Lowenstein-Jensen (LJ) medium was used for mycobacterial culture. This was incubated for 8 weeks. Bone marrow examination (BME) was considered positive if diagnostic findings were reported on histopathological evaluation or microbiological evaluation yielded evidence of specific infection. Diagnostic yield of BME was the proportion of total bone marrow samples showing specific diagnostic findings. Also the yield of newer techniques (PCR and Radiometric bacterial culture) was assessed. BME was considered a unique diagnostic modality if it was the only modality of diagnosis. Final diagnosis was reached on the basis of combined evaluation of history, clinical findings, laboratory investigations, and response to therapy.

Descriptive data is presented as mean with standard deviation for continuous variables and as proportions for categorical variables. For estimating cut-offs of haemoglobin and leukocyte counts in predicting diagnostic bone marrow, ROC curve was used. Statistical analysis was done on SPSS 11.0 for Windows.

Results

The total number of patients studied was fifty-two (thirty-four were males). The mean age was 34.8 +/- 7.4 years. Final diagnosis could be reached in 43 (82.7%) patients. Infectious aetiology was present in 32 (61.5%) patients. Table I shows the aetiological profile of patients. Among the three (5.8%) patients with non-infectious inflammatory disorders (NIID) one each had systemic lupus erythematosus, sarcoidosis, and adult onset Still's disease. Megaloblastic anaemia was the aetiology in two (3.8%) patients. No diagnosis could be reached in nine (17.3%) patients.

Table I: Aetiological profile of FUO patients.

Aetiology	Number of patients N-52
Infection	32 (61.5%)
M. tuberculosis	14
Kala-azar	6
Enteric fever	4
Malaria	1
Histoplasmosis	1
AIDS with disseminated tuberculosis	4
AIDS with disseminated fungal infection	2
Neoplasm	6 (11.5%)
Chronic lymphoid leukaemia (CLL)	1
Acute leukaemia	1
Non-Hodgkin's lymphoma (NHL)	1
Carcinoma stomach	1
Uncharacterised malignancy	2
Non-infective inflammatory disease (NIID)	3 (5.8%)
Miscellaneous	2 (3.8%)
Undiagnosed	9 (17.3%)

Thirty-six patients had pallor which was the commonest physical finding followed by hepatosplenomegaly (17 patients), and lymphadenopathy (11 patients). Routine laboratory test abnormalities were common but mostly non-specific. Liver enzyme abnormalities were present in 80% patients but helped in diagnosis in only one patient. Anaemia was present in 47 patients, 28 of whom had moderate to severe anaemia (< 8 g% in women, < 9 g% in men). Ten patients had leukocytosis and 17 had leucopenia.

Ultrasonography (US) of abdomen was done in 39 patients. It was abnormal though mostly non-specific in 29 patients detecting hepatomegaly (21 patients), splenomegaly (18 patients), lymphadenopathy (5 patients), and ascites (2 patients). One patient had necrotic retroperitoneal (RP) lymph nodes detected on US abdomen. Contrast-enhanced computed tomography (CECT) was done for chest in 38 patients and abdomen in 28 patients. The abnormalities detected consisted of hepatomegaly, splenomegaly, and lymphadenopathy. Seven patients had lymph node necrosis with rim enhancement (three in abdomen and four mediastinal) suggestive of tuberculosis and all responded to anti-tubercular therapy (ATT). Echocardiography was done in

18 patients and was helpful in diagnosis of one patient (tubercular pericarditis).

The invasive procedures performed included fine needle aspiration cytology (FNAC) and tissue biopsy. Abdominal lymph node FNAC was done in three patients of whom it showed AFB in one and malignant cells in another, and was inconclusive in the third patient. Peripheral lymph nodes were biopsied in 13 patients of whom only two were diagnostic. Other diagnostic invasive tests were mucosal biopsy from stomach showing adenocarcinoma in one patient, liver biopsy showing granulomatous hepatitis in one patient, and skin biopsy showing non-caseating granuloma in one patient (sarcoidosis). In three patients, response to empirical ATT led to the diagnosis of tuberculosis and three other patients had a positive Widal test and responded to antibiotics but did not grow *S. typhi* on culture. The diagnostic yield of various specific non-invasive and invasive tests other than the bone marrow is shown in Table II. In 20 (38.5%) patients, it was diagnostic of specific aetiology and in 14 (26.9%) of these it was the only diagnostic modality.

Table II: Diagnostic yield of various investigations other than bone marrow examination.

Diagnostic test	Final diagnosis	No. of patients
ANA and dsDNA (n=20)	SLE	1
Widal (n=52) and response to treatment	Enteric fever	3
CECT chest (n=38)	Tuberculosis	4
CECT abdomen (n=28)	Tuberculosis	3
Ultrasound abdomen (n=39)	Tuberculosis	1
FNAC abdominal LN (n=3)	Tuberculosis Malignancy	1 1
Cervical LN biopsy(n=3)	Histoplasmosis Tuberculosis	1 1
Stomach biopsy (n=1)	Adenocarcinoma	1
Liver biopsy (n=2)	Granulomatous hepatitis	1
Skin biopsy (n=1)	Sarcoidosis	1

Note: *All patients with final diagnosis of tuberculosis diagnosed only on the basis of imaging findings had shown therapeutic response to anti-tuberculosis treatment.*

The diagnostic yield of various pathological and microbiological tests conducted on bone marrow samples is shown in Table III. Microbiological investigations were diagnostic in seven (13.46%) patients. This included five patients with LD bodies, one patient with positive AFB smear and one patient with positive PCR for *M. tuberculosis* (who responded to ATT). PCR for *M. tuberculosis* was false positive in two (kala-azar & megaloblastic anaemia) patients. Culture for bacteria was sterile in all patients and so was culture for *M. tuberculosis* on Lowenstein-Jensen media. Fungal culture was positive in one patient who was having clinical AIDS. None of the patients showed malarial parasite on aspirate smear.

Table III: Diagnostic yield of various investigations conducted on bone marrow samples.

Test (n=52)	Positive	Diagnostic
AFB culture	0	0(0%)
PCR for *M. tuberculosis*	3	1(1.9%)
Bacterial culture	0	0(0%)
Fungal culture	1	1(1.9%)
Aspirate smear examination	9	9(17.3%)
Histopathology	17	17(32.7%)

The pathological examination of bone marrow aspirate showed evidence of leukaemia in two patients, features of megaloblastic anaemia in two and histoplasma in one. Pathological examinations of bone marrow trephine were diagnostic in 18 (34.61%) patients. This included finding of AFB in one patient (without granuloma), confirmation of findings of aspiration, i.e., LD bodies in five patients, histoplasma in one, features of megaloblastic anaemia in two, and malignany in two patients. The remaining diagnostic findings on trephine were granuloma in six patients – one of whom was AFB positive (five of them had tuberculosis and one had histoplasmosis) – and non-Hodgkin's lymphoma in one patient.

Since final diagnosis was made based on complete clinical and investigative profile as well as response to therapy, the cumulative yield of individual tests is more than the number of patients with diagnosis made as more than one modality may have contributed to diagnosing the disease. The various haematological and biochemical parameters among patients in whom bone marrow was diagnostic (positive group) and non-diagnostic (negative group) were compared. The haemoglobin level and total leukocyte count (TLC) level was significantly different between the two groups ($p<0.05$). ROC curve showed that, at level of haemoglobin below 7.7g%, diagnostic sensitivity of bone marrow was 70% and specificity was 72%. Similarly, TLC below 4,450/mm^3 had bone marrow diagnostic sensitivity of 70% and specificity of 84%.

Patients who remained undiagnosed were followed-up further. Of the nine undiagnosed patients, four had self

limiting fever, two expired, two were lost to follow-up and one patient is still under follow-up. Overall there were six mortalities. Among the patients who died, two were undiagnosed, two had tuberculosis, one had uncharacterised malignancy and one had AIDS with disseminated histoplasmosis.

Discussion

In our study, the diagnostic spectrum of FUO observed is typical of that seen in a developing country like India with infections accounting for majority of cases in contrast to Western series[4,5,6]. All the six patients with kala-azar were from the state of Bihar, which is endemic for kala-azar thus emphasising the need for finding out the geographical location of the patient. Haematological malignancies are the commonest neoplastic cause of FUO[7,8]. Of the five patients with malignancy, three had haematological malignancy in our series.

Although infection continues to be the leading cause of FUO in our series also, there were no cases of abscess and infective endocarditis. This changing pattern has been observed in other recent series as well[9]. Newer studies reflect not only the changing patterns of disease but also the impact of diagnostic techniques that make it possible to eliminate many patients with specific illnesses from the category of FUO. The widespread use of microbiologic cultures and the use of potent broad-spectrum antibiotics may have decreased the number of infections causing FUO. The wide availability of ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) has enhanced the detection of abscess, occult neoplasms and lymphomas in patients previously thought to have FUO. Likewise, the widespread availability of highly specific and sensitive immunologic testing has reduced the number of undetected cases of systemic lupus erythematosus and other autoimmune diseases. The easy availability of echocardiography to detect infective endocarditis has reduced its incidence as a cause of FUO. Malaria as a cause of FUO has been well-described[10]. There was no case in our series. This may be due to early detection of malaria by peripheral smear and buffy coat examination; and also, most patients often receive anti-malarial therapy empirically before coming to the hospital. Infections accounted for all the causes of FUO in AIDS patients, which is similar to the observations made in other series[11,12].

The diagnostic yield of bone marrow examination (BME) in classical FUO has varied from 2 - 20%[13,14,15]. A study conducted to look primarily for the diagnostic role of bone marrow examination in FUO by Ahmed *et al* in New York showed the diagnostic yield to be 16%[15]. Smear was diagnostic in one patient, culture in three patients, and pathological examination of trephine in four. Standard techniques of performing bone marrow aspiration have been described and the yield of aspirate in FUO has ranged from 0.6 - 10%[4,15,16]. The combined yield of various tests on bone marrow aspirate (15.4%) was higher in our study which may be explained by higher prevalence of infection as aetiology of FUO in India, especially LD bodies which can be identified easily on a bone marrow aspirate. Histopathological examination of bone marrow trephine also had a higher yield in our patients in contrast to other studies which report the yield to range from 2% to 18%[13], [14,15]. An interesting observation made by Fernandez-Aviles and colleagues was the higher and quicker diagnostic capability of BME in HIV infected patients[17]. HIV infected patients had a higher yield (50%) in our study as well.

Bone marrow cultures (BMC) are commonly obtained in the evaluation of fever of unknown origin. The yield of bone marrow cultures (aerobic, mycobacterial, and fungal) was nil in our series except for one patient with HIV infection who had positive bone marrow fungal culture (*Rhodotorula*). The low yield of BMC raises questions on their usefulness in FUO. Bacterial and fungal BMCs have been found to be useful in immunosuppresed patients with FUO in previous studies[18,19,20]. Small number of AIDS patients in our study makes any meaningful comparison difficult with respect to yield of cultures in this group of patients.

PCR by amplifying the MPB 64 gene of *Mycobacterium tuberculosis* is able to detect up to 5 - 10 Mycobacteria. This technique is more sensitive than culture methods and has the added advantage of being a rapid test – yielding results within two days of sampling. PCR has been shown to have good sensitivity and specificity in detecting *M. tuberculosis* in pulmonary as well as extrapulmonary specimens including bone marrow[21,22]. In our study, there were three patients whose bone marrow aspirate tested positive for *M. tuberculosis* PCR. Only one turned out to be true positive. The other two patients were diagnosed to have Kala-azar and megaloblastic anaemia respectively. The few studies on PCR for detecting *M. tuberculosis* in bone marrow samples have shown the yield to range from 42% to 82%[23,24]. Ritis *et al* found that of the 11 patients with extrapulmonary tuberculosis, PCR on bone marrow sample could diagnose 82% whereas the conventional method could diagnose only 27% of patients[23]. Ackan *et al* studied 48 patients with disseminated tuberculosis (diagnosed based on histopathology, culture, positive smear, or response to therapy)[24]. Bone marrow histopathological examination and PCR for *M. tuberculosis* was done in 41 patients. AFB smear was positive in 12%, histopathology in 29% and PCR in 73% patients. They

concluded that PCR is more reliable than histopathological studies for detection of tuberculosis in a bone marrow specimen. The yield in the current series was only 5.5%. Our results stand in contrast with the results of other studies with a very low diagnostic yield and significant false positivity rate. Presence of inhibitors have been postulated to account for false negatives, while the presence of dead bacilli or contamination of sample have been implicated in false positive results. The low yield of PCR may be due to the fact that bone marrow dissemination may not have been present in all tuberculosis patients. Usually, miliary tuberculosis patients have bone marrow involvement; but none of our patients had miliary tuberculosis[25].

An important observation made in our study was the high probability of having a positive bone marrow diagnostic finding in patients with anaemia and/or leucopenia. These may be the group of patients who should have BME early during the course of their evaluation of FUO. In conclusion, conventional bone marrow investigations have a good diagnostic yield in FUO. The newer techniques did not make any significant contribution. The role of these expensive tests is thus unclear and may need further refinements. Good clinical evaluation coupled with relevant investigations and judicious use of invasive procedures can lead to a definitive diagnosis in most of the cases.

References

1. Petersdorf R. Fever of unknown origin. An old friend revisited. *Arch Intern Med* 1992; 152: 21.
2. Durack DT, Street AC. Fever of unknown origin– re-examined and redefined. *Curr Clin Top Inf Dis* 1991; 11: 35-51.
3. Dar L, Sharma SK, Bhanu NV *et al*. Diagnosis of pulmonary tuberculosis by polymerase chain reaction for MPB64 gene: An evaluation in a blind study. *Indian J Chest Dis Allied Sci* 1998; 40: 5-16.
4. Sharma BK, Kumar S, Verma SC. Prolonged undiagnosed fever in northern India. *Trop-Georg-Med* 1992; 44: 32.
5. Knockaert DC, Vanneste LJ, Vanneste SB. Fever of unknown origin in 1980s. An update of the diagnostic spectrum. *Arch Int Med* 1992; 152: 51-5.
6. Howard P. FUO a prospective study of 100 patients. *Texas Med 1997*;73:56-59.
7. Vanderschueren S, Knockaert D, Adriaenssens T *et al*. From prolonged febrile illness to fever of unknown origin: the challenge continues. *Arch Intern Med* 2003; 163: 1033-41.
8. Saltoglu N, Tasova Y, Midikli D. Fever of unknown origin in Turkey: evaluation of 87 cases during a nine-year-period of study *J Infect.* 2004; 48: 81-5.
9. Zhiyong Z, Bingjun L, Xiaoju L. Fever of unknown origin: a report from China of 208 cases. *Int J Clin Pract.* 2003; 57: 592-6.
10. Shah N, Johnson K, Ghaly S. Fever of unknown origin. *J Natl Med Assoc.* 2003; 95: 1099-102.
11. Barbado F, Gomez-Cerezo J, Pena JM. Fever of unknown origin: classic and associated with human immunodeficiency virus infection. a comparative study. *J Med* 2001; 32: 152-62.
12. Miller RF, Hingorami AD, Foley NM. Pyrexia of undetermined origin in patients with human immunodeficiency virus infection and AIDS. *Int J STD AIDS* 1996; 7: 170-5.
13. Singh G. The study of prolonged fevers. *JAPI* 2000; 48: 454-55.
14. Kleijn EMHAD, Lier HJJV, Group TNFS. Fever of unknown origin (FUO). Diagnostic procedures in a prospective multicenter study of 167 patients. *Medicine (Baltimore)* 1997; 76: 401-414.
15. Ahmed S, Siddiqui A, Mehrotra B. Diagnostic yield of bone marrow examination in fever of unknown origin. *The American Journal of Medicine* 2003; 115: 591.
16. Bain BJ. Bone marrow trephine biopsy. *J Clin Pathol.* 2001; 54: 737-42.
17. Fernandez-Aviles F, Ribera JM, Romeu J. The usefulness of the bone marrow examination in the etiological diagnosis of prolonged fever in patients with HIV infection. *Med Clin (Barc).* 1999; 112: 641.
18. Volk EE, Miller ML, Kirkley BA. The diagnostic usefulness of bone marrow cultures in patients with fever of unknown origin. *Am J Clin Pathol* 1998; 110: 150-3.
19. Riley UBG, Crawford S, Barrett SP. Detection of mycobacteria in bone marrow biopsy specimens taken to investigate pyrexia of unknown origin. *J Clin Pathol* 1995; 48: 706-9.
20. Ker CC, Hung CC, Huang SY. Comparison of bone marrow studies with blood culture for etiological diagnosis of disseminated mycobacterial and fungal infection in patients with acquired immunodeficiency syndrome. *J Microbiol Immunol Infect.* 2002; 35: 89-93.
21. Cheng VC, Yam WC, Hung IF. Clinical evaluation of the polymerase chain reaction for the rapid diagnosis of tuberculosis. *J Clin Pathol.* 2004; 57: 281-5.
22. Manjunath N, Shankar P, Rajan L. Evaluation of PCR for diagnosis of tuberculosis. *Tubercle* 1991; 72: 21-7. leta
23. Ritis K, Tzoanopoulos D, Spes M, *et al*. Amplification of IS 6110 sequence for detection of *Mycobacterium tuberculosis* complex in HIV negative patients with fever of unknown origin and evidence of extra pulmonary disease. *Journal of Internal Medicine* 2000; 248: 415-24.
24. Akcan Y, Tuncer S, Hayran M. PCR on disseminated tuberculosis in bone marrow and liver biopsy specimens: Correlation to histopathological and clinical diagnosis. *Scand J Infect Dis* 1997; 29: 271-4.
25. Kinoshita M, Ichikawa Y, Koga H, et al. Re-evaluation of bone marrow aspiration in the diagnosis of miliary tuberculosis. *Chest* 1994; 106: 690-2.

ORIGINAL ARTICLE

JIACM 2013; 14(1): 28-32

Respiratory manifestations among patients with connective tissue disorders

SK Verma, S Saheer**, Puneet Kumar***, Manoj Kumar****, SK Das*****, Rajendra Prasad******, Ghulam Hassan********

Abstract

Background: Pulmonary physicians are often involved in the care of patients with connective tissue disorders having interstitial lung disease, so a comprehensive understanding is vital. With this aim this study was conducted in patients with connective tissue disorders in a hospital setting.

Methods: The present study was conducted between August 2009 and July 2010 at the Chhatrapati Shahuji Maharaj Medical University, Lucknow, India. The patients satisfying the American College of Rheumatology criteria for connective tissue disorders were included in the study and only those patients with any one or more respiratory complaints were evaluated in detail.

Results: During the study period 146 patients (105 females and 41 males) underwent evaluation. Dry cough and breathlessness were the major respiratory complaints. Chest radiograph was abnormal in 31 (21%) patients, high resolution computed tomography (HRCT) abnormalities in 87 (84%) patients and spirometry abnormalities in 91 (62%) patients. On spirometry, the most common abnormality was restrictive ventilation defect observed in 78 (62.4%) cases. Pleural effusion was noted in eight (5.47%) cases. Pulmonary arterial hypertension was observed in 31 (21.2%) patients, especially in progressive systemic sclerosis and mixed connective tissue disease whereas it was an uncommon presentation in rheumatoid arthritis and systemic lupus erythematosus, observed only in 7(9.85%) and 3 (9.7%) patients, respectively.

Conclusion: Interstitial lung disease is the most common pulmonary manifestation among patients with connective tissue disorders, and early detection and prompt treatment is expected to improve the outcome.

Key words: Connective tissue disorders, respiratory manifestations, interstitial lung disease, pulmonary arterial hypertension.

Introduction

In connective tissue disorders (CTDs) pulmonary manifestations are common. Inflammatory and/or fibrosing large-, and small airways disease, interstitial lung disease (ILD), pulmonary vascular or pleural disease may occur depending on the underlying collagen vascular disorder. ILD in progressive systemic sclerosis (PSS) is reported to be as high as 60% in pre-mortem and 100% in post-mortem studies[1], 80% in rheumatoid arthritis (RA) and 5 to 97% in polymyositis (PM)[2]. Pulmonary complications may precede the more typical systemic manifestations, for example in RA[3]. There are only few Indian studies demonstrating respiratory involvement in CTDs[4]. The present study – first of its kind in Uttar Pradesh state was undertaken to study the pulmonary manifestations in such disorders.

Materials and methods

The present study was conducted between August 2009 and July 2010, among the patient attending Pulmonary Medicine and Rheumatology Departments of the Chhatrapati Shahuji Maharaj Medical University, Lucknow, India. The patients satisfying the American College of Rheumatology (ACR)[5-10] criteria for CTDs were included in this study. All these patients were administered a questionnaire regarding the presence of the respiratory complaints, which included cough, expectoration, breathlessness, wheezing, chest pain, haemoptysis, stridor, and hoarseness of voice. Only the patients with one or more of these symptoms were evaluated in detail. Patients with pulmonary tuberculosis, human immunodeficiency virus (HIV) infection, smokers, and those with underlying cardiac disease were excluded from the study. 146 patients underwent evaluation through clinical picture, spirometry, relevant laboratory parameters, radiography, high resolution computed tomography (HRCT) and echocardiography. Spirometry was performed (using Spiro 232, Morgan Medical Ltd, England) as per the international quality

**** Professor, ** Junior Resident, Department of Pulmonary Medicine, *** Assistant Professor, Department of Rheumatology, **** Assistant Professor, Department of Radio-Diagnosis, ***** Professor and Head, Department of Rheumatology, ****** Professor and Head, Department of Pulmonary Medicine, ******* Post-doctoral Trainee, Department of Pulmonary Medicine, Chhatrapati Shahuji Maharaj (erstwhile King George) Medical University, Lucknow - 226 003, Uttar Pradesh.***

standards, and parameters like the forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and their ratio (FEV1/FVC) were taken into consideration for the purpose of analysis. These were interpretated as per ATS/ERS guidelines of 2005[11]. Diffusion capacity for carbon monoxide was not done due to lack of facility at our place, and HRCT of the thorax could not be done in some cases due to financial constraints. Amongst the patients who underwent HRCT (Philips Tomoscan, Best, Netherlands), serial slices were taken through the chest from the apex of the lung to base, each 1mm in width and 10mm apart, with scanning time of 2 s and reconstructed on a high resolution bone algorithm. All images were obtained at window levels appropriate for lung parenchyma settings (window width 13000 HU; window level-600 HU). Findings consistent with ILD were defined as the presence of interlobular and intralobular septal thickening[12]. The patients were treated with corticosteroids and/or immunosuppressive drugs, and were followed-up for a minimum period of one year.

Statistical analysis

Statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 15.0 statistical analysis software. Chi-square and Fisher's exact probability test were used and p values of less than 0.05 were considered significant.

Results

Majority of patients (71.9%) were females, mostly belonging to fifth decade of life (Table I). Twenty-six (17.8%) patients noticed respiratory complaints first and presented to the pulmonary medicine department. Among the various symptoms, cough was seen more in patients with mixed connective tissue disease (MCTD), RA and PSS in decreasing order of frequency (Table II). Similarly breathlessness was more prominent in MCTD, PSS and systemic lupus erythematosus (SLE) respectively. Chest pain was most observed in 80% cases with MCTD. No patient had stridor or hoarseness of voice. On spirometry, majority of the cases (78; 62.4%) were found to have restrictive pattern (Table III). It was normal in 34 (23.3%) patients. Only a minority (8.8%) had evidence of obstruction on spirometry. On HRCT, the most observed finding was reticulonodular pattern especially in patients of RA (Table IV). In PSS, honeycombing and traction bronchiectasis were the most frequent findings carrying highest statistical significance ($p < 0.05$). The ground glass appearance was prominent in all cases with MCTD. Pleural effusion was found in MCTD, SLE, and RA – again in decreasing order of frequency. The most common pulmonary involvement observed on HRCT thorax was ILD, noticed in 74 (50.7%) cases (Table 5). Overall, ILD was more common among females, but in RA it was predominantly observed in males (Table 5). Pulmonary arterial hypertension (PAH) was mostly found associated with MCTD (60%) and PSS (57.7%), and, least number of patients having PAH had ankylosing spondylitis (AS) (Table 6). Females were mostly observed to have PAH compared to males, and were prescribed appropriate medical therapy in addition to other drugs. During the study period two patients died due to chronic respiratory failure with hypoxaemia and eventual cardiac arrhythmias.

Discussion

Pulmonary involvement is one of the most frequent extra-articular manifestation of RA[13]. Most common lung manifestations include ILD and pleural effusions. In the present study, cough and exertional breathlessness were the most common respiratory complaints in patients of RA, and clubbing was noticed in 15 (21.1%) patients. In RA, restrictive ventilation defect was the most common spirometry abnormality detected in 43 (60.6%) patients. Nine (12.7%) patients had obstructive pattern who had associated bronchiectasis or bronchiolitis obliterans on HRCT. The reported prevalence of RA associated ILD varies from 10 to 63% and it depends upon the method of detection and the population examined[14]. In the present study, interstitial pattern consistent with ILD was observed in 39 (54.9%) patients. The most common type of ILD observed in patients of RA was usual interstitial pneumonia (UIP) in 30.8% cases. Pleural effusion was common in patients with high titres of rheumatoid factor and rheumatoid nodules. As per previous literature, symptomatic pleural effusion occurs in approximately 5% patients but it may be asymptomatic in around 70%[15]. However, in the present study it was observed only in four (5.6%) cases. Isolated PAH with clinical manifestations is rare in patients with RA but secondary PAH is common in patients with ILD[16]. Seven (9.86%) such patients had PAH in our study.

Lung disease in SLE causes a wide spectrum of symptoms ranging from mild chest pain to fulminant and rapidly fatal pulmonary haemorrhage. Pleuritis with or without pleural effusion is the most common manifestation in lupus[17]. On spirometry, restrictive ventilation defect was detected in eight (25.8%) patients. Although HRCT may demonstrate abnormalities consistent with ILD in as many as 38% of patients[18], incidence of these abnormalities in our study

Table I: Demographic characteristics of 146 patients with various CTDs.

Age group (years)	AS (n = 7)		MCTD (n = 5)		PM (n = 6)		RA (n = 71)		PSS (n = 26)		SLE (n = 31)		Total (n=146)	
	F	M	F	M	F	M	F	M	F	M	F	M	F (n = 105)	M (n = 41)
12 - 20	-	-	-	-	-	-	-	-	-	-	2	1	2	1
21 - 30	-	-	-	-	-	-	3	2	7	1	15	1	25	4
31 - 40	-	2	2	1	1	1	8	4	3	1	7	-	21	
41 - 50	-	3	2	-	3	1	13	6	10	1	1	1	29	12
51 - 60	-	2	-	-	-	-	20	7	1	2	3	-	24	11
> 60	-	-	-	-	-	-	4	4	-	-	-	-	4	4

AS = Ankylosing spondylitis; MCTD = Mixed connective tissue disease; PM = Polymyositis; RA = Rheumatoid arthritis; PSS = Progressive systemic sclerosis; and SLE = Systemic lupus erythematosus; M = Male; F = Female.

Table II: Respiratory symptoms in 146 patients with various CTDs.

Symptoms	AS (n=7)	MCTD (n=5)	PM (n=6)	RA (n=71)	PSS (n=26)	SLE (n=31)	p Value
Cough	4 (57)*	3 (60.0)	2 (33.3)	40 (56.3)	14 (53.8)	13 (41.9)	0.720
Expectoration	1 (14.3)	2 (40.0)	1 (16.7)	6 (8.5)	-	-	0.012
Breathlessness	4 (57.1)	5 (100.0)	4 (66.7)	55 (77.5)	22 (84.6)	28 (90.3)	0.216
Chest Pain	2 (28.6)	4 (80.0)	2 (33.3)	9 (12.7)	13 (50.0)	12 (38.7)	< 0.001
Haemoptysis	-	-	-	-	-	2 (6.5)	0.185

**Figures in parentheses indicate percentage*

Table III: Spirometry abnormalities in 146 patients with various CTDs.

Finding	AS (n=7)	MCTD (n=5)	PM (n=6)	RA (n=71)	PSS (n=26)	SLE (n=31)	p Value
Obstruction	-	1 (20.0)*	-	9 (12.7)	1 (3.8)	-	0.162
Restrictive	2 (28.6)	3 (60.0)	3 (50.0)	43 (60.5)	19 (73.1)	8 (25.8)	0.003
Mixed	-	-	-	2 (2.8)	-	-	0.829
Uncooperative	2 (28.6)	-	1 (16.7)	7 (9.85)	2 (7.7)	9 (29.0)	0.173
Normal	3 (42.9)	1 (20.0)	2 (33.3)	10 (14.1)	4 (15.4)	14 (45.2)	0.013

**Figures in parentheses indicate percentage*

was 90.4%. 38.7% patients had ILD, while Fenlon *et al* [12] have reported such abnormalities in 53% of patients, although the definitive diagnosis of ILD was justified in only 32% cases. Nonspecific interstitial pneumonia (NSIP) was the most common type of ILD which was observed in 33.3% of SLE patients. Clinically apparent pleural effusion has been reported in up to 50 per cent of patients with SLE and in up to 93 per cent of cases at autopsy[19]. In the present study, pleural effusion was noticed in 3 (9.7%) patients and it was exudative in nature. In 2 (6.5%) patients it was bilateral and one (3.2%) had unilateral involvement. The reported prevalence of PAH in SLE is between 5 to 14 per cent[20]. However, in the present study it was observed in three (9.7%) patients only.

The two most common pulmonary manifestations in PSS are ILD and pulmonary hypertension, and these manifestations alone account for 60% of PSS-related deaths[21]. Spirometry revealed restrictive ventilation defect in 19 (73.1%) of our cases. Obstructive defect was noticed in one (3.8%) patient only. About 74% of the affected patients are found to have interstitial fibrosis at autopsy[22]. In the present study, ILD was observed in 84.1% of these patients. Bronchiectasis and honeycombing were the most common tomographic abnormalities (in 84.2% and 78.9%, respectively). These observations are comparable to the study of Sergio Fernandes *et al*[23]. NSIP was the most common type of ILD observed in 63.1% of PSS patients in our study. PAH

Table IV: HRCT abnormality patterns in 146 patients of various CTDs.

Abnormality	AS (n=4)	MCTD (n=3)	PM (n=4)	RA (n=52)	PSS (n=19)	SLE (n=21)	p Value
Reticular	1 (25.0)*	1 (33.3)	-	3 (5.7)	4 (21)	2 (9.5)	0.265
Nodular	-	-	-	3 (5.7)	2 (10.5)	1 (4.7)	0.914
Reticulonodular	1 (25.0)	2 (66.7)	2 (50.0)	32 (61.5)	10 (52.6)	8 (38)	0.429
Honeycombing	-	-	1 (25.0)	5 (9.6)	15 (78.9)	-	0.009
Consolidation	-	1 (33.3)	3 (75.0)	4 (7.6)	5 (26.3)	2 (9.5)	0.003
Traction Bronchiectasis	2 (50.0)	2 (66.7)	1 (25.0)	11 (21.1)	16 (84.2)	3 (14.2)	<0.001
Ground glassing	-	3 (100.0)	4 (100.0)	36 (69.2)	12 (63.1)	6 (28.5)	<0.001
Lymphadenopathy	-	-	-	7 (13.4)	9 (47.3)	3 (14.2)	0.014
Pleural effusion	-	1 (33.3)	-	4 (7.69)	-	3 (14.2)	0.374

**Figures in parentheses indicate percentage*

in patients with PSS ranges from 6 to 60 per cent[24]. Risk factors for the progression of PAH over the course of disease include older age, limited skin disease, decreased diffusion and elevated pulmonary artery pressures at initial evaluation. This was noticed in 15 (57.7%) cases of our series. Of these, eight patients were having limited scleroderma[24].

The incidence of pulmonary involvement in AS varies from 0 to 30% in the literature[25]. None of our patients had any finding on physical examination. Spirometry showed a restrictive defect in two (28.6%) patients. The results were closer to the study of EI Maghraoui *et al*[26]. HRCT revealed abnormalities in 57.1% patients. In the present study, ILD was observed in 28.5% of the patients with AS. There was no specific ILD pattern in all the seven patients, and PAH was detected in one (14.3%) patient.

Polymyositis (PM) is less commonly associated with pulmonary involvement compared to other connective tissue diseases. The frequency of ILD in PM has been reported to range between 5 and 30[27]. Spirometry revealed restrictive pattern in three (50%) patients. Up to 30% of patients with PM have ILD[28] and in the present study the same was observed in two (33.3%) patients. The HRCT demonstrated mixed alveolar interstitial infiltrates. Again, these observations were close to the study by Gaude *et al*[4]. NSIP was the most common type of ILD observed in 50% of PM patients. PAH in PM can be secondary to either left ventricular failure from a dilated cardiomyopathy, hypercapnoeic respiratory failure from respiratory muscle weakness, or due to the presence of ILD[29]. In our study it was detected in two (33.3%) such patients.

Table V: Interstitial lung disease (ILD) in 146 patients of various CTDs.

Disorder	Males (No.)	Females (No.)	Total (No.)	p Value
Rheumatoid arthritis	24	15	39 (54.9)*	< 0.001
Systemic lupus erythematosus	3	9	12 (38.7)	0.0489
Progressive systemic sclerosis	5	11	16 (61.5)	0.1213
Ankylosing spondylitis	2	-	2 (28.5)	1.0000
Polymyositis	-	2	2 (33.3)	0.4667
Mixed connective tissue disease	1	2	3 (60)	1.0000
Total	**35(47.3)**	**39(52.7)**	**74(50.7)**	

Table VI: Pulmonary arterial hypertension in 146 patients of various CTDs.

Disorder	Males (No.)	Females (No.)	PAH (No.)	p Value
Rheumatoid arthritis	2	5	7 (9.85)*	0.0324
Systemic Lupus Erythematosus	3	-	3 (9.7)	1.0000
Progressive systemic sclerosis	12	3	15 (57.7)	1.0000
Ankylosing spondylitis	-	1	1 (14.3)	1.0000
Polymyositis	2	-	2 (33.3)	0.467
Mixed connective tissue disease	3	-	3 (60.0)	0.4000
Total	**22**	**9**	**31(21.2)**	

**Figures in parentheses indicate percentage.*

Pulmonary dysfunction may remain unrecognised during the early phase of MCTD. Overall respiratory involvement has been described in 20% to 80% of patients and abnormal pulmonary function tests are observed in 69% of such cases. Nearly half of the patients have restrictive pulmonary defect and about two-thirds of the patients have significantly reduced diffusing capacity[30]. In our study, restrictive ventilation defect was noticed in 3 (60%) and obstructive in one (20%) patient. Majority (60%) of patients in our study had ILD. NSIP was the most common type of ILD observed in 66.7% of MCTD patients. Pleural effusion was noticed in one which was unilateral and exudative in nature. Again PAH is a major cause of mortality and morbidity in patients with MCTD, and progressive PAH may be accompanied by severe vasculitic lesions in the lungs[30]. In our study PAH was noticed in only 3 (60%) of such patients.

In summary, pulmonary manifestations are common in patients of CTDs, but a high index of suspicion for significant respiratory disease among patients with CTDs is necessary if intervention is to impact the high morbidity and reduce premature death. Again, we emphasise the fact that further studies involving larger samples are needed to demonstrate the involvement of respiratory system in connective tissue disorders. It is also necessary that early detection using clinical scenario and more sophisticated diagnostic modalities improve the overall outcome.

Acknowledgement

Authors are grateful to all the patients for their co-operation and to Dr. Jabeed P, Dr. Jitendra Kumar Jatav and Dr. Bharath for their technical help.

References

1. Lamblin C, Bergoin C, Saelens J, Wallaert B. Interstitial lung disease in collagen vascular diseases. *Eur Respir J* 2001; 18:695-805.
2. Maini RV, Zuaifle N. Rheumatoid arthritis and other synovial disorders. In: Klipped JH, Dieppe PA, editors. Rheumatology. 2nd ed. London: Mosby. 1998:215-220.
3. Shiel W, Prete P. Pleuropulmonary manifestations of rheumatoid arthritis. *Semin Arthritis Rheum* 1984; 13:235-243.
4. Gaude GS, Mahishale V and Srivastava A. Pulmonary manifestations in connective tissue disorders: hospital based study at a tertiary care hospital. *Indian J Chest Dis Allied Sci* 2009; 51:145-151.
5. Arnett FC, Edworthy SM, Bloch DA *et al*. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1994; 31:315-324.
6. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40:1725.
7. Masi AT, Rodnan GP, Medsger TA Jr. Preliminary criteria for the classification of systemic sclerosis. *Arthritis Rheum* 1980; 23:581-590.
8. Tanimoto K, Nakano K, Kano S *et al*. Classification criteria for polymyositis and dermatomyositis. *J Rheumatol* 1995; 22:668-674.
9. Alarcon-Segovia D, Cardiel MH. Comparison between 3 diagnostic criteria for mixed connective tissue disease; study of 593 patients. *J Rheumatol* 1989; 16:328-334.
10. Dougados M, Van der Linden S, Juhlin R *et al*. The European Spondylarthropathy study group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; 34:1218-1227.
11. Miller MR, Hankinson J, Brusasco V *et al*. Series "ATS/ERS Task force: standardisation of lung function testing"- standardisation of spirometry. *Eur Respir J* 2005; 26:319-338.
12. Fenlon HM, Doran M, Sant SM, Breathnach E. High-resolution chest CT in systemic lupus erythematosus. *Am J Roentgenol* 1996; 166:301-307.
13. Turesson C, O'Fallon WM, Crowson CS *et al*. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis* 2003; 62:722-727.
14. Biederer J, Schnabel A, Muhle C *et al*. Correlation between HRCT findings, pulmonary function test and bronchoalverolar lavage cytology in interstitial lung disease associated with rheumatoid arthritis. *Eur Radiol* 2004; 14:272-280.
15. Balbir-Gurman A, Yigla M, Nahir AM, Braun-Moscovici Y. Rheumatoid pleural effusion. *Semin Arthritis Rheum* 2006; 35:368-378.
16. Udayakumar N, Venkatesan S, Rajendiran C. Pulmonary hypertension in rheumatoid arthritis-relation with the duration of the disease. *Int J Cardiol* 2008; 127:410-412.
17. Murin S, Wiedemann HP, Mathay RA. Pulmonary manifestations of systemic lupus erythematosus. *Clin Chest Med* 1998; 19:645-665.
18. Cheema GS, Quismorio FP Jr. Interstitial lung disease in systemic lupus erythematosus. *Curr Opin Pulm Med* 2000; 6:424-429.
19. Keane MP, Lynch JP. Pleuropulmonary manifestation of systemic lupus erythematosus. *Thorax* 2000; 55:159-166.
20. Pan TL, Thumboo J, Boey ML. Primary and secondary pulmonary hypertension in systemic lupus erythematosus. *Lupus* 2000; 9:338-342.
21. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007; 66:940-944.
22. Wiedemann HP, Matthay RA. Pulmonary manifestation of collagen vascular diseases. *Clin Chest Med* 1989; 10:677-721.
23. Jezler Sergio Fernandes de Oliveira, Santiago Mittermayer Barreto, Andrade Thamine Lessa *et al*. Interstitial lung disease in patients with progressive systemic sclerosis: a study of 58 cases. *J Bras Pneumol*. (serial on the Internet). 2005 Aug (cited 2010 Nov 17):31(4):300-306. (Availablefrom: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1806-37132005000400006&lng=en.Accesed on 11-04-2011).
24. Ungerer RG, Tashkin DP, Furst D *et al*. Prevalence and clinical correlates of pulmonary arterial hypertension in progressive systemic sclerosis. *Am J Med* 1983; 75:65-74.
25. Bouchea DK, Sundstrom WR. The pleuropulmonary manifestations of ankylosing spondylitis. *Semin Arthritis Rheum* 1989; 18:277-281.
26. El Maghraoui A, Chaouir S, Abid A *et al*. Lung findings on thoracic high-resolution computed tomography in patients with ankylosing spondylitis. correlations with disease duration, clinical findings and pulmonary function testing. *Clin Rheumatol* 2004; 23:123-128.
27. Ikezoe J, Johkoh T, Kohno N *et al*. High-resolution CT findings of lung disease in patients with polymyositis and dermatomyositis. *J Thorac Imaging* 1996; 11:250-259.
28. Fathi M, Vikgren J, Boijsen M *et al*. Interstitial lung disease in polymyositis and dermatomyositis: longitudinal evaluation by pulmonary function and radiology. *Arthritis Rheum* 2008; 59:677-685.
29. Lundberg IE. The heart in dermatomyositis and polymyositis. *Rheumatology* 2006; 45:18-21.
30. Prakash UB. Respiratory complications in mixed connective tissue disease. *Clin Chest Med* 1998; 19:733-746.

