

C O N T E N T S

Journal, Indian Academy of Clinical Medicine • Vol. 17, Number 3, July-September, 2016

Contains 92 pages from 165 to 256 (inclusive of all advertisements)

Viewpoint	Arise; awake, before it is too late 170 <i>BM Hegde</i>
Original Articles	<p>Prevalence and associations of cheiroarthropathy in patients with type 2 diabetes: A hospital based study from northern India 173 <i>N Saini, A Bhargava, A Sharma</i></p> <p>Association of HbA1c with liver fat, abdominal fat indices (visceral fat, subcutaneous fat) and CIMT (carotid intimal medial thickness) in non-diabetic subjects with NAFLD (nonalcoholic fatty liver disease): A cross-sectional analysis of cardiovascular risk in non-diabetic NAFLD subjects 178 <i>Karan Puri, Arun Gogna, Shabnam Bhandari Grover, Sunil Ranga</i></p> <p>Dengue: Clinical profile and management in reference to platelet transfusion 185 <i>SS Gupta, RK Singh, AK Gupta</i></p> <p>Gastrointestinal profile of corrosive injury in western Rajasthan 189 <i>Anil Sankhla, Chandra Prakash Mathur, Sunil Dadhich, Kishan Gopal Barupal, Rhythm Mathur, Mukesh Agarwal</i></p> <p>Spectrum of neurotuberculosis in HIV-infected patients: Clinical and radiological features 193 <i>Vandana V Ahluwalia, Shamrendra Narayan, Prerna S Saharan, TP singh, Dipti Agarwal</i></p> <p>Levels of vitamin D in patients with HIV infection and its correlation with CD4 cell counts 248 <i>RS Taneja, Pulin Kumar Gupta, Afroz Jamal, Ashok Kumar, BB Rewari, Anubhuti, Jyoti Aggarwal</i></p>
Short Communication	Knowledge of doctors, interns, and final year medical students on selected parameters of tuberculosis and RNTCP 198 <i>KB Gupta, Dinesh Mehta, Ruchi Sachdeva, Sandeep Sachdeva</i>
Review Articles	<p>Levosimendan: A new calcium sensitiser for inodilator therapy 201 <i>AS Dabhi, MVadivelan, Molly Mary Thabah</i></p> <p>Swine flu vaccination 205 <i>VK Katyal, Ashima Katyal, Aman Arora, Krishna Mohan, Kiran Bala</i></p> <p>Management of snakebite In India 209 <i>Shibendu Ghosh, Tanmoy Chatterjee, Prabuddha Mukhopadhyay</i></p>
Case Reports	<p>Tricuspid valve endocarditis in an intra-venous drug abuser caused by <i>Candida guilliermondii</i>: A rarely implicated fungus 219 <i>M Narang, S Prasad, R Chandel, R Bandsode</i></p> <p>Marfan syndrome 222 <i>Kavita Paul, Narendra Kumar Bairwa, Harbans Lal Kazal</i></p>

C O N T E N T S

Journal, Indian Academy of Clinical Medicine • Vol. 17, Number 3, July-September, 2016

Contains 92 pages from 165 to 256 (inclusive of all advertisements)

Case Reports	<p>Rosai-Dorfman disease mimicking meningioma – a diagnostic dilemma 225 <i>Gaurav Jain, Anshul Gupta, Satnam S Chhabra</i></p> <p>Kikuchi's disease with pleural effusion – A rare case report 227 <i>Kripa Shanker Jhirwal, Hemant Mahur, DP Singh</i></p> <p>Enteric duplication cyst presenting as stridor in a 2-month old infant 230 <i>Aparajita Shukla, Alpa Gupta, Pramod Sharma, Manju Saini</i></p> <p>Hypothyroidism masking myotonic dystrophy 233 <i>Neera Chaudhry, Vinod Puri, Yogesh Patidar, Geeta A Khwaja</i></p> <p>Coeliac disease presenting in association with rare transfusion reaction due to MNS mismatch 237 <i>Nitya Nand, Parveen Malhotra, Dhananjay Kumar, Dipesh Dhoot</i></p> <p>Unaccustomed exertion, opiate consumption, and dehydration leading to acute renal failure in a healthy male 240 <i>Monica Gupta, Mandip Bhatia, Sanjay D Cruz</i></p> <p>Disseminated tuberculosis with immune thrombocytopenia 242 <i>Bimal K Agrawal, Gaurav Aggarwal, Charu Batra Atreja, Aruna Bhagat Dubey</i></p> <p>An unusual presentation of rib caries without pleuro-pulmonary tuberculosis in an old male mimicking rib secondaries 245 <i>Pashaura Singh, Riputapan Singh, Saurabh Agarwal, Khushvinder Sherry, NS Neki</i></p>
Announcements	<p>Advertisement Tariff of the Journal, Indian Academy of Clinical Medicine (JIACM) 239</p> <p>Application form for IACM Membership/Fellowship 253</p>

The JIACM invites scientific and historical material of absorbing interest related to clinical medicine from all authors, whether or not Fellows or Members of the IACM. The editorials and articles do not represent the policy of the IACM unless this is specifically mentioned.

Self-addressed, sufficiently stamped envelopes must accompany all unsolicited manuscripts. Otherwise, material found unsuitable for publication will not be returned. The editor does not assume any responsibility for material submitted for publication.

The publication of an advertisement in this journal does not constitute an endorsement of the product by the Indian Association of Clinical Medicine, or by the Editor of the *Journal*. Advertisements carried in this journal are expected to conform to internationally accepted medical, ethical, and business standards.



Journal, Indian Academy of Clinical Medicine

EDITORIAL BOARD

Editor

DG Jain (New Delhi)

Associate Editor

MPS Chawla (New Delhi)

Secretary

Sumeet Singla (New Delhi)

Members

AK Gadpayle (New Delhi)

BB Rewari (New Delhi)

Vipin Mediratta (New Delhi)

Ex-officio Members

AK Gupta (New Delhi)

PC Mathur (Gwalior)

TP Singh (Agra)

ADVISORY BOARD

Vijay Achari (Patna)
AK Agarwal (New Delhi)
DP Agarwal (Agra)
Praveen Aggarwal (New Delhi)
KS Anand (New Delhi)
S Anuradha (New Delhi)
Vivek Arya (New Delhi)
BC Bansal (Noida)
D Bandyopadhyay (Kolkata)
Sunil Bansal (Agra)
Mujahid Beg (Aligarh)
Amalkumar Bhattacharya (Vadodara)
SK Bichile (Mumbai)
Anil Chaturvedi (New Delhi)
Maj Gen SS Chauhan (Panchkula)
RM Chhabra (New Delhi)
KK Dang (Agra)
Siddhartha Das (Cuttack)
Desh Deepak (New Delhi)
RM Dhamija (New Delhi)
S Dwivedi (Delhi)
Dhiman Ganguly (Kolkata)
Naveen Garg (Lucknow)
SN Gosavi (Pune)
B Gupta (New Delhi)
Pritam Gupta (New Delhi)
R Handa (New Delhi)
BM Hegde (Mangalore)
Alok Hemal (New Delhi)
Kamal Jain (Jaipur)

Neelima Jain (New Delhi)
PK Jain (Jhansi)
SN Kadam (Navi Mumbai)
T Kadiravan (Tirupati)
OP Kalra (Rohtak)
Ulka Kamble (New Delhi)
Umesh Kansra (New Delhi)
Madhuchanda Kar (Kolkata)
VN Kaushal (Agra)
GA Khwaja (New Delhi)
Dhanpat Kochar (Bikaner)
Anil Kulshrestha (Ahmedabad)
Ajay Kumar (Patna)
Rajat Kumar (Canada)
BM Singh Lamba (New Delhi)
AP Misra (New Delhi)
SK Mishra (Rourkela)
Alladi Mohan (Tirupati)
Sanjib Mohanty (Rourkela)
Sukumar Mukherjee (Kolkata)
YP Munjal (New Delhi)
G Narsimulu (Hyderabad)
NS Neki (Amritsar)
RP Pai (Mangalore)
KK Pareek (Kota)
Anupam Prakash (New Delhi)
Prashant Prakash (Agra)
CV Raghuveer (Mangalore)
Rajesh Rajput (Rohtak)
Y Sathyanarayana Raju (Hyderabad)

NR Rao (Manipal)
BK Sahay (Hyderabad)
JR Sankaran (Chennai)
Anita Sharma (Dehradun)
Brijesh Sharma (New Delhi)
GK Sharma (USA)
SK Sharma (New Delhi)
Ashok Shiromany (Agra)
RP Shrivastwa (Patna)
G Sidhu (Ludhiana)
RK Singal (New Delhi)
Harpreet Singh (Rohtak)
NP Singh (New Delhi)
Rajnish Singh (New Delhi)
RSK Sinha (New Delhi)
Sanjiv Sinha (New Delhi)
SB Siwach (Rohtak)
SH Talib (Aurangabad)
BO Tayade (Nagpur)
Vishal R Tandon (Jammu)
RS Taneja (New Delhi)
Nihal Thomas (Vellore)
Manjari Tripathi (New Delhi)
Sanjay Tyagi (New Delhi)
Rajesh Upadhyay (New Delhi)
SK Verma (Dehradun)
GS Wander (Ludhiana)
Sunil Wadhwa (New Delhi)
Madhur Yadav (New Delhi)
Pushpa Yadav (New Delhi)

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, Mahatma Gandhi Road, 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>)."

July-September, 2016 issue published on September 15, 2016

The statements and opinions contained in the articles of the
'Journal, Indian Academy of Clinical Medicine'

are solely those of the individual authors and contributors. The publisher and honorary editor disclaim any responsibility about the originality of contents. All the articles, however, are peer-reviewed.

The editor and publisher disclaim any responsibility or liability for the claims, if any, made by advertisers.