ORIGINAL ARTICLE

JIACM 2013; 14(1): 33-6

Prevalence of hyperhomocysteinaemia in chronic kidney disease and effect of supplementation of folic acid and vitamin B12 on cardiovascular mortality

N Nand, M Sharma**, N Mittal****

Abstract

***Objectives:** Cardiovascular disease (CVD) mortality is 16-times more in cases of chronic kidney disease (CKD). Elevated plasma homocysteine is an important risk factor for increased cardiovascular morbidity and mortality. It is elevated in 85 to 100% patients of CKD and can be an important modifiable risk factor for increased CVD risk. The present study was undertaken to see homocysteine levels in CKD and effect of folic acid and B12 supplementation on homocysteine and cardiovascular outcome.*

***Methods:** A randomised placebo-controlled trial on 100 cases was carried-out at our tertiary care hospital from May 2009 to November 2010. Adult patients of CKD having glomerular filtration rate (GFR) < 60ml/min were enrolled for the study. Patients were randomly assigned into two groups. Control group was given placebo and the interventional group was given folic acid and vitamin B12 supplementation for 6 months.*

***Results:** Mean baseline homocysteine levels were similar in the two groups. It was 32.61 µmol/L in the interventional group and 29.48 µmol/L in the placebo group ($p > 0.05$). The level decreased significantly to 19.69 µmol/L ($p < 0.001$) in the interventional group and it increased to 34.41µmol/L ($p > 0.05$) in the placebo group after 6 months. The homocysteine level had a negative co-relation with haemoglobin ($r = -0.19$), GFR ($r = -0.16$), folic acid ($r = -0.19$) and vitamin B12 ($r = -0.35$). There was no significant effect on total mortality, deaths due to CVD, total ischaemic events, hospitalisation due to unstable angina, heart failure, or venous thrombotic events after 6 months of supplementation therapy.*

***Conclusion:** Serum homocysteine is elevated in patients of CKD. Folic acid and vitamin B12 supplementation lowered homocysteine, but it did not reduce cardiovascular disease mortality.*

***Key words:** Glomerular filtration rate, unstable angina, venous thrombotic events.*

Introduction

Patients of CKD are at higher risk of mortality from cardiovascular disease[1]. Homocysteine is an independent risk factor for CVD[2]. In people with CKD, plasma homocysteine levels tend to increase with decreasing GFR[3] and may reach high levels in end-stage renal disease[4]. Folic acid, vitamin B12, and vitamin B6 play a critical role in the metabolism of homocysteine[5]. Although epidemiological studies have confirmed the association between homocysteine and cardiovascular risk, interventional studies designed to lower homocysteine have not shown any consistent benefit on clinical outcomes[6,7]. Several randomised control trials of lowering homocysteine with folic acid and B vitamins failed to find any reduction of major cardiovascular events or death in high risk patients[6,7]. However, most of the studies done were in Caucasian population[8]. There are no data available regarding their role in Indian population[8]. The present study was therefore conducted to evaluate the prevalence of hyperhomocysteinaemia in CKD patients and to see the effect of supplementation of folic acid and vitamin B12 on homocysteine level and CVD mortality in these Indian patients.

Materials and methods

This was a randomised placebo-controlled trial carried over the period from May 2009 till November 2010. It included 100 adult patients of CKD having GFR < 60 ml/min/1.73m^2. Patients taking vitamin supplementation more than 2.5 mg of folic acid and normal homocysteine level were excluded from the study. Pre-informed consent was obtained in each case and patients were divided into two group. Group A (interventional group) included 50 patients and they were given daily supplementation of 2.5mg folic acid, 50mg vitamin B6 and 1.5mg of vitamin B12, whereas Group B (control group) patients were given placebo. All the patients were examined in detail and all basal laboratory investigations were done with a special emphasis on renal and cardiovascular parameters. Serum homocysteine, vitamin B12 and folic acid were measured at baseline, at 3 months and at 6 months alongwith other renal parameters.

**** Senior Professor & Head, Department of Nephrology, ** Formerly Associate Professor of Biochemistry, *** Resident, Department of Medicine, Pandit B.D. Sharma Post-Graduate Institute of Medical Sciences (PGIMS), Rohtak, Haryana.***

Patients were evaluated every month for adherence to treatment, adverse effects, and clinical outcome. Homocysteine, vitamin B12 and folic acid levels were measured by ADVIA CENTOUR CP model using Siemen's kit.[9] Data was analysed by using student t – test (paired and unpaired), chi-square test and Pearson's correlation coefficient (r). Paired t-test was used for comparison within the same group and unpaired t-test was used for comparison in between two groups.

Results

The age of the patients ranged from 20 - 80 years. The mean age of the patients in group A was 50.48 ± 12.45 years and it was 46.68 ± 14.94 years in group B. There were 66 men and 34 women. Chronic glomerulonephritis was the commonest cause (46.6%), followed by diabetic nephropathy (15%). Anaemia was present in all the patients (mean Hb 9.38gm%) and was more severe in stage 5 CKD. There were 18 patients on dialysis in group A, and 16 in group B. Baseline biochemical parameters of two groups were alike/comparable and are shown in Table I. Homocysteine levels were elevated in 94.4% of the patients. Serum homocysteine levels decreased significantly (Fig. 1) in group A (interventional group) from 32.61 µmol/l to 23.64 µmol/l at 3 months ($p < 0.001$) and 19.69 µmol/l at 6 months ($p < 0.001$). In group B (control group) homocysteine continued to increase from 29.48 µmol/l at baseline to 30.13 µmol/l at 3 months ($p > 0.05$) and 34.41 µmol/l at 6 months ($p > 0.05$). The rise was more in patients receiving renal replacement therapy (RRT) in group B from 32.28 µmol/l at baseline to 33.58 µmol/l at 3 months ($p < 0.05$) and 41.25 µmol/l at 6 months ($p < 0.05$) in comparison to patients of group B, who were not receiving RRT ($p > 0.05$). The homocysteine levels had negative co-relation (Fig. 2 & 3) with haemoglobin ($r = -0.19$), GFR ($r = -0.16$), folic acid ($r = -0.19$) and vitamin B12 ($r = -0.35$). The p value was significant with vitamin B12 ($p < 0.05$).

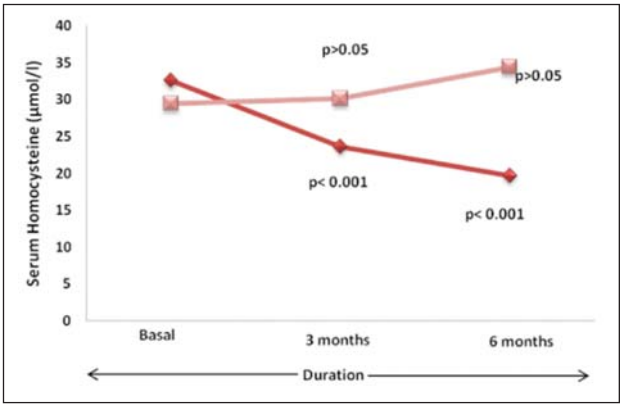


Fig. 1: *Showing homocysteine levels at the onset of the study and after 3 and 6 months of supplementation/placebo therapy.*

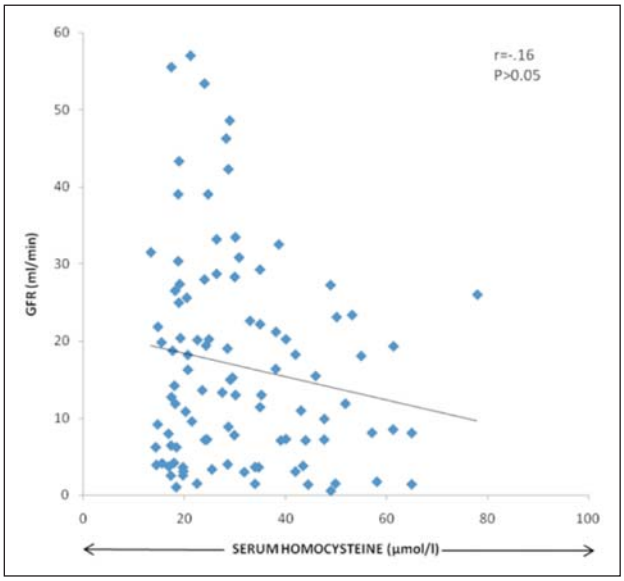


Fig. 2: *Showing negative correlation of homocysteine with GFR.*

Table I: Baseline characteristics of the participants in the two groups.

	Group A	Group B	Unpaired p value
Age (years)	50.48 ± 12.45	46.68 ± 14.94	> 0.05
Sex (M:F)	32:18	34:16	> 0.05
Patients on RRT	18	16	> 0.05
SBP (mmHg)	138 ± 22.32	140.44 ± 26.44	> 0.05
DBP (mmHg)	86.04 ± 11.68	88.76 ± 15.97	> 0.05
Haemoglobin (gm%)	9.38 ± 1.74	9.89 ± 1.86	> 0.05
Blood urea (mg%)	108.87 ± 52.25	105.78 ± 51.69	> 0.05
Serum creatinine (mg%)	4.45 ± 3.58	4.50 ± 3.09	> 0.05
Serum uric acid (mg%)	7.96 ± 2.32	7.85 ± 2.23	> 0.05
GFR (ml/min/1.73m^2)	15.92 ± 12.51	17.77 ± 14.22	> 0.05
Serum calcium (mg%)	9.06 ± 0.86	8.98 ± 0.91	> 0.05
Serum phosphorus (mg%)	5.07 ± 1.47	5.64 ± 2.24	> 0.05

SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

Serum folic acid levels were within the normal range in both the groups (Table II). Following supplementation, folic acid levels increased significantly in Group A both at 3 months and at 6 months ($p < 0.001$), while there was no significant change observed in folic acid levels of control group ($p > 0.05$). There was a significant fall in folic acid level in group B patients who were on RRT ($p < 0.05$). Serum vitamin B12 levels were in lower range in both the groups. Following supplementation, B12 levels increased significantly in Group A – both at 3 months ($p < 0.001$), and at 6 months ($p < 0.001$), while there was no significant

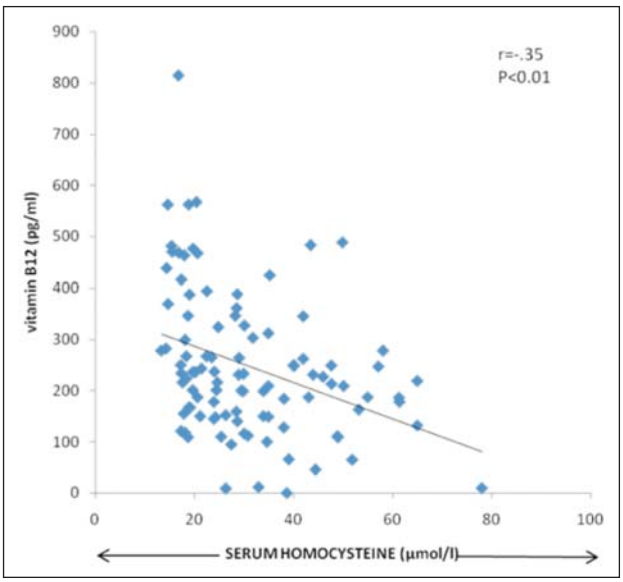


Fig. 3: *Showing negative correlation of homocysteine with vitamin B12.*

change in control group (p > 0.05). There was no significant difference observed in blood urea, serum creatinine, and GFR during follow-up in any group.

Table II: Plasma concentration of homocysteine, folic acid, and vitamin B12 at baseline, at 3 months, and at 6 months.

Parameters	Group A	Group B	Unpaired p value
Homocysteine (µmol/l)			
Baseline	32.61±14.14	29.48±13.89	>0.05
3 months	23.64±11.84*	30.13±13.41**	<0.001
6 months	19.69±8.41*	34.41±12.2**	<0.001
Folic acid (ng/ml)			
Baseline	11.93±6.14	12.89±6.54	>0.05
3 months	16.43±7.07*	13.16±5.63**	<0.01
6 months	17.73±7.32*	13.08±5.73**	<0.01
Vitamin B12 (pg/ml)			
Baseline	236.56±124.01	259.44±157.54	>0.05
3 months	371.18±168.18*	258.28±132.73**	<0.001
6 months	554.95±316.58*	253.67±123.38**	<0.001

Paired p value baseline to 3 months & baseline to 6 months comparison.
** = < 0.001; ** = > 0.05*

Although homocysteine levels declined significantly after 6 months, but there was no significant effect observed on clinical outcome (Table III). No adverse effect was observed due to folic acid and vitamin B12 and B6 therapy during the follow-up period.

Table III: Clinical events at 6-months follow-up in the two groups.

Clinical events	Group A	Group B	Unpaired p value
Total no. of deaths	10	11	> 0.05
Death from CVD	3	4	> 0.05
Total ischaemic events	6	7	> 0.05
Hospitalisation due to USA	3	4	> 0.05
Hospitalisation due to CHF	3	3	> 0.05
Venous thrombotic events	0	0	> 0.05

Discussion

Patients of CKD are at 16-times increased risk for mortality from CVD[1]. Further, patients on dialysis have a higher risk of left ventricular hypertrophy, congestive heart failure, and ischaemic heart disease, suggesting that the excess risk of CVD begins in the early stages of CKD[1]. Although traditional risk factors such as hypertension are more prevalent in this population, there has been an increasing emphasis on the role of nontraditional risk factors such as anaemia, hyperparathyroidism, and hyperhomocysteinaemia[10]. The association of elevated homocysteine levels with risk of CVD has drawn attention because of the nearly universal elevation of homocysteine in patients with CKD, the epidemiologic correlation between homocysteine and cardiovascular risk in CKD[11,12]. Supplementation of folic acid and vitamin B12 is known to lower homocysteine level in these patients[12,13]. However, only a limited number of interventional trials are available which show the effect of homocysteine lowering on CVD.

In this study, serum homocysteine levels were elevated in 94.4% of the cases. A significant reduction (p < 0.001) in homocysteine levels was seen after supplementation. A number of studies[8,14,15] have documented similar decline with supplementation of vitamin B12 and folic acid for a period ranging between 3.2 to 5 years. We found a 27% decline in homocysteine level at 3 months and 39% at 6 months which was comparable to other studies conducted over 3.2 to 5 years[8,14,15].

There was increase in homocysteine level in the control group, which was more in patients on dialysis suggesting that dialysis decreases folic acid level – probably by increasing the loss. Accumulation of uraemic toxins, decrease in homocysteine clearance and metabolism owing to a decreased functioning renal mass may also be responsible for this increase in homocysteine levels in ESRD patients[16].

Patients of group B who were on dialysis showed a significant decline in folic acid level during the follow-up

as compared to those who were not on dialysis. On the other hand, in patients of group A who were on dialysis, the folic acid levels actually rose. The decline in folic acid levels may be due to enhanced folate loss in patients who were on dialysis suggesting that these patients require a high folic acid level to maintain normal homocysteine levels.

Although folic acid, vitamin B12, and vitamin B6 treatment significantly reduced homocysteine, there was no significant difference on the total number of deaths, deaths due to CVD, total ischaemic events, hospitalisation due to unstable angina, and congestive heart failure (CHF). Similar observations have been reported by HOPE-2 and other investigators[8,14,15]. The failure to observe a sustainable benefit of supplementation therapy (B12 and folic acid) in cases of CKD was probably due to the fact that the underlying burden of disease is too great for a measurable benefit from lowering homocysteine. Although homocysteine levels were substantially reduced, amelioration of the consequences of hyperhomocysteinemia requires lowering to normal levels, an effect that was achieved in only some of our participants, despite administration of the high vitamin doses.

Therefore, on the basis of observations in this study, we conclude that though homocysteine levels are elevated in majority of CKD patients, reduction of homocysteine levels did not decrease the adverse cardiovascular outcome in CKD patients. Further, there was enhanced folate loss through dialysis causing more elevation of homocysteine level in those who received dialysis but were not on supplementation, suggesting that all cases of CKD especially on dialysis therapy require daily supplementation of folic acid and vitamin B12.

References

1. Foley RN. Clinical epidemiology of cardiac disease in dialysis patients. Left ventricular hypertrophy, ischemic heart diseaseand cardiac failure. *Semin Dial* 2003; 16: 111-7.
2. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA* 2002; 288: 2015-22.
3. Wollesen F, Brattstrom B, Refsum H *et al*. Plasma total homocysteine and cysteine in relation to glomerular filtration rate. *Kidney Int*. 1999; 55: 1028-35.
4. Mallamaci F. Homocysteine and risk in end-stage renal disease: a matter of context. *Kidney Int* 2006; 69: 204-7.
5. Finkelstein J. Regulation of homocysteine metabolism. Carmel R, Jacobsen DW, eds. In: *Homocysteine in Health and Disease*. Cambridge, UK: Cambridge University Press; 2001: 92-9.
6. Bønaa KH, Njolstad I, Ueland PM. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006; 354: 1578-88.
7. Lonn E, Yusuf S, Arnold MJ. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006; 354: 1567-77.
8. Johannes F, Mann E, Sheridan P, Matthew J *et al*. Homocysteine lowering with folic acid and B vitamins in people with chronic kidney disease-results of the renal HOPE-2 study. *Nephrol Dial Tranplant* 2008; 23: 645-3.
9. Burtis CA, Ashwood ER, Bruns DE. Analytical Techniques And Instrumentation. Burtis CA, Ashwood ER, Bruns DE, eds. In: Clinical Chemistry and Molecular Diagnostics. 4thedn. Elsevier, New Delhi, 2006, p84-5.
10. Muntner P, He J, Astor BC *et al*. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the Atherosclerosis Risk in Communities study. *J Am Soc Nephrol* 2005; 16: 529-38.
11. Robinson K, Gupta A, Dennis V *et al*. Hyperhomocysteinemia confers an independent increased risk of atherosclerosis in end-stage renal disease and is closely linked to plasma folate and pyridoxine concentrations. *Circulation* 1996; 94: 2743-48.
12. Jungers P, Joly D, Massy Z *et al*. Sustained reduction of hyperhomocysteinaemia with folic acid supplementation in predialysis patients. *Nephrol Dial Transplant* 1999; 14: 2903-06.
13. Bostom AG, Shemin D, Lapane KL. High dose-B-vitamin treatment of hyperhomocysteinemia in dialysis patients. *Kidney Int* 1996; 49: 147-52.
14. Jamison RL, Hartigan P, Kaufman JS, Goldfarb DS *et al*. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. *JAMA* 2007; 298: 1163-70.
15. Zoungas S, McGrath BP, Branley P. Cardiovascular morbidity and mortality in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) in chronic renal failure: A multicenter, randomised, controlled trial. *J Am Coll Cardiol* 2006; 47: 1108-16.
16. Massy ZA. Potential strategies to normalize the levels of homocysteine in chronic renal failure patients. *Kidney Int* 2003; 63: 134-6.

REVIEW ARTICLE

JIACM 2013; 14(1): 37-45

Coenzyme Q10 – A novel molecule

Pragati Kapoor, AK Kapoor***

Abstract

Coenzyme Q10 is a fat soluble vitamin-like substance produced by the human body. It is necessary for proper functioning of many organs and for basic functioning of cells. It is found throughout the body. Coenzyme Q10 is used both as a food supplement and as an important antioxidant. It is a component of the electron transport chain and plays a key role in producing energy in mitochondria in the form of ATP that functions like a rechargeable battery in the transfer of energy. Coenzyme Q10 levels are reported to decrease with age and to be low in cardiac conditions, Parkinson's disease, cancer, diabetes, muscular dystrophies, HIV/AIDs, etc. Some drugs also lower Coenzyme Q10 levels. It is not only used as an important nutrional supplement by millions of people all over world but is also used in a number of clinical conditions namely CHF, diabetes, gum disease, Huntington's disease, Parkinson's disease, etc. Coenzyme Q10 is fairly safe and well tolerated.

Key words : Coenzyme Q10, antioxidant,

Introduction

Coenzyme Q10 is a fat soluble vitamin-like substance found throughout the body but especially in heart, liver, kidney, and brain[1]. Coenzyme Q10 is produced by the human body and is required for the proper functioning of many organs and chemical reactions in the body. It helps provide energy to the cells and has powerful antioxidant activity. It is a component of the electron transport chain and participates in aerobic cellular respiration, generating energy in the form of ATP. Ninety-five per cent of energy of the human body is generated this way[2,3]. It is necessary for the basic functioning of cells as the body needs energy for cell growth and maintenance. It is vital to a number of activities related to energy metabolism. Coenzyme Q10 can be synthesised in the laboratory and is used both as a medicine and as a food supplement. CoQ10 is the third most sold dietary supplement in the United States after omega-3 fatty acids and multivitamins. Coenzyme Q10 is also known as ubiquinone, ubidecarenone, Coenzyme Q and abbreviated as CoQ10 or Q10 or Q. These days CoQ10 is being used by millions of people in Japan, Europe, Russia, Canada, and the US. It is now also available in India.

CoQ10 is used in the treatment of a variety of disorders primarily related to suboptimal cellular energy metabolism and oxidative injury. It appears most promising for neurodegenerative disorders such as Parkinson's disease and certain encephalo-myopathies for wihich CoQ10 has gained orphan drug status[4]. CoQ10 levels are reported to decrease with age and to be low in patients with some chronic diseases such as cardiac conditions, muscular dystrophies, Parkinson's disease, cancer, diabetes, and HIV/AIDS. Some drugs may also lower CoQ10 levels. CoQ10 levels in the body can be increased by taking CoQ10 supplements, although it is not clear that replacing 'low CoQ10' is beneficial.

Discovery and history

Coenzyme Q10 was first discovered from beef mitochondria by Prof. Fredrick L. Crane and colleagues at the University of Wisconsin – Madison Enzyme Institute in 1957[5]. In 1958, its chemical structure was reported by Dr. Karl Folkers. In 1961, Peter Mitchel proposed the electron transport chain of which Coenzyme Q10 is a component (being a vital proton motive role of CoQ10), and for this he was awarded the Nobel prize in 1978. From the 1980s onward, numerous scientists around the world started studies on this molecule in relation to various diseases including cardiovascular diseases (owing to demonstration of deficiency of CoQ10 in human heart diseases) and cancer. The antioxidant role of CoQ10 as a free radical scavenger was also widely studied.

Chemical property

Its molecular formula is C59H 90 O4 and its molecular mass 863.34 g mol[1]. Chemically, it is 1,4,-benzoquinone where Q refers to the quinone chemical group and 10 refers to the number of isoprenyl chemical subunits in its tail. The various kinds of Coenzyme Q can be distinguished by the number of isoprenoid subunits in their side chains. CoQ10 is present in most eukaryotic cells primarily in human mitochondria, hence it is the most common CoQ10 in human beings.

**** Junior Consultant, Indraprastha Apollo Hospital, Sarita Vihar, New Delhi, ** Professor and Head, Department of Pharmacology, Rohilkhand Medical College & Hospital, Bareilly, Uttar Pradesh.***

Sources of Q10

Besides endogenous synthesis, CoQ10 is also supplied to the organism by various foods.

Dietary sources

CoQ10 levels in selected food are as under[6]:

	Beef	Pork	Chicken	Fish	
Heart	113	118-128	116.2-132.2	Red flesh	43-67
Liver	39-50	22.7-54		White flesh	11-16
Muscle	26-40	13.8-45		Salmon	4-8
	Oils	**Nuts**			
Soyabean	54-280	Peanuts	27		
Olive	4-160	Walnuts	19		
Sunflower	4-15	Seasame seeds	18-23		
		Pistachio	20		
		Hazelnuts	17		
		Almonds	5-14		
Vegetables		**Fruits**			
Parsley	8-26	Avocado	10		
Broccoli	6-9	Grape	6-7		
Cauliflower	2-7	Black currant	3		
Spinach	10	Orange	1-2		
Chinese Cabbage	2-5	Apple	1		
		Strawberry	1		

CoQ10 levels are particularly high in organ meats such as heart, liver and kidney, as well as beef, soy oil, sardines, mackerel and peanuts; In short, meat and fish are the richest sources of dietary CoQ10. Dairy products are poor sources of CoQ10. Vegetable oils are also good sources. Vegetables (except parsley) and fruits (except avocado) are poor sources of CoQ10[6]. CoQ10 is manufactured by fermenting beets and sugarcane with special strains of yeast. The estimated daily intake of CoQ10 is 3 - 6mg per day derived primarily from meat. Cooking by frying reduces CoQ10 content by 14 - 32%.

Biosynthesis

The endogenous biosynthesis is quite a complex process. Starting from acetyl-CoA, a multi step process of mevalonate pathway produces farnesyl-PP (FPP), the precursor for cholesterol, CoQ10 and isoprenylated protein. The pathway involves HMG Co-A reductase The long isoprenoid side-chain of CoQ10 is synthesised by condensing FPP by enzymes.[7] The next step involves condensation of this polyisoprenoid side-chain with 4 hydroxybenzoate, catalysed by polyprenyl- 4 hydroxy-benzoate transferase. Hydroxybenzoate is synthesized from tyrosine or phenylalanine. In addition to mitochondria, these initial reactions also occur in the endoplasmic reticulum and peroxisomes indicating multiple sites of synthesis[8]. Increasing the endogenous biosynthesis of CoQ10 is an important strategy to fight CoQ10 deficiency.

Physiological role

1- CoQ10 is a component of electron transport chain and participates in aerobic cellular respiration, generating energy in the form of ATP. CoQ10 plays a key role in producing energy in mitochondria in the form of ATP. Thus, CoQ10 has a role in producing ATP, a molecule in body cells that functions like a rechargeable battery in the transfer of energy. 95% of the human body's energy is generated this way. Thus, those organs with the highest energy requirement such as heart, liver, and kidney have the highest CoQ10 concentrations[9,10]. There are three redox states of Coenzyme Q10, fully oxidized (ubiquinone), semiquinone (ubisemiquinone) and fully reduced (ubiquinol). CoQ10 exists in a completly oxidised form and completely reduced form which enable it to perform its function in electron transport chain and as an antioxidant.

As mentioned earlier, CoQ10 is primarily found in mitochondria and is also found in the membranes of many organelles. Since its primary function in cells is in generating energy, the highest concentration is found in the inner membrane of the mitochondrion. Some other organelles that contain CoQ10 include endoplasmic reticulum, peroxisomes, lysosomes, and vesicles.

CoQ10 and the electron transport chain

CoQ10 plays a unique role in the electron transport chain (ETC) and functions in every cell of the body to synthesise energy. In the inner mitochondrial membrane, electrons from NADH and succinate pass through to the ETC to the oxygen, which is then reduced to water. The transfer of electrons through ETC results in pumping of H^+ across the membrane causing a proton gradient across the membrane, which is used by ATP synthase (located on the membrane) to generate ATP. CoQ10 functions as an electron carrier from enzyme complex I and enzyme complex II to complex III in this process. This is crucial in the process, since no other molecule can perform this function.

Antioxidant function of CoQ10

CoQ10 functions as an antioxidant which protects the body from damage caused by harmful molecules known as free radicals. The antioxidant role of CoQ10 as a free radical scavenger was widely studied by Lars Emster. Antioxidants such as CoQ10 can neutralise free radicals and may reduce or even help prevent some of the damage they cause like damage to cell membranes, tamper with DNA, and cell death. The antioxidant nature of CoQ10 derives from its energy carrier function. As an energy carrier, the CoQ10 molecule is continually going through an oxidation reduction cycle. As it accepts electrons, it becomes reduced. As it gives up electrons, it becomes oxidised. In its reduced form, the CoQ10 molecule holds electrons rather loosely, hence this CoQ10 molecule will quite easily give up one or both electrons, and thus act as an antioxidant. CoQ10 inhibits lipid peroxidation by preventing the production of lipid peroxyl radicals. By preventing propogation of lipid peroxidation CoQ10 protects not only lipids, but also proteins from oxidation. Oxidation of the circulating LDL is thought to play a key role in the pathogenesis of atherosclerosis, which is the underlying disorder leading to heart attack and ischaemic strokes and CHD. Content of ubiquinol in human LDL affords protection against the oxidative modifications of LDL themselves, thus lowering their atherogenic potency. In addition, the reduced form of CoQ10 effectively regenerates vitamin E from, the α-tocopheroxyl radical and, thereby interfering with the propogation step. Furthermore, during oxidative stress, interaction of H_2O_2 with metal ions bound to DNA generates hydroxyl radicals and CoQ10 efficiently prevents the oxidation of bases, particularly in mitochondrial DNA. In contrast to other antioxidants, CoQ10 inhibits both the initiation and propogation of lipid and protein oxidation. It also regenerates other antioxidants such as vitamin E. The circulating CoQ10 in LDL prevents oxidation of LDL, therefore providing its benefits in cardiovascular disease. Additionally, CoQ10 is an indirect stabiliser of calcium channels to decrease calcium overload[11].

Coenzymes help enzymes work to digest food and perform other body processes, and they help protect the heart and skeletal muscles. It is also said to boost energy and speed recovery from exercise.

Pharmacokinetics

Absorption

CoQ10 is a crystalline powder that is insoluble in water. Absorption follows the same process as that of lipids and the uptake mechanism appears to be similar to that of vitamin E, another lipid soluble nutrient. In human beings, the process involves the secretion of pancreatic enzymes and bile into the small intestine that facilitate emulsification and micelle formation that is required for the absorption of lipophilic substances.

Food intake (and the presence of lipids) stimulates bodily biliary excretion of bile acids and greatly enhances the absorption of CoQ10.[12] Exogenous CoQ10 is absorbed from the small intestine and is best absorbed if it is taken with a meal. Peak plasma levels are achieved in 2 - 6 hours after oral administration. In some studies, a second plasma peak was also observed at about 24-hours after administration.[13]

Improving the bioavailability of CoQ10

In order to boost the bioavailability of CoQ10 after oral administration, several approaches have been adopted:

a. Reduction in particle size

The obvious strategy is reduction of the particle size to as low as the micro-and nano-scale. This approach has so far not proved to be very successful with CoQ10.[14]

b. CoQ10 in oil suspension

Using an emulsion to facilitate absorption from GIT and to improve bioavailability has been successful. Emulsions of soybean oil are being used in the form of oil-based soft gelatin capsules to enhance bioavailability. The significantly increased bio-availability of CoQ10 was confirmed for several oil-based formulations in most other studies[15].

c. Novel forms of CoQ10 with increased water solubility

Facilitating drug absorption by increasing its solubility in water is a common pharmaceutical strategy and has been shown to be successful with the use of aqueous dispersion of solid CoQ10 with tyloxapol polymer[16] formulations based on various solubilising agents, i.e., hydrogenated lecithin[17] and complexation with cyclodextrin[18]. Besides, some other novel carrier system like liposomes, nano- particles, dendrimer, etc., can be used to enhance the bioavailability of Coenzyme Q10.

Metabolism

Limited data are available. It appears CoQ10 is metabolised in all tissues, while a major route for its elimination is biliary and faecal excretion. The elimination half-time is 33 hours[19].

Measurement of CoQ10 levels

CoQ10 levels can be measured in plasma and these measurements reflect dietary intake rather than tissue status. Currently, CoQ10 levels are measured in cultured skin fibroblasts, muscle biopsies, and in blood mononuclear cells[20]. Cultured fibroblasts can be used to evaluate the rate of endogenous CoQ10 biosynthesis by measuring the uptake of 14C–labelled p-hydroxy-benzoate.

Inhibition of synthesis by statins and beta-blockers

Coenzyme Q10 shares a common biosynthetic pathway with cholesterol. The synthesis of an intermediary precursor of CoQ10, mevalonate, is inhibited by some beta-blockers and statins[21,22,23]. Statins can reduce serum levels of CoQ10 by up to 40%. Thus, it is logical to supplement CoQ10 as a routine to any treatment that may reduce endogenous production of CoQ10. It may be emphasised that till date there are no conclusive reports that support the role of CoQ10 deficiency in the pathogenesis of statin-related myopathy.

Deficiency of CoQ10

There are two major factors that lead to deficiency of CoQ10 in human beings:-

1. Reduced biosynthesis
2. Increased utilisation by the body.

Biosynthesis is the major source of CoQ10. Biosynthesis requires at least 12 genes and mutations in many of them cause CoQ10 deficiency. A few other genetic defects such as mutations of mitochondrial DNA can also influence, while the role of statins is controversial. Some chronic diseases such as cancer, heart disease, etc., may also reduce the biosynthesis and increase the demand for CoQ10 in the body.

It may be mentioned that CoQ10 levels are highest during the first 20 years of life. By age 80 years, the levels of CoQ10 are lower than that at birth It is not only time that uses up the body's store of CoQ10, smoking does, too.

Dose

The observed safe level (OSL) is intake up to 1,200 mg/day. However, the usual dose is 100-200 mg/day in deficiency states and other disease states.

Are there safety concerns?

CoQ10 is considered to be safe for most adults, and possibly safe for children when taken by mouth or when applied directly to the gums. Most people tolerate CoQ10 well, i.e., it causes minimal side effects.

Indications

CoQ10 is being used by millions of people all over world not only as a nutritional supplement but also in treating a variety of clinical conditions such as cardiac, neurologic, and immunologic disorders. It is being used for treating heart and blood vessel conditions like CHF, angina, high BP, and heart problems linked to certain cancer drugs. It is also used for diabetes, gum disease, breast cancer, Huntington's disease, Parkinson's disease, muscular dystrophy, chronic fatigue syndrome (CFS), Lyme disease and to treat hair loss related to warfarin. Coenzyme Q10 has also been tried for treating inherited or acquired disorders that limit energy production in the cells of the body (mitochondrial disorders), for improving exercise performance, for strengthening the immune systems of people with HIV/AIDS, male infertility, migraine headache and countering muscle pain sometimes caused by statins. Besides, it has also being tried for increasing the life span, since with advanced age CoQ10 levels decrease.

According to the Mayo Clinic, use of CoQ10 remains controversial and unproven as a treatment in many clinical conditions though it is approved for use as an orphan product in the treatment of Huntington's disease and mitochondrial cytopathies.

However, the effectiveness ratings for Coenzyme Q10 based on the Natural Medicines Comprehensive Database are as follows:

1. **Likely effective** –
   i. In cases of Coenzyme Q10 deficiency - Rare condition, 150 mg/day is administered.
   ii. Inherited or acquired disorders that limit energy production in the cells of the body (mitochondrial disorders). Improvement in symptoms are slow and the treatment 50 mg/day has to be continued for six months. CoQ10 is being approved for use as an orphan drug in mitochondrial cytopathies. Additionally, CoQ10 has shown positive trends in reducing symptoms associated with selected mitochondrial abnormalities including encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, Kearns-Seyre syndrome, and the myoclonus epilepsy with ragged-red fibers (MERRhF) syndrome[24,25,26].
2. **Possibly effective** –
   i. Congestive heart failure (CHF):

In CHF there is increased oxidative stress as well as there is evidence of CoQ10 deficiency as confirmed by tissue assays[27]. CoQ10 taken alone may not be effective in CHF, but it can be helpful when taken in combination with other medications of heart failure[28,29]. Dose 100 mg/ day BD. Double blind research suggest CoQ10 may reduce symptoms related to heart failure. CoQ10 is thought to increase energy production in heart muscle. Recent human studies, however have not supported these. Studies show that CoQ10 has little or no effect in treating heart failure or angina. A more recent trial using CoQ10 in combination with carnitine and taurine did find modest clinical improvement[30]. However, CoQ10 has been approved in Japan since 1974 for use in heart failure. Recently, CoQ10 plasma concentrations have been demonstrated as an independent predictor of mortality in chronic heart failure.

ii. Decreasing the risk of additional heart problems in people who have had a recent myocardial infarction:

When started within 72 hours of MI and taken for one year, CoQ10 significantly lowers the risk of heart-related events including non-fatal MI. Dose is 120 mg/day BD.

iii. Preventing blood vessel complications caused by coronary by-pass surgery:

There is some evidence that taking CoQ10 orally for a week before surgery might help to reduce blood vessel damage. Further, its use following cardiac surgery demonstrated improvements in myocardial isoenzyme levels, left ventricular functions, and post-operative recovery time (n=20)[31].

iv. Lowering high blood pressure:

Combining CoQ10 with other antihypertensive agents may permit decrease of antihypertensive dose as it can enhance the effects of antihypertensive medications. A recent meta-analysis (2007) concluded that CoQ10 in hypertensive patients can lower systolic blood pressure by up to17 mm of Hg, and diastolic blood pressure by up to 10 mm of Hg without significant side effects[32]. Dose of CoQ10 is 120 - 200 mg/day BD.

v. In isolated systolic hypertension:

Taking CoQ10 orally may lower systolic blood pressure by about 26% after 12-weeks of therapy in some people. Dose is 60 mg BD.

vi. Huntington's disease:

Ubiquinol, an altered form of CoQ10 has been granted, "orphan drug status" by the US FDA, However, taking CoQ10 in doses of 600 mg/day orally or less does not seem to be effective in slowing the progression of this rare neurological disorder[33].

vii. Preventing migraine headache (prophylaxis):

Oral CoQ10 helps in preventing migraine headache (prophylaxis)[34]. It can decrease the frequency of headaches by about 30%. However, CoQ10 does not seem to be effective in treating migraine once it have developed. Dose is 100 mg TDS. It has been used effectively in prophylaxis of migraine (300 mg/day) in combination with magnesium citrate 500 mg/day and riboflavin 400 mg/day[35].

viii. Parkinson's disease:

Lower levels of CoQ10 have been observed in people with Parkinson's disease. Increasing CoQ10 may increase the level of dopamine, which is thought to be lower in people with Parkinson's disease. It has also been suggested that CoQ10 might protect brain cells from damage by free radicals. The results of a 16-month trial suggested that CoQ10 – especially at 1,200 mg/day dose – had a significant reduction in disability compared to those who took placebo. A randomised, double blind, placebo controlled multicentre study of 80 patients observed that 1,200 mg/day of Coenzyme Q10 was associated with up to 44 per cent less functional decline in patients with Parkinson's diseases, including activities of daily living[36]. However, the results need further confirmation.

Oral CoQ10 may slow the decline in people with early Parkinson's disease but not in people with mid-stage Parkinson's disease[36,37].

ix. Improving the immune system of people with HIV/ AIDS:

CoQ10 is being used for strengthening the immune system of people with HIV/AIDS.

x. Muscular dystrophy:

Oral CoQ10 seems to improve physical performance in this inherited disorder in some patients. Dose is 100 mg/day.

3. CoQ10 has been used or recommended for use in the following conditions though more evidences and additional studies are required for its effectiveness –

i. Dental (periodontal) disease:

When applied directly to the teeth and gums or else oral administration of CoQ10 improves gingival health. Studies have shown that diseased gum tissue is deficient in CoQ10[38]. Thus CoQ10 may improve gingival health, immune response in gum tissues and reversal of the diseased gum conditions[39,40]. In addition to oral supplementation, topical application of CoQ10 on gum tissues has been shown to improve periodontitis and gingivitis conditions.

ii. Atherosclerosis:

Preliminary data imply benefit in the setting of atherosclerosis. As mentioned earlier, oxidation of the circulating LDL is thought to play a key role in the pathogenesis of atherosclerosis, which is the underlying disorder leading to heart attack, ischaemic strokes, and CHD[41,42]. It has been demonstrated that the content of ubiquinol in human LDL affords protection against the oxidative modifications of LDL themselves, thus lowering their atherogenic potency.

iii. In post-MI cases:

In a randomised, placebo-controlled trial of 73 patients following MI who were administered 120 mg/day of coenzyme 10 for one year, it was observed that coenzyme Q10 group demonstrated a significant decrease in total cardiac events including nonfatal MI and cardiac deaths[43]. This improvement has been attributed to possible attenuation of endothelial dysfunction[44].

iv. In cardiac arrest:

A recent study shows a survival benefit after cardiac arrest if CoQ10 is administered in addition to commencing active cooling of the body to 32 - 34°c[45].

v. Angina:

CoQ10 might improve exercise tolerance in angina. Evidences in angina pectoris cardiomyopathy and physical exercise capacity show conflicting results and require further study.

vi. Hypertrophic cardiomyopathy:

CoQ10 orally seems to decrease the thickness of heart wall and decrease symptoms of shortness of breath and fatigue. Several small trials have found CoQ10 may be helpful for certain types of cardiomyopathy.

vii. Cancer:

CoQ10 is being investigated as a treatment for cancer and as a relief from cancer treatment side-effects[46,47]. The AHRQ found no evidence to asses the efficacy of coenzyme Q10 for this use. Animal studies have shown that CoQ10 helps the immune system work better and makes the body better able to resist certain infections and types of cancer. In breast cancer, the results are not very conclusive, though oral CoQ10 might be helpful in advanced breast cancer along with surgery and conventional treatment plus other antioxidants and omega-3 and omega-6 fatty acids as relief from cancer treatment side-effects. Clinical trials have shown that CoQ10 helps protect the heart from the damaging side-effects of doxorubicin and daunorubicin (anti-cancer agents), or other anthracycline medications.

viii. Radiation injury:

CoQ10 dietary supplementation in rats reduced radiation damage to animal's blood[48].

ix. Improving athletic or exercise performance and reducing fatigue:

CoQ10 might help increase energy. This is because CoQ10 has a role in producing ATP. Thus, CoQ10 has been tried for treating inherited or acquired disorders that limit energy production in the cells of the body (mitochondrial disorders) and for improving exercise performance or athletic performance and reducing the sensation of fatigue[49]. The physical performance of subjects was found to increase in those who had taken 300 mg of CoQ10 and the subjects also reported feeling less fatigued.

x. Enhancing anti-inflammatory effects:

CoQ10, a powerful antioxidant produced by the human body, helps to reduce inflammation. It is observed that in elderly individuals, the anti-inflammatory effects of eating a Mediterranean-style diet – one rich in olive oil, fruits, and vegetables – are enhanced by addition of a daily 200 mg supplement of CoQ10, and that CoQ10 supplementation acts in synergy with a Mediterranean diet to control inflammatory responses and oxidative stress within cells[50].

xi. Improving blood sugar control in diabetics:

The effectiveness of CoQ10 in diabetes is controversial. A more recent trial using 100 mg CoQ10 twice daily suggested significantly improved blood pressure and glycaemic control[51]. However, two randomised controlled studies conducted earlier found that CoQ10 supplementation failed to find any effect on glycaemic control[52].

xii. Male infertility:

There is some evidence that CoQ10 treatment can improve the movement and density of sperm in men with certain type of infertility. Dose: 200 -300 mg/day.

xiii. Statins-induced myopathy:

Statins sometimes cause muscle pain. Oral CoQ10 might reduce this pain[53].

xiv. Reduction in muscle damage from exercise:

Too much exercise or strenuous exercise can cause oxidative stress, inflammation, and muscle damage, CoQ10 supplementation before strenuous exercise may lower the oxidative stress and inflammation in the body, lowering the chance of muscle damage[54]. CoQ10 group of runners showed a reduction in oxidative stress as suggested by milder increase in 8-OHdG levels, a decrease in isoprostanes generation and an increase in catalase and antioxidant status. Besides, CoQ10 decreased creatinine production, creatinine being the end-product of muscle metabolism and a key marker of muscle damage[54].

xv. Prevention of pre-eclampsia:

Evidences show that women who are at risk for developing this condition have a lower chance of getting it if they take oral CoQ10 from 20 weeks of pregnancy until delivery[55]. Dose: 100 mg/d.

xvi. In hair loss related to use of the warfarin:

Research is continuing to assess the potential of CoQ10 in this condition.

xvii. In Lyme disease.

xviii. Life span:

Low dosages of CoQ10 reduce oxidation and DNA double strand breaks, and a combination of a diet rich in polyunsaturated fatty acids and CoQ10 supplementation leads to a longer life span in rats[56,57]. Yet a few studies reported no increase in life span or decrease in ageing in mice or rats supplemented with CoQ10.