Papers which have been published in this *Journal* become the property of the *JIACM* and no part of this publication may be reproduced, or published in any form without the prior written permission of the editor.

Typesetting by: Columbia Press, 881, East Park Road, New Delhi - 110 005.

Published by Dr. D. G. Jain

for and on behalf of the Indian Association of Clinical Medicine

from Barnala House, 867, New Rohtak Road, 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,
Mahatma Gandhi Road, Agra - 282 002 (U.P.)

Founder-President: MC Gupta (Agra)

GOVERNING BODY

President

NK Soni (Ghaziabad)

President-Elect

PC Mathur (Gwalior)

Immediate Past-President

AK Gupta (Agra)

Vice-Presidents

Dipanjan Bandyopadhyay (Kolkata)

DP Agarwal (Agra)

Hony. General Secretary

TP Singh (Agra)

Hony. Editor, JIACM

DG Jain (New Delhi)

Associate Editor, JIACM

MPS Chawla (New Delhi)

Hony. Treasurer

Suresh Kushwaha (Agra)

Members

Subhash Chandra Gupta (Agra)

Prashant Prakash (Agra)

OP Kalra (New Delhi)

Vipin Mediratta (New Delhi)

PK Jain (Jhansi)

HS Pathak (North 24 Parganas)

Saikat Datta (Darjeeling)

Arvind Kumar (Meerut)

Zonal Members

North Zone

PN Gupta (New Delhi)

South Zone

YSN Raju (Hyderabad)

East Zone

Sujit Kumar (Bihar Sharif)

West Zone

Ram Pal (Kota)

Central Zone

Rama Kant Yadav (Saifai)

Organising Secretary

(IACMCON-2016)

Navneet Agrawal (Gwalior)

Organising Secretary

(IACMCON-2015)

Vikas Loomba (Ludhiana)

Joint Secretaries

AK Khanna (Agra)

Ashish Gautam (Agra)

Sumeet Singla (New Delhi)

Arise; awake, before it is too late

BM Hegde*

"Science produces ignorance, and ignorance fuels science. We have a quality scale for ignorance. We judge the value of science by the ignorance it defines. Ignorance can be big or small, tractable or challenging. Ignorance can be thought about in detail. Success in science, either doing it or understanding it, depends on developing comfort with the ignorance, something akin to Keats' negative capability."

– Firestein, Columbia University.

This is an appeal to all *thinking* humanitarians, from the heads of Governments in the world, especially our beloved Prime Minister, all those powers-that-be, politicians of all hues and colour, *scientists* of all grades, my colleagues in the healing arts, down to the last person in the world. This appeal concerns every living human (even other life forms) and their future in this world. Western conventional science, especially medical science, does not answer the questions raised in reality. Despite that we claim that ONLY our controlled double blind randomised studies are the gold-standard *science*. All that those studies tell us is that a particular treatment is better than the placebo or better than another treatment.

Take for example a patient has low backache. He will not benefit by knowing which drug works better than placebo or another drug or which surgery does good. This does not answer the question but does not tell the hapless sufferer if there is a better method of management, may be outside our system that might be much better for him. Western medicine, owned by the drug, surgery and device lobbies, has monopolised the whole area condemning every other system as unscientific! This has become so bad that inhuman treatments are thrust on terminal cancer victims and terminally ill patients in the name of science. Even death has been made *scientific* to make death most undignified today!

Thinking people and people in power have started slowly voicing their concerns. In 2010 the then Health Minister of the UK, Andrew Lansley, had this to say in the foreword to their document *Healthy Lives, Healthy People* where he wrote: Social factors are more important in health and disease than all the hi-Tec treatment methods. "We have to be bold because so many of the lifestyle driven disease we have today are already on alarming levels. We are the most

obese nation in Europe today. We have the worst rate of sexually transmitted diseases, relatively large population of drug users and rising levels of alcohol. Smoking alone causes 80,000 deaths per year. Experts feel that tackling poor mental health could reduce the overall disease burden by a quarter. We need a newer approach that empowers people to make healthy choices." Look at what George Bernard Shaw said in his toast to Albert Einstein: "*Science is always wrong; it never solves a problem without creating 10 more*". Modern western medical science has done just that.

In an article in *Nature* in 2011 Michel Crow, a senior science administrator and the President of Arizona State University, proposed a radical change in science policy. Most of the \$30 billion research budget of their NIH goes to funding molecular and genetic aspects of disease rather than looking at people's behaviour. He wanted new institutes to look at fundamental questions about human health from sociologic perspectives, next to look at health outcomes of our interventions which should draw on behavioural sciences, economics, technology, communications, and education along with fundamental biomedical research. Trying to find out a genetic or molecular leads to obesity have been totally misplaced. These are good signs. Indian powers-that-be should take notice as our aping the west has landed us in a worse situation than what obtains in the UK and USA while we ignored own methods where our country has been the birth place of many effective, economical and patient friendly disease care systems. Any one hearing this message?

One of the paradoxes of modern medicine in the recent two decades has seen the phenomenal growth of alternate systems (so called by the main line honchos) of treatment. Unfortunately, the main stream doctors who are brought up on mechanistic reductionistic science steeped in materialism do not understand the philosophy of holism and quantum world view where the human body is seen to be capable of self healing with a powerful immune system called the inner healer of a *closed system* of human biology, in contrast to the *open system*, where an outside intervention is a must for every deviation from the normal nurtured by the materialistic science. A couple of large western scientific studies have shown some powerful drugs and even complicated coronary revascularisation surgeries

***Padma Bhushan; Former Vice-Chancellor, Manipal University; Editor-in-Chief, The Journal of the Science of Healing Outcomes (JSHO); 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.**

are, in fact, placebo effect only!

Nature seems to be rebelling against the inhuman use of materialistic science in that lately the people's placebo effect seems to be growing by leaps and bounds. At present in USA the placebo effect is 56% more powerful and *in many cases drug companies are not able to get effective drugs that are more powerful compared to the placebo effect in the population*. The whole science of medicine has to change. The new system, evidence based Comparative effective study (CES) should replace the time tested RCTs, to look at the following: Rupert Sheldrake).

- Which method works best, including all alternate systems?
- Which method had the variability between practioners?
- Which methods were cost-effective?

Recently a large number of outcome researches in depression (of any severity) and even schizophrenia where psychotherapy was shown to be superior to drugs alone or drugs and psychotherapy have come out. The brain altering chemicals cannot do much to the human mind which is outside the brain activity. Are we listening? One of the problems with mechanistic medicine is its tunnel vision and its obsession with chemical drugs and surgical methods of treatment to the exclusion of all other methods. Medicine is taught that way in medical schools; in India we have taken the London University MBBS curriculum. And there is this biased funding system of medical research which excludes genuine studies for not only funding but even for publication of results in their so called "indexed" journals of repute. When one goes deep into those methods one finds that 17 papers had to be retracted in one year from *Science* and 7 from *Nature*, that much for their excellence!

Western science claims that it is totally objective but recent studies have shown that most, if not all leading scientific studies in science, are biased and are highly subjective. In one of his unguarded moments Nobel Laureate medical scientist, Peter Medawar, when asked if scientific research is a fraud in a BBC interview in 1963 answered in the affirmative, not about research as such but the way scientific papers are written! Linus Pauling with two Nobels, was shouting from house tops that cancer research is a fraud

tein was just 16-years-old when he dreamt that he was running faster than the speed of light and then imagined that time had stopped. All his future studies on relativity must have been biased. A couple of great Nobel Laureates are said have taken small doses of LSD to think deeply! Their names are excluded here to avoid any controversy. Nothing that a man does can be 100% objective. We have no right to criticize alternate systems being subjective. We all have our own world views in the new thinking of

biocentrism. Even animal studies are no exception as the animal's consciousness interacts with the researchers' 40-50 per cent differences in results of animal research could be seen depending on whether a man or a woman is the researcher. The animals can even sense the pheromones of the scientist!

Immortality is another one of the fantasies of western science. Starting with the Russian scientist, Leonid Krasin who tried to preserve Lenin's body in liquid nitrogen to be resurrected later, the trend continues to this day. However, the body decomposed under Krasin's very nose. It did not end there; even today people keep their dead frozen with liquid nitrogen for \$150,000 and neuro-freezing for \$90,000!

People have started freezing cord blood and what have you, all in the name of "science," the word that buys them clients. Keeping terminal cancer patients alive with poisonous chemotherapy, radiation and surgery is a daily affair, thanks to scientists flirting with human immortality. Reality is seen in a large prospective study quoted below, worth reading for every thinking man/woman who administers the research funds for science in general and medical science in particular.

One cannot defeat nature by science; science has to learn from nature. In the new science of quantum world view death is only a part of life. Consciousness persists even after death. Clinical evidence of that view is accumulating. Immortality is a myth. In conclusion, I shall quote above mentioned study of terminal cancer and leave it to the powers that be to wake up to have a new system for the future. In India we have our Ayurvedic legacy on which the new system can be built. It should be an all encompassing system drawing strength from western medicine for emergency care (2% of the total patient load) and for the rest of 98% patient load from all other systems like homeopathy, naturopathy, siddha, unani, osteopathy, chiropractic, acupuncture, and hypnosis. Before building such a system one has to take care to include only those measures that have been authenticated and are genuine. I would love to call this system as *Modern Ayurveda*; *modernity should arise out of our own antiquity and not come from the west as it is thought now in all formal colonial nations*. Modern medicine also started as mumbo-jumbo five thousand years ago on the Nile Valley. It has grown by refining itself to the present level where it has been useful for mankind to a certain extent. Unfortunately, it has become prohibitively expensive as it was hijacked by the money lobby early on in its course, thanks to materialistic science en route. Ayurveda has to do similar innovations as human wisdom grows. It is good that Ayurveda has the science base of holism which modern quantum physics swears by. Indian science has to grow out of its tunnel vision of

developing only natural sciences to the detriment of social sciences which today seem to have more to do with human life on this planet, human health and sickness. Almost all the research funds for science flow through the Indian Academy of Science and hardly anything comes to the Indian Academy of social sciences. The latter gets a step-motherly treatment by the science administrators' even in 2016!

Now is the large study of metastatic lung cancer funded by Cancer foundation in the USA. The patients were offered palliative care soon after diagnosis. They reported better outcomes, better quality of life, were less depressed and in fact, had *survived longer than those who received aggressive anti-cancer treatment.* (Temel et al, *early palliative care for small cell metastatic cancer of the lung.* *New England Journal of Medicine* 2010; 303: 733-742).

Arise; wake up all the science connected people and science administrators all over the world to this reality. Unless we start to change we will all perish before long, eaten up by this monster called reductionist illogical science which has been called a Golem (the scarecrow) by two physicists, Harry Collins and Trevor Pinch in a book by the same name- The Golem!

“Unless we put medical freedom into the constitution, the time will come when medicine will organise into an undercover dictatorship to restrict the art of healing to one class of men and deny equal privileges to others; the constitution of the Republic should make a special privilege for medical freedoms as well as religious freedom.”

– Dr. Benjamin Rush
(Signer of the Declaration of the US Constitution).

***In dwelling, live close to the ground.
In thinking, keep to the simple.
In conflict, be fair and generous.
In governing, don't try to control.
In work, do what you enjoy.
In family life, be completely present.***

– TAO TE CHING.

Prevalence and associations of cheiroarthropathy in patients with type 2 diabetes: A hospital based study from northern India

N Saini*, A Bhargava**, A Sharma***

Abstract

Background: Cheiroarthropathy, characterised by thickening of skin and limited joint mobility, has been documented in both type 1 and type 2 diabetes and occasionally in healthy subjects. It has been noted to be associated with microvascular complications in type 1 diabetes while the association in type 2 diabetes has been inconsistent.

Aims: We assessed the prevalence of cheiroarthropathy in patients with type 2 diabetes and non-diabetic controls, and its association with microvascular diabetic complications.

Methodology: This cross-sectional study was conducted over a year on 212 consecutive patients with type 2 diabetes and an equal number of non-diabetic subjects who were evaluated for the presence of cheiroarthropathy (using the prayer sign) and microvascular complications.

Results: Cheiroarthropathy was prevalent in 30.7% (95% CI: 24.5%, 37.3%) of type 2 diabetics and in 10.8% (95% CI: 7.0%, 15.8%) of controls ($p < 0.0005$). Cheiroarthropathy was strongly associated with the presence of neuropathy on multivariate analysis (adjusted OR: 7.10, 95% CI: 3.2, 15.9) while there were modest associations of cheiroarthropathy with the presence of retinopathy or nephropathy on univariate analysis. Cheiroarthropathy had moderate sensitivity (67%), higher specificity (85%) and a moderately high likelihood ratio for a positive test (4.5) for the presence of diabetic neuropathy.

Conclusion: There was a strong association between presence of cheiroarthropathy and selected microvascular complications like neuropathy in patients with type 2 DM neuropathy. Cheiroarthropathy can be elicited by any health worker at the peripheral level and could serve as a possible rule in test for the presence of diabetic neuropathy.

Keywords: Diabetes mellitus, cheiroarthropathy, limited joint mobility, microangiopathy.

Introduction

Diabetes has emerged as a major healthcare problem globally and in India. In 2004, the Prevalence Of Diabetes in India Study (PODIS) estimated the standardised prevalence of diabetes in India to be 4.3% with a significant difference in prevalence of diabetes in urban areas (5.6%) compared to rural areas (2.7%)¹. Recent surveys have indicated a rising trend of diabetes prevalence in both urban and rural areas with prevalence estimates for urban areas ranging from 10.9% to 14.2% and those for rural areas ranging from 3.0% to 8.3% in those over 20 years of age². The projected prevalence of diabetes for the entire country is of 62.4 million persons with diabetes, which constitutes the largest population of diabetics in the world².

In India, a large proportion of diabetics remain undiagnosed due to the lack of screening programmes, as has been documented in prevalence surveys. After diagnosis has been made, patients should have optimal glycaemic control to prevent diabetic complications, which are major causes of morbidity, premature mortality, disability, and economic loss. Diabetic microvascular

complication affecting the kidney, retina, and peripheral nerves are a common cause of renal failure, blindness in adults, and foot complications resulting in amputation. In India, most patients with diabetes do not get screened for these complications due to lack of awareness amongst both patients and healthcare providers, and poor availability of specialists like physicians and ophthalmologists in rural areas. There is a need for simple bedside tests which can be used by healthcare workers to detect diabetic complications.

Cheiroarthropathy – also known as limited joint mobility – has the potential as a marker for diabetic microvascular complications. Cheiroarthropathy is characterised by thickening of the skin resulting in inability to extend the fingers to fully flatten the hand and this can be detected easily using 2 simple bedside tests, viz., prayer sign and the table top test. This non-vascular complication was first reported in association with type 1 diabetes³ and later in patients with type 2 diabetes. The pathogenesis of this complication is uncertain, but it could be related to non-enzymatic glycosylation of collagen in diabetics⁴. The prevalence of this complication increases with the duration

*Resident, **Associate Professor, ***Professor and Head, Department of Internal Medicine, Himalayan Institute of Medical Sciences (HIMS), Swami Rama Himalayan University, Jolly Grant - 248 140, Dehradun, Uttarakhand.

of diabetes and in different studies has varied from 8% - 58%⁵. The presence of cheiroarthropathy indicating increased risk of microvascular complications in type 1 diabetes was noted in a study in 1981, but the association of cheiroarthropathy with microvascular complications in type 2 diabetes has been inconsistent⁶.

There is a paucity of studies from India on the prevalence and association of cheiroarthropathy with microvascular complications in patients with type 2 diabetes. To address this gap, we studied the prevalence and association of cheiroarthropathy in patients with type 2 diabetes and non-diabetic controls attending the outpatient department of a tertiary care hospital in Uttarakhand which caters to a large population of urban and rural patients drawn from Uttarakhand and the neighbouring districts of Uttar Pradesh. This was done to evaluate the potential of presence of cheiroarthropathy as a possible bedside marker of diabetic microvascular complications.

Material and methods

Study design: This was a cross-sectional case-control study conducted over a period of 1 year.

Sample size and sampling methods: 212 consecutive patients of type II diabetes presenting in the out-patient and in-patient departments of HIMS were included in the case group. An equal number of non-diabetic patients were included in the control group. This sample size was estimated to detect a difference in prevalence of cheiroarthropathy of 0.1 between diabetic and non-diabetic subjects with a power of 0.9 and an alpha error of 0.05.

Inclusion criteria: All patients aged more than 30 years and diagnosed to have type 2 diabetes on the basis of elevated fasting plasma glucose (FPG > 126 mg/dl), elevated random plasma glucose (RPG > 200 mg/dl) in the presence of symptoms and elevated glycosylated haemoglobin (HbA1c > 6.5 per cent), were included in the study. For the control group, subjects who had been screened for diabetes for any reason (e.g., preoperative screening) and found to have a



Fig. 1: 'Prayer sign'.

normal plasma glucose were included in the study.

Exclusion criteria: Patients with type 1 diabetes, or patients with type 2 diabetes with impaired consciousness or respiratory distress, rheumatological disorders like rheumatoid arthritis, scleroderma, and neurological disorders like peripheral neuropathy, stroke – and its complications, were excluded from the study.

Study tools: Diabetic cheiroarthropathy/limited joint mobility. This was assessed by the prayer sign using the method of Rosenbloom⁷.

Diabetic retinopathy: This was assessed by ophthalmoscopic examination.

Diabetic neuropathy: The patients were screened for the presence of diabetic neuropathy using the Michigan neuropathy screening score⁸.

Diabetic nephropathy: This was assessed by estimating the macroalbuminuria by semi-quantitative dipstick based testing of spot urine, and by estimating serum creatinine.

Statistical analysis: Descriptive statistics such as mean (standard deviation) were used to describe normally distributed continuous variables (e.g., heights), median (inter-quartile range) were used for variables with a skewed distribution (e.g., age) and percentages were used to describe categorical variables (e.g., gender, occupation), etc. Chi-square test was used to analyse associations between 2 categorical variables. A multivariable logistic regression analysis was performed with the presence or absence of cheiroarthropathy as the outcome variable while the co-variables were age, duration of diabetes, and presence of neuropathy, nephropathy, and retinopathy. Variables were included in the final model if the univariate analysis showed a p value < 0.25. Univariate and adjusted odds ratios with their 95% confidence intervals were estimated using STATA version 11 (STATA Corp, College Station, Texas USA).

Results

The distribution of study participants according to their select demographic characteristics is shown in Table I. There was a preponderance of males and those from urban areas in the study population, though with no significant difference in gender composition and location of residence between the diabetic and the non-diabetic subjects. The age of persons with diabetes was significantly higher than those who were in the non-diabetic group, while there was a higher proportion of farmers in the non-diabetic group ($p < 0.001$).

The anthropometric indices varied significantly between the diabetics and non-diabetic subjects as expected. The mean (sd) of weight in the diabetic group was 65.38 (12.12)

kg while it was 59.96 (11.56) in the non-diabetic group ($p < 0.0005$), while the body mass index was 24.60 (10.10) in the diabetic group compared to 22.65 (7.36) in the non-diabetic group ($p = 0.0318$). The diabetes related characteristics of the subjects are shown in Table II, which shows that the level of glycaemic control was suboptimal in this population.