Contraindications

No absolute contraindications are known for CoQ10.

Adverse effects

Adverse effects with CoQ10 are quite rare. Toxicity is not usually observed with high doses of CoQ10. A daily dose up to 3,600 mg is found to be well-tolerated by healthy as well as unhealthy persons though very high intakes are associated with mostly GIT adverse effects such as stomach upset, loss of apetite, nausea, vomiting, and diarrhoea. On an average, mild gastrointestinal discomfort is reported in less than one per cent of patients in clinical trials[58]. It can also cause allergic reactions and may lower BP in some people. Dividing the total daily dose by taking smaller amounts two or three times a day can reduce the side effects.

Precautions

i. Not enough is known about the use of CoQ10 during pregnancy or in breast feeding mothers or in young children. Hence it is better to avoid its use in them.

ii. CoQ10 might interfere with blood pressure control during and after surgery; hence stop using CoQ10 at least 2 weeks before a scheduled surgery. It may increase the effects of medications used to lower BP; hence monitoring is advised.

iii. Because of CoenzymeQ10's potential hypoglycaemic effects, monitoring is advised when using adjunctively with prescription medications.

iv. Smoking can use-up the body's store of CoQ10.

v. CoQ10 has not been carefully tested in combination with chemotherapy to see if it is safe and effective.

Drug Interactions

i. Antihypertensive agents:

CoQ10 seems to decrease BP. Taking CoQ10 along with other antihypertensive agents may cause BP to go too low.

ii. Warfarin :

Warfarin is used to decrease blood clotting while CoQ10 might increase blood clotting; thus CoQ10 might decrease the effectiveness of warfarin and increase the risk of dangerous clots[59]. Potential interactions with warfarin causing decreased international normalised ratio (INR) has been reported in case studies. However, a prospective placebo controlled trial of 24 stable patients taking warfarin and 100 mg CoQ10 over four weeks found no changes

in prothrombin time and INR levels[60].

iii. Oral contraceptives:

These agents significantly decrease serum levels of CoQ10 and alpha-tocopherol, the most biologically active form of vit E[61]. This is the outcome of a cross-sectional study conducted on 55 pre-menopausal women with regular menstrual cycles.

iv. Cancer chemotherapy:

CoQ10 being an antioxidant, it might decrease the effectiveness of some medications used for cancer, but it is too early to pass a judgement. Several doxorubicin trials, mostly in animal models have workers observed a reduction in cardiac coenzyme Q10 depletion and cardiotoxicity associated with co-administration of coenyzmeQ10. The clinical implications on disease state and adverse reaction profile with coenzymeQ10 supplementation in depleted states requires further investigation.

v. Statins:

Statin drugs or HMG-CoA reductase inhibitors which are used to lower cholesterol, may interfere with the body's production of CoQ10. A recent cross-over trial found no significant coenymze Q10 drop after initiation of selected statins[62].

vi. Tricyclic antidepressants:

Including amitryptyline, doxepin, and imipramine can lower the levels of CoQ10 in the body.

vii. Red yeast :

Red yeast might reduce CoQ10 levels. However, there are no known interactions with foods.

Dosage and standardisation

The majority of coenzyme Q10 products are symthesised in Japan. It is available in various formulations. This exhibits variation in bioavailability, bioequivalence, and dosage consistency[63].

Current status

CoQ10 has been used, recommended, or studied for numerous clinical conditions, but remains controversial as a treatment in many areas. It is a safe but expensive supplement with preliminary benefit in Parkinson's disease and mitochondrial cytopathies, and inconsistent results in cardiovascular disease requiring further multi-centric research evaluations.

References

1. Tran MT, Mitchell TM, Kennedy DT *et al.* Role of Coenzyme Q10 in chronic heart failure, angina, and hypertension. *Pharmacotherapy* 2001; 21: 797-808.
2. Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. *Biochimica et Biophysica Acta* 1995; 1271 (1): 195-204.
3. Dutton PL Ohnishi T, Darrouzet E e*t al.* Coenzyme Q oxidation reduction reactions in mitochondrial electron transport. In Kagan VE; Quinn PJ. Coenzyme Q: Molecular mechanisms in health and disease. Boca Raton: CRC Press. 2000; pp. 65-82.
4. Bonakdar RA, Guarneri E. Coenzyme Q10. *American Fam Physician* 2005; 72 (6): 1065-70.
5. Crane F, Hatefi Y, Lester R e*t al.* Isolation of a quinone from beef heart mitochondria. *Biochimica et Biophysica Acta* 1957; 25(1): 220-21.
6. Igor P, Katja Z, Janko Z. Coenzyme Q10 contents in foods and fortification strategies. *Critical Reviews in Food Science and Nutrition* 2010; 50 (4): 269-80.
7. Tran UC, Clarke CF. Endogenous synthesis of Coenzyme Q in Eukaryotes. *Mitochondrion* 2007; 7: S62-71.
8. Bentinger M, Tekle M, Dallner G. Coenzyme Q- biosynthesis and functions. Biochem. *Biophys Res Commun* 2010; 396(1): 74-79.
9. Okamoto T, Matsuya T, Fukunaga Y e*t al.* Human serum ubiquinol-10 levels and relationship to serum lipids. Int. J Vitamin, Nutrition Res. Internationale Zeitschrift fur Vitamin-und Ernahrungsforschung. *Journal International de vitaminologie et de nutrition* 1989; 59(3): 288-92.
10. Aberg F, Appelkvist EL, Dallner G e*t al.* Distribution and redox state of ubiquinones in rat and human tissues. *Archives of Biochemistry and Biophysics* 1992; 295(2):230-34.
11. Sugiyama S, Kitazawa M, Ozawa T *et al.* Antioxidative effect of Coenzyme Q10. *Experentia* 1980; 36: 1002-03.
12. Ochiai A, Itagaki S, Kurokawa T e*t al.* Improvement in intestinal coenzyme Q10 absorption by food intake. *Yakugaku Zasshi* 2007;127(8):1251-54.
13. Bhagavan H N, Chopra RK. Coenzyme Q10: Absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radical Research* 2006; 40(5): 445-53.
14. Joshi SS, Sawant SV, Shedge A e*t al.* Comparative bioavailability of two novel coenzyme Q10 preparations in humans. *Int J Clin Pharmacol Ther* 2003; 41(1):42-48.
15. Westesen K, Siekmann B. Particles with modified physicochemical properties, their preparation and uses. US6197349. 2001.
16. Ohashi H, Takami T, Koyama N e*t al.* Aqueous solution containing Ubidecarenone. US4483873.1984
17. Zmitek J, Smidovnik A, Fir M e*t al.* Relative bioavailability of two forms of a novel water-soluble CoenzymeQ10. *Ann Nutri Metabol* 2008; 52(4): 281-87.
18. Kagan, D, Madhavi D. A study on the bioavailability of a novel sustained-release Coenzyme Q10-ß-Cyclodextrin Complex. *Integrative Medicine* 2010;9(1): 20-24.
19. Tomono Y, Hasegawa J, Seki T e*t al.* Pharmacokinetic study of deuterium-labelled coenzyme Q10 in man. *Int J Clin Pharmacol Ther Toxicol* 1986;24(10): 536-41.
20. Montero R, Sanchez-Alcazar JA, Briones P e*t al.* Analysis of coenzyme Q10 in muscle and fibroblasts for the diagnosis of CoQ10 deficiency syndromes. *Clin Biochem* 2008;41(9): 697-700.
21. Kishi T, Watanabe T, Folkers K. Bioenergitics in clinical medicine XV. Inhibition of coenzyme Q10- enzymes by clinically used adrenergic blockers of beta-receptors. *Research Communications in Chemical Pathology and Pharmacology* 1977; 17(1): 157-64.
22. Mortensen SA, Leth A, Agner E e*t al.* Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase

inhibitors. *Molecular Aspects of Medicine* 1997; 18:S137-44.

23. Ghirlands G, Oradei A, Manto A e*t al.* Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. *J Clin Pharmacol* 1993; 33(3): 226-29.
24. Chan A, Reichmann H, Kogel A *et al.* Metabolic Changes in patients with mitochondrial myopathies and effects of coenzyme Q10 therapy. *J Neurol* 1998; 245: 681-5.
25. Chen RS, Huang CC, Chu NS. Coenzyme Q10 treatment in mitochondrial encepha-lopathies: short term double-blind, crossover study. *Eur Neurol* 1997; 37: 212-8.
26. Bresolin N, Doriguzzic, Ponzetto C *et al.* Ubidecarenone in the treatment of mitochondrial myopathies: a multicenter double-blind trial. *J Neurol Sci* 1990; 100: 70-8.
27. Folkers K, Vadhanavikit S, Mortensen SA. Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. *Proc Natl Acad Sci USA* 1985; 82: 901-04.
28. Khatta M, Alexander BS, Krichten CM e*t al.* The effect of coenzyme Q10 in patients with congestive heart failure. 2000; 132(8):636-40.
29. Singh U, Devaraj S, Jialal I. Coenzyme Q10 supplementation and heart failure. 2007; 65(6): 286-93.
30. Jeejeebhoy F, Keith M, Freeman M e*t al.* Nutritional supplementation with MyoVive repletes essential cardiac myocyte nutrients and reduces left ventricular size in patients with left ventricular dysfunction. *Am Heart J* 2002; 143: 1092-100.
31. Judy WV, Stogsdill WVV, Folkers K. Myocardial preservation by therapy with Coenzyme Q10 during heart surgery. *Clin Investing* 1993; 71 (8 Suppl): S155-61.
32. Rosenfeldt FL, Haas SJ, Krum H e*t al.* Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials. *J Human Hyperten* 2007; 21(4): 297-306.
33. Huntington Study Group. A randomized placebo-controlled trial of Coenzyme Q10 and remacemide in Huntington's disease. *Neurology* 2001; 57: 397-404.
34. Rozen TD, Oshinsky ML, Gebeline CA *et al.* Open label trial of coenzyme Q10 as a migraine preventive. *Cephalalgia* 2002; 22(2): 137-41.
35. Sandor PS, Di Clemente L, Coppola G e*t al.* Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology* 2005; 64(4): 713-15.
36. Shults CW, Oakes D, kieburtz K *et al.* Effects of Coenzyme Q10 in early Parkinson disease : Evidence of slowing of the functional decline. *Arch Neurol* 2002; 59: 1541-50.
37. Shults CW, Therapeutic role of coenzyme Q(10) in Parkinson's desease. *Pharmacol Ther* 2005; 107(1): 120-30.
38. Nakamura R, Littarru GP, Folkers K e*t al.* Study of CoQ10-Enzymes in gingiva from patients with periodontal disease and evidence for a deficiency of Coenzyme Q10. *Proc Natl Acad Sci USA*. 1974; 71(4): 1456-60.
39. Littarru GP, Nakamura R, Ho L e*t al.* Deficiency of Coenzyme Q10 in gingival tissue from patients with periodontal disease. *Proc Natl Acad Sci USA* 1971; 68(10): 2332-35.
40. McRee JT, Hanioka T, Shizukuishi S e*t al.* Therapy with coenzyme Q10 for patients with periodontal disease. *J Dent Health* 1993; 43(5): 659-66.
41. Witztum JL. The oxidation hypothesis of atherosclerosis. *Lancet* 1994; 344(8925): 793-95.
42. Parthasarathy S, Steinberg D, Witztum JL, The role of oxidized low-density lipoproteins in the pathogenesis of atherosclerosis. *Annual Review of Medicine* 1992; 43: 219-25.
43. Singh RB, Neki NS, Kartikey K *et al.* Effect of Coenzyme Q10 on risk of atherosclerosis in patients with recent myocardial infarction. *Mol Cell Biochem* 2003; 246: 75-82.
44. Kuettner A, Pieper A, Koch J *et al.* Influence of Coenzyme Q10 and cerivastatin on the flow-mediated vasodilatation of the brachial artery: results of the ENDOTACT study. *Int J Cardiol* 2005; 98: 413-19.
45. Damian MS, Ellenberg D, Gildemeister R e*t al.* Coenzyme Q10 combined with mild hypothermia after cardiac arrest: A preliminary study. *Circulation* 2004; 110(19): 3011-16.
46. Heller FR, Descamps O, Hondekjin JC. LDL oxidation: therapeutic perspectives. *Atherosclerosis* 1998; 137: S25-31.
47. Sakano K, Takahashi M, Kitano M e*t al.* Suppression of azoxymethane-induced colonic premalignant lesion formation by coenzyme Q10 in rats. *Asian Pacific Journal of Cancer Prevention* 2006; 7(4): 599-603.
48. Koryagin AS, Krylova EV, Luk'yanova LD. Effect of ubiquinone-10 on the blood system in rats exposed to radiation. *Bulletin of Experimental Biology and Medicine* 2002; 133(6): 562-64.
49. Mizuno K, Tanaka M e*t al.* Antifatigue effects of coenzyme Q10 during physical fatigue. *Nutrition* 2008; 24(4): 293-99.
50. Yubero-Serrano EM, Gonzalez-Guardia L e*t al.* Mediterranean diet supplemented with coenzyme Q10 modifies the expression of proinflammatory and endoplasmic reticulum stress-related genes in elderly men and women. *J Gerontol A Biol Sci Med Sci* 2012.
51. Hodgson JM, Watts GF, Playford DA e*t al.* Coenzyme Q(10) improves blood pressure and glycaemic control: a Controlled trial in subjects with type 2 diabetes. *Eur J Clin Nutr* 2002; 56: 1137-42.
52. Henriksen JE, Andersen CB, Hother-Nielsen O *et al.* impact of ubiquinone (Coenzyme Q10) treatment on glycemic control, insulin requirement and well being in patient with type 1 diabetes mellitus. *Diabet Med* 1999; 16: 312-18.
53. Caso G, Kelly P, McNurlan MA e*t al.* Effect of coenzyme Q10 on myopathyic symptoms in patients treated with statins. *Am J Cardiol* 2007; 99(10): 1409-12.
54. Diaz-Castro J, Guisado R e*t al.* Coenzyme Q(10) supplementation ameliorates inflammatory signaling and oxidative stress associated with strenuous exercise. *Eur J Nutr* 2011; 123: 6.
55. Teran E, Hernandez I e*t al.* Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. *Int J Gynaecol Obstet* 2009; 105(1): 43-5.
56. Quiles J, Ochoa JJ, Huertas JR e*t al.* Coenzyme Q supplementation protects from age-related DNA double-strand breaks and increases lifespan in rats fed on a PUFA-rich diet. *Experimental Gerontology* 2004; 39(2): 189-94.
57. Coles L, Harris S. Coenzyme Q10 and lifespan extension. *Advances in Anti-Aging Medicine* 1996; 1(1): 205-15.
58. Fuke C, KriKorian SA, Couris RR, Coenzyme Q10: a review of essential functions and clinical trials. *US Pharmacist* 2000; 25: 28-41.
59. Spigset O. Reduced effect of warfarin caused by ubidecarenone. *Lancet* 1994;344:1372-73.
60. Engelsen J, Nielsen JD, Hansen KF *et al.* Effect of coenzyme Q10 and ginkgo biloba on warfarin dosage in patients on long-term warfarin treatment. A randomized, double-blind, placebo-controlled cross-over trial (Danish). *Ugeskr Laeger* 2003; 165: 1868-71.
61. Palan PR, Magneson AT e*t al.* Effects of menstrual cycle and oral contraceptive use on serum levels of lipid-soluble antioxidants. *Am J Obstet Gynecol* 2006; 194(5): e35-38.
62. Bleske BE, Willis RA, Antohny M e*t al.* The effect of pravastatin and atorvastatin on coenzyme Q10. *Am Heart J* 2001; 143: E2.
63. Weis M, Mortensen SA, Rassing MR *et al.* Bioavailability of four oral coenzyme Q10 formulations in healthy volunteers. *Mol Aspects Med* 1994; (15suppl): S273-80.

REVIEW ARTICLE

JIACM 2013; 14(1): 46-9

Corrosive poisoining: No calm after the storm

Ashish Gautam, Upendra Nath Gupta*, Subhash Chandra*, Balvir Singh***

Abstract

Accidental, suicidal, or by any other means, ingestion of a corrosive even in a small amount can make the life of the victim miserable. Corrosive poisoning in acute phase is troublesome to manage and more frustrating is the failure to check the development of long-term complications by any means. Excessive use of chemicals with corrosive potential in home appliances like batteries, dish washers, toilet cleaners make them easily available for poisoning. Aspiration pneumonitis, mediastinitis, perforation are the leading cause of death in such cases. Endoscopic grading of the extent of injury and development of better and effective guidelines for management in acute phase reduced the mortality rate but not the long-term complications like stricture and malignancy. Endoscopic interventions like frequent oesophageal dilatation, stenting, etc. can reduce the strictures, still extensive surgeries are needed frequently to correct the complications.

Key words: Corrosive poisoning, oesophageal stricture, endoscopic stricture dilatation.

Introduction

Ingestion of a substance that causes a chemical reaction with mucosal tissue and injures the gastrointestinal and respiratory tract is corrosive poisoning. It is worst amongst all poisonings as it causes prolonged morbidity and severe long-term complications which make a victim's life miserable. The commonly involved corrosives are available at home and most incidences are associated with toilet cleaners. Examples of common available home use corrosives are mentioned in table 1.

Table 1: Common home use corrosives.

Acids		Alkalies	
Sulphuric acid	Car batteries	Sodium hypochlorite	Disinfectant (bleach)
Nitric acid	Metal cleaners	Sodium hydroxide	Laundry detergent
Hydrochloric acid	De scalers	Sodium carbonate	Dish washing agent
Hydrofluoric acid	Rust remover	Sodium phosphate	Dish washing agent
Oxalic acid	Rust remover		
Phenol	Disinfectant		

Epidemiology

Most (80%) of unintentional poisoning occurs in < 5 years old children [1]. The mean age is 27 years (range 16 - 60 years)[2,3]. Development of effective guidelines has reduced the short-term mortality rate from 20% to less than 1% in the past 30 years. Still the long-term morbidity is nearly same due to failure of all measures to prevent complications. Adults have more mortality and morbidity rates due to significant volumes of exposure and possible co-ingestion. Aspiration pneumonitis, mediastinitis, peritonitis, and multi-organ failure (MOF) are the leading cause of death. 12.9% of all cases expire due to any of above complications[5].

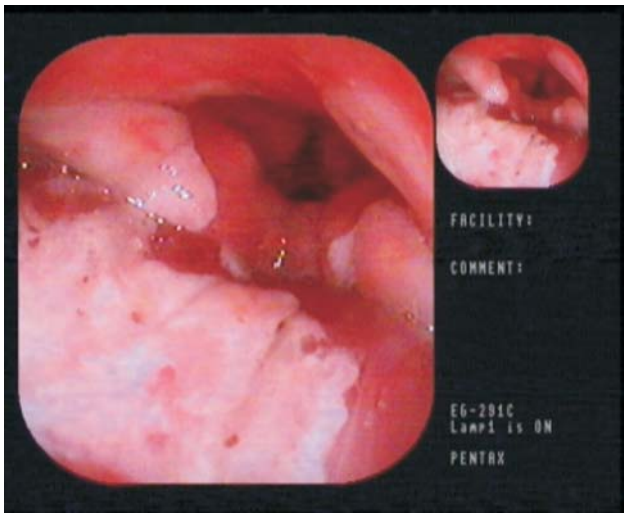


Fig. 1: *UGIE picture of corrosive poisioning.*

Pathology

The maximum corrosive potential depends on the pH of substance, i.e., pH < 2 or > 11, its concentration and duration of mucosal exposure[3]. Alkalies are potent solvents of lipoproteins and immediately damage the cell membrane by producing liquefactive necrosis of tissue thus rapidly penetrating into deeper tissue[6]. Thrombosis

**** Lecturer, **Associate Professor, P.G. Department of Medicine, S.N. Medical College, Agra - 282 002, Uttar Pradesh.***

of vessels further aggravates necrosis. Maximum damage occurs at 5 - 7 days.

Acidic corrosives produce relatively less damage than alkalis. Acidic corrosives cause coagulation of proteins and form precipitated protein (Eschar) layer[3]. Eschar prevents deep tissue damage and limits injuries. A second opinion for the above fact is that acids produce intense pain in the mouth at ingestion, so the corrosive is immediately expelled out, whereas alkalis are tasteless and odourless, thus a good amount is ingested before protective reflex is evoked. With acidic corrosives, most severe injuries develop at 3 - 4 days.

After oesophagus gastric antrum is usually most severely affected. Presence of food and water in stomach limits injuries. Long-term complications are same for both acids and alkalies.

Clinical features

1. **Early post-ingestion period**

   Symptoms depends on grade of injury. Persistent salivation with blood content, odynophagia, vomiting, burning and tearing pain in throat, mid-chest and epigastrium are common presentations[7]. Hoarseness of voice, dysphonia and stridor indicates larynx and upper respiratory tract involvement[8]. Examination may show oedematous lips with exudates and sloughed mucosa of oral cavity and pharynx. Teeth appear chalky white. 20 - 45% patients have mild erythema or minimal signs, but may have severe injuries in oesophagus and stomach. Presence of shock, large volume haematemesis, peritonitis, Hamman's sign, and subcutaneous emphysema suggest severe injuries or perforation, and require urgent surgical intervention[9].

   Other systemic manifestations:

   a. Metabolic acidosis.
   b. Methaemoglobinaemia in phenol poisoning.
   c. Haemolysis and hyperkalaemia.
   d. Pulmonary oedema and ARDS due to inhalation of fumes.

2. **Late post-ingestion period**

   Most patients with Zargar's grade 1 or 2 injuries gradually improve with resolution of burning but pain decreases more slowly and later persists on deglutition of solids only. Intermittent vomiting of undigested food indicates initiation of stricture formation.

3. **Weeks to months after**

   Globus sensation, early satiety, vomiting of undigested food, and weight loss suggest significant oesophageal stricture which actually develops in 1/3rd of corrosive poisoning patients commonly with grade 2(b) or 3 injuries[5]. Digested food in vomitus few hours after meals is due to gastric outlet obstruction.

4. **Decades after**

   Oesophageal carcinoma[3,4] (squamous cell).

Diagnostic evaluation

An upright chest and abdominal x-ray is mandatory for all patients. Oral water soluble contrast x-ray may be more helpful for suspected perforation. If general condition permits, water soluble contrast-enhanced CT scan of thorax and abdomen for suspected pneumomediastinum, pneumothorax, or pneumoperitonium is the most sensitive investigation.

Extent of injury is better ascertained with oesophago-gastroduodenoscopy (EGD)[6,12,13]. 40 - 80% of patients with corrosive injury do not show any injury or grade 1 or 2(a) injuries at EGD, and do not require aggressive treatment[5]. Most studies recommend EGD with flexible endoscope between 24 - 48 hrs or may be delayed up to 72 hours if condition is clinically stable. Besides this, EGD helps to explain the prognosis and guide further management. Mitani *et al* explained the utility of endoscopic ultrasound to provide a more accurate determination of depth of injury[10,11].

Zargar's grading of corrosive poisoining[5]

Zargar graded the corrosive injury of upper gastrointestinal tract on the basis of EGD findings. He advised diagnostic EGD between 24 to 48 hours to assess extent of damage if patient is stable. EGD is contraindicated if perforation is suspected on clinical grounds.

Grade 1	:	Erythema and oedema
Grade 2 (a)	:	Haemorrhage, erosion, blister, focal ulcer, exudates
Grade 2 (b)	:	Circumferential or deep ulcers.
Grade 3	:	Multiple deep ulcers with brown black or grey discolouration.
Grade 4	:	Perforation.

Management

Conservative treatment with management of ABC should be started promptly for all patients with hypotension or

respiratory distress. The immediate goal of treatment is to prevent perforation and reduce damage. Long-term target is to prevent and limit fibrosis and stricture. Presence of stridor, haematemesis, and respiratory distress or arterial blood gas abnormality indicates aspiration pneumonitis and mandates urgent flexible laryngoscopy. Patients with swollen, inflamed, engorged or necrotic laryngopharynx should not undergo endotracheal (ET) intubation; rather, tracheostomy is preferred and shows good outcomes. ET tube can be placed for mild erythema or erosion of larynx.

Neutralisation of acids by weak alkali or *vice versa* produces heat by exothermic reaction and adds to the injury, so is not recommended[14]. Avoid emesis or nasogastric tube placement to prevent re-exposure of oesophagus and aspiration[3]; use metoclopramide. Although nasogastric tube should be placed as soon as patient gets stabilised and no risk of perforation is present. Use of activated charcoal, carbonated drink, milk, butter do not have any benefit, also may obscure the endoscopic view. Dilution with plain water is worthwhile. Promote drinking water if there is no risk of aspiration and no evidence of perforation.

Presence of shock indicates massive gastrointestinal bleeding or perforation and calls for urgent surgical intervention. As emergency surgery has high mortality and morbidity, a pre-surgical endoscopic and/or contrast CT of neck, thorax and abdomen is mandatory to identify ideal timing and patient who can be benefited with surgery. Oesophagectomy or gastrectomies are the usual surgical procedures done[9]. Intravenous fluids to maintain hydration are initiated. Sucralfate in the dose of 1 gm 6 hourly is started. Intravenous proton pump inhibitor (PPI) or H_2-blocker is initiated to increase gastric pH and minimise the effect of gastric acid on the damaged mucosa. An average patient with grade 2(b) injury takes 10 - 15 days for symptomatic relief.

Antibiotics

Use of systemic antibiotics is not recommended, but patients with tracheo-laryngitis, intubated patients, or patients with tracheostomy need prophylaxis for pneumonia prevention. Use of antibiotics in other patients is individualised[15,16].

Steroids

Use of steroids is controversial. Animal studies with alkali injury with use of systemic steroids started within 24 hours of exposure shows reduced rate of oesophageal stricture formation by inhibiting granulation and fibroblast activity. A prospective randomised controlled trial in children by Anderson *et al* for both acids and alkalies did not show any prevention of stricture with steroids[18]. Use of local injection of steroids proved to be beneficial in some studies[17].

Clinically stable asymptomatic patients, and patients with grade 1 or grade 2(a) injuries, can be sent back home with liquid feeds and sucralfate for 3 - 5 days. A follow-up endoscopy is advised after 4 weeks to rule-out any stricture formation.

Treatment of late complications

1. **Stricture of oesophagus**

   A conservatively treated patient with grade 2(b) or 3 injuries develops oesophageal stricture from 2 weeks to months later. In a stable patient with visible oesophageal injury but spared stomach, an early placement of nasogastric tube is a must to avoid complete oesophageal stricture. Later repeated oesophageal dilatation[19] or placement of oesophageal stent[14] is helpful to maintain patency of oesophagus and re-institution of near-normal feeding.

2. **Gastric outlet obstruction**

   Antral and pyloric stricture manifests at 1 to 6 weeks[15]. An injured stomach calls for early endoscopic intervention, i.e., placement of nasojejunal tube. Gastric antrum is the most frequent part affected by corrosives. An early placement of nasogastrojejunal tube helps to maintain feeding in the patient. Injury up to such extent usually requires major surgical repair of strictures of upper gastrointestinal tract in future. Nasogastrojejunal tube this way helps to maintain patency of oesophagus and continued feeding which keeps the patient physically fit for surgery.

3. **Development of oesophgeal malignancy**

   Oesophageal squamous cell carcinoma is reported to develop after alkali injury usually after 40 years with approximate risk 1,000 times. Yearly endoscopic surveillance beginning 20 years after caustic oesophageal injury is recommended.

Oral findings

Patients with normal or grade 1 injuries can be started feeds in a day or so. Other patients should be started with liquid feeds as soon as the symptoms subside.

Conclusion

An early decision of treatment plan is rewarding in

corrosive poisoning. After managing ABC, i.e., airway, breathing, and circulation, an EGD is most helpful to deliver appropriate treatment. Placement of nasogastric or nasogastrojejunal tube not only helps to maintain feeding but also aids in managing complications like strictures. The decision to post a suitable patient for urgent surgery is a must as it could be life-saving. Follow-up EGD is recommended to exclude development of oesophageal malignancy.

References

1. Watson WA, Litovitz TL, Rodgers Jr GC e*t al.* 2002 annual report of the American Association of Poison Control Centres Toxic Exposure Surveillance System. *Am J Emerg Med* 2003; 21: 353-421.
2. Dilawari JB, Sing S, Rao PN e*t al.* Corrosive acid ingestion in man: a clinical and endoscopic study. *Gut* 1984; 25: 183-7.
3. Trowers E, Thomas C Jr, Silverstein FE. Chemical- and radiation-induced esophageal injury. *Gastrointest Endosc Clin N Am* 1994; 4: 657.
4. Isolauri J, Markkula H. Lye ingestion and carcinoma of the esophagus. *Acta Chir Scand* 1989; 155:269.
5. Zargar SA, Kochhar R, Nagi B *et al*. Ingestion of strong corrosive alkalis: spectrum of injury to upper gastrointestinal tract and natural history. *Am J Gastroenterol* 1992 Mar; 87(3): 337-41.
6. Christesen HB. Prediction of complications following caustic ingestion in adults. *Clin Otolaryngol Allied Sci* 1995; 20: 272.
7. Gaudreault P, Parent M, McQuigan MA e*t al*. Predictability of esophageal injury from signs and symptoms: A study of caustic ingestions in 378 children. *Pediatrics* 1983; 71: 767-70.
8. Lovejoy FH, Woolf AD: Corrosive ingestions. *Pediatr Rev* 1995; 16: 473-4.
9. Zhou JH, Jiang YG, Wang RW e*t al.* Management of corrosive esophageal burns in 149 cases. *J Thorac Cardiovasc Surg* 2005; 130: 449-55.
10. Kamijo Y, Kondo I, Soma K e*t al.* Alkaline esophagitis evaluated by endoscopic ultrasound. *J Toxicol Clin Toxicol* 2001; 39: 623.
11. Mitani M, Hirata K, Fukuda M, Kaneko M. Endoscopic ultrasonography in corrosive injury of the upper gastrointestinal tract by hydrochloric acid. *J Clin Ultrasound* 1996; 24: 40.
12. Poley JW, Steyerberg EW, Kuipers EJ e*t al.* Ingestion of acid and alkaline agents: Outcome and prognostic value of early upper endoscopy. *Gastrointest Endosc* 2004; 60: 372-7.
13. Bautista Casasnovas A, Estevez Martinez E, Varela Cives R e*t al.* A retrospective analysis of ingestion of caustic substances by children. Ten-year statistics in Galicia. *Eur J Pediatr* 1997; 156: 410-14.
14. Kirsh MM, Peterson A, Brown JW e*t al.* Treatment of caustic injuries of the esophagus. A ten-year experience. *Ann Surg* 1978; 188: 675-8.
15. Kikendall JW. Caustic ingestion injuries. *Gastroenterol Clin North Am* 1991; 20: 847-57.
16. Leape LL, Ashcraft KW, Carpelli DG e*t al.* Hazard to health: Liquid lye. *N Engl J Med* 1971; 284: 578-81.
17. Kochhar R, Sriram PV, Ray JD *et al*. Intralesional steroid injections for corrosive induced pyloric stenosis. *Endoscopy* 1998; 30: 734-6.
18. Anderson KD, Rouse TM, Randolph JG. A controlled trial of corticosteroids in children with corrosive injury of the esophagus. *N Engl J Med* 1990; 323: 637-40.
19. Broor SL, Raju GS, Bore PP e*t al.* Long-term results of endoscopic dilation for treatment of corrosive esophageal strictures. *Gut* 1993; 34: 1498-501.

REVIEW ARTICLE

JIACM 2013; 14(1): 50-6

Lung cancer – Where are we now?

Girija Nair, Aparna Iyer***

Abstract

Lung cancer is the leading cause of cancer deaths worldwide. Globally, the largest number of cancers detected are lung cancers – 1,350,000 new cases annually, i.e., 12.4% of total cancers diagnosed[1]. Despite the advent of newer diagnostic methods and advances in treatment and surgery, the prognosis remains dismal – with a 5-year survival rate of 15.6% in the United States and lower in other parts of the world. The epidemiology of lung cancer is undergoing a sea of change with an increasing incidence among women and in the developing countries. Also, as a result of better understanding of molecular genetics and its association with prognosis and treatment response, coupled with the advent of newer methods for detection of pre-invasive stages of the disease, the classification and treatment of lung cancer has changed dramatically over the past decade. This article aims at highlighting the changing nature of this very aggressive but preventable cancer and throw light on the latest developments in its diagnosis and treatment.

Key words: Lung cancer, bronchoscopy, newer therapies.

Introduction

Lung cancer is the leading cause of cancer deaths worldwide. Globally, the largest number of cancers detected are lung cancers – 1,350,000 new cases annually, i.e., 12.4% of total cancers diagnosed[1]. The single largest aetiological factor contributing to lung cancer remains smoking and ever since this causal relationship was established in 1950[2,3], the fight against tobacco smoke has been initiated by mankind. Although we have come a long way in detection and treatment of lung cancer, early detection of this disease still eludes us in most parts globally, leading to a dismal 5-year survival rate of 15.6% or less[1].

Epidemiology

The epidemiology of lung cancer has been undergoing a change in the last few decades. In the developed world, the incidence of lung cancer among men has shown a decreasing trend since the 1980s, and of late, its incidence in women too is on the decline. This lag has been attributed to the late peak noted in the proportion of women who were smokers. However increasing incidence is being noted in the developing world which contributes to around 50% of cases detected globally[1]. Histopathologically, although squamous and small-cell cancers are strongly associated with smoking and adenocarcinoma is commoner among 'never smokers', the use of filtered and low tar and nicotine containing cigarettes has led to greater distribution of smoke in the peripheral airways, leading to an increase in adenocarcinoma which is now the leading type of cancer detected globally. Other causes of lung cancer include environmental exposure to radon, pollution, second-hand tobacco smoke, pre-existing lung pathologies, and minerals like asbestos and metalloid elements like arsenic.

In India, tobacco use is prevalent both in chewed and smoked form. Local forms of inhaled tobacco including use of *beedi* and *hukkah* are commonplace. Around 63,000 new cancer cases are being diagnosed annually in India, although the age-standardised rate among males (7.4/100,000) and females (1.8/100,000) is lower than global figures[4]. Regional figures show that lung cancer is the leading cause of death in Mumbai, Bhopal, Chennai, Delhi, and Kolkata[5]. Highest incidence was noted in the north-eastern district of Aizwal[6]. The median age of detection is 54.6 years in males and 52.8 in females. Incidence among males remains higher, (M:F ratio 5.76-6.67). Beedi smoking has been associated with a higher risk of development of cancer as compared to cigarette, due to lack of filters and higher tar content[4,5]. Squamous cell type is the commonest variety detected in India in contrast to global figures. However, the incidence of adenocarcinoma has shown an increasing trend in the past decade. Most cancers were diagnosed at advanced stages with 51.8% showing metastasis to other parts when diagnosed[5].

Pathology

Historically, the 4 major histological types of lung cancer recognised were squamous cell, adenocarcinoma, large-cell and small-cell types. The classification of lung cancers has been modified and the recommendations by the International Association for the Study of Lung Cancer (IASLC) are now to be used for staging tumours (Table I). This staging evaluated the impact of single and multiple ipsilateral satellite nodules on survival, and reclassified them into T_3 and T_4 rather than M_1. Also, malignant pleural effusions and contralateral nodules have been included in a new stage M_{1a} with distant metastasis forming a separate substage M_{1b}[7].

**** Professor and Head, Department of Pulmonary Medicine, ** Assistant Professor, Department of Pulmonary Medicine, Dr. D.Y. Patil Hospital and Research Institute, Nerul, Navi Mumbai, Maharashtra.***

Table I: Lung cancer staging system. T staging parameters.

Tumour and sub-group[a]	Definition
T (primary tumour)	
T0	No primary tumour
T1	Tumour $\leq$ 3 cm[b] surrounded by lung or visceral pleura, not more proximal than the lobar bronchus
T1a	Tumour $\leq$ 2 cm[b]
T1b	Tumour $\geq$ 2 but $\leq$ 3 cm[b]
T2	Tumour > 3 but $\leq$ 7 cm[b] or tumour with any of the following[c] invades visceral pleura, involves main bronchus $\geq$ 2 cm distal to carnia, atelectasis/obstructive pneumonia extending to hilum but not involving the entire lung
T2a	Tumour > 3 cm but $\leq$ 5cm[b]
T2b	Tumour > 5 cm but $\leq$ 7 cm[b]
T3	
$T3_{>7}$	Tumour > 7 cm[b]
$T3_{Inv}$	Directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium
$T3_{Centr}$	Tumour in the main bronchus < 2 cm distal to the carina[d] or atelectasis/obstructive pneumonitis of entire lung
$T3_{Satell}$	Separate tumour nodule(s) in the same lobe
T4	
$T4_{Inv}$	Tumour of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, or carina
$T4_{Ipsi\ Nod}$	Separate tumour nodule(s) in a different ipsilateral lobe
N (regional lymph nodes)	
N0	No region node metastasis
N1	Metastasis in ipsilateral peribronchial or perihilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene, or supraclavicular lymph node(s)
M (distant metastasis)	
M0	No distant metastasis
M1a	
M1 $a_{Contr\ Nod}$	Separate tumour nodule(s) in a contralateral lobe
M1 $a_{Pl\ Dissem}$	Tumour with pleural nodules or malignant pleural dissemination[e]
M1 b	Distant metastasis
Special situations	
TX, NX	T or N status not able to be assessed
T_{is}	Focus of *in situ* cancer
T1[d]	
$T1_{ss}$	Superficial spreading tumour of any size but confined to the wall of the trachea or mainstem bronchus

[a] *These sub-group lables are not defined in the International Association for the Study of Lung Cancer publications[1-4] but are added for clarity.*

[b] *In greatest dimension.*

[c] *T2 tumours with these features are classified as T2a if less than or equal to 5 cm.*

[d] *The uncommon, superficial spreading tumour in central airways is classified as T1.*

[e] *Pleural effusions that are cytologically negative, nonbloody, transudative, and clinically judged not to be caused by cancer are excluded.*

To address the advances in oncology, molecular biology, pathology, and surgery of adenocarcinomas, a new multidisciplinary consensus classification has been proposed by the IASLC, ATS, and the ERS. This also addresses the issues of use of uniform terminology, approach to non resection biopsy specimens, and management of tissue specimens for molecular and immunohistochemical studies[8].