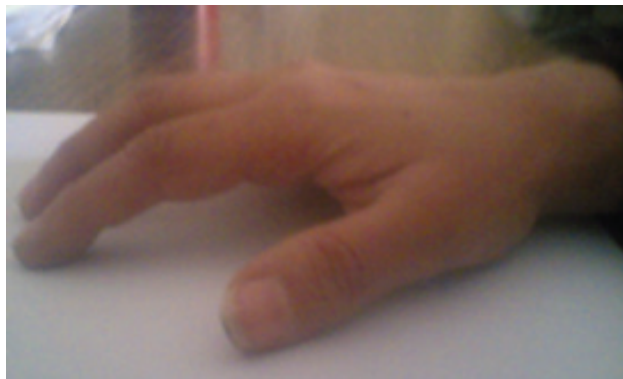


Fig. 2: 'Table top' sign.

On evaluation for presence of cheiroarthropathy, this was found in 65 of diabetic subjects (30.7%, 95% CI: 24.5%, 37.3%), while it was also found in 23 of non-diabetic subjects (10.8%, 95% CI: 7.0%, 15.8%) and this difference in proportions was statistically and clinically significant (chi-squared test, $p < 0.0005$).

Table I: Socio-demographic characteristics of cases and controls.

Characteristic		Diabetics (cases) n = 212	Non-diabetics (controls) n = 212	p value
Mean age (SD)		56 (± 12.44)	50.9 (± 14.27)	$p < 0.001^*$
Gender	Males	132 (62.3)	148 (69.8)	$p = 0.101^s$
	Females	80 (37.7)	64 (30.2)	
Residence	Rural	72 (34)	88 (41.5)	$p = 0.109^s$
	Urban	140 (66)	124 (58.5)	
Occupation	Housewife/total	80 (37.7)	61 (28.8)	$p < 0.001^s$
	Farmer/Labourer	50 (23.6)	79 (37.3)	
	Govt. Service	47 (22.2)	30 (14.2)	
	Private Service/ Business	35 (16.5)	42 (19.8)	

* t-test; ^sChi-square test; figures in parenthesis indicate percentages.

The presence of cheiroarthropathy in the controls was associated with higher age of the subjects and this difference was statistically significant ($p < 0.00005$).

Cheiroarthropathy was associated with smoking status ($p = 0.036$), but there was no association with consumption of alcohol.

Table II: Characteristics related to diabetes in the study population (duration, glucose, and levels of glycosylated haemoglobin).

Parameter	Mean(SD)	Median (IQR)
Duration of DM (years)	7.70 (6.62)	4 (2,8)
Mean FBS (mg/dl)	171.3 (64.06)	158.5 (127.5, 192)
Mean PPBS (mg/dl)	209.9 (73.48)	194 (164, 243)
Mean HbA _{1c} (%)	9.17 (2.55)	8.2 (7.3, 11)

DM = Diabetes mellitus; FBS = Fasting blood sugar; PPBS = Postprandial blood sugar; HbA_{1c} = Glycosylated haemoglobin.

The associations of cheiroarthropathy in the non-diabetic controls are shown in Table III.

Table III: Association of cheiroarthropathy in non-diabetic controls.

Characteristic	Cheiroarthropathy present (n = 23)	Cheiroarthropathy absent (n = 189)	P value
Age, mean (sd)	68 (11.17)	48.94 (13.19)	$P < 0.00005^*$
Gender			
Male	18 (11.3)	141 (88.7)	$P = 0.702^s$
Female	5 (9.4)	48 (90.6)	
Smoking	14 (60.9)	72 (38.1)	$P = 0.036^s$
Alcohol	12 (52.2)	82 (43.4)	$P = 0.423^s$

*Mann-Whitney test, ^sChi-squared test.

The prevalence of different types of microvascular complications in the diabetic subjects is mentioned in Table IV. Diabetic nephropathy was the most frequent microvascular complication present in 50% of our subjects, followed by retinopathy, and diabetic peripheral neuropathy.

Table IV: Prevalence of microvascular complications in diabetic subjects.

Type of microvascular complication	No. of patients with complications	Prevalence (percentage) n = 212
Diabetic neuropathy*	64	30.2
Diabetic retinopathy ^s	96	45.3
Diabetic nephropathy [#]	106	50.0

Table V shows the OR (odds ratio) of various factors which were significantly associated with the presence of cheiroarthropathy on univariate analysis and the adjusted ORs obtained after performing a multivariable logistic

regression analysis. In univariate analysis there was a strong association between the presence of diabetic neuropathy and diabetic cheiroarthropathy, while there was a modest association of presence of diabetic retinopathy and nephropathy with the presence of cheiroarthropathy. In the multivariable regression analysis, the presence or absence of cheiroarthropathy was the outcome variable while the co-variables were age, duration of diabetes, and presence of neuropathy, nephropathy, and retinopathy. The variables significantly associated with the presence of cheiroarthropathy were age of patients, and the presence of neuropathy. The associations of duration of diabetes, alcohol intake, retinopathy, and nephropathy with presence of cheiroarthropathy which were significant in univariate analysis, did not remain significant when adjusted for other co-variables in the multiple logistic regression model. We also evaluated the positive prayer sign as a diagnostic test for the presence of neuropathy. The results are shown in Table VI.

A positive prayer sign had a moderate sensitivity but higher specificity for the presence of diabetic neuropathy. The likelihood ratio for a positive prayer sign was 4.5 which indicates a moderate increase in the likelihood of diabetic neuropathy.

Discussion

Our study evaluated the prevalence and associations of cheiroarthropathy in 212 patients with diabetes of varying duration seen at a tertiary care centre and in an equal number of non-diabetic hospital-based subjects using a cross-sectional study design. We found a significant prevalence of cheiroarthropathy in diabetic subjects (30%) which was almost three-fold higher than that in non-diabetic subjects. In non-diabetic controls the presence of cheiroarthropathy was associated with higher age and smoking status. In diabetic subjects, there was a significant association between cheiroarthropathy and duration of diabetes and the presence of microvascular complications on univariate analysis, and the strength of the association varied with the type of complication. The strongest association was observed between the presence of cheiroarthropathy and neuropathy where patients with cheiroarthropathy had an odds ratio (OR) of 11.63 (95% CI: 5.53, 24.67). This means that in persons with cheiroarthropathy there were 11.6 higher odds of having diabetic peripheral neuropathy. The association of cheiroarthropathy with nephropathy; OR 2.16 (95% CI: 1.14, 4.12) and retinopathy; OR 2.6 (95% CI: 1.37, 4.97) were also statistically significant but the associations were weaker compared to the association with neuropathy. On multivariate logistic regression analysis, the association of

cheiroarthropathy was limited to neuropathy. If we consider the presence of cheiroarthropathy as a bedside marker of diabetic neuropathy, then cheiroarthropathy may serve as a 'rule in' test for diabetic neuropathy as it has a good specificity (85%) and a moderately high likelihood ratio of a positive test⁹. This is a useful finding as the presence of cheiroarthropathy determined by a positive prayer sign can be assessed by any healthcare worker and this could suggest the presence of underlying diabetic neuropathy, which in turn can put the foot at high risk of development of complications like infection, ulceration, and consequently amputations.

Table V: Univariate Odds Ratios (ORs) and adjusted ORs for variables associated with diabetic cheiroarthropathy after logistic regression analysis.

Variable	Univariate OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age (in years)	1.12 (1.08, 1.16)	< 0.0005	1.10 (1.06, 1.15)	< 0.0005
Duration of diabetes (in years)	1.06 (1.01, 1.1)	0.01	0.99 (0.94, 1.04)	0.716
Alcohol intake	2.57 (1.41, 4.67)	0.002	1.96 (0.90, 4.26)	0.09
Neuropathy	11.63 (5.8, 23.2)	< 0.0005	7.10 (3.2, 15.9)	< 0.0005
Retinopathy	2.6 (1.4, 4.7)	0.002	0.84 (0.37, 1.9)	0.68
Nephropathy	2.16 (1.18, 3.93)	0.012	1.66 (0.75, 3.7)	0.213

(*t = test; [§]Chi-square test; [#]Mann whitney test; IQR = Interquartile range).

Table VI: Sensitivity, specificity, likelihood ratios of positive prayer sign for detection of diabetic neuropathy

	Sensitivity	Specificity	Correctly classified	Positive likelihood ratio (LR ⁺)
Use of positive prayer sign for presence of diabetic neuropathy	67.19%	85.03%	79.62%	4.49

The prevalence of diabetic cheiroarthropathy in our patients as well as non-diabetic controls is consistent with those reported in the literature. The association of cheiroarthropathy with increasing age and smoking status has been described in other reports¹⁰. The prevalence of cheiroarthropathy in diabetic subjects has been reported to be between 8% and 50%¹¹. In the landmark study in patients with type 1 diabetes by Rosenbloom it was 30%, which is similar to the prevalence in our study¹². A recent study from Lucknow on 200 patients with diabetes, noted a prevalence of cheiroarthropathy of 40.5%¹³. In a study on a similar number of patients (216) in patients with type 2

diabetes mellitus and age and gender matched controls in Sri Lanka¹⁴, the prevalence of cheiroarthropathy was 18.5% in diabetics and 4.6% in the control group, which is lower than the prevalence in our patients. Our study had some limitations. The study population included patients attending a tertiary care centre in Uttarakhand, and is not representative of patient populations at other levels of health care. The sampling method involved was a convenience sample rather than a random sample, which does impact on the reliability of some of the probability estimates.

Acknowledgement: The cooperation extended by Dr. J.P. Sharma, Medical Superintendent of the Himalayan Hospital for the conduct of this study is gratefully acknowledged.

References

1. Sadikot S, Nigam A, Das S *et al.* The burden of diabetes and impaired glucose tolerance in India using the WHO 1999 criteria: prevalence of diabetes in India study (PODIS). *Diabetes Research and Clinical Practice* 2004; 66 (3): 301-7.
2. Anjana RM, Pradeepa R, Deepa M *et al.* Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research – IndiaDIABetes (ICMR–INDIAB) study. *Diabetologia* 2011; 54 (12): 3022-7.
3. Hordon L, Nathan D, Mudler J. Limited joint mobility in diabetes mellitus. *Uptodate* (homepage on Internet). 2012; Available from: <http://www.uptodate.com>.
4. Monnier VM, Vishwanath V, Frank KE *et al.* Relation between complications of type I diabetes mellitus and collagen-linked fluorescence. *New England Journal of Medicine* 1986; 314 (7): 403-8.
5. Arkkila PE, Kantola IM, Viikari JS. Limited joint mobility in type 1 diabetic patients: correlation to other diabetic complications. *J Intern Med* 1994; 236 (2): 215-23.
6. Rosenbloom AL, Silverstein JH, Lezotte DC *et al.* Limited joint mobility in childhood diabetes mellitus indicates increased risk for microvascular disease. *N Engl J Med* 1981; 305 (4): 191-4.
7. Rosenbloom AL. Limitation of finger joint mobility in diabetes mellitus. *J Diabet Complications* 1989; 3 (2): 77-87.
8. Feldman EL, Stevens M, Thomas P *et al.* A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care* 1994; 17 (11): 1281-9.
9. Singleton JR, Smith AG, Russell J *et al.* Polyneuropathy with impaired glucose tolerance: Implication for diagnosis and therapy. *Current Treat Options Neurol* 2005; 7 (1): 33-42.
10. Eadington DW, Frier BM. Association between connective tissue changes and smoking habit in type 2 diabetes and in non-diabetic humans. *Diabetes Res Clin Pract* 1991; 11 (2): 121-5.
11. Cherqaoui R, McKenzie S, Nunlee-Bland G. Diabetic cheiroarthropathy: a case report and review of the literature. *Case Rep Endocrinol* 2013; 2013: 257028.
12. Kim RP, Edelman SV, Kim DD. Musculoskeletal complications of diabetes mellitus. *Clinical Diabetes* 2001; 19 (3): 132-5.
13. Pandey A, Usman K, Reddy H *et al.* Prevalence of hand disorders in type 2 diabetes mellitus and its correlation with microvascular complications. *Ann Med Health Sci Res* 2013; 3 (3): 349-54.
14. Grundy SM, Cleeman JI, Daniels SR *et al.* Diagnosis and management of the metabolic syndrome an American Heart Association/ National Heart, Lung, and Blood Institute scientific statement. *Circulation* 2005; 112 (17): 2735-52.

**Organ donation does not in any way go against religious teaching and
is as good as the donation of food and money.
This is a great human value; there is no doubt about it.**

– MAULANA WAHIDUDDIN KHAN.

Association of HbA1c with liver fat, abdominal fat indices (visceral fat, subcutaneous fat) and CIMT (carotid intimal medial thickness) in non-diabetic subjects with NAFLD (nonalcoholic fatty liver disease): A cross-sectional analysis of cardiovascular risk in non-diabetic NAFLD subjects

Karan Puri*, Arun Gogna**, Shabnam Bhandari Grover***, Sunil Ranga****

Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is associated with existing cardiovascular diseases independent of classical risk factors, and hence obesity may act as co-factor for the link between serum HbA1c level and NAFLD. Previous studies provide support to the hypothesis that in the absence of diabetes, homeostatic glycaemic control is a risk factor for atherosclerosis.

Aims of study: This study was undertaken to investigate the association of HbA1c with various abdominal fat indices and liver fat and carotid intimal medial thickness (CIMT) in non-diabetic NAFLD subjects.

Methodology: 50 non-diabetic subjects with NAFLD were recruited into this study. Subjects were further divided into three groups as per quartiles of HbA1c (HbA1c < 5.0%, HbA1c = 5.0-5.7%, HbA1c = 5.7 - <6.5%) given by the American Diabetic Association (2010). Study parameters included demographic, clinical, anthropometric parameters, biochemical profile and sonographic parameters (grade of fatty liver, visceral fat, subcutaneous fat, carotid intimal medial thickness).

Results and conclusions: HbA1c was significantly and positively correlated with the grade of fatty liver (p value < 0.001), visceral fat (p value = 0.006), right common carotid intimal thickness (p value = 0.019) and left common carotid intimal thickness (p value = 0.004). Although, a positive correlation was seen between HbA1c and subcutaneous fat, but the result was not statistically significant (p = 0.125). Positive relationship between HbA1c and liver fat, visceral fat, right and left CIMT reveals a possible association between HbA1c and cardiovascular risk in non-diabetic NAFLD patients. Considering the potential link between HbA1c and cardiovascular risk in such non-diabetic NAFLD patients; even non-diabetic individuals with NAFLD should be screened for cardiovascular risk.

Key words: Cardiovascular risk, fatty liver, homeostatic glycaemic control, sonographic parameters.

Introduction

Non alcoholic fatty liver disease (NAFLD) is known to be associated with obesity, i.e., visceral and subcutaneous fat, type 2 diabetes, insulin resistance and cardiovascular risk¹. NAFLD was first described by Ludwig in 1980 as an unnamed liver disease that histologically mimics alcoholic hepatitis and that also may progress to cirrhosis. Most patients in Ludwig's study were moderately obese, and many had obesity-associated diseases, such as diabetes mellitus. Presence of hepatomegaly and mild abnormalities of liver function were common clinical findings in these patients². NAFLD is associated with existing cardiovascular diseases independent of classical risk factors, glycaemic control, medications, and metabolic syndrome features³.

Visceral fat has been reported to be associated with nonalcoholic fatty liver disease (NAFLD) and the metabolic syndrome. Seul-Ki Jeong *et al* study showed that increased

visceral fat content is significantly associated with both NAFLD and the metabolic syndrome⁴. The study done by Han *et al* assessed HbA1c and visceral fat levels as cardiovascular diseases risk factors in health check-up examinees that were not yet diagnosed with diabetes. Visceral fat levels in their study were significantly associated with HbA1c in the group of HbA1c > 5.7. The observations of these authors suggests that subjects who have high levels of HbA1c should be carefully monitored during prediabetes and should have a chance to have health education programmes⁵. Sookoian *et al* reviewed the literature and they found that carotid plaques were more frequently observed in NAFLD patients in comparison with controls and hence these authors concluded that routine measurement of CIMT might be implemented in NAFLD patients⁶.

It is important to determine whether NAFLD is an independent predictor of cardiovascular morbidity and mortality and several studies have suggested that there is

*Post-Graduate Resident, **Professor and Consultant, Department of Medicine, ***Professor and Consultant, Department of Radio-Diagnosis, ****Senior Pathologist, Department of Lab. Medicine, Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital, New Delhi - 110 029.

an association between NAFLD and cardiovascular disease⁷⁻¹². It is hypothesized that NAFLD is not merely a marker of cardiovascular disease but may also be involved in its pathogenesis⁸. Since HbA1c is indicated to be a marker of cardiovascular risk, the elevated HbA1c reported in elderly NAFLD patients in the various studies may partially interpret why NAFLD increases the risk for cardiovascular disease¹³. The Atherosclerosis Risk In Communities (ARIC) study in normoglycaemic individuals also provides support to the hypothesis, that in the absence of diabetes, glycaemic control is a risk factor for atherosclerosis¹⁴.

There is very limited literature on the association between HbA1c and subclinical cardiovascular diseases in non diabetic population. In the above context, the present study was conducted in non-diabetic NAFLD subjects to investigate the association of HbA1c with various abdominal fat indices and liver fat and CIMT.

Material and methods

The study was conducted in the department of medicine and department of radio diagnosis at Vardhman Mahavir Medical College and Safdarjang Hospital, New Delhi, India from January – December, 2012. It was a cross-sectional study in which 50 non-diabetic patients with NAFLD attending medicine out-patient department, with age group between 15 - 60 years were recruited in the study. NAFLD was defined as cases in whom ultrasound examination shows fatty liver of grades 1 to 3 and when other causes of fatty liver particularly significant alcohol intake (more than 140 g weekly in men, 70 g weekly in women) and medication use were rigorously excluded, and patients with otherwise unexplained ALT and AST elevation at least 1.5 times above upper border of normal; and in whom metabolic risk factors were present¹⁵.

The following patients were excluded from study:

1. Diabetic patients were excluded using ADA 2013 guidelines: HbA1c \geq 6.5% (in the absence of unequivocal hyperglycaemia repeat testing is required) or FPG \geq 126 mg/dl (in the absence of unequivocal hyperglycaemia repeat testing is required) or 2-hour plasma glucose \geq 200 mg/dl during an OGTT (75 - g); (in absence of unequivocal hyperglycaemia repeat testing is required) or random plasma glucose \geq 200 mg/dl in patients with classic symptoms of hyperglycaemia.
2. Patients with alcoholic liver disease, patients with hepatitis B, hepatitis patients with acute fatty liver of pregnancy, patients taking drugs like amiodarone, methotrexate, diltiazem, expired tetracycline, HAART

(highly active antiretroviral therapy), tamoxifen, glucocorticoids, patients with inflammatory bowel disease, environmental poisons like phosphorus, mushroom poisoning, HIV, malnutrition, hypothyroidism, patients on total parental nutrition and patients having gastric bypass, jejunio-ileal bypass surgeries.

Informed consent was taken from all subjects recruited in the study and the Institute Ethics Committee at Safdarjang hospital and VMMC approved the study.

Detailed physical examination was carried out with emphasis on cardiovascular examination: blood pressure, pulse, height, weight, waist-hip ratio, waist circumference and body mass index.

Laboratory investigations: Fasting and 2-hour post-prandial blood glucose, HbA1c, blood urea, serum creatinine, liver function test, thyroid function test.