Highlights of the changes include the following:

1. The terms BAC (bronchoalveolar carcinoma) and mixed subtype adenocarcinomas are no longer used.
2. The terms adenocarcinoma in situ (AIS) and minimally invasive adenocarcinomas (MIA-invasion $\geq$ 5mm) have been introduced for resected specimens in order to identify patients, who, if treated with complete resection will have 100 to nearly 100% disease-free survival.
3. Invasive adenocarcinomas are classified by predominant pattern after comprehensive histological subtyping. This classification also applies to small biopsy specimens, as these form the bulk (70%) of present day diagnostic samples.
4. The use of the term non small-cell carcinomas (NSCLC) not otherwise specified should be minimised and tumours in advanced stages are to be further classified into squamous cell, adenocarcinomas for the following reasons:
    a) Adenocarcinomas and NSCLC of unspecified types should undergo testing for epidermal growth factor (EGFR) mutations as their presence predicts response to newer drugs like EGFR tyrosine kinase inhibitors.
    b) Adenocarcinomas have better outcome with premetrexed therapy as compared to squamous type.
    c) Potentially life-threatening haemorrhage may occur with use of bevacizumab (VEGF inhibitor) in squamous cell types.

If this is not possible with histology alone, use of immunohistochemistry markers such as thyroid transcription factor-1 (TTF-1) for adenocarcinomas, p63 for squamous type and additional stains such as mucin stains is advocated.

Early detection of lung cancer

The dismal survival rates noted in lung cancer are mainly due to the fact that lung cancers become symptomatic only in advanced stages and no effective screening tool is yet in place for detection of the same.The recently published National Lung Screening Study (NLST), a prospective, randomised controlled trial, has shown that screening with low-dose spiral computed tomography (CT) results in early stage detection and 20.3% reduction in mortality from lung cancer[9]. A few problems relating to the routine use of CT as a screening tool include high false-positive (95%) rates, over-diagnosis, resection of benign nodules, radiation exposure, and high costs.

Sputum cytology and X-ray have not been effective in reducing mortality rate and are not recommended as screening tools.

Pre-invasive lung cancer

Tobacco smoke causes changes in the respiratory epithelium and a progressive model with transition from metaplasia to dysplasia, carcinoma in situ, and finally invasive lung cancers, has been postulated[10].

Detection of these lesions may be done with the help of bronchoscopy.The conventional white light bronchoscope (WLB) has limited ability to pick up these lesions and this has led to development of the auto-fluorescence bronchoscope (AFB). Dysplastic lesions, CIS, and invasive carcinoma have different auto-fluorescence properties. When blue light from a helium-cadmium laser (at 442 nm) is used to illuminate the tissue, normal bronchial epithelium seems green, whereas abnormal areas in the bronchial epithelium seem reddish-brown on the monitor.

Studies have shown improvement in detection rates from about 50% to 73% in sensitivity for the WLB plus AFB group as compared to conventional methods.It is essential to obtain a biopsy from suspicious areas for confirmation of diagnosis.

Other markers for detecting pre-invasive changes include detection of mutations in the K-ras oncogene, p53 tumour suppressor gene, aneuploidy, and loss regions of DNA or loss of heterozygosity on chromosomes 3, 5, and 9[11].

Distinguishing these lesions is essential as mild and moderate dysplasias are rarely progressive; however, 50% of CIS lesions tend to progress to invasive cancers within 3 months of diagnosis[12].

Because severe dysplasia and CIS have to be treated with local therapy, several endobronchial therapies may be effective in treating these lesions while preserving lung function. These include:-

1. Photodynamic therapy (PDT) – Use of a photo-sensitiser with narrow-band width light resulting in tumour death in the presence of oxygen.

2. Brachytherapy – Placement of a radioactive source through the bronchoscope near or within the lesion.
3. Electrocautery – Uses high-frequency electrical current that generates heat to coagulate and vaporise tumour tissue.
4. Cryotherapy – Uses nitrous oxide-driven cryo-probes, and exerts its effects from selective cellular necrosis caused by tissue freezing and loss of vascular supply.

Advances in radiology of lung cancer

Imaging in lung cancer has made major advances in the last decade. Compared to chest radiography, computerised tomography leads to better and earlier detection of nodules in the chest.

CT FEATURES OF LUNG CANCER INCLUDE[13] (Fig. 1):-

a) Peripheral tumour – Mass lesion with spherical or oval configuration, solitary pulmonary nodule. Edges are usually irregular, may be spiculated, lobulated, or may show single or multiple parenchymal strands around the lesion (corona radiata).
b) Central lesion – Usually squamous cell or small-cell. The mass is usually accompanied by collapse or consolidation of the lung beyond the tumour. Effusions may also be noted in addition (Fig. 2).
c) Volume doubling time, i.e., a 25% increase in diameter within a period of 1 to 18 months is suggestive of malignant aetiology.

Apart from this, cavitation, eccentric or irregular calcification may be noted. Associated features like enlargement of lymph nodes, thickening of interstitium (lymphangitis), involvement of surrounding tissues and vascular structures should also be looked for.

CT can also prove useful in peripheral lesions wherein a diagnostic biopsy can be done under guidance.

VIRTUAL BRONCHOSCOPY: Uses 3-D reconstruction of CT images to provide images simulating those visualised during bronchoscopy.

ELECTROMAGNETIC NAVIGATION (EMN): Combines real-time three-dimensional CT images with virtual bronchoscopy and uses a locatable guide that has active steering capability to guide more readily and accurately to peripheral lung lesions.

PET-CT: Positron emission tomography using fluorodeoxyglucose as a marker of metabolic activity has evoked much interest. PET is a functional imaging test that detects hypermetabolism in cells. The tracer 18-FDG is a radio-labelled glucose analog that is selectively taken-up by metabolically active cells. The active lesions are detected as 'hot spots'[14].

Indications of PET in lung cancer:-

1. Diagnosis and characterisation of pulmonary nodules.
2. Staging of the mediastinum and detection of occult metastasis.
3. Assessing recurrence/response after therapy.

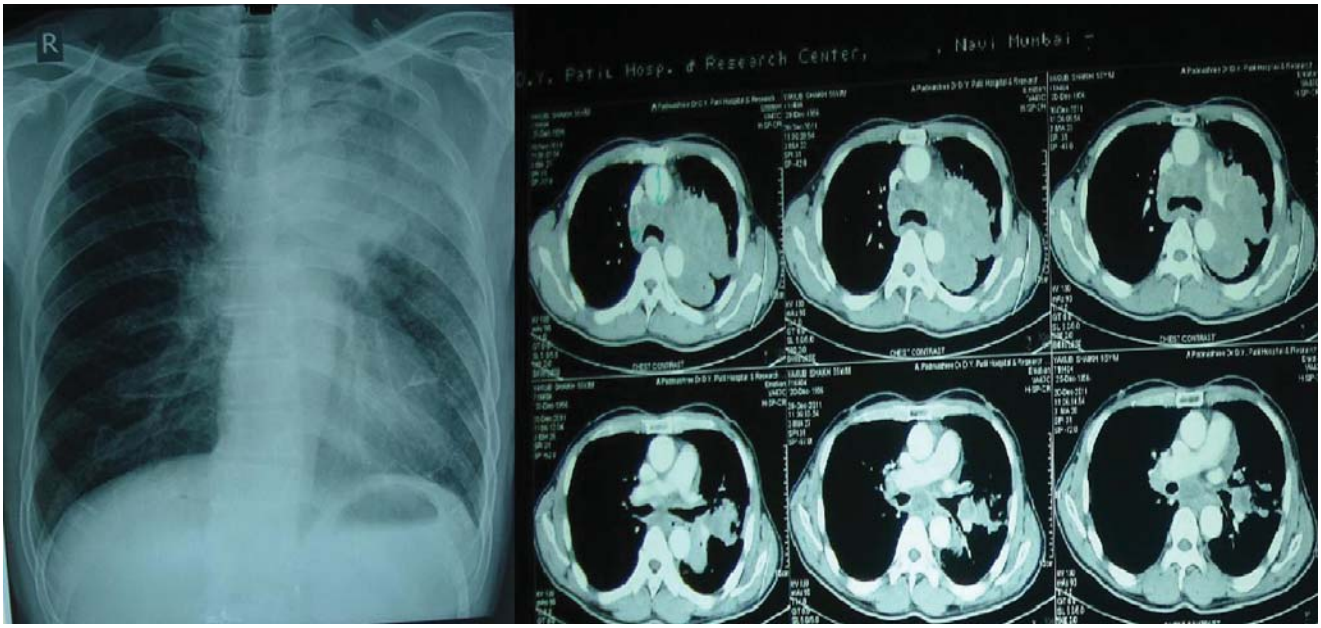


Fig. 1: *Chest X-ray and CT scan of a patient with bronchogenic (small-cell) carcinoma.*

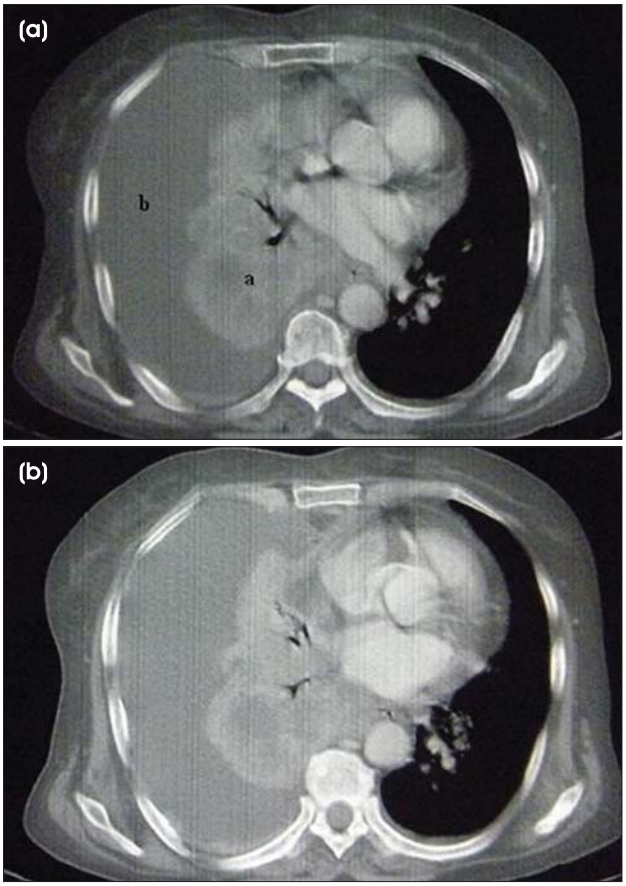


Fig. 2: *Large central tumour (a) with malignant pleural effusion (b) .*

Advantages:

1. Non invasive unlike thoracoscopy/mediastinoscopy.
2. More sensitive than CT for detection of mediastinal lymph nodes.
3. Helps in up-staging/down-staging lesions so as to decide appropriate treatment intervention(s).
4. Effective roadmap for further diagnostic and staging interventions. PET followed by mediastinoscopy resulted in fewer futile interventions than mediastinoscopy alone.

Disadvantages:

1. High cost.
2. May miss slow-growing tumours.
3. Inflammatory processes such as granulomas, infections, may produce false-positive results.

Integration of PET with CT (PET-CT) helps in precise localisation of the tissues and structures responsible for the increased uptake.

Advances in bronchoscopy

Use of the bronchoscope now forms a vital part in the diagnosis and management of lung cancer.

ROLE OF BRONCHOSCOPY IN LUNG CANCER:-

1. Diagnosis:
   a) Pre-invasive lesions: Detection of pre-cancerous and CIS lesions by narrow-band imaging, auto-fluorescence bronchoscope.
   b) Invasive lesions: Visualisation of endobronchial mass, mucosal irregularity, narrowing of bronchus followed by confirmation with biopsy (Fig. 3).
   c) Peripheral solitary nodules: Endobronchial ultrasound (EBUS) guided biopsy.
2. Staging:
   a) Extent of tumour and involvement of tracheo-bronchial tree.
   b) Transbronchial needle aspiration (TBNA) – both conventional and EBUS-guided – of mediastinal lymph nodes.
3. Therauputic:
   a) Pre-invasive lesions: Ablation/destruction by photodynamic therapy/cryotherapy/brachy-therapy.
   b) Palliative: Relieve airway obstruction due to tumours by:
      - Mechanical debulking with a rigid scope.
      - Use of the argon plasma coagulator (APC) probes, cryotherapy, electrocautery, brachy-therapy, lasers through flexible scope.
      - Achieving airway patency by any of the above methods followed by airway stenting with silicon, metal, or combined stents.

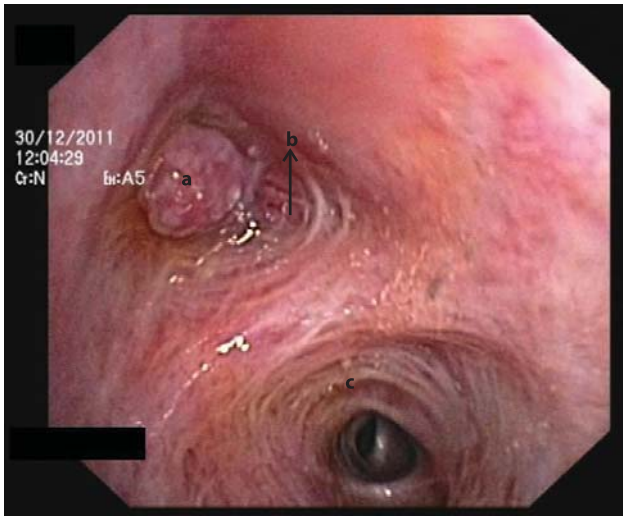


Fig. 3: *Bronchoscopic image of left upper lobe mass lesion. Biopsy of the mass revealed bronchogenic CA (small-cell). (a) Mass; (b) Left upper lobe bronchus; (c) Lingula.*

Advances in therauputics for non small-cell lung cancer

With the advances in understanding of the genetics of lung cancer and molecular biology and advent of targeted therapy, better options are now available for treatment of even advanced lung cancers[15].

1. Advances in chemotherapy:
   a) Bevacizumab – Anti-angiogenesis factor, monoclonal antibody to vascular endothelium derived growth factor (VEGF), causes tumour shrinkage.
   b) Pemetrexed – Anti-folate chemotherapy targeting multiple enzymes involved in folate metabolism, including thymidylate synthase.

   Predictive markers: Advances in immune-histochemistry have enabled detection of markers and mutations that predict response to cancer therapy. Some of these markers are:

   - Excision repair cross-complementing 1(ERCC1) gene – Higher levels detected by IHC or RT-PCR predict good prognosis, less aggressive tumour and better response to platinum-based chemotherapy.
   - Ribonucleotide reductase M1(RRM1) gene – Target for the chemotherapeutic drug gemcitabine. Higher levels predict good response to gemcitabine.
   - Breast cancer 1 (BRCA1) gene is a tumour suppressor gene. BRCA-1 is a potential predictive biomarker for chemotherapy, with decreased expression associated with cisplatin sensitivity, and increased expression predictive of benefit from taxanes.
   - Thymidylate synthase – Key enzyme in folate metabolism. It is a major target of several chemotherapies, including pemetrexed, and is currently being evaluated as a predictive biomarker of benefit in patients with non-squamous cell NSCLC.

2. Gene therapy:

   Gene therapy involves modification of the genetic make-up of cells. Delivery of genetic material can be accomplished through[16]:

   a) Vectors – Viruses, liposomes, polymers, molecular conjugates.
   b) Antisense therapy – Suppression of gene expression through delivery of targeted oligonucleotide sequences leading to reduced mRNA transcription. The material can be delivered intravenously or into the tumour – e.g., TGFâ (transforming growth factor â) suppression for NSCLC

Studies in lung cancer are ongoing and the following strategies are being studied:

a) Replacement of tumour suppressor genes like p53 and FUS1 that have lost their function due to mutations.
b) Vaccines – Killed tumor cells used for vaccination.
c) Immunotherapy – Established tumours have evolved many ways to evade or overwhelm the immune system, and thus some sort of exogenous stimulus is needed to enable the immune system to effectively eliminate tumour cells. Potential methods for the above include:-
   - Delivery of chemokines or cytokines into tumours
   - T-cell transfers
   - Blocking tumour-induced immunosupression

Gene therapy, if successful, can alter the natural course and improve the prognosis. However, the most efficacious, cost effective, and practical way to reduce lung cancer mortality is primary prevention by smoking cessation.

Discussion

Lung cancer, although a preventable disease, still contributes to the largest fraction of cancer deaths. Early detection and treatment is essential for improvement in survival rates. Changing trends in socio-economic conditions and increasing pool of smokers have led to an increased contribution to the cancer burden from developing countries. In India, high levels of air pollution in cities, widespread use of the 'chullah' as cooking fuel contribute to indoor and outdoor pollution leading to higher chances of developing lung cancer. Also indigenous forms of smoked tobacco such as bidi, hookah are commonplace.

Screening and therapeutics in lung cancer have shown remarkable progress in the past decade. Fibreoptic bronchoscopy is widely carried-out at many specialised centres in India. Biopsies of masses, transbronchial aspirations of lymph nodes can yield the diagnosis, and on distinguishing the cell type, the patient can be staged and sent for surgery when the tumour is resectable; else, chemotherapy can be instituted. Fibreoptic bronchoscopy also plays a vital role in diagnosis and treatment of early lesions and helps in palliation of progressive tumour-related airway narrowing. Newer chemotherapeutic drugs

available help in speedy regression of tumours especially those with good prognosis. Molecular diagnosis and immuno-histochemistry have in a big way contributed to understanding of lung cancer genetics and its role in predicting tumour progress, prognosis, and response to chemotherapy. The newer therapies like gene therapy and targeted chemotherapy hold promise for the future of lung cancer management.

Early diagnosis is the urgent need of the hour, and hence the pressing need to refer all suspected patients of lung cancer to centres where speedy diagnosis may be achieved, followed by prompt management so as to ensure better survival rates for this very aggressive cancer.

References

1. Jemal A, Bray F, Center MM *et al*. Global cancer statistics. *CA Cancer J Clin* 2011; 61(2): 69-90.
2. Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma; a study of 684 proved cases. *J Am Med Assoc* 1950; 143(4): 329-36.
3. U.S. Public Health Service, office of the Surgeon General: The health consequences of smoking. National Clearing House for Smoking Health; 1972.
4. Ganesh B, Sushma S, Monika S, Suvarna P. A case control study of risk factors for lung cancer in Mumbai, India. *Asian Pacific J Cancer Prev*. 12: 367- 2.
5. Behera D, Balmugesh T. Review article. Lung cancer in India. *Indian J Chest Dis Allied Sci* 2004; 46: 269-28.
6. National Cancer Registry Programme and World Health Organization. Development of an atlas of cancer in India "First All India report 2001-2002, Mapping patterns of cancer in India." Available at http://canceratlasindia.org/map.htm. Last accessed on 12/5/2012.
7. Goldstraw P, Crowley J. The International Association for the Study of Lung Cancer. International Staging Project on Lung Cancer. *J Thorac Oncol* 2006;1(4): 281-6.
8. Pathology of Lung Cancer. William D. Travis, MD. *Clin Chest Med* 32 (2011) 669-92.
9. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; 365: 395-409.
10. Auerbach O, Stout AP, Hammond EC *et al*. Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. *N Engl J Med* 1961; 265: 253-67.
11. Devereux TR, Taylor JA, Barrett JC. Molecular mechanisms of lung cancer. Interaction of environmental and genetic factors. *Chest* 1996; 109: 14S–9S.
12. Bota S, Auliac JB, Paris C *et al*. Follow-up of bronchial precancerous lesions and carcinoma in situ using fluorescence endoscopy. *Am J Respir Crit Care Med* 2001; 164: 1688-93.
13. Neoplasms of the lungs, airway and pleura. Peter Armstrong. Imaging of diseases of the chest. 3rd edition. Pg 306-315.
14. Chang C, Rashtian A, Gould MK. The Use and Misuse of Positron Emission Tomography in Lung Cancer Evaluation. *Clin Chest Med* 32 (2011); 749-62.
15. Gettinger S, Lynch T. A decade of advances in treatment for advanced non small cell lung cancer. *Clin Chest Med* 32 (2011); 839-51.
16. Vachani A, Moon E, Wakeam E *et al*. Gene therapy for lung neoplasms. *Clin Chest Med* 32 (2011); 865-8.

FORM IV (See Rule 8)

The following particulars regarding the ownership of the **'JOURNAL, INDIAN ACADEMY OF CLINICAL MEDICINE'** are published as called for by Rule 8 of the Registration of Newspaper (Central) 1956.

1.	Place of Publication	–	Barnala House, 867, Guru Gobind Singh Marg, New Delhi - 110 005.
2.	Periodicity of Publication	–	Quarterly
3.	Printer's Name	–	Dr. D. G. Jain
	Nationality	–	Indian
	Address	–	Barnala House, 867, Guru Gobind Singh Marg, New Delhi - 110 005.
4.	Publisher's Name	–	Dr. D. G. Jain
	Nationality	–	Indian
	Address	–	Barnala House, 867, Guru Gobind Singh Marg, New Delhi - 110 005.
5.	Editor's Name	–	Dr. D. G. Jain
	Nationality	–	Indian
	Address	–	Barnala House, 867, Guru Gobind Singh Marg, New Delhi - 110 005.

6. Name and address of individuals who own the newspaper and partners or shareholders holding more than one per cent of the total capital.
   – Indian Association of Clinical Medicine, Headquarters: Post-graduate Department of Medicine, Sarojini Naidu Medical College, Agra - 282 002 (U.P.)

I, Dr. D. G. Jain, hereby declare that the particulars given above are true to the best of my knowledge and belief.

Sd/-
Dr. D. G. Jain
Signature of Publisher

Date:
January 15, 2013

CASE REPORT

JIACM 2013; 14(1): 57-8

Warfarin thromboprophylaxis – a boon or bane?

B Gupta, K Guleria**, A Sharma***, S Jain****, NB Vaid******

Abstract

Warfarin given for prophylaxis in atrial fibrillation can prove-near fatal if not cautiously monitored.

Key words: Warfarin overdose, coagulopathy, atrial fibrillation.

Introduction

Atrial fibrillation (AF) is an independent risk factor for stroke – especially in elderly patients. Vitamin K antagonist warfarin, which is given for stroke prophylaxis in AF requires close monitoring and frequent dose adjustments[1]. Spontaneous bleeding is one of the well reported and most common adverse effect of warfarin which can be life-threatening[2]. We discuss a case in which warfarin prophylaxis proved nearly fatal.

Case report

A 43-year-old female, Mrs. T, P3L3, presented to the emergency in shock. She had severe pallor, pulse was feeble (150 beats per minute), brachial and peripheral pulses were not palpable. Blood pressure was not recordable, and respiratory rate was 35 per minute. On auscultation, heart rate was 100 beats per minute, irregularly irregular, with a mid-diastolic murmur and loud S1. Bilateral air entry was normal and there were no added sounds. There were multiple large ecchymotic patches on her hands, thighs, abdomen, and back – the largest measuring 12 x 15 cms. Although the rest of her systemic and abdominal examination was normal, per vaginum examination revealed 500 ml of clots in the vagina. Uterus was normal in size and there was a tender mass about 10 x 12 cm in the pouch of Douglas.

Immediate resuscitative measures were undertaken. A venous cut down was done and dopamine was started at 5µ/kg/minute. Arterial blood gas sample was taken which was normal. Crystalloids and colloids were infused to maintain blood volume and meanwhile blood was arranged.

History was taken from the relatives and previous records were reviewed. The patient was a known case of rheumatic heart disease with severe mitral stenosis with tricuspid regurgitation with pulmonary artery hypertension and atrial fibrillation. She was taking frusemide 40 mg BD, digoxin 0.25 mg OD 5/7 and atenolol 50mg OD. She had been started on warfarin 2 mg OD twenty days back, and since the INR was low the dose of warfarin was increased to 5 mg OD 10 days back. The patient had started heavy bleeding per vaginum after 5 days of increasing the dose. There was no history of bleeding from other sites, no h/o trauma, and no signs/symptoms suggestive of hypothyroidism, tuberculosis and lump in abdomen. Her previous menstural cycles were regular.

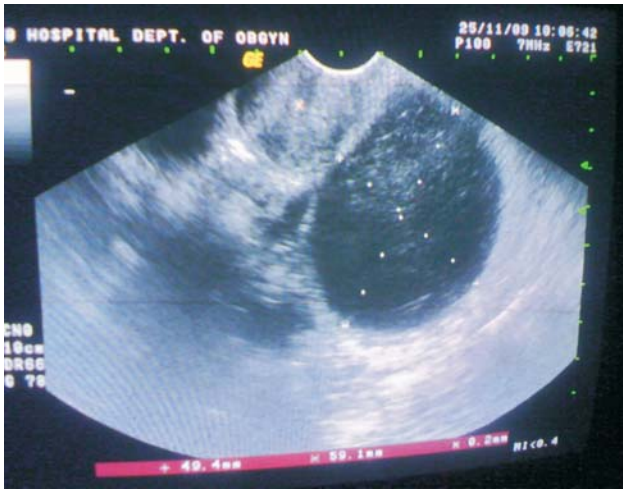


Fig. 1: *Pelvic haematoma seen on USG.*

Laboratory investigations revealed haemoglobin 5 gm%, platelet count 300,000, prothrombin time (PT) and activated partial thromboplastin time (APTT) were more than 2 minutes. ECG showed features suggestive of atrial fibrillation, and X-ray chest was normal. Ultrasound revealed a large pelvic haematoma (12x14 cms) in the pouch of Douglas and there was no free fluid in the abdomen. Rest of the investigations like liver function tests, kidney function tests were normal

**** Pool Officer, ** Professor, *** Specialist, **** Lecturer, ***** Director-Professor and Head of the Department of Obstetrics & Gynecology, University College of Medical Sciences (UCMS) & Guru Teg Bahadur (GTB) Hospital, Dilshad Garden, Shahdara, Delhi - 110 092.***

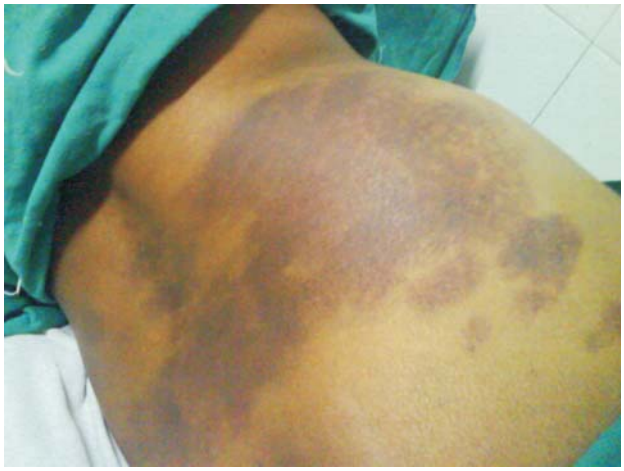


Fig. 2: *Ecchymotic patches on the back.*

Keeping a provisional diagnosis of warfarin overdose, she was given 7 packs of fresh frozen plasma (FFP) and 4 packs of red cell concentrate. Warfarin was stopped. She was given 3 doses of vitamin K, and antibiotics for infective endocarditis prophylaxis. She received intravenous tranexamic acid and oral progestogen (norethisterone 5 mg) to control per vaginum bleeding.

She was kept in the obstetric ICU for 48 hours. Her dopamine was slowly tapered and her cardiac drugs – except warfarin – were restarted. Her repeat PT and APTT were 19/14 and 37/30; INR 1.36. She was discharged after cardiac consultation after 21 days in a stable condition. After 6 months the patient had resumed her normal menses, was not started on warfarin, and the mass had regressed to 3 x 4 cms.

Discussion

It is estimated that at least 1% of people on warfarin experience serious bleeding and the mortality rate amongst warfarin-induced complications is 0.5%[3]. Warfarin is the most popular and widely used oral anticoagulant. It has a complex dose-response relationship and exerts its action by inhibiting vitamin K dependent coagulation factors (II, VII, IX, and X). It also inhibits the synthesis of natural anticoagulants in the blood, protein C and S. Due to the difference in the half life of "coagulation factors" and "anticoagulants", the coagulation system may be transiently biased towards clotting after starting warfarin. The target international normalised ratio (INR) is maintained around 2 - 3[4]. Hence it is important to gradually increase the dose, do the INR after 72 hours of initiation of therapy, repeat again after 72 hours before increasing the dose. Sudden increase in dose results in haemorrhagic complications as in our case.

Various factors determine the bleeding complications of Warfarin. These include older age, dose, and duration of therapy, drug interaction, and occult diseases[4]. Expected net clinical benefit of warfarin therapy is highest among patients with the highest untreated risk for stroke, which includes the oldest age category[5].

For patients with an elevated international normalised ratio (INR) with mild or no bleeding, withhold the warfarin and recheck INR in 1 to 2 days; if INR > 5, add oral vitamin K supplementation. For major bleeding and elevated INR, hospital admission, vitamin K, fresh frozen plasma, and frequent monitoring are needed. Emergent situations call for hospitalisation, clotting factor replacement, and vitamin K administered by slow intravenous infusion[6]. A similar management was carried out in the present case.

Various studies have been done to reduce this dreaded complication. An increased thrombomodulin level is a marker for haemorrhagic complications[7]. A newer agent like ximelagatran, the first of the oral direct thrombin inhibitors, has a wider therapeutic margin and low potential for drug interactions, allowing fixed dosing without anticoagulation monitoring. There is absolute reduction in stroke and systemic embolic events with ximelagatran compared with warfarin of 1.6% per year versus 2.3% per year, respectively[1].

To conclude, warfarin therapy is a double-edged sword. The safety margin is very narrow. Times have come when better anticoagulants with similar efficacy and fewer side effects should be tried. Patients on warfarin should be on stringent monitoring to prevent such untoward incidents.

References

1. Olsson SB, Halperin JL. Prevention of stroke in patients with atrial fibrillation. *A Semin Vasc Med* 2005; 5(3): 285-92.
2. Levine MN, Raskob G, Landefeld S, Hirsh J. Hemorrhagic complications of anticoagulant treatment. *Chest* 1995; 108: 276S-90S.
3. Maimon N, Penner T, Demajo W. Warfarin-induced gastric bleeding and intestinal obstruction. *Eu J Int Med* 2006; 17: 211-2.
4. Subramanian S, Marappa GS, Thirunarayanan A *et al*. Retroperitoneal hemorrhagic shock in a patient on warfarin therapy. *Emerg Trauma Shock* 2009; 2(2): 137-8.
5. Singer DE, Chang Y, Fang MC. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med* 2009; 151(5): 297-305.
6. Prasad S, Wootten MR, Kulinski N, Chapman SA. What to do when warfarin therapy goes too far. *J Fam Pract* 2009; 58(7): 346-52.
7. Ohlin AK, BiLind M, Boman K *et al*. Thrombomodulin as a marker for bleeding complications during warfarin treatment. *Arch Intern Med* 2009; 169(13): 1210-5.

CASE REPORT

JIACM 2012; 13(4): 59-61

Marchiafava-Bignami disease – A rare presentation of chronic alcoholism

*SJ Wagh***, AS Dabhi*, PB Thorat*, JF Vasava**, JP Modia***, MJ Shah****

Abstract

Herein we report the case of an alcoholic patient with highly suspicious Marchiafava-Bignami disease(MBD) who developed acute neurologic dysfunction and showed characteristic abnormalities in the corpus callosum on the brain MRI.

Key words: Alcoholism, low signal lesion, callosal atrophy, corpus callosum.

Introduction

Alcohol addiction and alcohol withdrawal are associated with a variety of neuropsychiatric syndromes, some of which are associated with significant morbidity and mortality. Marchiafava-Bignami disease (MBD) is a rare, alcohol-associated disorder characterised by demyelination and necrosis of the corpus callosum[1]. It is a radiological diagnosis as clinical features are variable and non-specific[2].

Herein we report a case of Marchiafava-Bignami disease who had a history of chronic alcoholism, and clinical presentation and MRI findings were consistent with the diagnosis.

Case report

A 55-year-old right-handed man with a history of chronic alcohol abuse was admitted in the medical ward with history of unconsciousness for two days. The patient then developed complex partial seizures involving the left side of the body. There was no history of fever, headache, vomiting, jaundice, head injury, and ear or nasal bleed. Alcohol abuse was ongoing for the last 25 years and he used to drink 1 - 2 litres of country-made liquor a day. Neurologically, no significant past history was present. On admission, neurological examination showed a Glasgow Coma Scale of E2M2V3. The oculo-cephalic reflex was normal. Examination of cranial nerves showed normal pupillary size and reaction. The fundus examination was normal. Motor examination revealed hypotonia in all 4 limbs with exaggerated deep tendon reflexes. Bilateral extensor plantar response was present. No meningeal signs were present. Further physical examination and review of other systems was normal.

Laboratory results revealed normal biochemistry profile. CXR and ECG were normal. CSF studies were normal. CT scan of the brain, which was performed immediately on admission in the emergency department, showed no significant abnormalities. MRI brain on T2W and FLAIR images showed a high signal lesion in the body and splenium of corpus callosum (sandwich sign) with relative sparing of rostrum, genu, and peripheries of body and splenium as seen on sagittal and axial view. T1W images revealed hypointensity in the same areas On apparent diffusion coefficient image (ADC) it is hypointense and hyperintense on diffusion weighted image (DWI) and these areas are showing restricted diffusion. On the basis of history, clinical features, and imaging studies, the diagnosis of acute form of MBD was made. Patient was treated with thiamine, vitamin B complex, and with anticonvulsants (injectable phenytoin sodium and sodium valproate).

Discussion

Although first described by Carducci in 1898 in Italian red wine drinkers, it was in 1903, that the Italian pathologists Marchiafava and Bignami described a unique alteration of the corpus callosum in three alcoholic patients who died after having seizures and coma. The disease affects persons in middle and late adult life. With a few exceptions, the patients have been males and severe chronic alcoholics[3]. The underlying mechanism of the disease is still not understood. It is probably caused by the combination of alcohol abuse and malnutrition, leading to metabolic, toxic, and vascular disturbances[4]. There are no characteristic clinical presentations of Marchiafava-Bignami disease. Clinical clues for the disease are reduced consciousness, psychotic and emotional symptoms, depression and apathy, aggression, seizures, hemiparesis, ataxia, apraxia, and frequently leading to coma and death[5]. The course of he disease may be acute, subacute, or chronic, and may lead to death within weeks to months. Marchiafava-Bignami disease may present in various clinical forms[6].

Acute Marchiafava-Bignami disease includes seizures,

**** Associate Professor, ** Assistant Professor, *** Resident, Department of Medicine, Medical College and SSG Hospital, Jail Road, Vadodara - 390 001, Gujarat.***

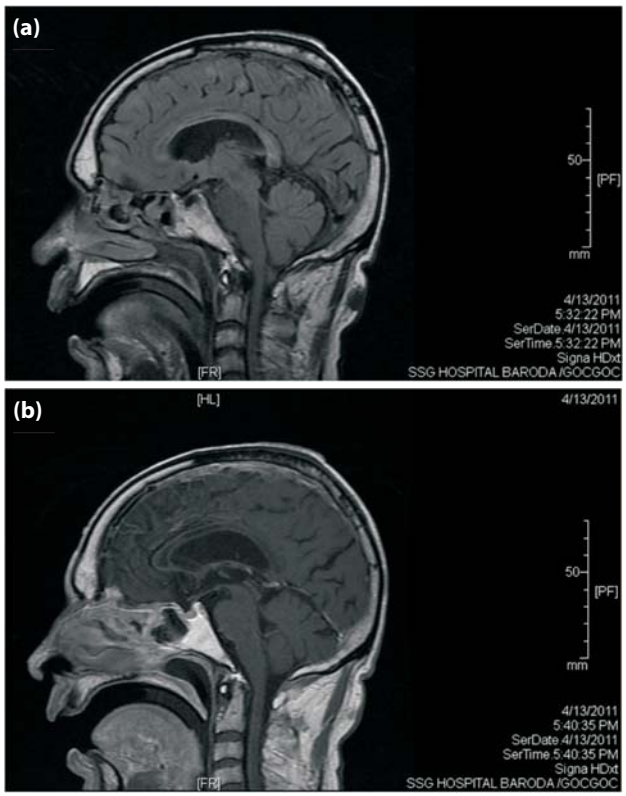


Fig. 1: *Saggital MRI showing lesion in the body of corpus callosum which is hypointense on T1 image (a) and hyperintense on T2 image(b). Sandwich sign is positive.*

impairment of consciousness, and rapid death.

Subacute Marchiafava-Bignami disease includes variable degrees of mental confusion, dysarthria, behavioural abnormalities, memory deficits, signs of interhemispheric disconnection, and impairment of gait.

Chronic Marchiafava-Bignami disease, which is less common, is characterised by mild dementia that is progressive over years.

Until recently, the definite diagnosis was confirmed at autopsy. However, in the era of modern imaging technology, diagnosis could be based on clinical profiles, history of alcoholism, and specific localisations of pathological lesions in the corpus callosum demonstrated by CT and MRI[4]. The corpus callosum appears hypoattenuated on CT scans, with the exception of cases that are characterised by subacute bleeding, in which it may be iso-hyperattenuated. However, if callosal damage is mild or the lesion is small, it may not be obvious and thus easily missed on CT, as in our patient. MRI is currently the most sensitive diagnostic tool[4]. Conventional MRI typically detects lesions as hyperintense on T2- phase and FLAIR signal intensity, and hypointense on T1-weighted images in the body of the corpus callosum, sometimes extending into the genu, and the splenium[8]. Mainly the central layers of the corpus callosum are affected, with sparing of the dorsal and ventral layers (sandwich sign on MRI)[4]. The entire corpus callosum is rarely involved. Similar lesions may also be found in the middle cerebellar peduncles and in the hemispheric white matter involving the centrum semiovale and extending, in some cases, into the adjacent convolutional white matter. These lesions usually do not have mass effect and may show peripheral contrast enhancement during the acute phase. As lesions become chronic, cystic lesions are likely to develop. Pathology may also be seen on diffusion-weighted imaging and ADC as areas of restricted diffusion. Greater the restriction, worst the prognosis[8]. After a few months, signal intensity alterations become less evident but residual atrophy of the involved structure usually is present[7].

The diagnosis of MBD rests mainly on evidence of these callosal lesions. The corpus callosum may also be affected in other diseases such as ischaemic stroke, contusion, multiple sclerosis, and lymphoma. MBD, however, is distinguished from these disorders by the symmetry of the callosal lesions with relative sparing of thin upper and lower edges[9]. Other neuropsychiatric conditions associated with chronic heavy drinking are: Wernicke's encephalopathy, Korsakoffs psychosis, alcoholic dementia, cerebellar degeneration, central pontine myelinolysis, alcoholic amblyopia, alcoholic pellagra encephalopathy, and peripheral neuropathy.

Because the aetiology of the disease is uncertain, a specific therapy is not available. Cessation of alcohol intake is mandatory. Therapy with thiamine and vitamin B complex, including vitamin B-12 and folate, has been used in many patients who have recovered. However, identical therapy has been used in patients who did not recover. Seizures and coma are treated symptomatically. A favourable response has been reported after the use of corticosteroids in some cases. Some patients survive for many years in a demented condition or occasionally even show partial or complete recovery. Patients who survive should stop alcohol consumption, receive rehabilitation and nutritional counselling.

References

1. Heinrich A, Runge U, Khaw AV. Clinicoradiologic subtypes of Marchiafava-Bignami disease. J neurol 2004; 251: 1050-9.
2. Gohar SC, Faria N, Singh A *et al*. Marchiafava-Bignami Syndrome. *J Assoc Physicians India* 2007; 55: 130.
3. Ropper AH, Brown RH. Diseases of the nervous system due to nutritional deficiency. In: Ropper AH, Brown RH eds. Adams and

Victor's Principles of Neurology. 9th ed. New York: McGraw-Hill. 2009; 1124-1126.

4. Haas L, Tjan D, Die JV *et al*. Coma in an alcoholic: Marchiafava-Bignami disease. *Journal New Zealand Medical Association* 2006; 119: 1244.
5. Helenius J, Tatlisumak T, Soinne L *et al*. MarchiafavaBignami disease: two cases with favourable outcome. *Eur J Neurol* 2001; 8: 269-72.
6. Schwalm JD, Phillips C, Silva J. Marchiafava-Bignami & *Mycobacterium tuberculosis. McMaster University Medical Journal* 2006; 3: 22-25.
7. Anna G, Andrea F, Lucia M *et al*. MarchiafavaBignami Disease: Longitudinal MR Imaging and MR Spectroscopy Study. *Am J Neuroradiology* 2003; 24: 249-53.
8. Me´ne´gon P, Sibon I, Pachai C *et al*. Mar chiafava–Bignami disease: Diffusion weight ed MRI in corpus callosum and cortical lesions. *Neurology* 2005; 65: 475-7.
9. Johkura K, naito M, Naka T. Cortical Involvement in Marchiafava-Bignami Disease. *Am J Neuroradiology* 2005; 26: 670-3.

"One of the essential qualities of the doctor is interest in humanity, for the secret of the care of the patient is in caring for the patient."

– Frances Weld Peabody in "The Care of the Patient".

CASE REPORT

JIACM 2013; 14(1): 62-3

Lithium-induced sinus node dysfunction at therapeutic concentration

Tarun Kumar, Surender Deora**, Ashish Agarwal*, R Rangraj***, S Patil****, CN Manjunath******

Abstract

The present report describes a case of sinus node arrest in a patient of manic-depressive illness being treated with lithium carbonate with a therapeutic serum level of lithium. The patient responded to symptomatic treatment and lithium was withdrawn in consultation with psychiatrist. A review of literature revealed case reports in which both therapeutic and toxic levels of lithium were associated with sinus node dysfunction and bradyarrhythmias. The probable mechanism for sinus node dysfunction is lithium-induced sodium channel blockade as sodium channels are critically important in pacemaker activity.

Key words: Lithium, sinus node dysfunction, cardiac sodium channels.

Introduction

We describe a 48-year-old diabetic male with a history of bipolar depression who was maintained on 1,200 mg/day of lithium carbonate, 8 mg/day trihexphenydyl, 8 mg/day risperidone for the last 20 years, but on irregular follow-up. He presented in the Emergency department, with a history of giddiness on-and-off for 1 week. There was no previous personal or family history of cardiovascular disease. The 12-lead ECG showed sinus node arrest (Figure 1) with an idioventricular escape rhythm at 30 - 40 beats/min.

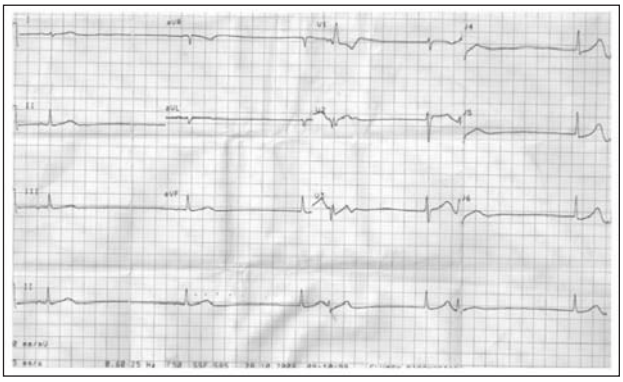


Fig. 1: *12-lead ECG during symptomatic phase showing sinus node arrest with an idioventricular escape rhythm.*

During evaluation in the Emergency department, the patient had syncope followed by cardio-respiratory arrest from which he was resuscitated (inj. atropine, inotropic support, mechanical ventilation, and temporary pacemaker [Figure 2]). Patient reverted to sinus rhythm after about 12 hrs, was haemodynamically stable and symptomatically improved. All supports were gradually withdrawn.

Investigations including random blood sugar, cardiac biomarkers, thyroid profile, and serum electrolytes (including calcium) were within normal limits. Serum lithium level was 1.16 mEq/L (N = 0.6 -1.2 mEq/L). CXR was normal. Transthoracic echo showed normal study. A diagnosis of lithium- induced sinus node dysfunction was made in the absence of any other competing diagnosis.

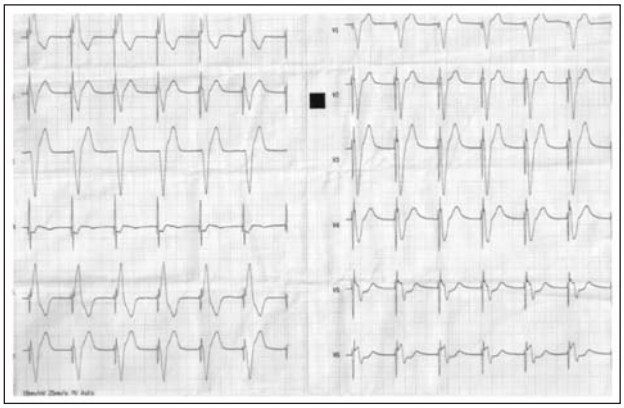


Fig. 2: *12-lead ECG after temporary pacemaker insertion.*

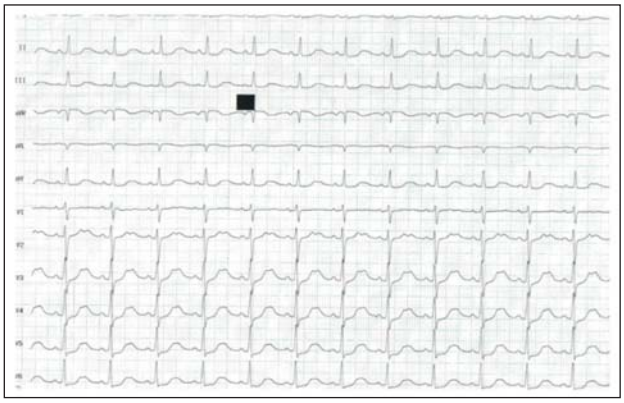


Fig. 3: *12-lead ECG during recovery phase showing normal sinus rhythm.*

**** 3rd Yr. DM Student, ** Post-DM, *** Professor, **** Associate Professor, ***** Director-Professor and Head, Department of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bangalore, Karnataka.***

Discussion

Lithium is a small monovalent cation. In 1949, it was found to be sedative in animals and to exert beneficial effects in manic patients. Its use for this purpose was delayed until 1970, in part due to uncontrolled use of lithium as a salt substitute and instances of toxicity in patients with cardiac disease. Subsequently, the importance of maintaining a narrow range of serum lithium concentration was realised and unequivocal evidence of its efficacy was obtained. Lithium is established as the standard anti-manic and mood stabilising drug. The most common ECG changes associated with therapeutic doses of lithium carbonate are T wave abnormalities[1,2]. Flattening or occasional inversion of the T waves is seen in 20 - 30% of lithium-treated patients which is reversible within 2 weeks after the drug is discontinued. Isolated cases of lithium toxicity causing supraventricular and ventricular tachyarrhythmias, AV and intraventricular conduction defects, QT prolongation have been described[1]. In a number of case reports, lithium caused sinus node dysfunction, including marked sinus bradycardia, sinus pauses, and sino-atrial (SA) block[1-5]. Such effects, however, are uncommon relative to the number of population taking the drug. In a study, of 97 consecutive patients receiving lithium, only 2 had sinus node depression possibly caused by lithium[3]. Here we have reported a case with severe symptomatic lithium-induced sinus arrest causing syncope at therapeutic serum level, which could be fatal; hence the need for regular ECG monitoring of patients on lithium therapy.

Mechanishm

The effect of lithium on the sinus node seemed to be intrinsic and was not caused by increased parasympathetic tone[6]. The putative mechanism of lithium associated bradyarrhythmias has been linked to hypercalcaemia and hypothyroidism[7,8]. But case reports, including our case, have shown sinus node dysfunction in patients on lithium who were euthyroid and normocalcaemic.

The demonstration that lithium can unmask Brugada syndrome has provided a crucial link to lithium-induced sinus node dysfunction[9]. Indeed, lithium chloride caused a concentration dependent block of the peak sodium current, with the concentration required for 50% inhibition being 6.8+ 0.4 micromole[9], which is consistent with permeation in native voltage-gated sodium channels via a multi-ion mechanism[10]. Sodium channels are expressed in SA node and surrounding tissue and their mutation has been linked to sinus arrest (failure of impulse generation) and exit block (failure of conduction into adjacent atrial myocardium)[11-14]. In humans also, loss of function due to mutation of sodium channel has been linked to atrial standstill[15] and conduction system disease[16].

The recognition that only a fraction of patients on lithium therapy will manifest sinus nodal dysfunction and its occurrence after a long time following the initiation of lithium therapy is consistent with a multifactorial mechanism for sinus nodal pacing activity, which implies that the other intrinsic and/or extrinsic factors may also play an important role. Important factors are:-

1. Variation in serum level of lithium[8].
2. Degree of cardiac sympathetic and parasympathetic tone.
3. Age-dependent accumulation of interstitial fibrosis and decrease of intrinsic sinus rate.
4. Inter-individual variation of cardiac sodium current (due to variable sodium channel expression)[15].

References

1. Mitchell J E, Mackenzie TB. Cardiac effects of lithium therapy in man: *J Clin Psychiatry* 1982; 43: 47.
2. Tilkian AG, Schroeder JS, Kao JJ *et al*. The cardiovascular effects of lithium in man. *Am J Med* 1976; 661: 665.
3. Hagman A, Arnman K, Ryden L. Syncope caused by lithium treatment: Report of two cases and a prospective investigation of the prevalence of lithium -induced sinus node dysfunction. *Acta Med Scand* 1979; 208: 467.
4. Wellens HJJ, Cats VM, Duren DR. Symptomatic sinus node abnormalities following lithium carbonate therapy. *Am J Med* 1975; 59: 285.
5. Wilson JR, Krauss ES, Bailas MM *et al*. Reversible sinus node abnormalities due to lithium carbonate therapy. *N Engl J Med* 1976; 294: 1223.
6. Rosenqvist M, Bergfeldt L, Aili H, Mathe AA. Sinus node dysfunction during long-term lithium treatment. *Br Heart J* 1993; 70: 371-375.
7. Wolf ME, Ranade V, Molnar J *et al*. Hypercalcemia, arrhythmia, and mood stabilizers. *J Clin Psychopharmacol* 2000; 20: 260-4.
8. Livingstone C, Rampes H. Lithium: A review of its metabolic adverse effects. *J Psychopharmacol* 2006; 20: 347-55.
9. Darbar D, Yang T, Churchwell K *et al*. Unmasking of brugada syndrome by lithium. *Circulation* 2005; 112: 1527-31.
10. Favre I, Moczydlowski E, Schild L. On the structural basis for ionic selectivity among Na^+, K^+, and Ca^{2+} in the voltage gated sodium channel. *Biophys J* 1996; 71: 3110-25.
11. Maier SK, Westenbroek RE, Yamanushi TT *et al*. An unexpected requirement for brain-type sodium channels for control of heart rate in the mouse sinoatrial node. *Proc Natl Acad Sci USA* 2003; 100: 3507-12.
12. George AL Jr. Inherited disorders of voltage gated sodium channels. *J Clin Invest* 2005; 115: 1990-9.
13. Veldcamp MW, Wilders R, Baartscheer A *et al*. Contribution of sodium channel mutations to bradycardia and sinus node dysfunction in LQT3 families. *Circ Res* 2003; 92: 976-83.
14. Benson DW, Wang DW, Dyment M *et al*. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). *J Clin Invest* 2003; 112: 1019-28.
15. Bezzina CR, Shimizu W, Yang P *et al*. Common sodium channel promoter halotype in asian subjects underlies variability in cardiac conduction. *Circulation* 2006; 113: 338-44.

CASE REPORT

JIACM 2013; 14(1): 64-5

Acute inflammatory large bowel wall abscess: An unusual presentation

SL Margekar, N Singh*, VG Margekar**, SS Jayant**

Abstract

Overall, the infectious colitis are typically diagnosed clinically. This is a rare report of bowel wall abscess which was diagnosed incidentally on ultrasonography of abdomen in a patient where the clinical symptoms were not straightforward.

Key words: Bowel wall abscess, colitis, ultrasonography.

Introduction

Intestinal abscesses can be caused by appendicitis, intestinal diverticulitis, inflammatory bowel disease (IBD), parasitic infections in the intestines, or other conditions[1].

Inflammatory conditions of intestines are: ulcerative colitis (UC), Crohn's disease (CD), infectious colitis (tuberculosis, typhoid, amoebiasis), pseudomembranous colitis, ischaemic colitis, radiation colitis, and chemical colitis (resulting from harsh chemicals into the colon from an enema or other procedures). An abscess may form in the intestinal wall – sometimes causing it to bulge out. Intra-abdominal abscesses usually contain a mixture of aerobic and anaerobic bacteria from the gastrointestinal tract. They are highly variable in presentation.Common symptoms include persistent diarrhoea, urgency of defaecation, tenesmus, often associated with spiking fever, persistent abdominal pain, and weight loss[2]. If not diagnosed timely and left untreated, it may rupture into adjacent organs or cavities, or the process continues until bacteraemia develops, which then progresses to generalised sepsis and shock.

Indeterminate colitis (IC) refers to those 10 - 15% of cases of inflammatory bowel disease in which there is difficulty distinguishing between ulcerative colitis and Crohn's disease on colonoscopy, in colonic biopsies, or in colectomy specimens. Clinically, most patients with IC evolve to a definite diagnosis of UC or CD on follow-up[3].

Case report

This case involved a previously healthy non alcoholic, non smoker, non diabetic 53-year-old male presenting with a 10-days history of pain in abdomen, fever, and vomiting. There was no history of any recent travel, exposure to sick contacts or animals, trauma or any abdominal surgery. Also, there was no history of flare-ups, abdominal cramps, persistent and recurrent diarrhoea, urgency of defaecation, tenesmus, blood, pus-or mucus-mixed stools, rectal bleeds, or weight loss. There was no family history of IBD, and the patient had not received any antibiotics prior to complaints.

Upon examination, the patient appeared unwell, with a pulse of 98/min and BP of 110/80 mmhg. Abdominal examination revealed generalised tenderness with normal bowel sounds. No extraintestinal manifestations of skin, eyes, joints, or of the liver and biliary system were present. Blood tests were normal except for mild anaemia (haemoglobin-8.6 gm%). Emergency ultrasonography was performed which yielded a grossly thickened wall involving the caecum, ascending colon, and transverse colon, with a few rounded well-defined, hypoechoic lesions measuring around 1 cm in the wall of the hepatic

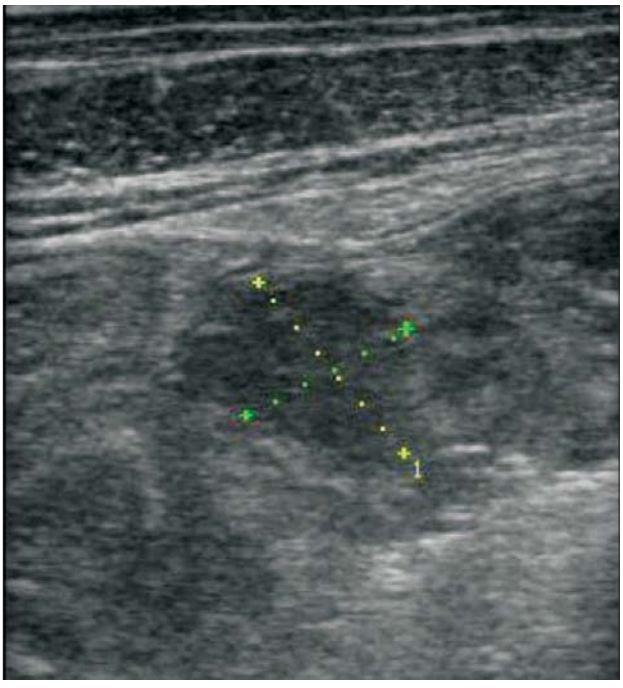


Fig. 1: *USG of abdomen showing rounded, well-defined, hypoechoic lesions measuring around 1 cm in the wall of the hepatic flexure of colon and ascending colon suggestive of bowel wall abscess.*

**** Assistant Professor, ** Post-Graduate student, Department of Medicine, G.R. Medical College, Gwalior - 474 009, Madhya Pradesh.***

flexure of colon and ascending colon suggestive of bowel wall abscess with surrounding inflamed mesentery with mild ascites (Figures 1, 2, and 3).

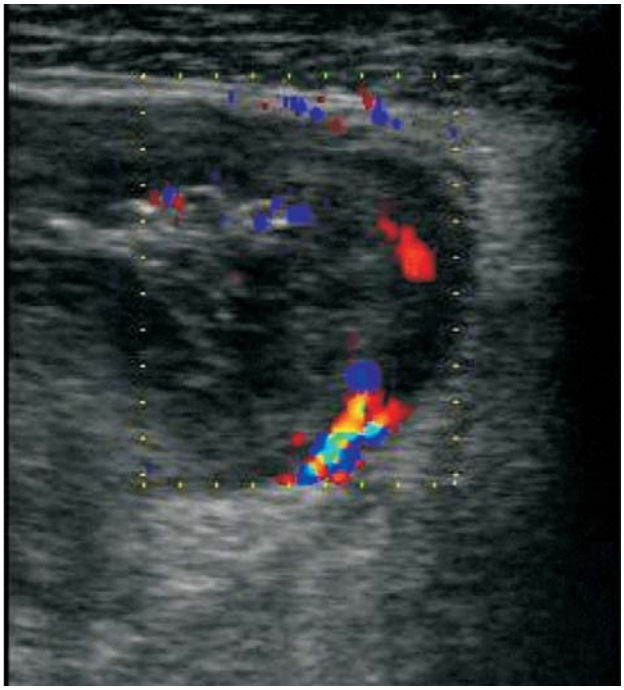


Fig. 2: *USG of abdomen showing rounded, well-defined hypoechoic lesions with no vascularity, suggestive of bowel wall abscess.*

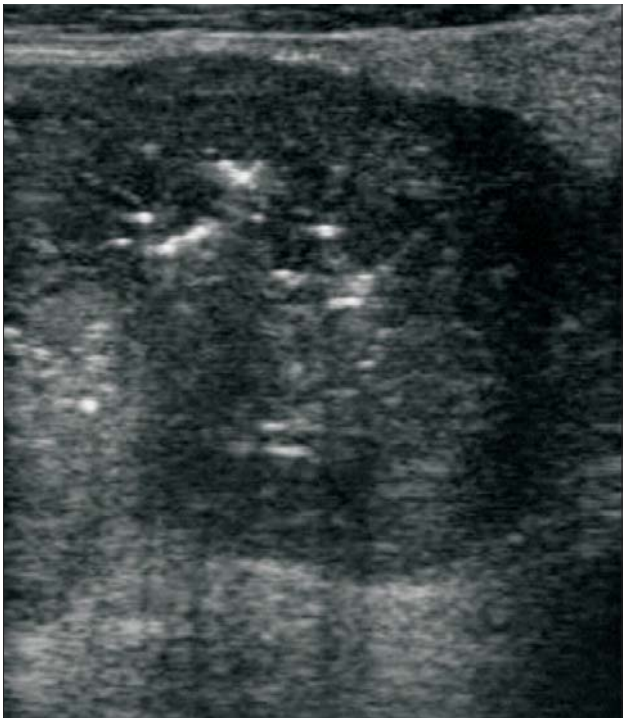


Fig. 3: *USG of abdomen showing grossly thickened bowel wall involving caecum.*

He was put on IV fluids, antibiotics (IV cefotaxime, metronidazole and pazufloxacin) and supportives, to which he responded well. In view of bowel wall abscess, colonoscopy was done to assess the intraluminal involvement and extent of the lesion which revealed a few shallow ulcers in the sigmoid colon, with normal anal canal and rectum. The patient was relieved/discharged on day 10 on oral antibiotics. A follow-up with repeat ultrasound of abdomen on day 17 showed thickened bowel loops in the right iliac fossa and lumbar region (caecum and ascending colon). There was no abscess or collection seen in the bowel wall.

Discussion

The initial ultrasonographic (USG) findings of bowel wall abscess is a rare occurence almost never reported. The presence of thickened caecum and ascending colon in follow-up USG after a course of antibiotics and the presence of a few shallow ulcers in the sigmoid colon suggests an ongoing inflammatory process in the large intestine. Whether it was Crohn's disease, ulcerative colitis, or any other infectious colitis, remains to be determined. Capsule endoscopy and biopsy of the lesion would have led to a definitive diagnosis.

In a prospective study it was found that increased bowel wall thickness, localised in the right lower quadrant, in combination with inflammatory masses or an abscess, suggests Crohn's disease[4].

Amoebiasis is a major cause of colitis in developing countries and should be included as one of the differential diagnoses of acute abdomen and bowel wall abscess[1].

Conclusion

Bowel wall abscess is a rare entity and is of particular significance for patients possessing a paucity of risk factors for portal or systemic sepsis. A high index of suspicion is crucial for diagnosis, and is essential to avoid unnecessary complications and surgery. Ultrasound being easily available, affordable, and not involving ionizing radiation, can be used as a reliable screening tool in the initial evaluation of any abdominal pain.

References

1. Ng DCK, Kwok SY, Chung CC *et al*. Colonic amoebic abscess mimicking carcinoma of the colon. *Hong Kong Med J* 2006;12: 71-3.
2. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2004; 99: 1371-85.
3. Guindi M, Riddell RH. Indeterminate colitis. *J Clin Pathol* 2004; 57: 1233-44 .
4. Worlicek H, Lutz H, Heyder N, Matek W. Ultrasound findings in Crohn's disease and ulcerative colitis: A prospective study. *Journal of Clinical Ultrasound* 1987; 15: 153-63.

CASE REPORT

JIACM 2013; 14(1): 66-8

A rare presentation of definitive ocular tuberculosis in a health-care worker

G Bharti, T Dewan**, S Vashisth***, D Shrivastav****, MD Singh******

Abstract

***Case report:** A young healthy health-care worker presented in the eye OPD with complaints of floaters and decreased vision in her left eye. Examination revealed a chorio-retinal mass lesion in the affected eye. No systemic association was found. Based on ocular findings, a strong suspicion of a choroidal tuberculoma was made and the patient advised to start corticosteroid therapy and ATT, while she was investigated further. HRCT chest picked up Pott's spine of D11-12, and Gold TB-Quantiferon test came out to be positive. The lesion regressed on a full course of ATT.*

***Conclusion:** Tuberculosis can present with multi system involvement. A seemingly innocuous ocular involvement could be associated with significant systemic tuberculosis and thus requires thorough investigations.*

***Key words:** Choroidal tuberculoma, Pott's spine, ATT.*

Introduction

Tuberculosis is a multisystem disease with myriad manifestations and presentations. Ocular tuberculosis is a rare but known complication of tuberculosis. Ocular involvement can occur through either direct entry or as an immunological reaction to the organism. The organism can enter the eye from both the epithelial and the haematogenous route. The latter being the favourable route of spread. The ocular manifestations of tuberculosis vary from involvement of the lid and adnexa, orbital cellulitis, dacroadenitis, periocular lymphadenopathy to phlyctenules, conjuctival granuloma, scleritis , iridocyclitis in the anterior segment. The posterior segment can be involved in the form of vitritis, pars planitis, chorio-retinitis, choroiditis and optic neuritis[1]. Multisystem tuberculosis may present for the first time with ocular signs. Inadequate systemic workup may falsely classify such cases as extra-pulmonary tuberculosis and thus assign them to a different category of DOTS[2].

Case report

A 29-year-old health care provider presented in the out-patient department of our tertiary care hospital with complaints of redness, pain and blurred vision in her left eye for the past one month, and a floater noticed in the same eye for about a week. The redness had no aggravating or relieving factors and no other association. There was no history of metamorphopsia, flashes, or field loss. On detailed questioning, a systemic history of draining of a forearm abscess under broad spectrum antibiotic cover was present. However, the incision site continued to ooze serous fluid till date. Rest of the systemic history was not contributory. Her best corrected vision at the time of presentation was 6/6 in right eye and 6/9 in left eye. The examination findings were normal for right eye. Detailed examination of her left eye revealed a localised area of congestion in the nasal bulbar conjunctiva suggestive of episcleritis. Slit lamp biomicroscopy revealed presence of vitreous cells and flare. On indirect ophthalmoscopy, an elevated mass in the inferonasal quadrant just next to the ora with a distinct component in the retinal plane having a collar-stud appearance was seen. It was about 5 disc diameter size with sub-retinal exudates, and the superficial retinal vessels arched over it. The surrounding vitreous showed marked vitritis (Fig. 1). Another lesion was seen in the supero-temporal quadrant, near to the equator. It was

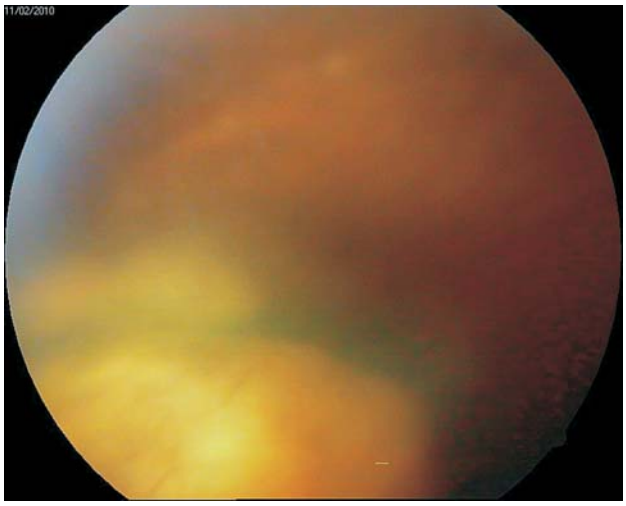


***Fig. 1:** Colour photograph of fundus showing elevated choroidal mass with retinal vessels arching over it.*

** Senior Resident, ** Specialist, *** Head of the Department of Ophthalmology, **** Consultant in Medicine, ***** Senior Specialist, Ophthalmology, PGIMER, Dr. RML Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.*

almost the disc size, flat, and having a localised area of retinal mottling with overlying vitreous haze. On B-Scan, the lesion in the infero-nasal quadrant was seen to be in relation with the inner layers of the eyeball. It was cystic with a moderate initial spike and no internal echoes, suggestive of abscess or a tuberculoma. There was no evidence of choroidal excavation or any calcifications. The maximum width of the lesion was 9 mm with max height 3.05 mm. The overlying and surrounding retinal spikes were normal. FFA done at the centre showed marked hyperfluorescence around the lesion in the early phase, which increased in size and intensity over the mid- and late phases. The lesion showed an early hypofluorescence with the appearance of dye within the lesion only in the mid-phase. This intra-lesional hyperfluorescence increased gradually over the later phases till the appearance of a homogenous hyperfluorescence. Hyperfluorescence was seen in some peripheral retinal vessels suggestive of vasculitis. No leakage of dye was noted in the vitreous or extracellular compartment. Right eye FFA was normal. Her ocular examination and the FFA findings were collaborative for an inflammatory lesion, though a rare possibility of a neoplasm was also thought for which the patient was investigated further.

On the basis of the above findings, a presumptive diagnosis of ocular tuberculosis was made. In view of the vision-threatening consequences, the patient was advised a depot steroid (triamcinolone) injection in the affected eye. As the patient refused any form of parentral therapy, oral steroids were started and systemic investigations ordered to know the cause of the lesion. Prolonged systemic steroids are know to significantly increase the risk of tuberculosis[3] in the general population. Also, a case of tuberculosis, where the diagnosis has been missed (and the patient is not on systemic ATT), if given steroids, can have detrimental effects[4]. Thus, in our case, a medical consultation was sought to rule out systemic tuberculosis. The physician found her general physical examination to be normal except for the continuing ooze from the forearm abscess. Her blood profile and biochemistry was normal except for a mildly raised ESR. Mantoux test was strongly positive (with necrosis). ELISA TB was negative for both IgG and IgM and the quantiFERON-TB gold test was positive. PCR from the forearm ooze was requested but denied by the biochemist because of the possibility of contamination. Chest X-Ray and ultrasound abdomen were normal. HRCT chest was also advised at the same time.

The patient did not respond to oral steroids alone. In view of the vision-threating lesion, and to give her the full benefit of the ATT, it was decided to treat her as a category 1 patient, even though extrapulmonary tuberculosis is classically treated under category 3 of the DOTS regime. This decision to put her in category 1 at this stage might seem controversial to some pulmonologists, but we considered chorioretinitis as a serious vision-threatening condition. The HRCT chest was done and it came out to be normal; but it reported an incidental finding of a psoas abscess which on further MRI was confirmed as a case of Pott's spine of the D10 and D11 vertebrae (Fig. 2). An orthopaedics consultation was sought and the abscess drained under ultrasound guidance. About 25 ml of pus was drained which stained positive for AFB. Patient was continued on ATT with an intensive phase on HRZE for 2 months and continuation phase on HR for 6 months. The patient was reviewed again by the treating physician and was advised to continue ATT for another 2 months. The ooze from the forearm lesion soon stopped, and the ocular lesion regressed – leaving a pigmentary scar – in 6 weeks.

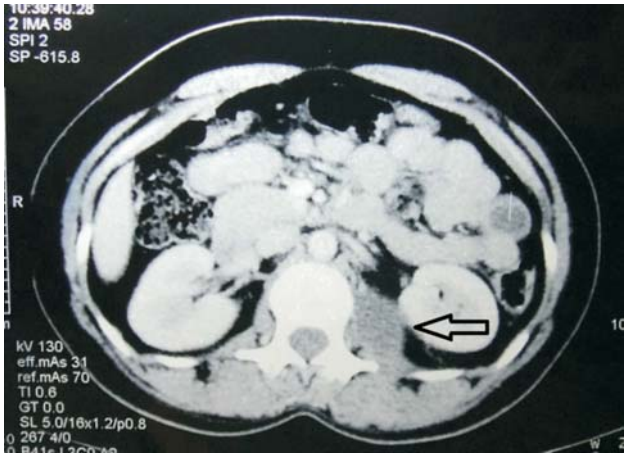


Fig. 2: *MRI of the patient showing psoas abscess.*

Discussion

Ocular tuberculosis usually occurs in apparently healthy individuals. A small, insignificant, and unnoticed tuberculous lesion elsewhere in the body can lead to irreparable, vision threatening damage to the eye leading to permanent blindness[5]. On the other hand, a seemingly innocuous ocular involvement may be associated with significant systemic tuberculosis. As in our case, sometimes the ocular finding can help the treating physician to make a diagnosis of systemic tuberculosis. There are only a few reported cases of solitary choroidal tuberculoma, and it may present with or without active pulmonary tuberculosis. A lesion like this can even masquerade a choroidal melanoma, for which enucleations have been performed[6]. Thus a thorough knowledge of the manifestations is very important to the treating ophthalmologist. The diagnosis of ocular tuberculosis is usually presumptive and depends upon indirect evidence.

Extrapulmonary TB is more difficult to diagnose than pulmonary disease, often requiring invasive procedures (to obtain a diagnostic specimen) and more sophisticated laboratory techniques. A definitive diagnosis requires an inter-speciality interaction and a high clinical suspicion. History of tuberculosis exposure, ATT in the past, clinical examination, positive tuberculin test, and x-ray chest had been used in the past for evaluating patients of retinal vasculitis for systemic evidence of tuberculosis. These tests are now complemented with tests with better specificity like the PCR and Gold TB-quantiFERON[7,8]. Since HRCT scan detects subtle, early, and small lesions, it is very useful in detecting mediastinal lymphadenopathy. Our patient being a health-care provider, had an exposure to *Mycobacterium tuberculosis* and thus a positive Mantoux test. But the lesion in the eye is usually secondary to a focus somewhere else. Definitive diagnosis in such cases is difficult but not impossible if the patient is given the full benefit of all the relevant tests. Treatment of extrapulmonary tuberculosis is another challenge for the treating ophthalmologist. The DOTS programme does not put ocular tuberculosis under any category[2]. Ideally it should be recommended that ocular tuberculosis, with potentially vision-threatening complications be categorised as seriously ill extrapulmonary TB. Thus giving the patient the full advantage of the category 1 ATT regime.

References

1. Sheu SJ, Shyu JS, Chen LM *et al*. Ocular manifestations of tuberculosis. *Ophthalmology* 2001;108(9): 1580-5.
2. World Health Organization (WHO). Treatment of Tuberculosis: Guidelines for National Programmes, 3rd edition. WHO/CDS/TB2003.313 Geneva, Switzerland: WHO, 2003.
3. Pal D, Behera D, Gupta D *et al*. Tuberculosis in patients receiving prolonged treatment with oral corticosteroids for respiratory disorders. *Ind J Tub* 2002; 49: 83.
4. Davis LE. Danger of corticosteroid administration in meningitis due to misdiagnosed agent. *Pediatric Neuro* 1994; 10(4): 338-9.
5. Sahu GN, Mishra N, Bhutia RC *et al*. Manifestations in ocular tuberculosis. *Ind J Tub* 1998; 45: 153
6. Hakan Demirci, Shields CL, Jerry A *et al*. Ocular tuberculosis masquerading as ocular tumors. *Survey of ophthalmology* 2004; 49(1): 78-89.
7. Gupta V, Gupta A, Rao NA. Intraocular tuberculosis- An Update. *Survey of Ophthalmology* 2007; 52(6): 561-87.
8. Albini TA, Rao NA, Karakousis PC. Interferon-ã Release Assays in the Diagnosis of Tuberculous Uveitis. *American Journal of Ophthalmology* 2008; 146: 486-8.

"To be a doctor, then, means much more than to dispense pills or to patch up or repair torn flesh and shattered minds. To be a doctor is to be an intermediary between man and God."

– from "To Be a Doctor" by Felix Marti-Ibanez.

CASE REPORT

JIACM 2013; 14(1): 69-70

Cerebral malaria caused by *Plasmodium vivax*

*NS Neki**

Abstract

Cerebral malaria is a diffuse encephalopathy characterised by unarousable coma of more than 30 minutes duration associated with or without seizures in which the bacterial meningitis and locally prevalent viral encephalitis has been excluded by relevant clinical and laboratory investigations. Usually cerebral malaria is caused by P. falciparum, but rarely it could be the presenting complication or occurring during the course of P. vivax. We report 2 cases of cerebral malaria caused by Plasmodium vivax complicated by seizures and symptoms of encephalitis. Both cases were successfully treated with parenteral artesunate without any sequelae.

Keywords: Cerebral malaria, plasmodium vivax.

Introduction

Cerebral malaria is usually secondary to *P. falciparum* infection. It is a grave complication and is manifested by either acute widespread bilateral, symmetrical encephalopathy producing hypertonia, brisk deep tendon reflexes, extensor plantar response, extensor posturing, decerebrate rigidity/decorticate rigidity, and sustained upward deviation of eyes[1]. About half of the total reported cases of cerebral malaria caused by *P. vivax* occur in children[2].

Case report

Two male patients in the age of 42 and 49 years, presented with high grade intermittent fever of 5 days and impaired consciousness of 4 days duration. The fever was associated with chills and rigors. Both had a history of generalised tonic-clonic convulsions prior to admission. On examination, both patients were severely dehydrated, comatosed. Pulse was 110/min regular, BP was 110/80 mmHg, respiratory rate was 22/min. Chest and CVS examinations were unremarkable. Abdominal examination revealed splenomegaly. There were no signs of meningeal irritation; deep tendon reflexes were brisk with extensor plantar response. Laboratory investigations of Hb, TLC, DLC, platelet count, blood sugar, urea, creatinine, serum electrolytes, LFT, and ECG were within normal limits. CT of brain, CSF, and EEG were noncontributory. Peripheral blood smear of both cases was positive for trophozoites of *P. vivax*. Antigen test for *P. vivax* was positive, while it was negative for *P. falciparum* in both cases. Both were given treatment in the form of supportive therapy along with intravenous artesunate in the recommended dosage for five days. Peripheral blood smears taken subsequently were negative for parasites in both the patients. They were discharged in a clinically stable condition and were advised to take primaquine for 14 days, in order to destroy the hypnozoite (exoerythrocytic schizozoite of *P. vivax* or *P. ovale*) phase in the liver, after excluding G-6PD deficiency. After one month of follow-up, both cases showed no neurological deficit.

Discussion

Malaria is a major health problem in the world. An estimated 300 - 500 million cases and 1.2 - 7 million deaths occur each year due to malaria[3]. In India, over the past two decades, the incidence of malaria has been fluctuating between 2 - 3 million each year. India accounts for 40% of all malaria cases outside Africa[4]. *P. vivax* infection is responsible for 60 - 70% of malaria cases in India and it is the most important cause of morbidity. It is usually presumed to cause only uncomplicated malaria but in the last few years, there have been many reports regarding cerebral vivax malaria[5,6]. In a study by Kocher *et al*[5], *P. vivax* can cause both sequestration-related and non sequestrated-related complications of severe malaria, all of which are commonly associated with *P. falciparum* infection. Sachdeva and Mohan[7] studied a clinico-laboratory profile of six patients with vivax cerebral malaria. The presenting features were of acute febrile encephalopathy, convulsions and coma, while one patient had focal neurological signs. In a study by Sarkar *et al*[6], out of 3 patients of cerebral malaria caused by *P. vivax*, two had predominantly meningeal signs, while in the third patient, the features were purely of encephalitis. Cerebral vivax malaria may cause status epilepticus, or cerebral malaria subjects may have a seizure disorder as documented by Ozen *et al* in their study[2].

**** Professor of Medicine, Government Medical College & Guru Nanak Dev Hospital, Amritsar - 143 001, Punjab.***

References

1. WHO. Severe Falciparum Malaria. Transitions of the Royal Society of Tropical Medicine and Hygeine 2000.
2. Ozen M, Gungor S, Atambay M, Daldal N. Cerebral malaria owing to *Plasmodium vivax*: Case report. *Ann J Pediatr* 2006; 26:141-4.
3. WHO 2000. WHO expert committee on malaria. Twentieth report World Health Organization, Geneva, Technical Report Series, No. 892.
4. Pareek A, Nandy A, Kocher D *et al*. Efficacy and safety of a/b Artemether for treatment of acute Plasmodium falciparum Malaria. *American Journal of Trop Med Hyg* 2006; 75(1): 139-42.
5. Kocher DK, Saxena V, Singh N *et al*. Plasmodium Vivax Malaria. *Emerg Infect Dis* 2005; 11: 132-4.
6. Suman S, Prithwis B. Cerebral malaria caused by Plasmodium vivax in adult subjects. *Indian J Crit Care Med* 2008; 12(4): 204-5.
7. Sachdev HP, Mohan M. Vivax cerebral malaria. *J Trop Pediatr* 1985; 31: 213-5.

CASE REPORT

JIACM 2013; 14(1): 71-2

Hashimoto's encephalopathy

Neelkanth Bapat, Vinayak Hingane**, Pavan Hanchnale***

Abstract

Hashimoto's encephalopathy is a rare but treatable cause of encephalopathy. High index of suspicion is necessary to diagnose such patients. The available literature is in the form of case reports and some case series. We discuss the case of 70-year-old lady who presented with convulsions and later on the diagnosed to have Hashimoto's encephalopathy. She was treated with steroids and improved significantly.

Key words: Hashimoto's encephalopathy, steroid responsive encephalopathy.

Case report

A 70-year-old hypertensive lady was admitted for convulsions in November 2009.There was no significant past history. She did not have any residual neurodeficit then. Her haemogram, renal function tests, sugar levels and electrolytes were normal. CT scan of the brain was unremarkable except for senile atrophy. An electroencephalogram was done which was normal. TSH level was not done. The patient was diagnosed as late onset epilepsy and was started on sodium valproate and discharged in an asymptomatic condition.

After a one-month asymptomatic period, the patient was again admitted in the ICU with altered mental status and anorexia. She also had a painful left knee and fever. Her clinical examination revealed septic arthritis of the left knee, which was confirmed with arthroscopic synovial biopsy.The patient was obtunded but there was no localising neurodeficit. She deteriorated rapidly due to sepsis and developed acute lung injury. She was suspected to have encephalopathy secondary to sepsis. An arthroscopic knee lavage was given. She was started on amoxicillin and clavalunate, which was upgraded to piperacillin-tazobactum. Patient improved haemodynamically, her knee inflammation settled, and she was shifted out of the ICU. Her sensorium remained dull and gradually worsened and she was re-admitted in the ICU.

Her blood ammonia levels were ordered (to look for valproate toxicity), but turned out to be normal. Her CSF examination was unremarkable. The metabolic parameters also were non contributory. Her thyroid stimulating hormone level was distinctly high (20.19).This prompted the thought of autoimmune thyroiditis as a cause of encephalopathy. The patient's thyroid microsomal antibody titre was ordered which turned out to be positive. She was started on steroids and thyroxin supplementation. Thereafter, she showed a significant improvement in her sensorium. She became conscious and fully oriented, and was discharged within a week of steroid treatment.

Discussion

Hashimoto's encephalopathy, also known as steroid responsive encephalopathy with autoimmune thyroiditis is a rare but important syndrome. It is included in the list of treatable dementias[1]. The differential diagnoses include viral encephalitis, Creutzfeldt-Jacob disease, stroke, metabolic and paraneoplastic encepalopathies[2]. The available data about Hashimoto's encephalopathy mostly consist of case reports and case series.

The accepted diagnostic criteria include a spectrum of clinical features, presence of thyroid antibodies (TPO or microsomal), euthyroid or mild hypothyroid state, exclusion of infective, neoplastic, structural, or vascular aetiology, and responsiveness to steroid therapy[2,3].

Clinical features include encephalopathy manifested by cognitive impairment and 1 or more of the following: neuropsychiatric features (e.g., hallucinations, delusions, or paranoia), myoclonus, generalised tonic-clonic or partial seizures, or focal neurologic deficits[2]. Antithyroid antibodies are positive in almost all patients but their role as aetiological agent is unclear. There is evidence that cerebrospinal fluid titres of antithyroid antibodies are pathognomic[4]. Hashimoto's encepalopathy could be associated with mild hypothyroidism, or patient may develop hypothyroidism afterwards, but treatment with thyroxin is not useful in suppression of encephalopathy. Response to high-dose glucocorticoid therapy was obsereved in around 50% of patients. There is a population of patients who do not respond to steroid

**** Consultant Physician, ** DNB Resident, Department of Medicine, Deenanath Mangeshkar Hospital, Erandwane, Pune - 411 004, Maharashtra.***

therapy and plasmapheresis was tried with variable success in such patients.