Sonographic evaluation was done for:

(a) Grading of fatty liver, (b) Visceral and subcutaneous fat, (c) Carotid intimal media thickness as per standard techniques^{1,16,17,18}, figures 4a and 4b:

Liver fat: Three gradings of fatty liver were used: Grade 1: (mild steatosis) slightly increased liver echogenicity with normal vessels and absent posterior attenuation; Grade 2: (moderate steatosis) moderately increased liver echogenicity with partial dimming of vessels and early posterior attenuation. Grade 3: (severe steatosis) diffusely increased liver echogenicity with absence of visible vessels and heavy posterior attenuation¹.

Visceral fat: The distances between the posterior edge of the abdominal muscles and the lumbar spine were measured using electronic calipers and this was taken as visceral fat thickness. The transducer was placed on a straight line between the left and right midpoint of lower rib and iliac crest. Measurements were made at the end of a quiet expiration¹⁶.

Subcutaneous fat thickness: The thickness of subcutaneous fat was measured by placement of ultrasound probe perpendicular to the skin on the epigastrium. Longitudinal scans were obtained along the middle line (linea Alba). The thickness of the subcutaneous fat is defined as the distance between the anterior surface of linea Alba and the fat-skin barrier¹⁷.

CIMT: The subject was supine on an examination couch with the head turned 45 degrees away from the side being scanned. The Radiologist obtained longitudinal B-mode images of the left and right common carotid arteries, immediately proximal to the carotid bifurcation and measured the intimal thickness with electronic calipers¹⁸.

Statistical analysis

Levels of HbA1c among different groups of NAFLD (grade 1 to grade 3), visceral fat, and subcutaneous fat were compared using one-way analysis of variance, followed by bonferroni correadd multiple comparisons. HbA1c in each group were compared on different groups of abdominal fat using chi square test. The mean values of CIMT were compared in HbA1c groups using one way ANNOVA. The correlation between the mean values of variables was ascertained using Pearson's correlation coefficient. A P-value of < 0.05 was considered to be statistically significant.

Results

50 NAFLD subjects included in study were divided into three groups as per quartiles of HbA1c laid down by ADA 2010. Out of 50 subjects: 17 (34%) were in group 1, 22 (44%) were in group 2 and 11 (22%) were in group 3. The mean age was 44.7 ± 7.5 years mean weight was 73.9 ± 5.7 kg and mean height was 166.6 ± 7.4 cms (Table I).

Out of total 50 subjects: 23 had grade 1 fatty liver, 22 had grade 2 fatty liver, and 5 had grade 3 fatty liver. In subjects having grade 1 fatty liver, mean HbA1c was 4.8 ± 0.4 .

In subjects having grade 2 fatty liver, mean HbA1c was 5.4 ± 0.5 . In subjects having grade 3 fatty liver, mean HbA1c was 5.5 ± 0.5 (Table II). As the grade of fatty liver increases, mean HbA1c also increases from 4.8 in grade 1 fatty liver to 5.5 in grade 3 fatty liver, and this is statistically significant (p value < 0.001).

Table II: Table showing association between HbA1c and grades of fatty liver.

	No. of subjects	Mean HbA1c	Standard deviation	95% confidence interval
Grade 1 fatty liver	23	4.8	0.44	4.6 - 5.0
Grade 2 fatty liver	22	5.4	0.56	5.2 - 5.7
Grade 3 fatty liver	5	5.5	0.58	4.8 - 6.2
	50	5.2	0.59	5.0 - 5.3

As grade of fatty liver increases mean HbA1c increases "p value < 0.001"

**P value less than 0.05 taken as statistically significant.*

Among all 50 subjects, the mean visceral fat was 8.2 ± 2.4 cms, and the mean subcutaneous fat was 2.1 ± 0.7 cms (Table I). HbA1c was found to be positively correlated with

Table I: Table showing demographic and sonographic parameters among study subjects.

		No. of subjects	Mean	Standard deviation	95% confidence interval	Association with HbA1c (p value)
Age		50	44.7 years	7.58	42.6 - 46.9	0.33
Weight		50	73.9 kg	5.70	72.3 - 75.6	0.88
Height		50	166.6 cm	7.44	164.5 - 168.7	0.26
Visceral fat	Group 1	17	7.5 cm	2.51	6.3 - 8.8	0.075
	Group 2	22	8.3 cm	2.19	7.3 - 9.3	0.48
	Group 3	11	9.2 cm	2.62	7.5 - 11.0	0.48
	Total	50	8.2 cm	2.43	7.6 - 8.9	0.006*
Subcutaneous fat	Group 1	17	1.9 cm	0.73	1.5 - 2.3	0.44
	Group 2	22	2.0 cm	0.72	1.7 - 2.3	0.36
	Group 3	11	2.5 cm	0.71	2.0 - 3.0	0.25
	Total	50	2.1 cm	0.74	1.9 - 2.3	0.125
Right CIMT	Group 1	17	0.6 mm	0.16	0.5 - 0.6	0.76
	Group 2	22	0.7 mm	0.16	0.6 - 0.7	0.89
	Group 3	11	0.8 mm	0.10	0.6 - 0.8	0.94
	Total	50	0.7 mm	0.16	0.6 - 0.7	0.019*
Left CIMT	Group 1	17	0.6 mm	0.15	0.5 - 0.6	0.84
	Group 2	22	0.6 mm	0.17	0.5 - 0.7	0.109
	Group 3	11	0.7 mm	0.11	0.6 - 0.8	0.81
	Total	50	0.6 mm	0.16	0.5 - 0.6	0.004*

**Statistically significant at p value < 0.05*

visceral fat with a Pearson correlation of + 0.386 and this is statistically significant (p value = 0.006). Furthermore, we found that HbA1c was also positively correlated with subcutaneous fat with a Pearson correlation of + 0.220 but this is not statistically significant (p value = 0.125).

In HbA1c group 1, the mean visceral fat was 7.5 ± 2.5 cm. In HbA1c group 2, the mean visceral fat was 8.3 ± 2.1 cm. In the HbA1c group 3, the mean visceral fat was 9.2 ± 2.6 cm (Table I). As we move from HbA1c group 1 to group 3, the mean visceral fat increases from 7.5 cms to 9.2 cms, but this is not statistically significant (p value = 0.20).

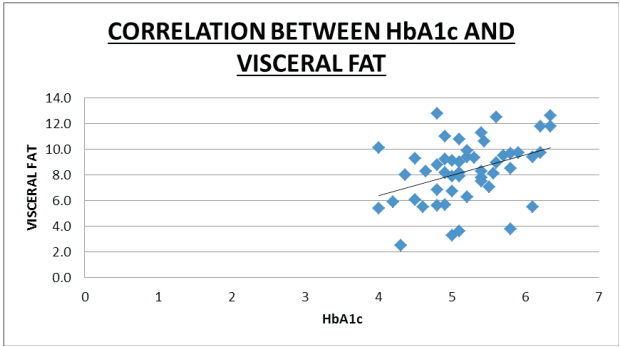


Fig. 1: Showing Pearson correlation of HbA1c with visceral fat.

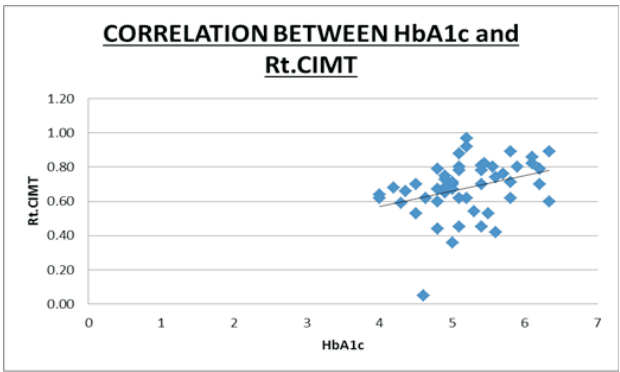


Fig. 2: Showing Pearson correlation of HbA1c with right CIMT.

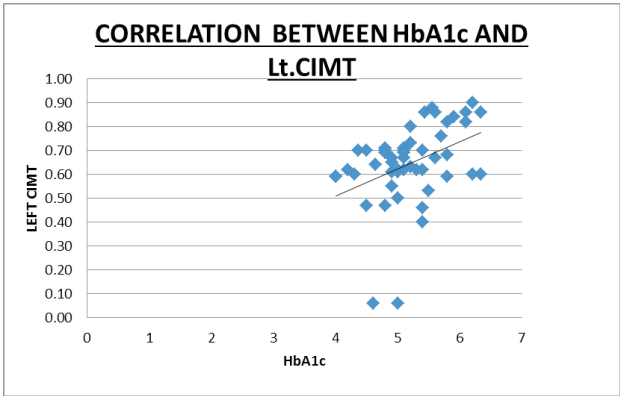


Fig. 3: Showing Pearson correlation of HbA1c with left CIMT.

In the HbA1c group 1, the mean subcutaneous fat was 1.9 ± 0.7 cm. In the HbA1c group 2, the mean subcutaneous fat was 2.0 ± 0.7 cm. In the HbA1c group 3, the mean subcutaneous fat was 2.5 ± 0.7 cm (Table I). As we move from group 1 to group 3, the mean subcutaneous fat increases from 1.9 cm to 2.5 cm, but this is not statistically



Fig. 4 (I): Ultrasound images showing fatty liver (grade 1).

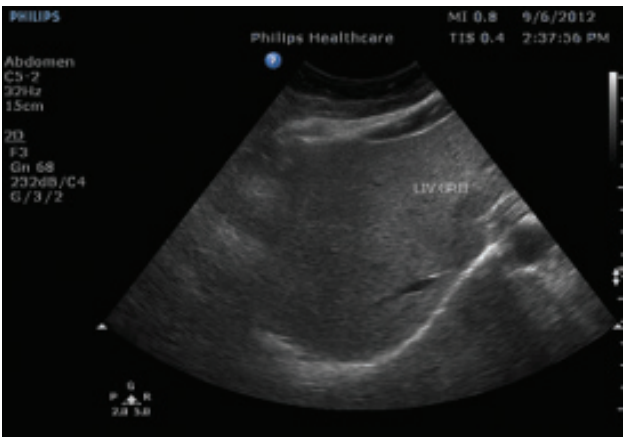


Fig. 4 (II): Ultrasound images showing fatty liver (grade 2).