Our patient was misdiagnosed at first presentation as late-onset epilepsy. During second admission, her encephalopathy was attributed to sepsis. We could diagnose her with the help of raised TSH and positive antithyroid antibodies, after ruling-out infective and structural causes for her encephalopathy. Her response to steroid treatment confirmed the diagnosis. Hashimoto's encephalopathy, though rare, should be suspected highly as it is treatable in most of patients.

References

1. Ghika-Schmid F, Ghika J, Regli F *et al*. Hashimoto's myoclonic encephalopathy: an underdiagnosed treatable condition? *Mov Disord* 1996; 11: 555-62.
2. Pablo Castllo, Bryn Woodruff *et al*. Steroid responsive encepalopathy associated with autoimmune thyroiditis. *Arch Neurol* 2006; 63: 197-202.
3. Shaw PJ, Walls TJ, Newman PK, Cleland PG. Hashimoto's encephalopathy – a steroid responsive disorder associated with high anti-thyroid antibody titers. Report of 5 cases. *Neurology* 1991; 41: 228-33.
4. Ferracci F, Moretto G, Candeago RM *et al*. Antithyroid antibodies in the CSF: their role in the pathogenesis of Hashimoto's encephalopathy. *Neurology* 2003; 60: 712-4.

CASE REPORT

JIACM 2013; 14(1): 73-5

A presentation of wandering spleen as pelvic mass

KC Nayak, Surendra Kumar**, BR Sandeep***, Varun Kulkarni***, Ashwani Vyas***, Nagendra Thalor***, Prabhudayal Barala****

Abstract

A wandering spleen is a rare clinical entity characterised by splenic hypermobility due to laxity or maldevelopment of the supporting splenic ligaments. It is commonly discovered in children while investigating for abdominal mass. Among adults, it is most commonly found in women of reproductive age, in whom acquired laxity of the splenic ligaments is usually the cause.

This case report presents a diagnosis of wandering spleen in a 26-years-old-female while evaluating for pain abdomen and anaemia. Clinically felt as a hypogastric mass and with the aid of imaging modalities (ultrasonography, CT scan), the patient was found to be having an enlarged spleen in the pelvic region.

Key words: Wandering spleen, ultrasonography, pelvic mass, splenectomy, splenopexy.

Case report

A 26-year-old female presented to our hospital with a two weeks history of pain abdomen and anorexia. On examination she had pallor, and her abdominal examination revealed hepatomegaly and a large ovoid mass with a notch facing medially, felt in the hypogastric region and extending to the right iliac fossa. Laboratory tests showed Hb-6.3 g%; WBC and platelet counts were in normal limits; and liver function tests were normal.

Ultrasonography and CT scan of abdomen-pelvis revealed absence of spleen in its normal position (Fig. 1 & 2) and a well-defined soft-tissue density/mass in pelvis in midline and right lateral aspect suggestive of enlarged spleen, measuring approximately 8.2 x 15.5 x 12.5 cm just anterior to the uterus and urinary bladder (Fig. 3 & 4).

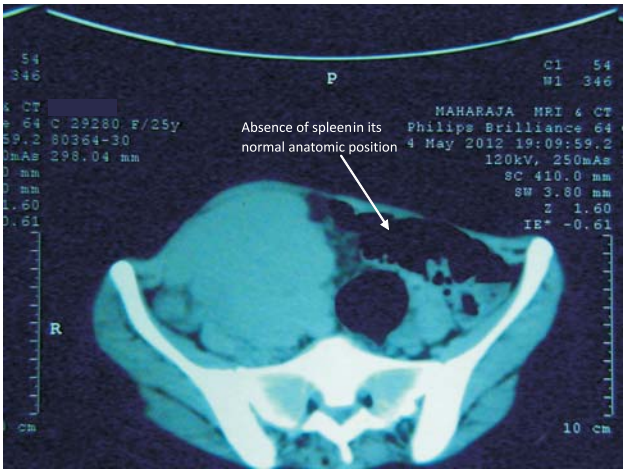


Fig. 1: *CT scan abdomen showing absence of spleen in its normal anatomic position.*

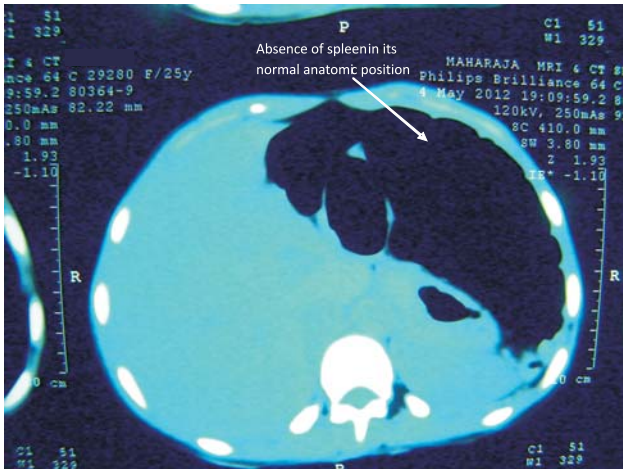


Fig. 2: *CT scan abdomen showing absence of spleen in its normal anatomic position.*

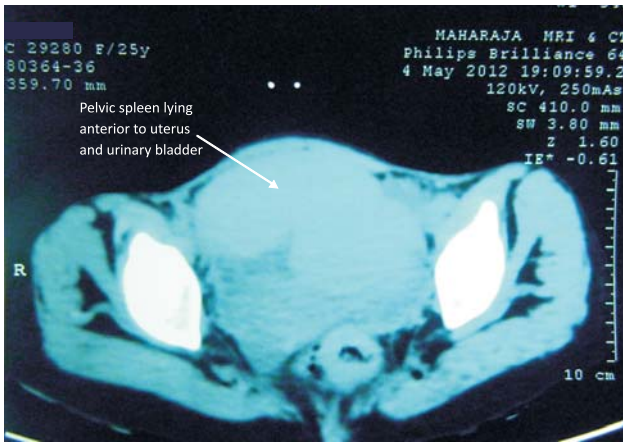


Fig. 3: *CT abdomen showing pelvic spleen lying anterior to uterus and urinary bladder.*

**** Professor and Head of Department, ** Associate Professor, *** Resident, Department of Medicine, S.P. Medical College, Bikaner - 334 003, Rajasthan.***

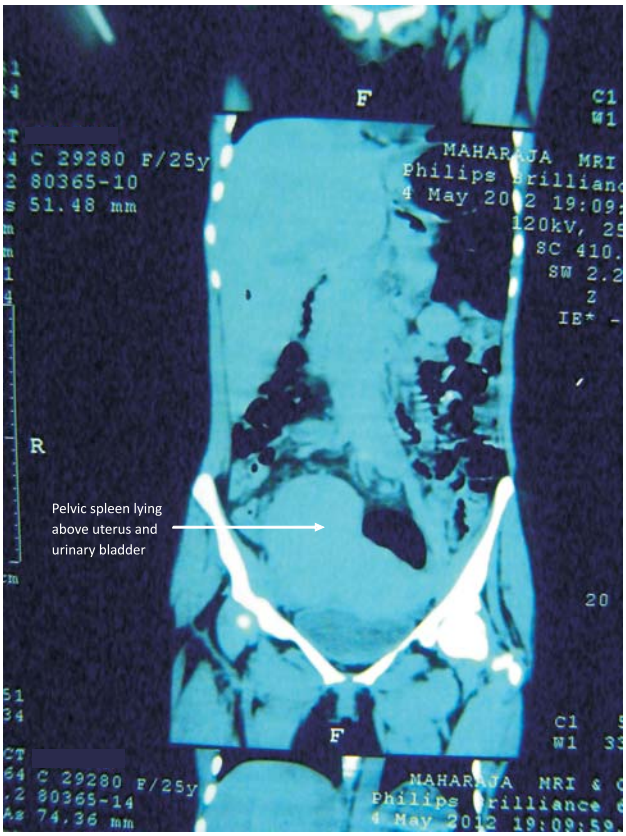


Fig. 4: *CT abdomen showing pelvic spleen lying above uterus and urinary bladder.*

Patient gave history of three normal vaginal deliveries without any complications, but unfortunately patient did not have any previous records or investigations regarding pelvic mass or wandering spleen.

A diagnosis of a wandering (pelvic) spleen with enlargement was made, and the patient was treated to correct her anaemia, and referred to a general surgeon for further management.

Discussion

Before discussing this rare case let us recapitulate the development and anatomy of spleen. The spleen develops from the mesoderm in the dorsal mesogastrium. It lies in the left hypochondrium behind the stomach, and is about 12 cm long and 7 cm broad[1]. The spleen is fixed in position by the lieno-renal and gastro-splenic ligaments; the phrenico-colic ligament provides additional support.

Wandering spleen is defined as a mobile spleen that is attached only by an elongated vascular pedicle, allowing it to migrate to any part of the abdomen or pelvis. It is a result of congenital anomalies in the development of the dorsal mesogastrium and the absence or malformation of normal splenic suspensory ligaments[2, 3]. However, acquired anomalies have been described and are attributed to laxity of the ligaments due to weakness of the abdominal wall, multiple pregnancies, hormonal changes, or increase in the size in the spleen[4].

Wandering spleen is most commonly diagnosed in young children[5] as well as women between the ages of 20 and 40[6]. Even so, the disease is very rare, fewer than 500 occurrences of the disease have been reported as of 2005[5], of which around 148 (including both children and adult cases) were documented to have been from between 1960 and 1992[7]. Less than 0.5% of all splenectomies, i.e., surgical removal of the spleen, are performed due to having this disorder[8].

The clinical presentation of a wandering spleen is variable; patients may be asymptomatic, or they may have acute abdominal crisis or chronic vague lower abdominal pain[9]. The most common presentation in children is an acute surgical abdomen occurring due to infarction from torsion of the splenic pedicle[10, 11]. Physical factors may cause ischuria, constipation, as well as numerous spleen-related diseases such as hypersplenism, thrombocytopenia, and lymphoma[7].

The clinical diagnosis of wandering spleen may be quite difficult and the haematological and biochemical investigations may be non-specific. Laboratory tests may reveal elevated inflammatory markers and evidence of hypersplenism or functional asplenia[12]. Non-invasive imaging procedures such as ultrasonography, scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI) are usually diagnostic. However, ultrasonography is still being considered to be the most reliable for diagnosis of wandering spleen[13]. The non-invasiveness of ultrasonography makes it an acceptable modality, especially in children.

In the absence of infarction, thrombosis and hypersplenism, in patients presenting with an acute abdomen, detorsion and splenopexy is a recognised surgical option[14]. Splenic preservation is highly recommended in very young patients, those under 1 year of age up to those in the third decade of life, who are at particular risk for overwhelming post-splenectomy sepsis[15]. But if there is no blood flow after unwinding the spleen through detorsion, then splenectomy must be performed[6]. Recently, laparoscopic procedures have been introduced for splenic surgery and it has been shown to offer the benefits of minimally invasive surgery[12, 15].

Conclusion

Wandering spleen is a rare condition and difficult to

diagnose clinically, only imaging modalities will help to establish the abnormal location of spleen. It is an important condition about spleen to be known as some of these patients may present with acute abdomen. When wandering spleen is diagnosed, the treatment of choice is splenopexy in asymptomatic and even symptomatic patients without the presence of splenic necrosis. If splenic necrosis is present, a splenectomy is usually required.

References

1. Singh I. Essentials of anatomy. New Delhi: Jaypee Brothers Medical Publishers Ltd. 2002, P 283.
2. Liu HT, Lau KK. Wandering spleen: an unusual association with gastric volvulus. *AJR Am J Roentgenol* 2007 Apr; 188(4): W328-30.
3. Chawla S, Boal DK, Dillon PW, Grenko RT. Splenic torsion. *Radiographics* 2003 Mar-Apr; 23(2): 305-8.
4. Stringel G, Soucy P, Mercer S. Torsion of the wandering spleen: splenectomy or splenopexy. *J Pediatr Surg* 1982 Aug; 17(4): 373-5.
5. Alawi MH, Khalifa A, Bana SH. Wandering Spleen: A Challenging Diagnosis (PDF). *Pakistan Journal of Medical Sciences* 2005; 4.
6. Safioleas MC, Stamatakos MC, Diab AI, Safioleas PM. Wandering spleen with torsion of the pedicle. *Saudi Med* 2007; J28(1): 135-6. PMID 17206307.
7. Satyadas T, Nasir N, Bradpiece HA. Wandering spleen: case report and literature review. *J R Coll Edinb* 2002; 47: 512-4.
8. Kinori I, Rifkin MD. A truly wandering spleen. *J ultrasound Med* 1988; 7: 101-5.
9. Alawi MH, Khalifa A, Bana H. Wandering spleen: A Challenging diagnosis. *Pak J Med Sci* 2005; 21(4): 482-4.
10. Buchner M, Baker MS. The wandering spleen. *Surg Gynecol obstet* 1992; 175: 373-87.
11. Abel I. Wandering spleen with torsion of the pedicle. *Ann Surg* 1933; 98: 722-5.
12. Fiquet-Francois C, Belouadah M, Ludot H, Defauw B. Wandering spleen in children: multicenter retrospective study. *J Pediatr Surg* 2010 Jul; 45(7): 1519-24.
13. Tait NP, Young IR. The wandering spleen: an ultrasonic diagnosis. *J Clin ultrasound* 1985; 13: 45-6.
14. Hirose R, Kitano S, Bando T *et al*. Laparascopic Splenopexy for Paediatric wandering spleen. *J paediatric Surg* 1998; 33: 1571-3.
15. Soleimani M, Mehrabi A, Kashfi A *et al*. Surgical treatment of patient with wandering spleen: report of six cases with a review of the literature. *Surg Today* 2007; 37(3): 261-9.

CASE REPORT

JIACM 2013; 14(1): 76-9

Recurrent herpes zoster related myelitis in an immunocompetent child

GA Khwaja, S Raghuvanshi***, M Gupta*, D Chowdhury**, M Hirve***, A Kulkarni***, A Batla****

Abstract

Cases of varicella-zoster virus (VZV) myelitis have been reported in immunocompromised adults, but we report the rare occurrence of recurrent VZV myelitis in an immunocompetent child who initially developed myelitis with paraparesis after a right-sided T11-L1 distribution herpes zoster or shingles. Recurrent cervico-dorsal myelitis caused by VZV, five-and-a-half months later, was verified by the presence of new-onset clinical symptoms and signs, extensive spinal cord lesion on MRI and evidence of anti-VZV IgM antibodies in the serum.

Introduction

Herpes zoster is more common in the elderly and myelitis or myelopathy is a rare complication that usually develops in the immunocompromised host. We report a rare case of recurrent HZ related myelitis in an immuno-competent child.

Case history

An 11-year-old girl, reported to us with a one-and-a-half months history of weakness in all the four limbs with decreased sensation below the clavicles. Her history revealed that seven months prior to admission, she had developed a vesicular eruption over the T11 to L1 dermatomes on the right side of the body. The eruptions subsided within ten days of onset but were followed 4 days later by the development of an acute onset asymmetric paraparesis (R > L) along with sensory loss below the umbilicus (T11 level) and retention of urine for which she was catheterised. The illness evolved over 10 days and then remained static for the next two weeks. This was followed by a complete recovery over the next one month, without any specific treatment. Subsequently she remained asymptomatic and ambulatory for the next 2 months. Around 5 months after the onset of the initial problem she underwent surgery for right-sided nephrolithiasis under general anaesthesia, without any complications. One month post-surgery she developed an acute onset quadriparesis (lower limbs > upper limbs) which evolved over 7 days and was accompanied by decreased sensation below the clavicles (T2 level) but without any bladder or bowel involvement. There was no history of a preceding skin rash during this recurrent episode. The upper limb weakness started improving within a week and recovered significantly over the next 15 days, but the lower limb weakness persisted without much improvement over the next one month. Besides a history of chicken pox at 4 years of age, the past history was insignificant.

On examination at the time of presentation, her vitals were maintained. General examination was unremarkable except for the presence of hyperpigmented, healed scar marks on the skin over the T11 to L1 dermatomes on the right side (Fig. 1). There was no bony tenderness or

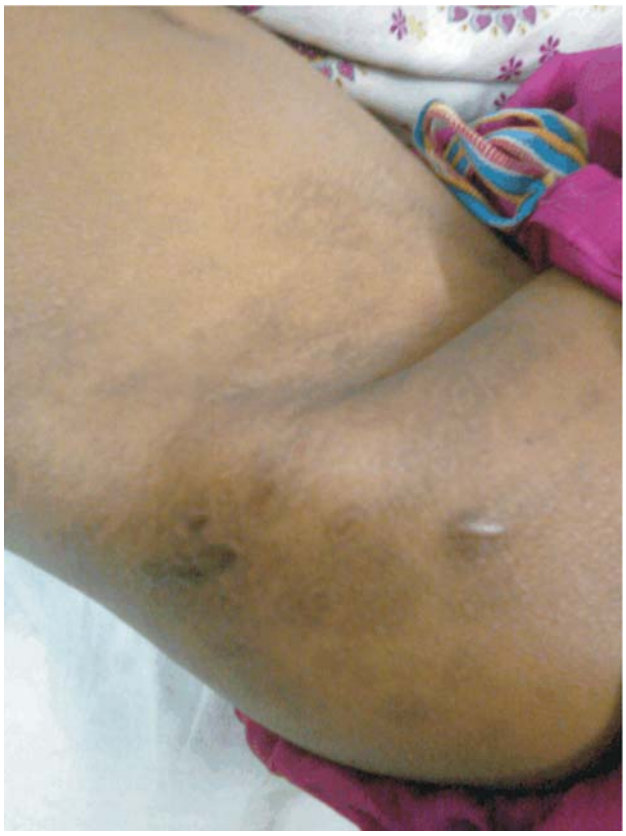


Fig. 1: *Hyperpigmented, healed scar marks on the skin over the T11 to L1 dermatomes on the right side.*

**** Director-Professor, ** Professor, *** Senior Resident, Department of Neurology, G.B. Pant Hospital, Jawaharlal Nehru Marg, New Delhi - 110 002.***

deformity of the spine. On examination, higher mental functions and cranial nerves were intact. Tone was normal in the upper but increased in both the lower limbs. Power was grade IV/V in both the upper limbs, and grade II/V in both the lower limbs. All DTRs were brisk and plantars were bilaterally extensor, with retained abdominal reflexes. She had a 50% loss of sensation for touch and pain below the T2 spinal level, with bilateral impaired vibration and joint position sense.

Laboratory data revealed normal complete blood count, blood biochemistry, and connective tissue profile. Her HIV status was negative. X-ray chest, cervical and dorsal spine were normal. MRI of the cervico-dorsal spine revealed a hyperintense intramedullary signal involving the cord from C6 to D8 level on T2-weighted images and a post-gadolinium enhancement of the cord at the mid-dorsal level suggestive of myelitis (Fig. 2). CSF examination was essentially normal (no cells; protein - 46 mg%; sugar - 71mg%). ELISA test for varicella-zoster IgM antibodies was negative in the CSF but positive in the serum, suggestive of a recent exposure to the virus. CSF-PCR for VZV-DNA was not done due to financial constraints.

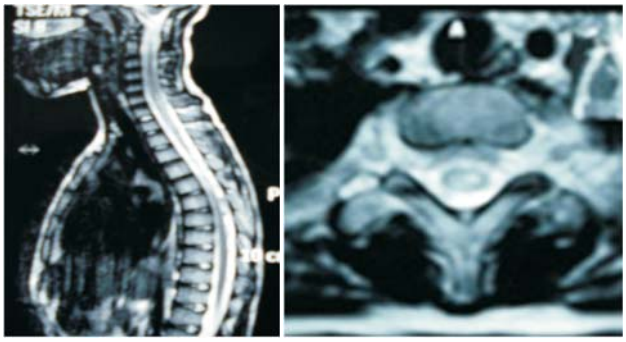


Fig. 2: *T2-weighted saggital and axial MRI images of the cervico-dorsal spine showing a hyperintense intramedullary signal involving the cord from C6 to D8 level.*

A diagnosis of recurrent herpes zoster related myelitis was made. She was treated with oral acyclovir, 400mg five times daily for 14 days and also given IV methyl-prednisolone pulse therapy in a dose of 500mg/day for 5 days followed by tapering doses of oral steroids over a period of one month, with a significant recovery of 50% at one month post-treatment follow-up.

Discussion

Varicella-zoster virus (VZV) is an exclusively human, highly neurotropic, alpha-herpes virus[1]. Primary infection causes chickenpox, after which the virus becomes latent in cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia along the entire neuraxis[1]. Decades later, reactivation of the latent infection can result in herpes zoster (HZ) with dermatomal vesicular rash or shingles, usually restricted to one to three dermatomes or zoster sine herpete (pain without rash)[1,2]. Neurological complications of HZ include: dorsal root or cranial nerve ganglionitis, post-herpetic neuralgia, segmental sensory loss or zoster paresis, polyradiculoneuritis, aseptic meningitis, meningo-encephalitis, ventriculitis, leukoencephalopathy, vasculopathy, necrotising angiitis, and transverse myelitis or myelopathy[3].

Usually, primary varicella is a disease of childhood, whereas its reactivation infection, herpes zoster is encountered in the aged with declining VZV-specific cell-mediated immunity[1,3]. Of all patients with zoster, more than 66% are older than 50 years; fewer than 10% are younger than 20 years, and only 5% are younger than 15 years[4]. Varicella in infancy can predispose to zoster earlier in adulthood[1]. Our patient had suffered from chickenpox at 4 years of age and developed shingles at 11 years of age.

Approximately 25% of patients with human immunodeficiency virus (HIV) and 7 - 9% of transplant patients experience a bout of zoster, and recurrent herpes occurs almost exclusively among people who are immunosuppressed[3]. In children, zoster is more likely to be encountered in the setting of acute lymphocytic leukaemia or malignancy[3]. Our patient however had neither and was not immunocompromised but developed recurrent zoster-related myelitis.

Around 25 - 40% cases of transverse myelitis are caused by viral infections[3]. Myelitis or myelopathy however, is a rare complication of HZ that usually develops in the immunocompromised host[2]. It was first reported by Hardy in 1876, but most subsequent reports have described either single or a few cases only[5]. The reported frequency of transverse myelitis during or after varicella infection is around 0.3 to 0.8% only[2,3]. Moreoever, the occurrence of recurrent myelitis is rare and more so in the immunologically normal patients, as was the case with our patient. There are only a few case reports of recurrent VZV myelopathy developing weeks to months and even years after an initial episode of myelopathy in immuno-competent adults but none in childhood[6,7,8,9,10]. McAlpine *et al* and O'Donell *et al* reported patients with recurrent myelitis assosciated with encephalitis and Nakano *et al* reported a patient with pure recurrent myelitis[7,8].

Onset of herpes zoster myelitis is usually acute or subacute with a mean delay of 2 weeks between the initial vesicular rash and the neurological disturbance[2]. The temporal course is variable and the disease usually evolves over 1 to 3 weeks[2]. Neurological symptoms usually begin unilaterally, ipsilateral to the rash, but subsequently

become bilateral. Motor manifestations usually predominate, followed by spinothalamic and posterior column sensory abnormalities or bladder dysfunction. A self-limiting, monophasic, spastic paraparesis with or without sensory features and sphincter problems usually occurs in the immunocompetent patients[1]. An insidious, progressive, and sometimes fatal myelitis is seen mostly in immunocompromised patients[1]. A chronic or remitting exacerbating myelopathy may also be encountered[2].

The diagnosis of HZ myelitis is usually not difficult when the neurological symptoms develop in temporal proximity to the rash[2]. It is however, important to remember that VZV myelitis may develop in the absence of a skin rash also[6]. In our case, the first attack of transverse myelitis developed within 2 weeks of the appearance of the rash but the second attack occurred after a delay of five-and-a-half months and without a recurrence of the rash. Only a few cases of recurrent VZV myelitis without a preceding skin rash have been reported in the literature so far[6]. No diagnostic test is completely accurate for VZV myelitis. Magnetic resonance imaging (MRI) is nonspecific and usually shows longitudinal enhancing cord lesions, in proximity of the involved dermatome[1]. In our case however, the MRI during the recurrent attack of myelitis, revealed signal changes extending several segments above the initial site of the skin rash. CSF (cerebrospinal fluid) profile usually includes a mononuclear pleocytosis with normal or elevated protein[2]. The diagnosis is confirmed by finding VZV-specific DNA or anti-VZV IgG in cerebrospinal fluid but the virus cannot usually be isolated from the blood or CSF[1,3]. Evidence of active VZV infection is supported by any of the following positive tests: anti-VZV IgM in serum or cerebrospinal fluid; anti-VZV IgG in cerebrospinal fluid; VZV DNA in blood mononuclear cells or cerebrospinal fluid[1]. In our case, ELISA test for Varicella-Zoster IgM antibodies was negative in the CSF but positive in the serum, suggesting a recent exposure to the virus.

The pathogenesis of VZV myelitis is unclear. Both, direct viral invasion of the cord and an abnormal immune response to the infectious agent involving allergic and vascular mechanisms have been implicated[3]. Demonstration of the VZV antigen in CSF cells by immunofluorescence or isolation of VZV from the CSF is a confirmative evidence for viral infection of the central nervous system but is rarely successful[3]. Pathologic and virologic analyses of the spinal cord from fatal cases has however, revealed frank invasion of VZV in the parenchyma and, in some instances, spread of the virus to adjacent nerve roots[1].

Previous neuro-pathological reports of HZ myelitis have reported findings of a necrotising inflammatory myelopathy with or without associated vasculitis[1]. Demyelination has also been reported and may be secondary to viral infection and destruction of oligodendrocytes, since Cowdry type A inclusions have been detected in these cells[2]. Pathological involvement in HZ myelitis is usually most severe in the dorsal root entry zone and posterior horn of the spinal cord segment corresponding to the involved dermatome with a variable spread both horizontally and vertically. The major neuropathological findings in 9/13 patients with HZ myelitis in a study by Devinsky *et al*, included posterior horn abnormalities in all 9 patients, demyelination in 6/9 patients, and vasculitis with necrosis in 4/9 patients[2]. The spinal cord pathology suggests four principal mechanisms of injury: direct infection and/or immune-mediated destruction of oligodendrocytes with resultant demyelination; infarction secondary to vasculitis; leptomeningitis; and infection of other components including neurons, astrocytes, and ependymal cells[1].

Our patient is a unique and rare case of recurrent herpes zoster related myelitis in an immunocompetent child in which the first attack of myelitis followed the occurrence of shingles within 2 weeks but the second attack of myelitis occurred not only after a long gap of five-and-a-half months of the initial attack, but also at a site much higher than the initial site, and without a recurrence of active shingles. The first attack from which the patient recovered spontaneously, appears to be related to direct viral invasion of the spinal cord at the site of infection. Whether the second attack represents a recurrent active ascending viral infection of the cord or a delayed immune-mediated hypersensitivity reaction at a site distant from the primary site of infection remains debatable.

The spectrum of clinical outcomes in VZV myelitis ranges from spontaneous recovery to ascending progression and death. Rapid progression and flaccidity below the level of lesion carry a poor prognosis[3].

Antiviral drugs, can prevent multiplication and spread of the virus in the CNS and prevent or attenuate the evolving myelopathy[2, 11]. Treatment decisions about zoster should take into account the patient's age and immune status. In immunocompromised patients, intravenous acyclovir (5 to 10 mg/kg three times daily for 5 to 7 days) is recommended[1]. In immunocompetent patients age 50 and older, treatment with oral antiviral drugs – acyclovir (800 mg 5 times a day), famciclovir (500 mg three times a day), or valacyclovir (1g three times a day) is recommended for 10 - 14 days[1]. In immunocompetent patients younger than age 50, antiviral drugs are not

required, but speed healing of the rash[1]. Our patient was however given a course of oral acyclovir in view of the recurrence of myelitis.

Steroids have also been used for treatment, but the benefit is unknown and double-blind, placebo-controlled studies to confirm additional efficacy are also lacking. In certain cases it may be worthwhile to explore the use of corticosteroids under antiviral coverage[2]. There is a case report of recurrent HZ myelitis resistant to acyclovir, responding to methylprednisolone pulse therapy[1]. We also used methylprednisolone pulse therapy and oral steroids in our patient. Human interferon alpha has also been used to treat recurrent HZ myelitis[12].

In conclusion, our case exemplifies that physicians must maintain a high index of suspicion in atypical cases of myelitis. Moreover, early diagnosis and treatment of VZV myelitis with antiviral therapy is important to arrest the evolving myelopathy and prevent its recurrence.

References

1. Nagel MA, Gilden DH. Protean manifestations of Varicella-Zoster Virus infection. *Cleveland Clinic Journal of Medicine* 2007; 74: 490-504.
2. Devinsky O, Cho E-S, Petito CK, Price RW. Herpes Zoster myelitis. *Brain* 1991; 114: 1181-96.
3. Yýlmaz S, Köseoðlu HK and Yücel E. Transverse Myelitis caused by Varicella Zoster: Case Reports. *The Brazilian Journal of Infectious Diseases* 2007; 11(1):179-81.
4. Janniger CK, Driano A N. Zoster – e medicine. Updated: Mar 1, 2010.
5. Hardy M, Du zona. Gazette des Hospitaux Civils et Militaires 1876; 49: 827-8.
6. Gilden D, Nagela MA, Ransohoff RM *et al*. Recurrent Varicella Zoster virus myelopathy *J Neurol Sci* 2009 January 15; 276(1-2): 196-198.
7. McAlpine D, Kuriiwa *et al*. Acute demylienating disease complicating herpes zoster. *J Neurol Neurosurg Psychiatry* 1959; 22: 120-3.
8. O'Donnell PP, Pula TP, Sellman M, Camenga DL. Recurrent herpes zoster encephalitis. A complication of systemic lupus erythematosus. *Arch Neurol* 1981 Jan;38(1): 49-51.
9. Baik JS, Kim WC, Heo JH, Zang HY. Recurrent Herpes Zoster myelitis. *JKMS* 1997; 12: 360-3.
10. Gilden DH, Beinleich BR, Rubinstien EM *et al*. Varicella-Zoster virus myelitis: an expanding spectrum. *Neurology* 1994; 44: 1818-23.
11. SM de Silva, Mark AS, Gilden DH *et al*. Zoster Myelitis: Improvement with antiviral therapy in two cases. *Neurology* 1996; 47: 929-31.
12. Nakano T, Awaki E, Araga S *et al*. Recurrent Herpes Zoster myelitis treated with human interferon alpha: a case report. *Acta Neurol Scand* 1992 May; 85(5): 372-5.

CASE REPORT

JIACM 2013; 14(1): 80-2

Thyroid hormone resistance – An uncommon cause for elevated thyroid hormones

Yogendra Singh,CS Bal**, Anubhuti***, Bindu Kulshreshtha*****

Abstract

The occurrence of thyroid hormone resistance has been described earlier, albeit rarely. The condition usually presents with an eumetabolic state inspite of elevated levels of circulating thyroid hormones T3 and T4. Here, we describe a 45-year-old female patient who presented with a clinical and hormonal profile suggestive of thyroid hormone resistance.

Introduction

Thyroid hormones are essential for multiple aspects of basic metabolic processes in adults, and growth and development during intranatal period and childhood. Resistance to the action of thyroid hormone has been described *albeit* rarely. It usually presents as an autosomal dominant disorder characterised by reduced tissue responsiveness to thyroid hormones[1]. Refetoffet first described this syndrome in 1967[2,3]. While some cases of patients with thyroid hormone resistance have been reported from the West, to the best of the our knowledge there are only two previous cases of thyroid hormone resistance reported from India[4,5].

The thyroid hormone secretion is stimulated by TSH, which in turn is under a negative feedback regulation of thyroid hormones. The RTH (resistance to thyroid hormone) is characterised by high levels of circulatory thyroid hormones and inappropriately normal or elevated values of TSH[6]. The clinical profile of patients with RTH includes hyperthyroidism, hypothyroidism, or a combination of both. This is due to different tissue distribution of receptor isoforms TRA1, TRB1, and TRB2[7,8].

Case report

A 45-year-old female patient visited a private clinic for the evaluation of weight loss, night sweats, and palpitations on and off for 8 months. She was empirically started on anti-tuberculosis treatment (ATT) which she received for 6 months. There was no history of fever, cough, or lymphadenopathy. ATT was stopped 2 months prior to endocrine evaluation. She also complained of heat intolerance, altered bowel habits, and increased hair loss from the scalp. There was no history of neck swelling. She also experienced paraesthesias in hands and feet for 6 months. She had developed secondary amenorrhoea for the past one year. Inspite of treatment with ATT, palpitations and weight loss continued for which she was advised thyroid function tests and referred to the endocrine clinic for further evaluation. On examination, she was average built, height was 160 cm and weight 49 kg. Blood pressure was 106/70 mmHg and pulse rate 96 beats/min. Her thyroid gland was soft and symmetrically enlarged. There was no exophthalmos, and myxoedematous skin lesions were absent. The systemic examination including nervous system evaluation was normal.

Laboratory investigations revealed elevated free T4 and free T3 with normal TSH levels. We repeated the thyroid hormone profile twice and found similar results (Table 1). Anti-TPO antibody was negative. USG of neck revealed diffuse enlargement of the thyroid gland. Prolactin and cortisol levels were normal. LH and FSH were high (47.1 mIU/ml and 39.4 mIU/ml) along with low oestradiol levels (43.24 pmol/L).

We investigated this patient further with T4 suppression test and MRI of brain. In T4 suppression test we used 100 µgm of levothyroxin thrice a day for 10 days. Thyroid function test and radioactive iodine uptake were performed before and after thyroxine administration. There was suppression of TSH level over 10 days to 0.142 (Table I). Basal radio-iodine uptake (RAIU) 2-hour was 2.2 % and 24-hour uptake was 13.5%. Post-thyroxine, there was no suppression in RAIU (2-hour uptake was 5.5% and 24-hour uptake was 17.5%). Surprisingly patient reported gradual improvement in paraesthesias after T4 suppression test. At this stage, nerve conduction velocity test was normal. MRI brain revealed normal pituitary gland. The patient's brother, sister, and daughter had normal thyroid profile. Other family members did not report for evaluation.

Senior Resident, Department of Endocrinology, *** Assistant Professor, Department of Biochemistry, * Assistant Professor, Department of Endocrinology, PGIMER, Dr. RML Hospital, Baba Kharak Sing Marg, New Delhi - 110 001; ** Professor, Department of Nuclear Medicine, AIIMS, Ansari Nagar, New Delhi - 110 029.***

Table I:

S. No.	TSH (µm/ml) (0.5-5)	Free T3 (pg/dl) (0.7-2)	Free T4 (ng/dl) (2-4.4)
1.	1.59	14.3	4.17
2.	1.06	12.4	4.53
3.	1.12	11.3	4.32
Post-T4 suppression test	0.142	7.36	4.42

Discussion

RTH (resistance to thyroid hormone) is characterised by reduced clinical and biochemical manifestations of thyroid hormone action inspite of elevated circulating thyroid hormone levels. Thyroid hormones act by binding to thyroid hormone receptor which is encoded by the THRalfa (Thyroid hormone receptor alpha) and THRbeta genes located on chromosome 3 and 17 respectively[9]. Although THRalfa1and THRbeta1 are ubiquitously expressed, THRalfa1 is primarily expressed on heart and bone, where as THRbeta1 is more abundant in the liver, kidneys, and thyroid. THRbeta2 expression is limited to pituitary, hypothalamus, retina, and inner ear; and THRbeta3 expression has been detected mainly in the heart and kidney[10,11]. The linkage between RTH and thyroid receptor beta (TRB) gene was described first in 1988[11,12,13]; since then approximately 100 mutations have been detected in this gene[13].

It usually presents as autosomal dominant transmission but *de novo* mutations have also been reported. RTH without a structural THRbeta gene defect has also been described and occurs in approximately 10% of cases[15]. It has been postulated that cofactor interacting with THR may be responsible for the manifestations of RTH[15].

Most patients of RTH are clinically euthyroid, some individuals may appear to be hypothyroid or hyperthyroid. Furthermore, the same subject can manifest signs and symptoms of hypothyroidism in one tissue, while the findings may be suggestive of thyrotoxicosis in other tissues. Kong *et al* reported a patient with thyroid hormone resistance, who presented with palpitations and diffuse goitre but no other signs of hyperthyroidism[16].

The prevalence of RTH is reported to be about 1 case per 40,000 live births[17]. Familial occurrence of RTH has been documented in approximately 75% of cases[18]. On the basis of clinical features, two different forms of RTH have been described[9,10,14]: generalised RTH (GRTH) and pituitary RTH (PRTH).

GRTH is the most common form. Affected individuals appear eumetabolic despite elevated levels of thyroid hormones that are maintained by the hypersecretion of TSH in response to hypothalamic TRH. Around 15% patients who share the same biochemical phenotype exhibit clinical features of hyperthyroidism. PRTH patients usually manifest with symptoms and signs of hyperthyroidism.

Treatment of RTH should be based on assessment of tissue sensitivity to thyroid hormones. In most cases of GRTH, tissue RTH appears to be adequately compensated for by the increase in endogenous thyroid hormones, and no treatment is required. For GRTH patients who have features of hypothyroidism, or who cannot compensate by increasing thyroid hormone secretion because of prior erroneous diagnosis and ablative therapy, supraphysiological doses of thyroid hormones are recommended. Patients with PRTH who exhibit hyperthyroid features at tissue levels generally require treatment to reduce the elevated thyroid hormone levels. 3, 5, 3'-Triiodothyroacetic acid (TRIAC), a physiological metabolite of T3, can reduce TSH and endogenous thyroid hormone levels and alleviate symptoms[21]. However, the efficacy of TRIAC is variable, and its effect on heart rate is often minimal, probably because the decrease in thyroid hormone levels is offset by the intrinsic thyromimetic effect of the drug[22]. The differential diagnosis of RTH in face of increased FreeT4 and FreeT3 with normal or increased TSH include TSH secreting tumours[23]. In T4 suppression test, decreased RAIU post thyroxine is observed in 90 % cases of RTH, while usually not so in TSH secreting tumours.

The diagnosis of TRH in the present patient was based on clinical features, biochemical profile and MRI of pituitary. This patient presented with palpitations, which improved with propanolol. Surprisingly paraesthesias in our patient improved while on thyroxine therapy that had been given for a diagnostic T4 suppression test. Paraesthesia have been reported with hypothyroidism in around 64% of patients[24]. Thus, this was described a rare case of a 45-year-female with resistance to thyroid hormone.

References

1. Refetoffs. The thyroid, 9th edition, Philidelphia, Lippincott Wilkins, 2005;1109-29.
2. Kim JY, Chol ES, Lee JC *et al*. Resistance to thyroid hormone, missense mutation in thyroid hormone beta gene. *Korean J Internal Medicine* 2008; 23: 45-8.
3. Yun YS, Hong SK, Ahn CW *et al*. Mutation in thyroid hormone receptor-beta with patient with generalised resistance and pituitary resistance to thyroid hormone. *J Korean Soc. Endocrinology* 2000; 15; 113-20.
4. Agrawal NK, RastogiA, Naik D *et al*. Thyroid hormone resistance,

Postgrad Med J 2008; 84(995): 473-7.

5. Garg MK, Saini JS. A case of familial euthyroid hyperthyroxinemia: *J Association Physician India* 1999; 47(3): 340-1.
6. Refetoff S, Weiss RE, Vsala SJ. The syndromes of resistance of thyroid hormone. *Endocrinology Rev* 1993; 14: 348-99.
7. Refetoff S, DeWind LT, DeGroot LJ. Familial syndrome combining deaf-mutism, stippled epiphysis, goitre. *Clinical Endocrinology and Metabolism* 1967; 27: 279-94.6
8. Usala SJ, Menke JB, Watson TL *et al*. A homozygous deletion in the c-erbAb thyroid hormone receptor gene in a patient with generalized thyroid hormone resistance: Isolation and characterization of the mutant receptor. *Molecular Endocrinology* 1991; 5 327-35.
9. Ji Hye Kim, Tae Sun Park, Hong Sun Baek, Ji Hyun Park. A Newly Identified Insertion Mutation in the Thyroid Hormone Receptor-Gene in a Korean Family with Generalised Thyroid Hormone Resistance. *J Korean Med Sci* 2007; 22: 560-3.
10. Williams GR. Cloning and characterisation of two novel thyroid hormone receptor beta isoforms. *Mol Cell Bio* 2000; 20: 8329-42.
11. Lafranchi SH, Snyder DB, Sesser DE *et al*. Follow-up of newborns with elevated screening T4 concentrations. *J Pediatric* 2003; 143: 296-301.
12. Usala SJ, Bale AE, Gesundheit N *et al*. Tight linkage between the syndrome of generalised thyroid hormone resistance and the human c-erb A beta gene. *Mol Endocrinology* 2: 1217-20.
13. Brucker-Davis F, Skarulis MC, Grace MB, Weintraub BD. Genetic and clinical features of 42 kindred's with resistance to thyroid hormone. *Ann Intern Med* 1995; 123: 572-83.
14. Beck-Peccoz P, Chatterjee VK, Chin WW *et al*. Nomenclature of thyroid hormone receptor beta-gene mutations in resistance to thyroid hormone: consensus statement from the first workshop on thyroid hormone resistance, July, 1993, Cambrige, United Kingdom. *J Clin Endocrionolgy Metabolism* 1994; 78: 990-3.
15. Pohlenz J, Weiss RE, Macchia PE *et al*. Five new families with resistance to thyroid hormone not caused by mutations in the thyroid hormone receptor beta gene. *J Clin Endocrinology Metabolism* 1999; 84: 3919-28.
16. Kong APS, Lam CW, Chan AOS *et al*. Resistance to thyroid hormone in Chinese family. *Hongkong Med Jou* 2005; 11: 125-9.
17. Lafranchi SH, Snyder DB, Sesser DE *et al*. Follow-up of newborns with elevated screening T4 concentrations. *J Pediatric* 2003; 143: 296-301.
18. Refetoff S. Resistance to thyroid hormones. *Thyroid* 2005; 1109-293.
19. Beck-Peccoz P, Chatterjee VK. The variable clinical phenotype in thyroid hormone resistance syndrome. *Thyroid* 1994; 4: 225-32 .
20. Refetoff S, Dumitrescu AM. Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transportors and deiodination. *Clinical Endocrinology and Metabolism* 2007; 21(2): 277-305.
21. Refetoff S. Resistance to thyroid hormone. Current therapy in endocrinology and metabolism. 6th ed. St Louis: Mosby; 1997.
22. Kunitake JM, Hartman N, Henson LC *et al*. 3,5,3'-triiodothyroacetic acid therapy for thyroid hormone resistance. *J Clin Endocrinol Metab* 1989; 69: 461-6.
23. Cho by-clinical thyroidology. 2nd edition, Seoul: Korea Medical Book, 2005 .
24. Duffy RF, Van Denbosch J, Laman DM *et al*. Neuromuscular finding in thyroid dysfunction : A prospective clinical and electrodiagnostic study. *J Neurol Neurosurg Psychiatry* 2000; 68: 750-5.

"Diagnosis is not the end, but the beginning of practice."

– Frances Weld Peabody in "The Care of the Patient".

PICTORIAL CME

JIACM 2013; 14(1): 83-90

MRI spectrum of CNS tuberculosis

Vandana V Ahluwalia, Dayananda Sagar G**, TP Singh****, Nitish Arora**, Shamrendra Narayan***, MM Singh******

Abstract

Tuberculosis (TB) remains a major global problem and a public health issue of considerable magnitude. TB in any form is a devastating disease, which in its most severe form involves the central nervous system (CNS), with a high mortality and morbidity. There is a wide spectrum of CNS involvement in TB. Early diagnosis of CNS TB is crucial in appropriate management and in reducing morbidity and mortality. Noninvasive imaging modalities such as computed tomography (CT) scan and magnetic resonance imaging (MRI) are routinely used in the diagnosis of neurotuberculosis with MRI offering greater inherent sensitivity and specificity than CT scan. In addition to conventional MRI imaging, magnetisation transfer, diffusion and magnetic resonance spectroscopy techniques are also being evaluated for better tissue characterisation in CNS TB. The current pictorial essay describes the MRI spectrum of CNS TB.

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*[1], accounts for eight million deaths worldwide annually. Tuberculous involvement of the central nervous system (CNS) is an important and serious type of extra-pulmonary involvement. Approximately 10% of all patients with tuberculosis have CNS involvement[2]. However, its prevalence is greater in immunocompromised patients and is seen in upto 15% of cases of acquired immunodeficiency syndrome-related TB[3,4]. CNS TB usually results from haematogenous spread. However, it may result from direct rupture or extension of a subpial (beneath the pia mater) or subependymal focus (Rich focus). Granulomatous inflammatory reaction in CNS may involve the meninges, brain, spinal cord, and the bones covering the brain and spinal cord. It may manifest in a variety of forms including parenchymal and leptomeningeal tuberculomas, abscesses, cerebritis, vasculitis, infarction, meningitis, and osteomyelitis.

Spectrum of lesions in CNS TB

- TB meningitis
- Tuberculous granuloma (tuberculoma)
- Miliary and leptomeningeal granuloma
- Tuberculous cerebellar abscess
- Tuberculous encephalopathy
- Tuberculous cerebritis
- Vasculitis and infarction
- Cranial neuropathy
- Non-osseous spinal cord tuberculosis
- Calvarial tuberculosis, subdural and epidural abscess

TB meningitis (TBM)

TB meningitis is the most common manifestation of CNS TB in all age groups[4]. It may result from either haematogenous spread or rupture of Rich focus. Generally, pre-contrast MR imaging cannot detect pathological signal from meningeal inflammation or basal exudates in early stages. However, in later stages there may be

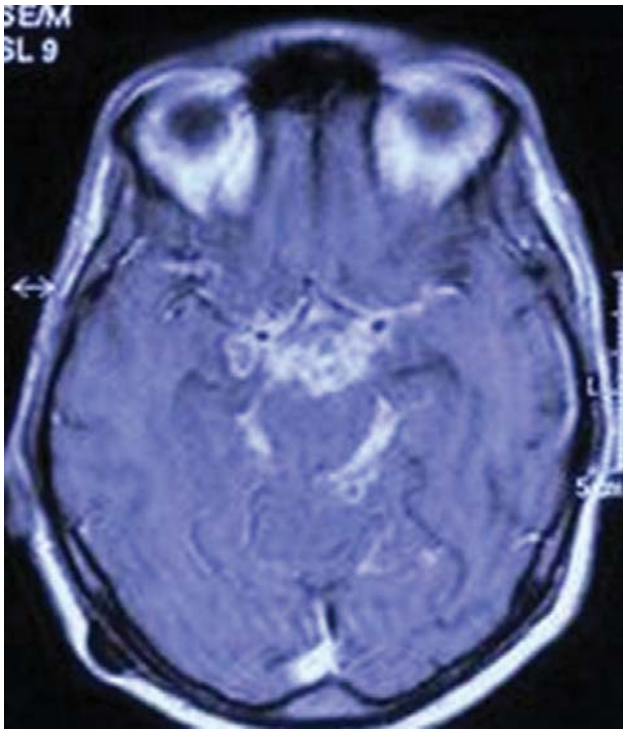


Fig. 1: *Tuberculous meningitis: Axial T1W post-contrast image shows meningeal enhancement in and around the basal cisterns.*

**** Associate Professor, ** Junior Resident, *** Lecturer, Department of Radiodiagnosis, **** Associate Professor, ***** Professor, Department of Medicine, Sarojini Naidu Medical College, Agra - 282 002, Uttar Pradesh.***

widening of subarachnoid spaces with associated T1 and T2 shortening of CSF. Post-contrast T1 images show diffuse meningeal enhancement around basal cisterns and sylvian fissures (Fig.1). This appearance is nonspecific and has a wide differential diagnosis that includes meningitis from other infective agents, inflammatory diseases such as rheumatoid arthritis, and sarcoidosis and neoplastic causes.

Magnetisation transfer spin echo (MT-SE) imaging following contrast injection is superior to conventional post-contrast imaging in demonstrating meningeal inflammation. Quantitative MT ratio is also of value in differentiation of TB meningitis from other chronic meningitis. Significantly lower MT ratio is seen in TB meningitis than pyogenic and fungal meningitis and significantly higher MT ratio than viral meningitis.

The most common complication is a communicating hydrocephalus and is caused by blockage of the basal cisterns by inflammatory exudates.

Ischaemic infarcts are also common, being seen in 20 - 40% cases, mostly within basal ganglia and internal capsule regions, and result from vascular compression and occlusion of small perforating vessels[3,5,6]. Cranial nerve involvement is seen in 17 - 70% cases, most commonly affecting second, third, fourth, and seventh cranial nerves.

Parenchymal granuloma (tuberculoma)

Tuberculoma is the most common parenchymal lesion in CNS TB. This lesion may be solitary, multiple, or miliary, and may be seen anywhere within the brain parenchyma, although it most commonly occurs within the frontal and parietal lobes. These granulomas usually involve the cortico-medullary junction and periventricular region as expected from haematogenous dissemination.

Non-caseating granuloma: It is usually iso-/hypo-intense on T1 and hyper-intense on T2-weighted images. Homogeneous enhancement is seen with gadolinium.

Caseating solid granuloma: It is usually hypo-intense on T1 and strikingly hypo-intense on T2-weighted images[7] (Fig. 2a, b. This relative hypo-intensity is attributed to the granulation tissue and compressed glial tissue in the central core resulting in greater cellular density than the brain parenchyma.

Granuloma with central liquefaction: It appears centrally hypointense on T1, and hyper-intense on T2-weighted images with a peripheral hypo-intense rim on T2W images. The low signal intensity of the capsule may be related to a layer of collagenous fibres with high protein concentration and low water content and a layer of outer inflammatory cells. Gd-DTPA-enhanced T1W images show rim enhancement in caseating granulomas. The oedema surrounding the granuloma is relatively less than pyogenic abscess (Fig. 3a, b). However, at times it is significant in the early stage.

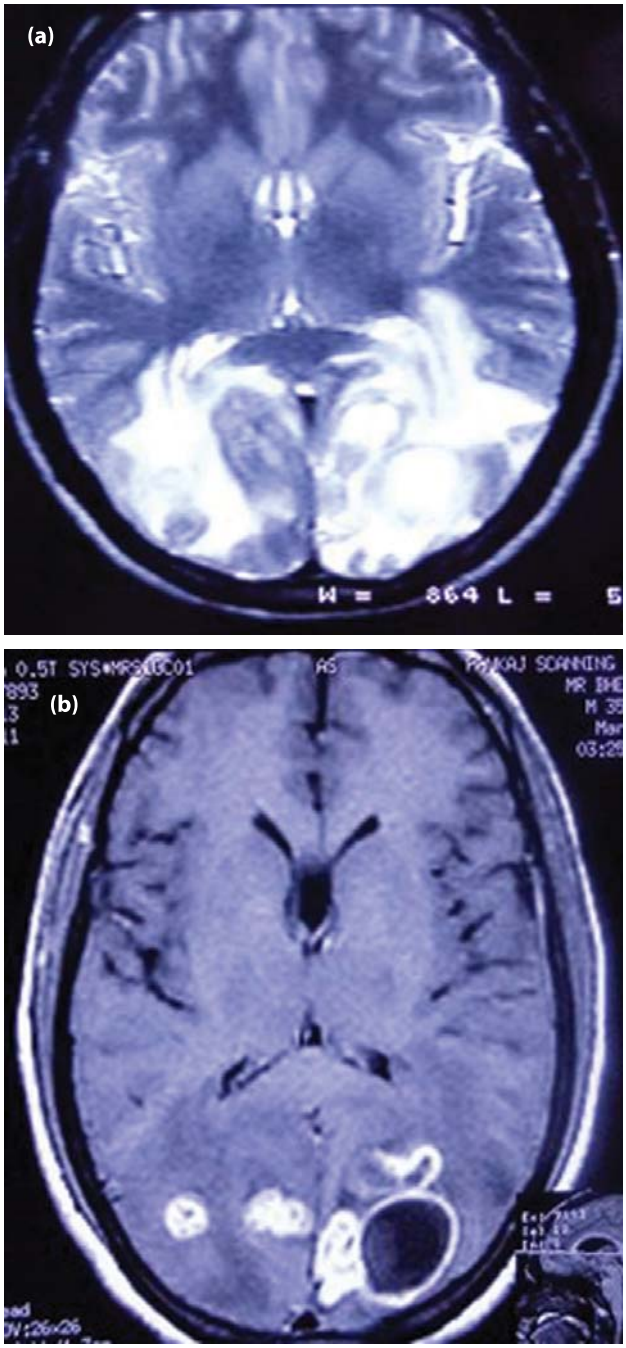


Fig. 2 a, b: *Parenchymal granulomas: Axial T2W (a) and post-contrast T1W (b) shows round hypointense lesion in Fig. a (tuberculous granuloma with caseation) and T2W hyper-intense lesion in the left occipital region with ring enhancement (tuberculous abscess).*

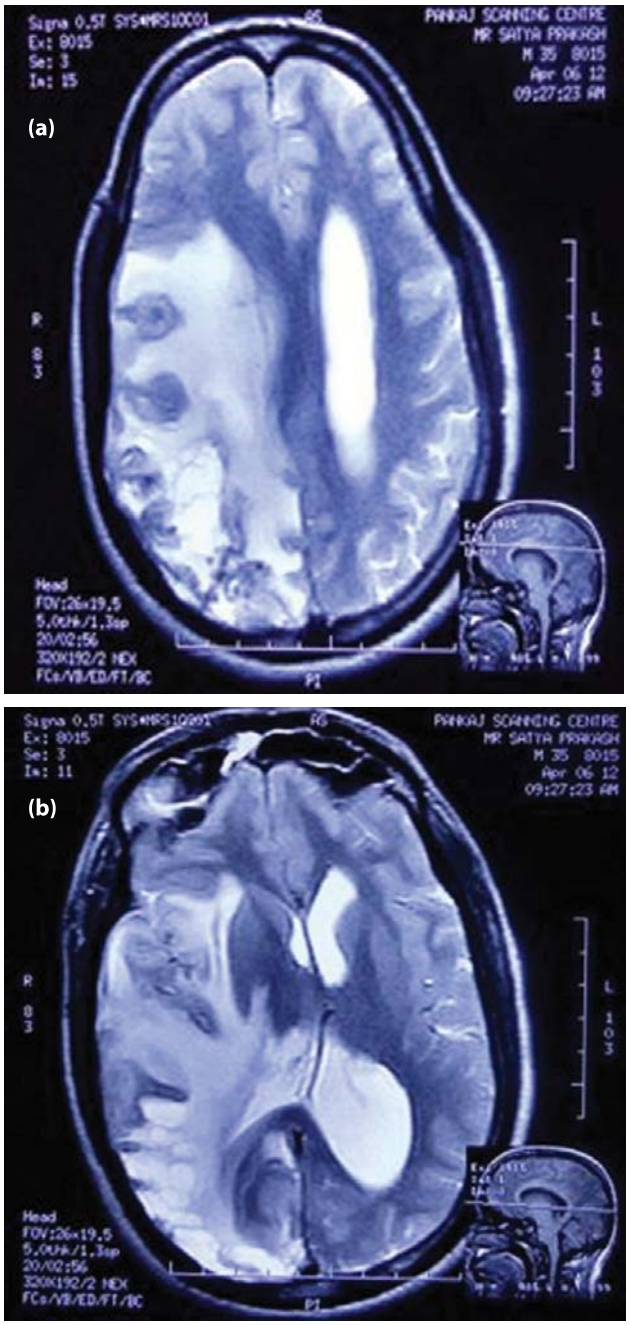


Fig. 3 a, b: *Granulomas in various stages of caseation: Axial T2W image showing granulomas in various stages of caseation with oedema and mass effect.*

MR spectroscopy shows prominent lipid peaks in tuberculomas as compared to other lesions such as metastasis and high-grade gliomas which shows lipid peaks in addition to other metabolite peaks like choline.

***Disseminated/miliary tuberculoma*:** This condition is a subtle clinical event demonstrated in patients with miliary pulmonary tuberculosis who have no clinical brain

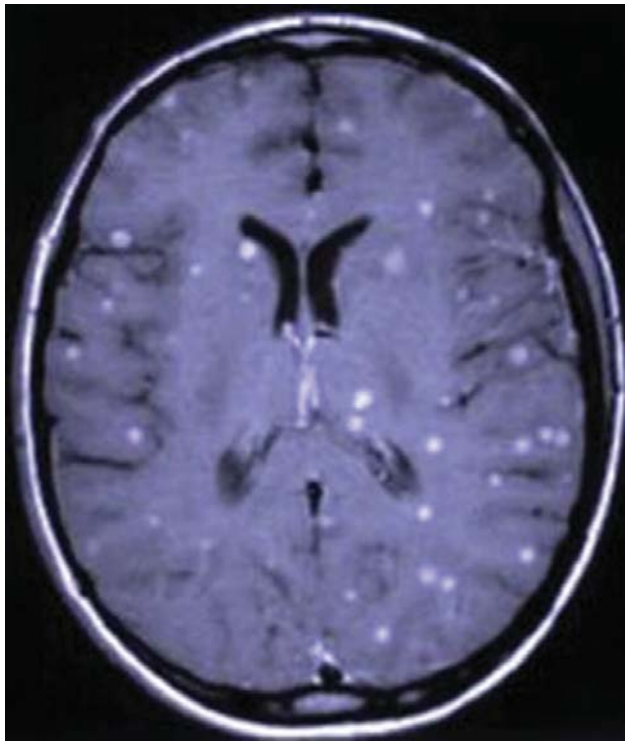


Fig. 4 : *Miliary tuberculosis: Axial post-contrast image shows multiple < 2 mm well-defined solid enhancing lesions.*

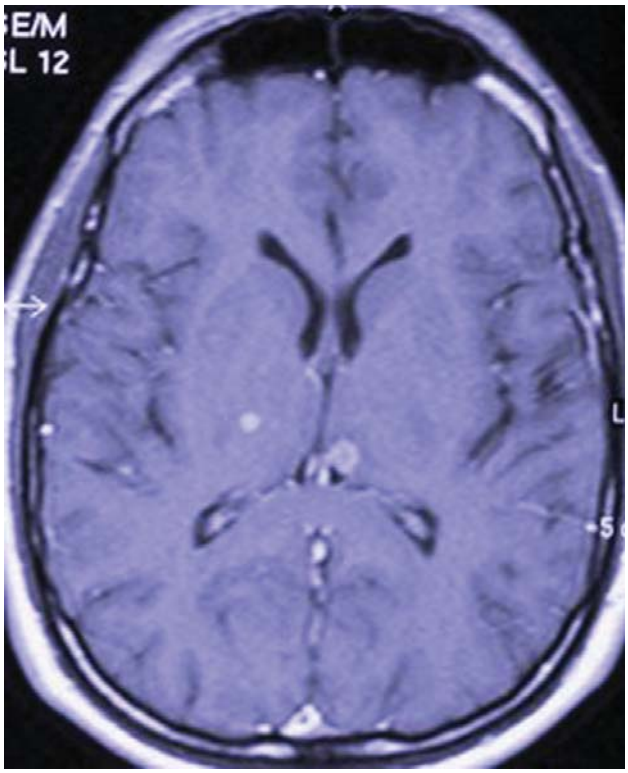


Fig. 5: *Leptomeningeal tuberculosis: Axial post-conrast T1W image shows a few solid enhancing nodules on cortical surface and in sulcal spaces.*

involvement. They may also occur in patients with TB meningitis. It is characterised by diffuse infiltration of brain by multiple small granulomas (< 2 mm) which have high or low signal on T2-weighted images (Fig. 4). Post-contrast shows numerous round areas of intense enhancement. Leptomeningeal granulomas show similar appearance; however, they are seen located in the sulcal spaces and basal cisterns (Fig. 5).

Tuberculous abscess

Tuberculous abscesses are occasionally seen. They occur in less than 10% of patients with CNS TB and are more common in the elderly and immunocompromised. They may be solitary or multiple and are frequently multiloculated. On imaging, a TB abscess may be indistinguishable from a caseating tuberculoma or a pyogenic abscess. However, TB abscess has thinner and smoother enhancing walls, is larger (> 3 cm in diameter), and it has peripheral oedema and mass effect (Fig. 6a, b).

Differentiation of TB abscess from pyogenic abscess can be done with MR spectroscopy and magnetisation transfer (MT) imaging[8]. On MR spectroscopy, TB abscess does not demonstrate aminoacids at 0.9 ppm as compared to pyogenic abscess which shows amino acids at 0.9 ppm. MT ratio in a TB abscess is lower than that found in a pyogenic abscess.

Tuberculous encephalopathy

Tuberculous encephalopathy, a syndrome exclusively present in infants and children, has been described by Udani and Dastur[9] in Indian children with pulmonary tuberculosis. The characteristic features of this entity are the development of a diffuse cerebral disorder in the form of convulsions, stupor, and coma, without signs of meningeal irritation or focal neurological deficit. Pathologically, there is diffuse oedema of cerebral white matter with loss of neurons in the grey matter. Neuroimaging shows severe unilateral or bilateral cerebral oedema. On T2-weighted images, hyper-intensity is seen in white matter suggesting myelin loss. These patients also show diffuse alteration of MT ratio in white matter which reverts back to normal after clinical recovery.

Tuberculous cerebritis

TB cerebritis is rare but has specific clinical, radiological, and pathological manifestations. The involved areas show extensive inflammatory exudates, Langerhans' giant cells, reactive parenchymal changes, and diffuse caseating and noncaseating microgranulomas in the cortex. On MR imaging, focal cerebritis appears hypo-intense on T1, hyper-intense on T2 and small areas of patchy enhancement on post-contrast scan (Fig. 7a,b).

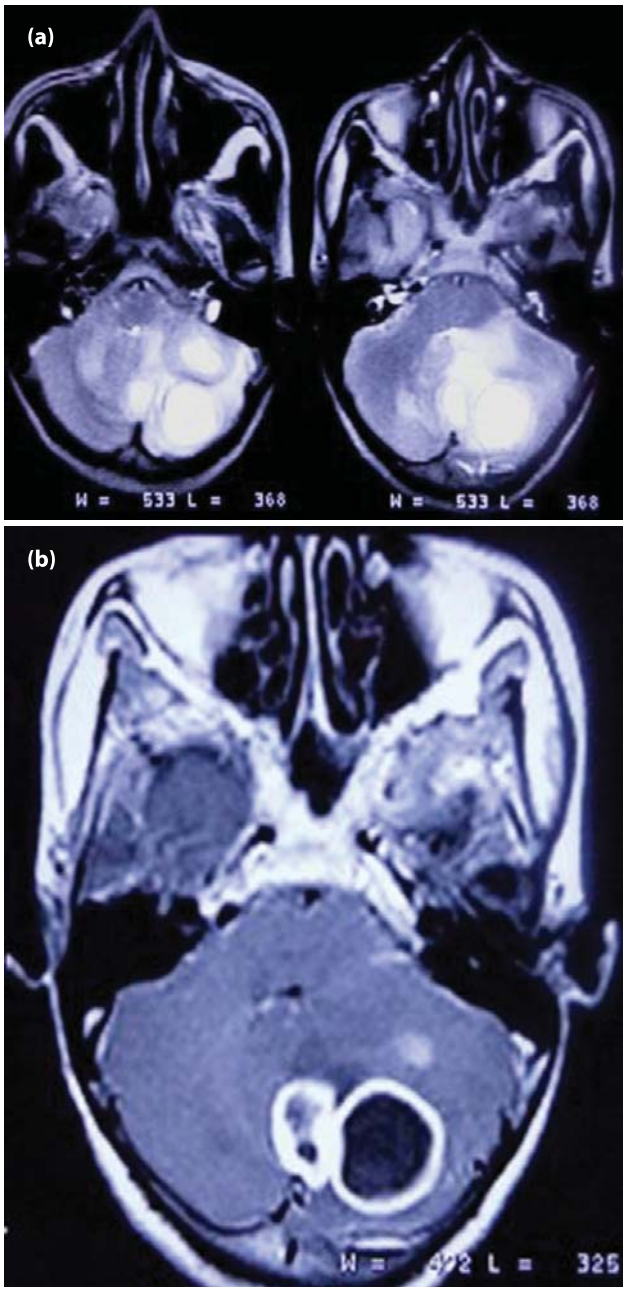


Fig. 6 a, b: *Tuberculous cerebellar abscess: Axial T2W (a) and post-contrast T1W (b) shows ring-enhancing well-defined regular thin-walled abscess.*

Vasculitis and infarction

Intracranial vaculitis is a common finding in patients dying from TB meningitis and a major factor contributing towards residual neurological deficits. Vasculitis is initiated by direct invasion of vessel wall by mycobacteria or may result from secondary extension of adjacent arachnoiditis. Infarction resulting from vascultits is more common in infants and children and is most frequently seen at basal ganglia, cerebral cortex, pons, and cerebellum. The middle

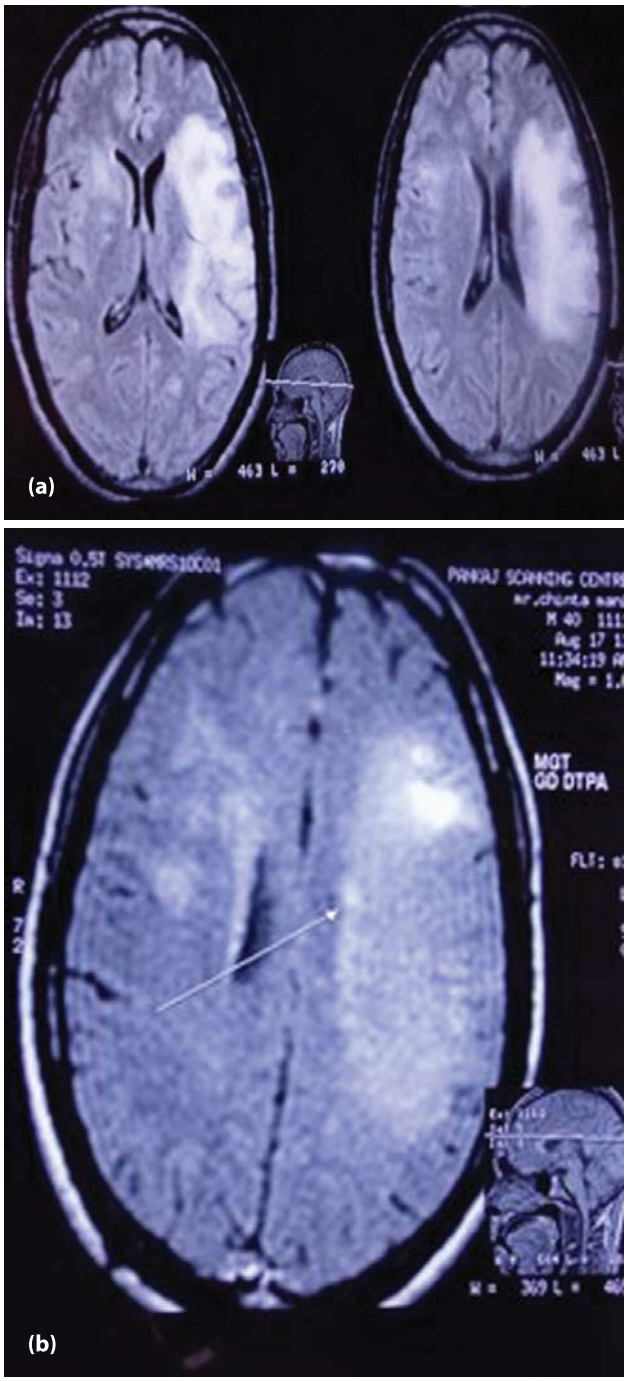


Fig. 7 a, b: *Tuberculous cerebritis: Axial T2W FLAIR image (a) shows well-defined round hypo-intense tuberculous nodule with caseation and post-contrast T1W image (b) shows patchy enhancement.*

cerebral artery territories are commonly affected and the infarcts are frequently bilateral.

MR imaging shows areas of hyper-intensities on T2-weighted images. Diffusion weighted images are the gold standard in acute infarctions seen as increasing hyper-intensity with increasing b values (Fig. 8 a, b).

Cranial neuropathies

Cranial neuropathies are seen commonly in association with TB meningitis. These are partly due to vascular

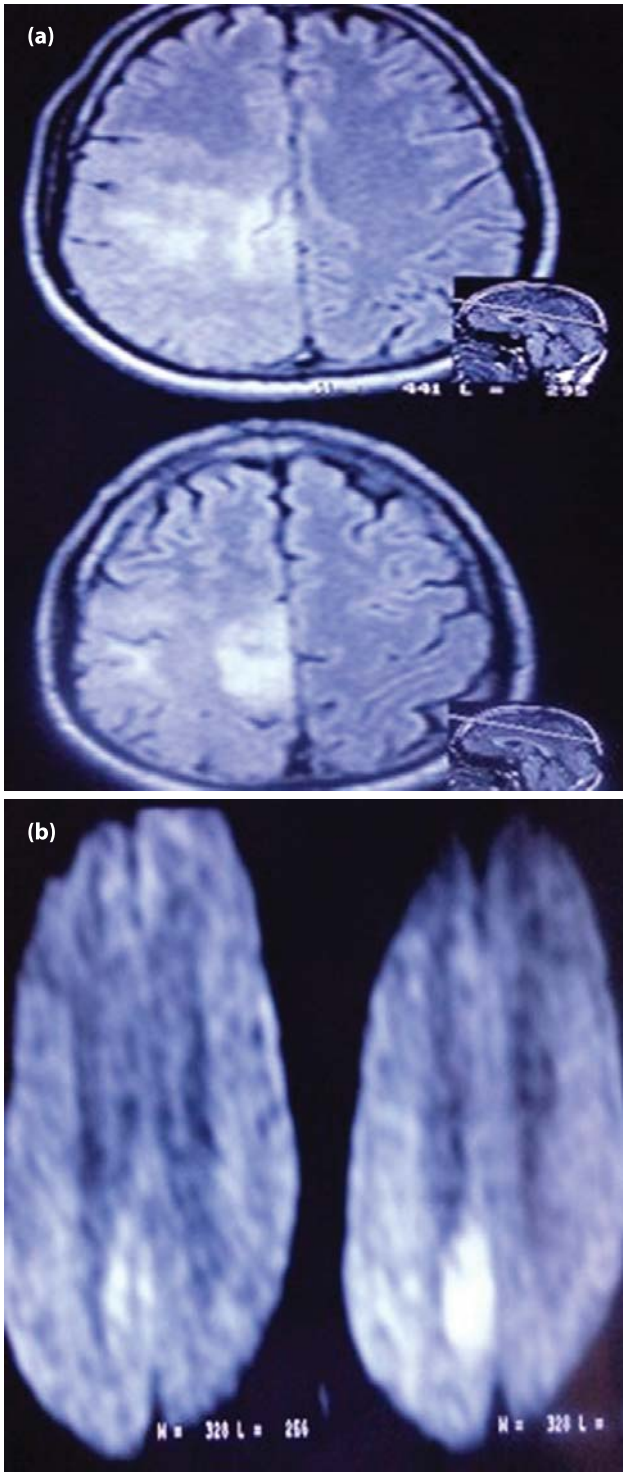


Fig. 8 a, b: *Infarct secondary to TB vasculitis: In a patient with TB meningitis, axial T2W FLAIR image (a) shows diffuse hyper-intensity in the right parasagittal region with restriction on DWI (b).*

compromise resulting in ischaemia of nerve or may be due to entrapment of nerves by the exudates. Large tuberculomas may also compress the nerves, resulting in compression neuropathy. Commonly affected are II, III, IV, and VII cranial nerves. On MR imaging, the affected nerves appear thickened and may show hyper-intensity on T2-weighted images. On contrast, the proximal portion of the nerve root is commonly affected and may show enhancement (Fig. 9a, b).

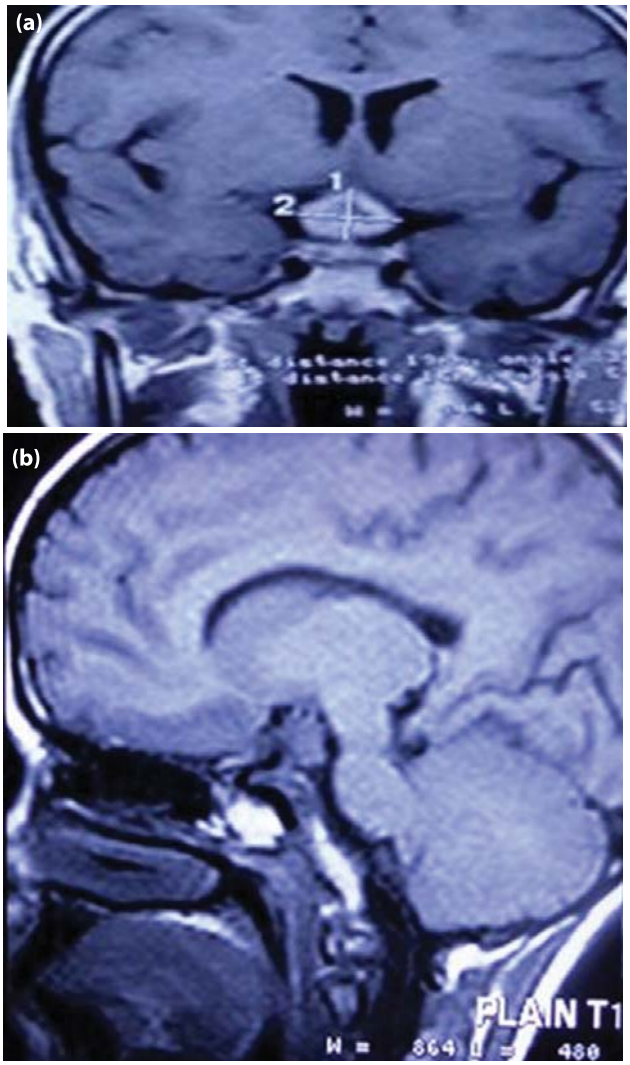
Non-osseous spinal cord tuberculosis

Non-osseous spinal cord tuberculosis can occur in the form of tuberculomas. Extramedullary lesions are more common; of them, the majority being extradural. Intramedullary tuberculomas are very rare. Cervico-thoracic cord is commonly involved. The pathophysiology of spinal meningitis is similar to that of TBM: a submeningeal tubercle forms during primary infection and ruptures into the subarachnoid space eliciting mediators of delayed hypersensitivity. As with intracranial lesions, there is granulomatous inflammation with areas of caseation and tubercles with eventual development of fibrous tissue in chronic or treated cases. The clinical features are indistinguishable from those of any extramedullary or intramedullary tumour, although acute worsening may occur.

MRI features include CSF loculation, and obliteration of the spinal subarachnoid space with a loss of outline of the spinal cord in the cervico-thoracic spine, and matting of the nerve roots in the lumbar region. Sometimes, patients who appear normal on unenhanced MRI images may show nodular, thick, linear, intradural enhancement, often completely filling the subarachnoid space on post-contrast images[10,11]. Spinal cord involvement in the form of infarction and syringomyelia may occur as a complication of arachnoiditis. Parenchymal TB myelitis and tuberculoma formation may also occur (Fig. 10a, b, c).

Calvarial tuberculosis, subdural, and epidural abscesses

Calvarial involvement in tuberculosis is rare. Before the advent of effective chemotherapy, calvarial tuberculosis was estimated to represent 0.2 - 1.3% of all cases of skeletal tuberculosis. About 50% of the cases reported in the



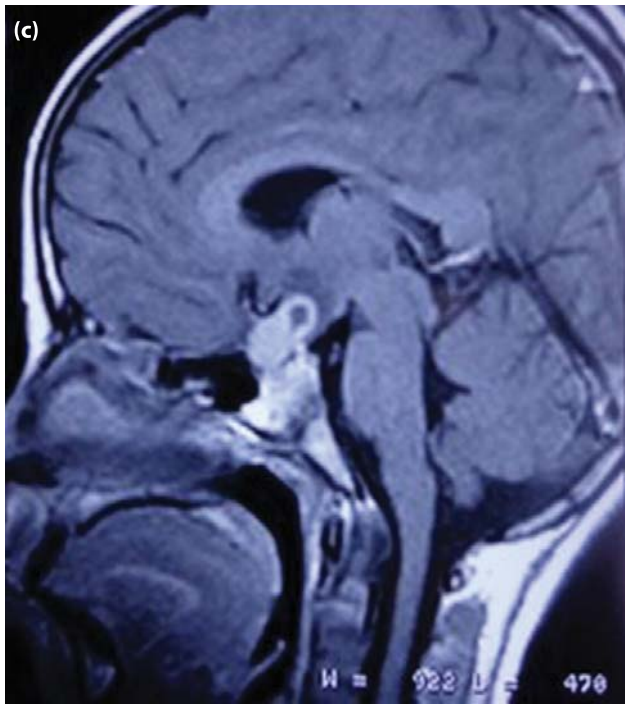


Fig. 9 a, b, c: *Tuberculoma causing compression neuropathy of optic nerve: In a patient with visual symptoms, post-contrast T1W image (a) revealed enhancing lesions in the suprasellar cistern compressing the optic chiasma. Sagittal plain T1W image (b) and post-contrast T1W image (c) shows contrast enhancement. The visual symptoms were due to optic chiasma compressed by the TB granuloma.*

literature were in patients younger than 10 years, and 70 - 90% were younger than 20 years. The disease is rarely seen in infants. It is believed that calvarial tuberculosis occurs by haematogenous seeding of bacilli into the diploic space. Lymphatic dissemination of tuberculosis, common in other bones, is not thought to occur in the skull[12,13]. Tuberculosis may present as a subgaleal swelling (Pott's puffy tumour) with a discharging sinus when the outer table is involved (Fig.12a, b). Involvement of the inner table is associated with formation of underlying extradural granulation tissue.

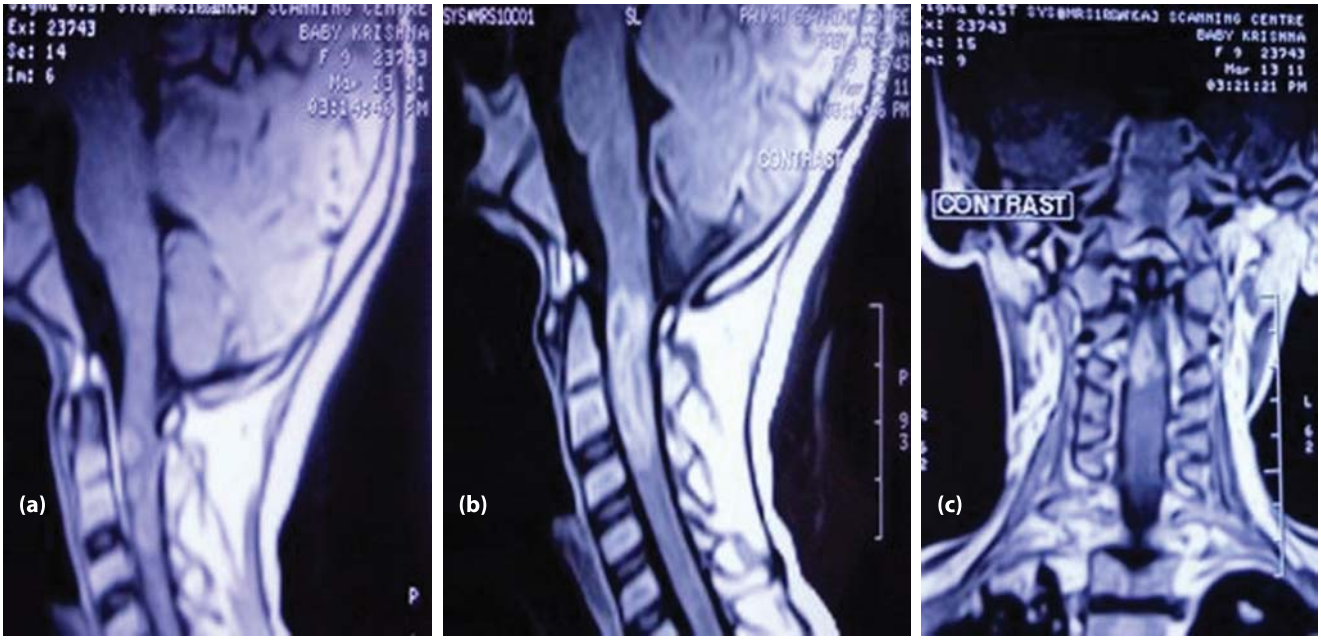


Fig.10 a, b, c: *Intramedullary granulomas: Post-contrast T1W images (a, b & c) show multiple intramedullary ring-enhancing lesions in the upper cervical cord with adjacent dural enhancement.*

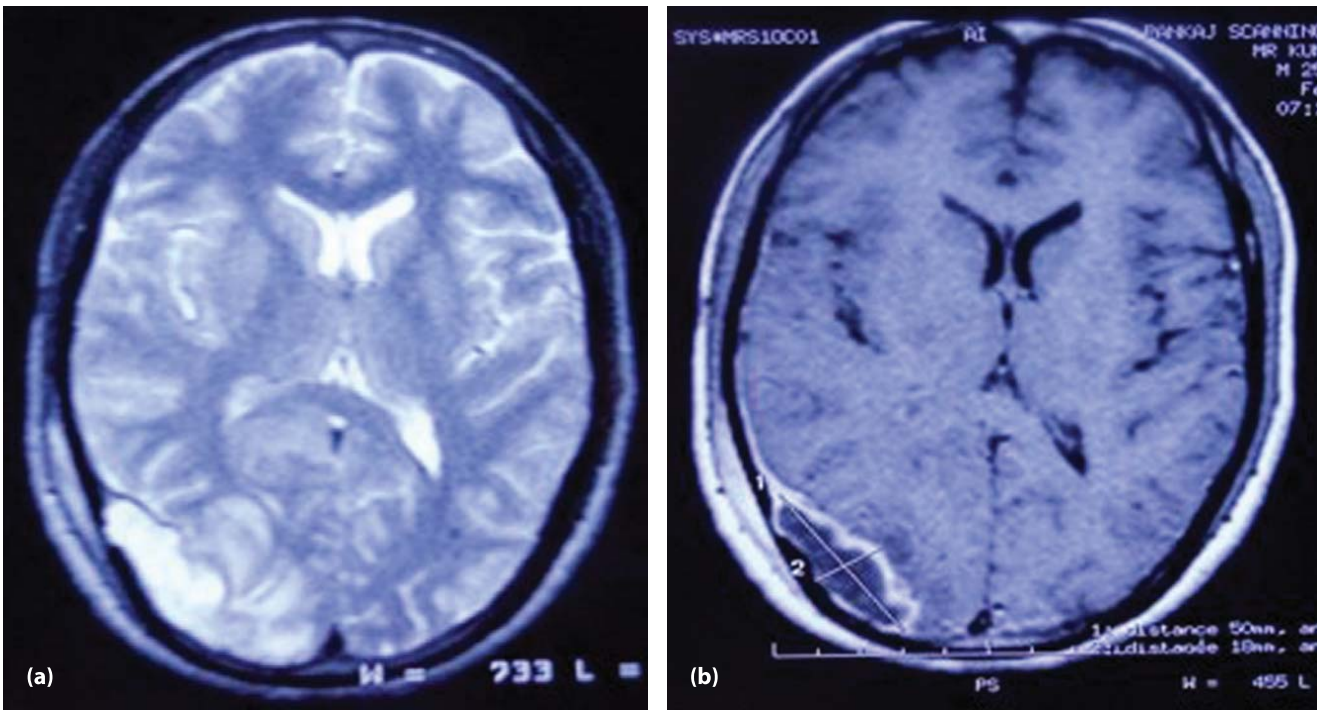


Fig. 11 a, b: *Epidural abscess with osteomyelitis: Axial T2W image (a) shows a well-defined epidural hyperintense focus with thinning of adjacent inner table of skull and extracranial soft-tissue swelling. Post-contrast T1W image (b) shows ring enhancement and dural tail.*

MR imaging, in most cases, leads to a conclusive diagnosis. Proton density and T2-weighted images show a high-signal-intensity soft-tissue mass within the defect in bone. This may project into the subgaleal and/or epidural spaces and show peripheral capsular enhancement on the contrast-enhanced image (Fig.11a,b). MR imaging is sensitive in demonstrating changes in the meninges and the ventricular walls and in detecting parenchymal foci of involvement.