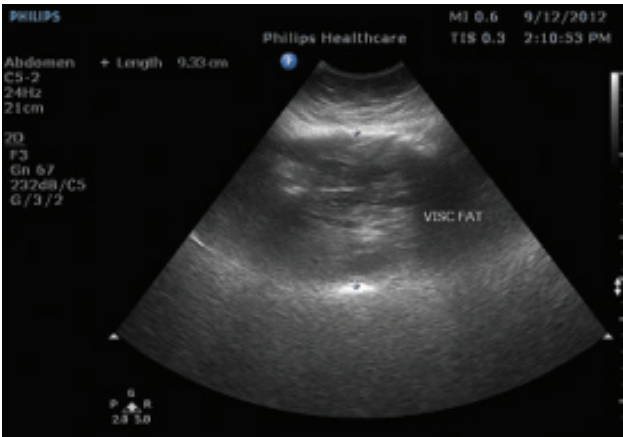


Fig. 4 (III): Ultrasound images showing visceral fat (9.33 cms).

significant (p value 0.116).

Among 50 subjects, the mean right common carotid intimal thickness was 0.7 ± 0.1 mm, and the mean left common carotid intimal thickness was 0.6 ± 0.1 mm (Table I). We found a statistically significant (p value = 0.019) positive Pearson correlation of + 0.332 between HbA1c and right CIMT and there was also a statistically significant (p value = 0.004) positive Pearson correlation of + 0.395 between HbA1c and left CIMT.

In HbA1c group 1, the mean right common carotid intimal medial thickness was 0.6 ± 0.1 mm and the mean left common carotid intimal medial thickness was 0.6 ± 0.1 mm. In HbA1c group 2, the mean right common carotid intimal medial thickness was 0.7 ± 0.1 mm and the mean left common carotid intima thickness was 0.6 ± 0.1 mm. In HbA1c group 3, the mean right common carotid intimal thickness was 0.8 ± 0.1 mm and the mean left common carotid intimal medial thickness was $0.7 \text{ mm} \pm 0.1$ (Table I). Further, as we move from the HbA1c group 1 to group 3, the mean right common carotid intimal medial thickness increases from 0.6 mm to 0.8 mm and this is statistically

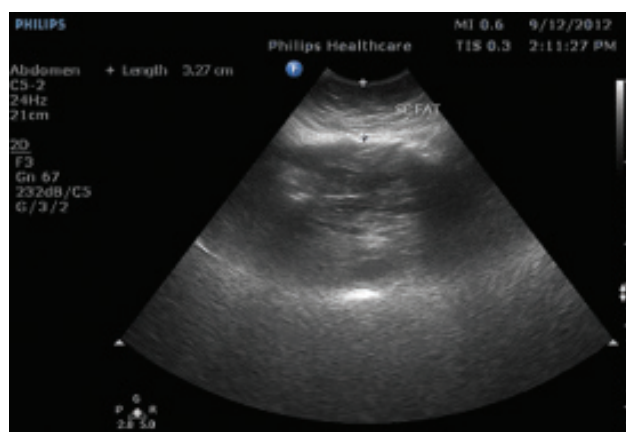


Fig. 4 (IV): Ultrasound images showing subcutaneous fat (3.27 cms).



Fig. 4 (V): Ultrasound images showing left CIMT (0.062 cms).

significant (p value = 0.043). Furthermore, as we move from the HbA1c group 1 to group 3, the mean left common carotid intimal medial thickness increases from 0.6 mm to 0.7 mm; and this is also statistically significant (p value = 0.029).



Fig. 4 (VI): Ultrasound images showing right CIMT (0.054 cms).

Discussion

Various studies had been conducted showing association of HbA1c with obesity indices and carotid intimal medial thickness (a marker of cardiovascular risk) in diabetic patients with NAFLD but till now very few studies had been done in nondiabetic NAFLD subjects^{4,5,13}.

Ma *et al* in 2013 reported in their study among the 949 elderly non-diabetic chinese subjects that prevalence of NAFLD was positively associated with serum HbA1c level. These authors further excluded subjects with obesity and/or the metabolic syndrome and they concluded that serum HbA1c was independently associated with NAFLD¹⁹. Chon *et al* in 2012 reported in their prospective study that individuals with fatty liver showed a higher HbA1c level after 5 years and concluded that HbA1c levels increased with time in individuals with the fatty liver²⁰.

In our study, as the grade of fatty liver increases, the mean HbA1c also increases. Therefore, the results of our study are comparable to the studies done by Ma *et al* and Chon *et al*.

Han *et al* reported in their study amongst health check-up examinees who were not yet diagnosed with diabetes that visceral fat levels were significantly associated with HbA1c ≥ 5.7 ⁵. Ford *et al* concluded that approximately one in three nondiabetic adults in the United States have Impaired fasting glucose (IFG) and obesity. IFG is known to be related to all components of the metabolic syndrome, including strong associations with obesity²¹. These authors, however, have not correlated the association of HbA1c with subcutaneous fat.

In our study, the mean visceral fat was found to be positively correlated with HbA1c and this was statistically significant. Therefore the results of our study are comparable to the studies done by Han *et al* and Ford *et al* with regard to visceral fat. However, our study is unique in that we have studied the association of HbA1c with subcutaneous fat as well. In our study there was a positive correlation of HbA1c levels with subcutaneous fat, although it was not statistically significant; reason for this could be a smaller sample size in our study.

Huang *et al* reported in Chinese subjects with normal glucose tolerance that higher HbA1c was significantly associated with elevated CIMT independent of age, sex, BMI, smoking and alcohol intake status, blood pressure, serum lipid levels, and even fasting plasma glucose²². Temelkova-Kurktschiev *et al* reported in German subjects without clinically diagnosed diabetes that fasting glucose, glucose measured 2 hours after an oral glucose load (2-hour glucose), and HbA1c were each associated with increasing CIMT after adjusting for age and sex²³. McNeely *et al* reported in individuals without evident diabetes that higher HbA1c levels were associated with increasing common carotid and internal carotid medial thickness after adjustment for cardiovascular risk factors²⁴. Vitelli *et al* in the ARIC study in normoglycaemic individuals found significant relationship between HbA1c level and carotid intimal medial thickening. Hence their hypothesis that in the absence of diabetes, glycaemic control is a risk factor for atherosclerosis was established¹⁴.

In our study mean right common carotid intimal thickness and left common carotid intimal thickness was found to be positively correlated with HbA1c and both these correlations were statistically significant. Furthermore, as we move from the HbA1c group 1 to group 3, both mean right and left common carotid intimal media thickness increases and this was also found to be statistically significant. Therefore the results of our study are comparable to the studies done by Huang *et al*, Temelkova-Kurktschiev *et al*, McNeely *et al*, and Vitelli *et al*.

Our study supports the observations made by the previous studies regarding cardiovascular risk in non diabetic NAFLD subjects. The demonstration of a positive and statistically significant relationship between HbA1c and liver fat, visceral fat, right and left CIMT reveals possible link between HbA1c and cardiovascular risk in non-diabetic NAFLD patients. Considering the growing incidence of obesity and NAFLD worldwide and the potential link between HbA1c and cardiovascular risk in such NAFLD patients, even non diabetic individuals should be screened extensively for cardiovascular risk if they have NAFLD.

The limitation of our study was a small sample size. So more number of studies with larger sample size would be

beneficial to the non-diabetic subjects with NAFLD for assessment of cardiovascular risk.

References

1. Agarwal AK, Jain V, Singla S *et al*. Prevalence of non-alcoholic fatty liver disease and its correlation with coronary risk factors in patients with type 2 diabetes. *J Assoc Physicians India* 2011; 59: 351-4.
2. Ludwig J, Viggiano TR, McGill DB *et al*. Non-alcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980; 55 (7): 434-8.
3. Targher G, Bertolini L, Poli F *et al*. Non-alcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. *Diabetes* 2005; 54 (12): 3541-6.
4. Misra A, Wasir JS, Vikram NK *et al*. Cut-offs of abdominal adipose tissue compartments as measured by magnetic resonance imaging for detection of cardiovascular risk factors in apparently healthy adult Asian Indians in North India. *Metab Syndr Relat Disord* 2010; 8 (3): 243-7.
5. Han AL, Shin SR, Park SH *et al*. Association of Haemoglobin A1c with Visceral Fat Measured by Computed Tomography in Nondiabetic Adults. *J Agric Med Community Health* 2012; 37 (4): 215-22.
6. Sookoian S, Pirola CJ. Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. *J Hepatol* 2008; 49 (4): 600-7.
7. Ishizaka N, Ishizaka Y, Yamakado M *et al*. Association between metabolic syndrome and carotid atherosclerosis in individuals without diabetes based on the oral glucose tolerance test. *Atherosclerosis* 2009; 204 (2): 619-23.
8. Rajala U, Päivänsalo M, Laakso M *et al*. Associations of blood pressure with carotid intima-media thickness in elderly Finns with diabetes mellitus or impaired glucose tolerance. *J Hum Hypertens* 2003; 17 (10): 705-11.
9. Bonora E, Kiechl S, Oberhollenzer F *et al*. Impaired glucose tolerance, Type II diabetes mellitus and carotid atherosclerosis: prospective results from the Bruneck Study. *Diabetologia* 2000; 43 (2): 156-64.
10. Faeh D, William J, Yerly P *et al*. Diabetes and pre-diabetes are associated with cardiovascular risk factors and carotid/femoral intima-media thickness independently of markers of insulin resistance and adiposity. *Cardiovasc Diabetol* 2007; 6: 32.
11. Choi SW, Shin MH, Yun WJ *et al*. Association between haemoglobin A1c, carotid atherosclerosis, arterial stiffness, and peripheral arterial disease in Korean type 2 diabetic patients. *J Diabetes Complications* 2011; 25 (1): 7-13.
12. Folsom AR, Eckfeldt JH, Weitzman S *et al*. Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Stroke* 1994; 25 (1): 66-73.
13. Fabs CA, Smith DL, Horn GP *et al*. Impact of excess body weight on arterial structure, function, and blood pressure in firefighters. *Am J Cardiol* 2009; 104 (10): 1441-5.
14. Vitelli LL, Shahar E, Heiss G *et al*. Glycosylated haemoglobin level and carotid intimal-medial thickening in non-diabetic individuals. The Atherosclerosis Risk in Communities Study. *Diabetes Care* 1997; 20 (9): 1454-8.
15. Farrell GC, Larter CZ. Non-alcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; 43 (2 Suppl 1): S99-S112.