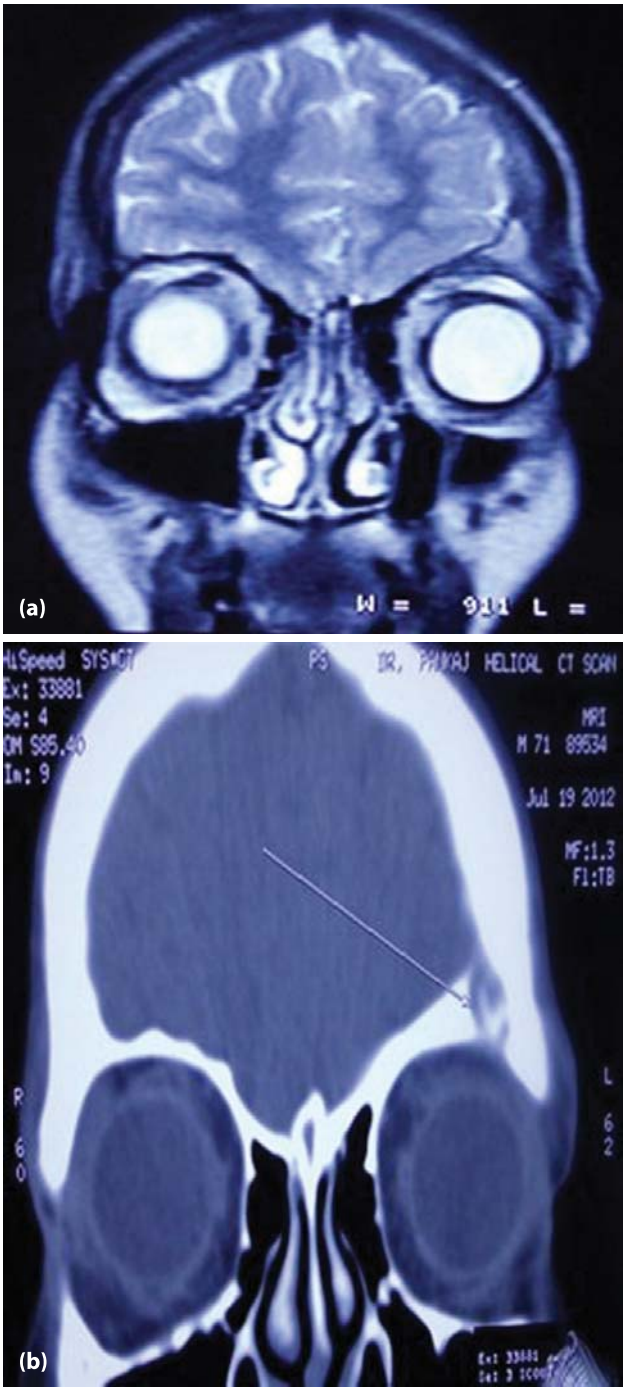


Fig. 12 a, b: *Osteomyelitis with intracranial extension: Coronal T2W image (a) shows an extra-dural well-defined hyper-intense soft-tissue lesion in the left basi-frontal region overlying the roof of orbit laterally. CT (b) correlation revealed bone erosion with sinus tract formation.*

Dural and subdural pathology: Tuberculous pus formation occurs between the dura and the leptomeninges and may appear loculated. It appears hyper-intense on T2W and iso- to hypo-intense on T1W images. The dural granulomas appear hypo- to isointense on T2W, and iso-intense on T1W images. Rim enhancement can be seen on post-contrast images.

Epidural TB: Lesions generally appear to be iso-intense on T1W images, and have mixed intensity on T2W images. In post-contrast images, uniform enhancement can be seen if the TB inflammatory process is phlegmonous in nature whereas peripheral enhancement is seen if true epidural abscess formation or caseation has developed [11]. Epidural tuberculous abscess may occur as primary lesions or may be seen in association with an underlying tuberculous focus.

Conclusion

CNS TB is a major cause of morbidity and mortality in patients with tuberculosis. MR imaging plays a crucial role in diagnosis because of its inherent sensitivity and specificity in detecting CNS lesions earlier than CT. We conclude that conventional imaging supplemented by advanced MRI techniques helps in improved detection and characterisation of CNS tuberculosis and may help in better management of these patients.

References

1. Tandon PN, Pathak SN. Tuberculosis of the central nervous system. In Tropical Neurology (Ed., Spillane JD), Oxford University Press: New York;1973. p. 37-62.
2. Wood M, Anderson M. Chronic meningitis. *Neurological infections; major problems in Neurology, vol 16.* 1998 (WB Saunders, Philadelphia), pp 169-248.
3. Whiteman ML. Neuroimaging of central nervous system tuberculosis in HIV-infected patients. *Neuroimaging Clin N Am* 1997; 7(2): 199-214.
4. Morgado C, Ruivo N. Imaging meningo-encephalic tuberculosis. *Eur J Radiol* 2005; 55(2): 188-92.
5. De Castro CC, de Barros NG, Campos ZM, CerriGG. CT scans of cranial tuberculosis. *Radiol Clin North Am* 1995; 33(4): 753-69.
6. Jinkins JR, Gupta R, Chang KH, Rodriguez-Carbajal J. MR imaging of central nervous system tuberculosis. *Radiol Clin North Am* 1995; 33(4): 771-86.
7. Salgado P, Del Brutto OH, Talamas O *et al*. Intracranial tuberculoma: MR imaging. *Neuroradiology* 1989; 31: 299-302.
8. Gupta RK, Vatsal DK, Husain N *et al*. Differentiation of tuberculous from pyogenic brain abscesses with *in vivo* proton MR spectroscopy and magnetization transfer MR imaging. *Am J Neuroradiol* 2001; 22: 1503-9.
9. Udani PM, Dastur DK. Tuberculous encephalopathy with and without meningitis: clinical features and pathological correlations. *J Neurol Sci* 1970; 10: 541-61.
10. Kumar A, Montanera W, Willinsky R *et al*. MR features of tuberculous arachnoiditis. *J Comput Assist Tomogr* 1993; 17: 127-30.
11. Gupta RK, Gupta S, Kumar S *et al*. MRI in intraspinal tuberculosis. *Neuroradiology* 1994; 36: 39-43.
12. Tirona JP. The roentgenological and pathological aspects of tuberculosis of skull. *AJR Roentgenol* 1954; 72: 762-8.
13. Davidson PT, Horowitz I. Skeletal tuberculosis. *Am J Med* 1970; 48: 77-84.

CLINICAL RESEARCH

JIACM 2013; 14(1): 91-5

Is hypertension 'essential'? – A new hypothesis

BM Hegde , I Shetty**, KG Likhita**, S Charu**, C Christina**, AS Jennie**, M Poonja***, HJ Shetty****, KR Shenoy*****, Calidas Krishnaswami*******

Secondary hypertension is a disease where there is a cause (causes) for the elevated blood pressure. However, that enigma called idiopathic, essential hypertension has so far eluded the search for a cause. Way back in 1988, one of us (BMH) had presented a paper that was later published in the *JAPI* to show that there could be a cause for the essential hypertension as well. We do not think that there is any reaction in Nature without an initial action. Medical academic world did not pay much heed to that paper for obvious reasons. It was not padded with lots of statistical data as is seen in any research paper. Recent revelation that obstructing the brachial artery in normal people would lead to pre-conditioning of the myocardium (as if there was an obstruction to the epicardial coronary vessels). This rekindled our curiosity in the old hypothesis which was put forward by one of us (BMH) earlier in that paper as also in the 1993 book *Hypertension – Assorted Topics* by one of us (BMH)

The hypothesis

When the blood supply to any organ gets reduced due to vascular blocks in any part of the body, the arterial pressure head goes up to compensate for that obstruction, lest the blood supply to the ischaemic organ should get compromised. Human body is built with a robust repair mechanism for most, if not all, eventualities where its working gets affected. This is a teleological view. Therefore, essential hypertension, by itself, is not a disease. Forced bringing down the elevated pressure head using chemical drugs might even harm the system. If the obstruction is corrected in time, before any secondary changes of elevated pressure are felt in other parts of the human system, the elevated pressure head should return to normal.

Experimental study

Recently there was a study which showed that if the arterial blood supply to the hand is obstructed using a BP cuff, the coronary supply area in the normal heart gets changes similar to pre-conditioning of the cardiac muscle cells akin to coronary blocks in the epicardial vessels. This gave us enough courage to attempt this study based on our original hypothesis published years ago.

School children are our study material. They were selected selected randomly, care being taken to see that they do not suffer from any illness at the time of the study. Ethical clearance has been obtained. Unlike the conventional studies we do not propose to comlicated statistical methods in this case as statistics based science has been shown to be flawed.

Procedure

One researcher checks the systolic pressure of the child at rest using the child blood pressure cuff. The pressure is recorded. The other researcher wraps another BP cuff of similar dimensions on to the opposite arm. The first examiner now raises the systolic pressure in the first cuff 10 mm of Hg above the systolic pressure and keeps it there for a few seconds while the second examiner quickly checks the systolic pressure in the opposite hand and records the same. Each such experiment is repeated three times to get the average reading with a gap of five minutes before recordings.

A computerised data sheet is available for proper documentation and the same is stored for analysis. The examiners never discuss their readings between them to avoid any expectation errors in BP recordings.

Clinical confirmation

We already have enough circumstantial evidence in our patient studies that when the obstruction to a vascular block is reversed, the BP comes down to normal as described above. However, future planned studies could be done with adequate angiographic controls to prove the same hypothesis in the clinical set-up.

Results

Data Scan

a) Entire data consisting of 549 pairs of readings (Normal BP and Obstructed BP) was scanned.

**** Retired Vice-Chancellor, Manipal University, Karnataka, *** Editorial Secretary, **** Engineering Teacher, ***** Retired Bank Chairman and a Statistician of repute, World Academy of Authentic Healing Sciences and the Journal of the Science of Healing Outcomes, Mangalore; ****** Clinical Professor of Medicine and Chief, TAG/VHS Diabetes Research Centre, Chennai, Tamil Nadu; ** Medical Students, Fr. Muller's Medical College, Mangalore, Karnataka.***

b) There are 7 cases where only one reading, namely, Normal BP is recorded.

c) There are as 44 cases where Obstructed BP levels are lower than the Normal BP level.

Therefore, 51 cases covered under 2a and 2b above, have been excluded from the purview of the present analysis. Even then, the number of cases included comes to 498, which is a very large sample by any reckoning.

Data Arrangement

i)	**Statement 1**	**col 1** Name	**col 2** Age	**col 3** x-normal	**col 4** y-obstructed	**col 5** d-response (x-y)

ii) **Statement 2 (Frequency Table)**

col 1 d-response	**col 2** f-frequency

Analytical tools used

a) Scattered diagram (x - normal, y - obstructed) Graph 1.

b) Correlation co-efficient (r)

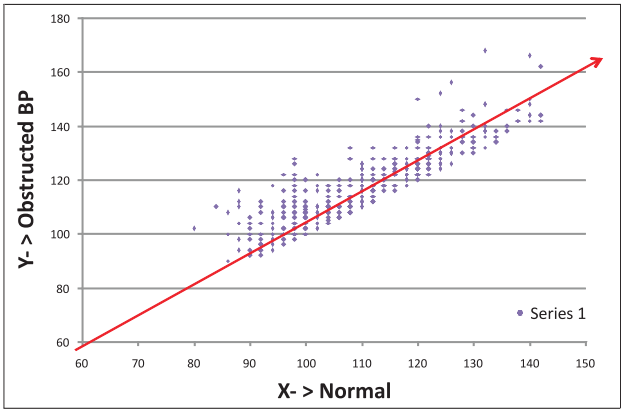
c) Frequency polygon for different levels of responses d = y-x and their frequencies of occurrence (f)

d) Smoothened curve super-imposed on the frequency polygon.

e) Empirical principle- 3Sigma Limits

Results

a) Scattered diagram (Graph 1) shows a close knit upward sloping formation of points with very few outliers. The pointer line clearly shows an upward direction. (It may be noted that this is not the line of Best Fit but only a direction pointer.) This is indicative of high +ve correlation between x and y.



Graph 1

b) Co-efficient of correlation of the sample of 498 pairs of readings, works out to 0.89 which is very high. Normally, $-1 < r < +1$.

c) 3Sigma Limits: Dispersion of computed values of responses (d) from their Mean (d-bar).

Mean (d-bar) = 7. Standard Deviation - s = 6.

Expected dispersion of values of d from the mean d-bar:

		Approx.	Actual
dbar + or – Sigma, i.e., 7+ or –6	1 to 13	68%	76%
dbar + or – 2Sigma, i.e., 7+ or –12	–5 to 19	95%	94%
dbar + or – 3Sigma, i.e., 7+ or –18	–11 to 25	99.7%	98%

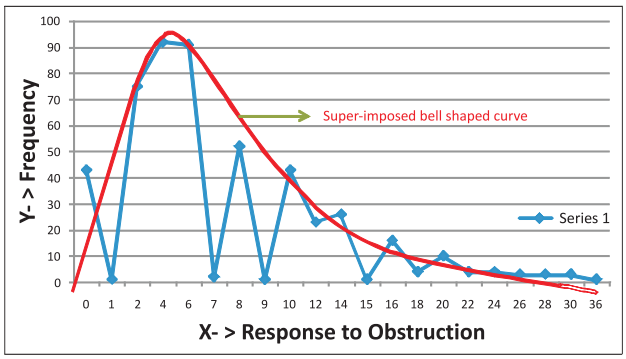
Inference

High-positive correlation between x and y indicates that for a given constant level of obstruction, (10 mm of Hg), different Normal BP levels (x) reach different Obstructed BP levels (y), in such a way that the rise is orderly and more or less proportionate, with least or no random fluctuations or disturbances. The inference holds good when the obstruction is removed and y moves down to x, because r (xy) = r (yx).

The empirical analysis with 3Sigma Limits shows that the relative variations between individual values of responses (d) and their mean (d-bar) lie within reasonably compact intervals (3Sigma limits) indicating gradual and smooth relative responses free from large swings. This further supports the pattern of rise and fall in the BP reading as observed in the immediately preceding paragraph.

Attachments

a) Statement 1; b) Statement 2; c) Graph 1; d) Graph 2



Graph 2

Discussion

What is blood pressure that we measure with the sphygmomanometer? Is it the lateral pressure exerted on the vessel wall by the flowing blood? Is the blood flow laminar? In that case the flowing blood does not (cannot) exert any lateral pressure! Richard Asher, a thinking physician at the Central Middlesex Hospital, London for forty years wondered, in his book *Talking Sense*, about Riva Rocci turning in his grave looking at the abuse and misuse

that we have put his innocent tool to make life miserable for the patients!

Do we know man well? No, says Nobel Laureate Alexis Carrel in his beautiful book, *Man, the Unknown*. Biology in general and, human physiology in particular, does not have a very sound scientific base!: (1) After all "science is making models, mostly mathematical constructs which, with verbal jargon, are supposed to work", writes John von Neumann, a Hungarian born American scientist. With that in view, biology is still in search of its Holy Grail, a mathematical model for itself. Human physiology is still worse, what with the human consciousness added on to the already complicated picture of a whole man. Animals and plants also do have their consciousness but, then, human consciousness is much wider and more evolved in comparison (http://www.plantneurobiology.org/). The present linear model based on the inanimate sciences of physics and chemistry does not work in human physiology. To date, all our so-called "scientific" medicine has been following the same inanimate science model with disastrous consequences. (2) Time has come to think seriously of this fundamental question in biology and human physiology lest we should be held responsible for all the misery that we cause to mankind because of the misconception of reductionist linear scientific base for human physiology as correct science of medicine.

Human blood pressure is so closely related to the human mind (consciousness) that to have a correct scientific model for BP is, at the moment, a near impossibility. The following passage from the noted biologist Rupert Sheldrake explains our science today very aptly.

"……..can be explained by the tendency of the mind to seek and find order in experience: the ordered structure of mathematics, creation of the human mind, are superimposed onto experience, and those that do not fit are discarded; thus the process resembling natural selection, those mathematical formulae that fit best are retained. In this view scientific activity is concerned only with the development and empirical testing of mathematical models of more or less isolated and definable aspects of the world; it cannot lead to any fundamental understanding of REALITY."

This explanation fits our world of blood pressure research and practice today. It has very little to do with reality. Come to think of it, in science what is reality? Hans Peter Durr, Emeritus Director of Max Planck Institute, says that there is ***no reality***. There are only ***potentialities.*** He uses the best German word *Wircklicheit* for the reality in the world. Indian sages called the same world as *Maya*. Modern medicine has been content calling blood pressure as the mathematical model of the product of cardiac output and peripheral resistance. Neither of the latter could be correctly assessed, in the first place, as they are linear laws in a non-linear human body. The heart is not a cone, round, sphere, or an oblong. How then do we apply Euclidean geometric rules to the heart to measure its output? In addition, the cardiac output is closely related to the pre-load and after-load, both of which depend on the heart rate, the latter in turn is intimately related to the human mind (consciousness). Naturally it changes from second to second! Similar physics problems arise with peripheral resistance! However, this inadequate science helps us in our work with the success of reductionism in showing the recorded BP coming down with chemical molecules given to patients, a surrogate end-point that we use to claim treatment success! The final outcome of what happens to the patient in the long run has not been adequately studied. Recent long-term audits like the recently concluded MRFIT study reports suggest that the so called risk factors like BP could be successfully reduced with our treatment but they DO NOT reduce the *risks* of fatal outcomes. "As far as this study is concerned, there are no such things as risk factors" was their final conclusion! This much for our faulty reductionist science of today. It brings to mind the still unresolved issue of the moon going round the earth which Isaac Newton wrote was due to the gravitational pull, but Albert Einstein thought that it is because the moon's path itself is curved!!

New ideas are available in this area. Blood flow inside the vascular system might not be laminar after all. Scientists have now demonstrated that blood flows by whirling inside the vessel collecting energy for flow as the blood flows down. A simple muscular heart of 300 gms weight will find it difficult to push blood, if it were to pump blood all the way, through nearly half-a-million kilometers of capillaries in an adult. Even RBCs can not move easily inside those thin capillaries; the reason why nature has given them the dumbbell shape. Energy for blood flow is generated by the whirling as in a cyclone! If the flow is not laminar then all our BP theories will fall by the way-side.

Now let us see what happens when the blood vessels are blocked? One of us (BMH) proposed the hypothesis years ago that the blocks should result in the pressure head going up to keep the end-organs properly perfused to the extent possible – a teleological view. Teleology is the main anchor of scientific research as otherwise science will always remain incomplete like the *fish-net hypothesis* of Sir Arthur Eddington, the famous British astrophysicist. The physics of vessel blocks is again very complicated based on the Bournelli Effect. Let us not get into that confusion here. This teleological view is in keeping with the natural laws where the human body tries to keep the system going as far as possible since we were designed

in nature not with the anticipation that the medical profession will find ways to get the blood pressure head down artificially using chemical molecules, a nascent misadventure. Charles Sherrington, a Nobel Laureate physiologist, way back in 1899, when he became the professor of physiology at the Liverpool University, had noted that positive sciences can never answer the question "why"; they could at best answer "how" or "how much" but not "why." Ratio rei, he said, was not reason why? Why does the pulmonary artery start to become stiff and thicken to raise the pulmonary artery pressure when the mitral valve on the left side of the heart gets smaller due to mitral stenosis (to prevent flooding of the lungs)? Same teleology was used by Paul Wood, the father of British cardiology, to explain this, a good analogy for blood pressure going up when blood vessels get blocked. Quantum physics today shows that matter and energy are the two faces of the same coin and reality in the world is only a myth. In the human body, like in the world outside, uncertainty is the only certainty. Medicine deals with uncertainty all the time but tries to use the reductionist science of certainties to deal with uncertainty. This world, in the words of Hans Peter Durr, the Emeritus Director of Max Planck Institute of Physics in Munich, is Wirchlikiet. (Changing drama)

Both physics and chemistry have undergone a paradigm shift. It is curious that biology, which is based on the laws of the former two, completely excuses itself from the former changes. Even though quantum theory has shown that a reductionistic, mechanistic and materialistic description of reality is an impossibility, many biologists think that "Science, by this analysis, is mechanism and materialism. And all that Darwin did was to show that mechanism and materialism applied to biology, too." There is nothing right about this. "The non-classical coherence of states in the realm of potentiality suggests that the nature of reality is that of indivisible *Wholeness*. Everything that comes out of the Wholeness belongs to the Wholeness, including our consciousness. This aspect of physical reality has led countless physicists, and others, to the conclusion that "spirit or consciousness is a cosmic property," writes Lothar Schafer, and adds that "Even though these forms are trans-empirical, they are real, because they have the potential – Aristotelian *potentiality* – to manifest themselves in the empirical world. As the famous Johns Hopkins physicist, Richard Conn Henry, put it in 2005, "This world is immaterial – mental and spiritual." Atoms are made out of invisible energy; not tangible matter. Quantum physics speaks a strange language of "now you see it, now you don't." Each atom or molecule has its own unique energy signature.

The world of blood pressure inside the blood vessels and its physics are much more complicated compared to the theory of evolution of Darwin! Every fluid flow in this world is by whirling. How come the flow of blood inside the blood vessels alone is laminar? There are now newer suggestions that blood also flows inside the vessels by whirling, collecting energy as it flows to be able to go through thousands of kilometers of capillaries requiring very high energy levels that can never be generated by a single contraction of a 300 gm muscular structure called the human heart! Even if we accept our old view that blood flow is laminar, the flow then can never exert lateral pressure on the blood vessels wall (our definition of BP) as Cosine 90 is zero. With our present thinking fin this area, like in all other areas of biology seems to be flawed. We need newer insights into human physiology. This work is an attempt at that.

One of us (BMH) is also aware of some anecdotal experience of patients whose blood pressures came down to normal without drugs after their peripheral blood vessels blocks were bypassed. Similar stories abound in the area of coronary artery bypass. One of his patients with resistant hypertension (with almost all drugs being used) came down to normal after her abdominal aortic block was bypassed!

This study was undertaken to test our hypothesis. The study has certain unique features. It used willing medical students during their free time to generate the data. Their enthusiasm was contagious. They were supervised and audited by seniors all the time. Although some of us do not believe in using statistics to prove our point (in this study it is not needed) as the results are overwhelmingly in favour of the hypothesis. Yet we got the best statistical brain available (KRS) to analyse the data using the latest computerised gadgets. All the authors worked for free and it was a novel method of doing medical research without getting funds from any source; consequently, without any strings attached to the results which are not doctored. The maximum that students got was a meal or a cup of tea at the end of a hard day's work, not regularly though. The subjects were also willing students and other workers who were keen to help knowledge growth. All in all, this was work with a smile on all sides. This has some novel features. Conventional peer reviewers with a closed mindset might find this objectionable, but if they stretch their imagination a bit more, they will soon see the new light in medical research here. In this study, the person himself/herself is his/her control, thus eliminating the main objection to the much hyped RCTs of cohort matching.

As a useful byproduct of this study, during our pilot project before the main study was started, we found, not surprisingly though as one of us (BMH) had reported this earlier in his book, that while raising the pressure in the

BP arm cuff we recorded the systolic pressure when the pulse just disappeared as reading number 1. Then we kept the cuff inflated to look for the stethoscope to record the systolic pressure based on the Korotkoff's sounds as reading number 2. The second reading consistently was much higher than the first. So we decided to stick to the palpatory method for estimating the systolic pressure for the purposes of this study. This cannot be faulted as we were not studying hypertension anyway. This incidental finding adds to the weight of this study result as it confirms that obstructing any blood vessels even for a short while pushes the pressure up, sometimes significantly. Is this not one of the reasons why we have an exponential rise in the incidence of so called hypertension in society in recent years?

Conclusions

This simple study, the like of which was not done in the past to the best of our knowledge has given us some important clues to this enigma called hypertension, which at best is only a risk factor, but has lately been elevated to the status of a full fledged disease. First lesson is that a significant number of our mild to moderate hyopertensives could in fact be normotensive only if we take care to record the pressure carefully. Secondly we have been able to show clearly that any obstruction to the flow of blood results in reflex increase in the systolic pressure head. Could arterial blocks anywhere be one of the aetiologic factors of the so called idiopathic, essential, or primary hypertension? More studies need to be done to reproduce our results and also to unravel further mysteries in this area.

Acknowledgement

We thank all those connected with the colleges, schools, and convents from where we got our study subjects. We are grateful to the subjects themselves who willingly and happily gave their time for us to do this study. We are grateful to all our friends, especially Professor CV Krishnaswami, Chief of the TAG-VHS diabetes Research Centre, Chennai, India, who gave constructive suggestions during the study period.

References

1. Schafer L. Quantum reality and the evolution theory. Jr. of Cosmology 2009; 3: 547-557.
2. Durr HP. Matter is not made out of matter.
3. Eddington AS. The Nature of the Physical World. New York: Macmillan, 1929.
4. Heisenberg W. Physics and Philosophy. New York: Harper Torchbook, 1962.

INVITATION FOR NOMINATIONS FOR ORATION AWARDS FOR 2013 AND 2014

Suggestions are invited from Fellows/Members for the following **Orations for the year 2013 and 2014** so as to reach Dr. Ashok Shiromany, Honorary General Secretary, Indian Association of Clinical Medicine, on the official address given below by **30th June 2013** :

1. **Prof. B.C. Bansal - Mrs. Uma Bansal Oration**
2. **Dr. G.S. Sainani - Dr. Mrs. Pushpa G. Sainani Oration**
3. **Dr. G.B. Jain Oration**
4. **Founder-President Prof. M.C. Gupta Oration**

- The suggestions are to be made for above Orations to be awarded during IACMCON-2013, (Kota) and IACMCON-2014 (Agra). Nomination Form is on page 86.
- The suggestions are to be made only by Fellows/Members of the Association, and must be accompanied with reasons for recommending the particular person showing the value of his/her research and accompanied with eight copies of three of his/her best publications. All the relevant papers in connection with suggestions such as Bio-data, List of Publications etc., should be submitted in **EIGHT SETS** by the proposer.
- The recipient of the above awards should deliver a lecture pertaining to his/her work at the Annual Conference of the Association in 2013 and 2014.

Members of the Governing Body of the Association are not eligible to receive the orations.

Eligibility Criteria:

1. The Nominee should have minimum 3 years standing in the Association as a Fellow/Member (kindly mention the Fellowship number and date of award).
   i. The member should have a standing of minimum three years in the Association.
   ii. The member should have participated in the annual conferences, scientific programmes, contributed to the *Journal* and actively engaged in the organisation of the annual conference of IACM.
   iii. For Founder-President Dr. M. C. Gupta's Oration, the subject of Oration should be related to cardiology.

Dr. Ashok Shiromany, *Hony. Gen. Secretary, Indian Association of Clinical Medicine,*
Post-graduate Department of Medicine, Sarojini Naidu Medical College, Agra-282 002, U.P.
E-mail : iacmnational@rediffmail.com

FORMAT FOR NOMINATION FOR IACM ORATION AWARDS

(Eight copies of format and eight copies each of important publications to be sent)

1. Name (in full) : .....
2. Designation : .....
3. Address : .....

   ..... Pin Code : .....

   Phone : ..... Fax : .....

   E-mail : .....
4. Oration for which nominated : .....
   (A person can be nominated for more than one oration simultaneously but can be awarded only one oration in his life time)
5. Field of interest and subject/title of oration, if awarded : .....
6. Bio-data and Justification for Nomination : .....
   (Please use separate sheets)

Signature ..... (Proposer)

Name:

Fellowship/Membership No.:

Signature ..... (Seconder)

Name:

Fellowship/Membership No.:

CONSENT OF NOMINEE

I hereby agree for the above nomination and undertake to deliver the oration if awarded at the appointed day and time. I have not been awarded any oration by the "Indian Association of Clinical Medicine" earlier.

Signature

(Name of Nominee)

Fellowship/Membership No. .....

RULES FOR ORATIONS/ORATORS:

1. No TA/DA shall be provided to the orator.
2. It is obligatory and compulsory for the awardee of oration to deliver it at the appointed day and time during the annual conference. No alternations shall be possible.
3. Oration if not delivered shall lapse and shall not be carried forward ordinarily.
4. A person can be nominated for any or all the orations and shall be considered for the orations he has been nominated for. However, only one oration can be awarded.

Please send your Nominations for Orations to:

Dr. Ashok Shiromany, Hony. Gen. Secretary, IACM, P.G. Department of Medicine, S.N. Medical College, Agra-282 002, U.P.

INSTRUCTIONS TO AUTHORS

General information

1. Send all articles in triplicate (with a floppy 3½", wherever possible) by registered post/courier. Please label the floppy with file name & programme on which it is made, e.g., MS-Word, Word Perfect, Pagemaker.
2. All articles must be accompanied by a covering letter signed by all authors confirming that the article has not been published or submitted elsewhere, either in part or in whole. This restriction does not apply to abstracts published in connection with scientific meetings.
3. The editorial board may modify the article partially or wholly to bring it to the set pattern of the journal to ensure continuity in style.
4. The views expressed in an article will remain the opinion of the author(s), and the editorial board accepts no responsibility for the same.
5. The papers which are published in *JIACM* become the property of the *Journal* and should not be published or reproduced in full or in part elsewhere without the permission of the Editor.

Original articles

- Should be typed double-space on A4 size bond paper with a 3 cm margin all around. Type on one side of paper only.
- Articles should not exceed 10-12 typewritten pages, including references, but excluding tables.
- The sequence of an article should be as follows :
  - Title page
  - Abstract
  - Keywords
  - Introduction
  - Material & Methods
  - Results
  - Discussion
  - Acknowledgment
  - References
  - Tables
  - Legends to figure(s)

A. Titles and Author(s) name

- On a separate page.
- Concise & descriptive title.
- Author(s) name be given as initials followed by surname.
- The academic degree and designations with name of institution be given at bottom of page after superscribing individual authors names with asterisks.
- Give address (postal as well as e-mail) for communication at bottom of page alongwith telephone and fax numbers.

B. Abstract

- This should be given on a separate page.
- Should not exceed 250 words for original article and 100 words for a case report, and should contain 3-10 keywords at conclusion of abstract.
- Should include background, aims of study, methodology, results, and conclusion. The problem(s) being addressed in the study, and conclusion of its result, must be expressed clearly in the abstract.

Review Articles and Update Articles should also be preferably sent alongwith an abstract.

C. Key words

- These are required for indexing of the article and the *Journal*.
- The key words should not include words in title as title is automatically indexed.
- The key words may be taken from Medical Subjects Headings (Me SH) published under these headings.
- Discussion should avoid repetition of results or review of literature.
- Text should not contain data given in tables.
- Abbreviations must be avoided in title, subtitle, and summary.
- Only the generic name of a drug should be used. Brand names may be used in material & methods section only when these have been used in research.
- Materials taken from other sources must be accompanied by a written statement from the author and the publisher giving permission to the *Journal* for reproduction of the same.

D. Statistical methods

- Describe methods used, in detail.
- Present the results in a logical sequence in the text, tables, and illustrations.
- In discussion, emphasise newer aspects of the study and the conclusions that follow from them.

E. Tables

- Type each table double-space on a separate page.
- Provide a title for each table, and indicate its position in the text.
- Number the tables in Arabic numerals.

- Put explanatory note in the footnote (and not in the heading).
- Do not use internal horizontal and vertical rules.
- Number of tables should be in proportion to length of the text.

F. Illustrations

- As far as possible, the figures should be professionally designed, on glossy paper, and large enough to be legible even after reduction, so as to fit the width of a single column.
- The back of each figure should have the name of author, sequence number, and proper orientation (e.g., 'top') marked in pencil.
- Figures should be unmounted.
- Photographs and illustrations should be 7x7x7 cm or 14 cm.
- Electron micrographs should have internal scale markers.
- Photographs of patient(s) should be accompanied by permission, or the subject should not be identifiable.
- Legends for illustrations should be triple-spaced on a separate paper.
- Colour prints are encouraged. Send both transparencies and glossy prints for this purpose.
- **Abbreviations.** If a term appears repeatedly, an abbreviation may be introduced in parentheses at the initial mention of the term and used thereafter in place of the term.
- **References to drugs.** The generic name of a drug should be preferred as a general rule. However, the full name, or the commercial name of the drug, as well as the name and location of the supplier, may be given if appropriate.
- **Copyright.** Material that has appeared elsewhere must be submitted with a legal release from the holder of the copyright.
- **Ethical consideration.** Reports on biomedical research involving human subjects must include a statement that the informed consent was obtained from each subject, or from his/her guardian. Reports on human experimentation must include a statement of approval by a local Human Investigations Committee, in accordance with the precepts established by the Helsinki Declaration.
- **Conflict of interest.** The author is required to disclose any commercial or other association that may constitute a conflict of interest in connection with the submitted manuscript.

G. References

1. The Vancouver system of references should be used.
2. References in text should be given as a number within brackets (rather than superscript figures).
3. The number of references should not exceed 30 for an original article, 10 for a short article, 8 for a case report, and 3 for a letter to the editor.
4. References should be numbered in order of their appearance in the text and not alphabetically.
5. Personal communications are to be identified in the text and not in the reference.
6. Cross references ("Quoted by _____") should be avoided.
7. As far as possible, Indian references should be preferred.
8. Names of all authors (upto four) should be mentioned; if there are more than four, then the first three names are mentioned followed by '*et al*'.
9. The author is wholly responsible for accuracy and completeness of the references.
10. As far as possible, only recent references should be included.

The form of references is as follows:

From a Journal

Name of Author(s). Title of the Article. Name of Journal Year; Vol: Page No(s).

From a chapter in a book

Name of Author. Name of Topic. Name of Editors. Name of Book. Place of Publication. Name of Publishers, Year; Vol: Page(s).

From a book

Name of Author or Editor. Name of Book. Place of Publication. Name of Publisher, Year; Vol: Page(s).

Reference to Personal Communications and to unpublished material must be incorporated, in parentheses, at the appropriate place in the text.

References to Congress abstracts should be cited in the reference section if they have been published previously in an official book of abstracts from the Congress.

H. Correspondence

Letter to the editor may comment on articles published in the journal, or may provide additional original data or information. The text should not exceed 500 words and a maximum of 3 references are permitted. The letter must be received within six weeks of the article's publication.

I. Review and actions

The editorial board examines the manuscripts and sends them to reviewers. The author(s) of an article not accepted for publication will be informed within six weeks usually, but decision on potentially acceptable articles may take longer.

IACMCON-2013
ABSTRACT FORM

26-27 October, 2013
Kota, Rajasthan

IACMCON-2013 - Registration No.:

(For office use only)
Abstract No. :

Category :

Title :

Name (Presenting Author Underlined), City :

- Only registered delegates can submit abstracts (If registration number is not mentioned abstract will not be considered).
- Abstract must be submitted on an original abstract form with 3 photocopies along with CD.
- In case you have more than one abstract, you can use high quality photocopies of the enclosed abstract form.
- Do not fold the abstract form.
- Abstracts sent by Fax will NOT be accepted.
- Abstract must be typed single-space in English using atleast 9 point size font and must fit inside the designated space.
- Type the abstract in order of title, authors, institution and text which should be left aligned and include aims & objects of the study, methods, results, and conclusions.
- Name of the presenting author should be underlined.
- Standard abbreviations are acceptableand uncommon abbreviations must be put in parenthesis and preceeded by full word the first time it appears in the text.
- Tables and graphs can be included if they can fit within the rectangle, Photographs will not be accepted.
- The presenting author must also be a registered delegate of the conference.
- Abstract must be submitted by **15th September, 2013**.

Please read instructions carefully before submitting abstracts.

Name of Corresponding Author : .....
(Surname followed by initials)

Designation : .....

Address for Correspondence : .....

.....

.....

Phone : ..... Fax : .....

Mobile : ..... E-mail : .....

Dr. B.B. Rewari (Chairman, Scientific Committee)
C/o Initials
E-39, Flatted Factory Complex, Jhandewalan, New Delhi-110 055
Mobile : +91-9811267610 E-mail : bbr.iacmcon2013@gmail.com

Signature of Author : .....

Indian Association of Clinical Medicine

Headquarters: P.G. Department of Medicine, S.N. Medical College, Agra - 282 002, U.P.

MEMBERSHIP / FELLOWSHIP FORM

No. ..... Date .....

The Honorary General Secretary,
Indian Association of Clinical Medicine (IACM)

Photograph

We hereby propose the admission of

Name (in full): .....
Qualifications: .....
(Branch of Medicine for P.G. Degree)
University: .....
Year of obtaining the first Postgraduate Qualification: .....
Address: .....
.....
..... Pin Code: .....
Phone (with STD code): .....

as an Associate Life Member/Life Member/Fellow of the Indian Association of Clinical Medicine.

To the best of our knowledge and belief, the above particulars are correct and we consider him/her a fit and proper person to be admitted as Associate Life Member/Member/Fellow of the 'Association'.

A D.D. No. ..... Dated ..... drawn on .....
..... for Rs. ..... is enclosed herewith.

Signature ..... (Proposer)
Name: .....
Fellowship/Membership No.: .....

Signature ..... (Seconder)
Name: .....
Fellowship/Membership No.: .....

Subject to approval of the Governing Body, I agree to become Associate Life Member/Member/Fellow, and if admitted, to abide by the Rules and Regulations of the 'Association'.

. . . . . .
(Signature of the Candidate)

Note by the Hony. General Secretary

- Fellowship Subscription: Rs. 5,250/-
  (Minimum 10 Years Standing after P.G. Qualification).
- Life Membership Subscription: Rs. 2,000/-
  (Minimum Qualification: Post-graduate Qualification as specified in the Constitution of IACM).
- Associate-Life Membership Subscription: Rs. 2,000/-
  (Diploma, or Postgraduate Qualification not covered as per Constitution of IACM).
- Please attach attested photocopy of P.G. Degree/Diploma.
- Cheques shall not be accepted. Demand Draft should be in favour of **"Indian Association of Clinical Medicine"** payable at Agra.

Correspondence Address:
Dr. Ashok Shiromany, Hony. Gen. Secretary, IACM, P.G. Department of Medicine, S.N. Medical College, Agra-282 002, U.P.