16. Stolk RP, Wink O, Zelissen PM *et al.* Validity and reproducibility of ultrasonography for the measurement of intra-abdominal adipose tissue. *Int J Obes Relat Metab Disord* 2001; 25 (9): 1346-51.
17. Armellini F, Zamboni M, Rigo L *et al.* The contribution of sonography to the measurement of intra-abdominal fat. *J Clin Ultrasound* 1990; 18 (7): 563-7.
18. O'Leary DH, Polak JF. Intima-media thickness: a tool for atherosclerosis imaging and event prediction. *Am J Cardiol* 2002; 90 (10C): 18L-21L.
19. Ma H, Xu C, Xu L *et al.* Independent association of HbA1c and non-alcoholic fatty liver disease in an elderly Chinese population. *BMC Gastroenterol* 2013; 13: 3.
20. Chon CW, Kim BS, Cho YK *et al.* Effect of nonalcoholic Fatty liver disease on the development of type 2 diabetes in nonobese, non-diabetic Korean men. *Gut Liver* 2012; 6 (3): 368-73.
21. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *J Am Coll Cardiol* 2010; 55 (13): 1310-7.
22. Huang Y, Bi Y, Wang W *et al.* Glycated haemoglobin A1c, fasting plasma glucose, and two-hour post-challenge plasma glucose levels in relation to carotid intima-media thickness in Chinese with normal glucose tolerance. *J Clin Endocrinol Metab* 2011; 96 (9): E1461-5.
23. Temelkova-Kurktschiev TS, Koehler C, Henkel E *et al.* Post-challenge plasma glucose and glycaemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care* 2000; 23 (12): 1830-4.
24. McNeely MJ, McClelland RL, Bild DE *et al.* The association between HbA1C and subclinical cardiovascular disease: the multi-ethnic study of atherosclerosis. *Diabetes Care* 2009; 32 (9): 1727-33.

***When you get into a tight place and everything goes against you,
till it seems as though you could not hang on a minute longer,
never give up then, for that is just the place and time that the tide will turn.***

– HARRIET BEECHER STOWE.

Dengue: Clinical profile and management in reference to platelet transfusion

SS Gupta*, RK Singh**, AK Gupta***

Abstract

Aim: To study the clinical profile of patients of dengue fever with thrombocytopenia and the role of platelet transfusion in its management.

Method: Serologically confirmed 68 cases of dengue infection who were hospitalised were included in the study. Detailed clinical examination, various laboratory parameters of blood counts, coagulation profile, biochemical investigations like renal and hepatic function tests were done. Patients were followed-up from admission to recovery or death. Data was analysed with statistical package version (SPSS) 14.0. The Chi square test was used for analysis of variables. A value of $P < 0.05$ was considered significant.

Observation: This study included 68 patients with a M:F ratio of 1.4: 1. Patients presented or developed complications like shock, hepatic or renal dysfunction, DIC, haemorrhage and multi-organ dysfunction. There is no role of prophylactic platelet transfusion. Rapid correction of shock is the key component of management.

Introduction

Dengue is a self-limiting acute mosquito transmitted disease characterised by fever, headache, muscle pain, rash, nausea, and vomiting. Dengue is caused by an arbovirus and the vector is the *Aedes aegypti* mosquito. A few patients may develop dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) which could be life-threatening if not managed properly. The crux in management of dengue fever is intravenous fluid therapy. Triage and management decisions are critical in the positive clinical outcome of patients.

The short interval between the onset of haemorrhage and death, especially in young children, makes rapid medical intervention a critical factor for survival. Successful treatment of dengue depends upon symptom recognition and careful fluid management. A simple dengue disease classification scheme is required. Dengue virus induces anti-platelet and anti-endothelial antibodies which are responsible for development of DHF/DSS due to lysis of platelets via complement activation and capillary leakage due to endothelial damage causing pleural, peritoneal, and pericardial effusion.

Material and methods

A total of sixty-eight ($n = 68$) serologically confirmed patients who were hospitalised were included in the study. IgM anti dengue antibodies using the IgM antibody capture – enzyme linked immunosorbent assay (MAC – ELISA) according to NVBDCP guidelines for diagnosis of dengue

were done. Patients were followed-up from the date of admission until recovery or death. Patients with fever with negative serology of dengue infection, positive for other infections like malaria, typhoid, and patients with any other cause identified for thrombocytopenia/hypotension were excluded. The criteria for admission were acute febrile illness of 2 - 7 days duration with positive serology for dengue infection presenting with hypotension, inproportionate tachycardia with fever, haemorrhagic manifestation like petechiae, ecchymosis, purpura, bleeding from mucosa, bleeding from GI tract and from injection sites, serous fluid accumulation (pleural effusion, pericardial effusion, and ascites), dehydration, persistent vomiting, unable to tolerate the oral fluid, organ impairment, thrombocytopenia, renal failure.

Detailed clinical examination was done at admission, blood samples were collected, and all haematological, coagulation profile and biochemical investigations for renal and hepatic function were done.

Results

The study group consisted of 68 patients with a male and female ratio of 1.4:1 and age ranging from 12 to 75 years (mean age: 35.6 years). Common clinical features were fever (100%), arthralgia and myalgia (98.53%), rash (86.76%), petechiae (92.65%) and other bleeding manifestation. Shock was observed in 24 patients (35.29%) without predilection to any particular age group during the critical phase, i.e., 3 to 7 days after onset of fever (Table I). Strong association between shock and presence of severe

*Assistant Professor, **Senior Resident, ***Professor and Head, Department of Medicine, FH Medical College and Hospital, Tundla, Firozabad, Agra 282 004, Uttar Pradesh.

bleeding ($p = 0.004$) was observed. Mortality rate among patients with shock was 45.8% ($n = 11$). Significant plasma leak was seen in the form of pleural effusion ($n = 14$). A total of twenty eight ($n = 28$) patients had fluid accumulation in serous cavities (Table III), of these 16 patients were in shock. Mean haematocrit at admission was 43.47% and 11 patients had haematocrit $> 50\%$ at admission (Table IV). The most common finding was thrombocytopenia ($n = 49$) with platelet count $< 50,000/\mu\text{l}$ at presentation (Table IV). We observed hepatic dysfunction in 54 patients with rise in $\text{AST} > \text{ALT}$, while 24 patients had serum bilirubin $> 2 \text{ mg/dl}$. Renal dysfunction was observed in 24 patients having serum creatinine $> 1.4 \text{ mg/dl}$, while three patients had acute renal failure. Among the patients studied there were eleven (16.17%) deaths (male $n = 10$, female $n = 1$) without predilection to any particular age group. Out of 11, seven patients who died had a platelet count in the range of 20,000 to 49,000/ μl ; one had platelet count $< 20,000/\mu\text{l}$, and three patients had platelet count $> 50,000/\mu\text{l}$. All eleven patients who died were in shock at the time of presentation and seven of them received platelet transfusion for the haemorrhagic manifestations.

Table I: Clinical features of patients with dengue.

Clinical feature	No. of cases	%
Fever	68	100
Myalgia /athralgia	67	98.5
Rash	59	86.76
Retro-orbital pain	16	23.52
Petechiae	63	92.64
Mucosal /gingival bleed	23	33.82
GI bleed	14	20.58
Menorrhagia	5	17.64
Systolic blood pressure $< 90 \text{ mmHg}$	24	35.29

Table II: Bleeding manifestations seen in patients under study.

Bleeding manifestations	Patients	%
Petechiae	63	92.64
Subconjunctival haemorrhage	8	11.76
Epistaxis	1	1.47
Gingival/oral bleeding	23	3.82
Haematemesis	9	13.23
Malena	4	5.88
Bleeding PR	1	1.47
Menorrhagia	5	17.85

Table III: Showing 28 out of 68 patients had pleural effusion, pericardial effusion, and ascites.

Fluid accumulation in serous cavities	Number of patients
Pleural effusion only	14
Pericardial effusion only	1
Pleural + pericardial effusion	2
Ascites only	8
Pleural effusion + ascites	3

Table IV: Hematological profile at admission.

Investigation (parameter)	No. of cases	Percentage (%)
Haematocrit $> 50\%$	11	16.17
WBC $< 4,000/\mu\text{l}$	18	26.47
Platelet count $> 1100,000/\mu\text{l}$	1	1.47
Platelet count 50,000 - 100,000/ μl	18	26.47
Platelet count 20,000 - 49,000/ μl	48	20.58
Platelet count $< 20,000/\mu\text{l}$	1	1.47

Table V: Haematocrit at admission in patients with shock (24 cases).

Haematocrit at admission	No. of cases
$> 50\%$	10
40 - 49%	10
30 - 39%	2
$< 30\%$	2

Table VI: Platelet counts at admission and during stay in hospital.

Platelet count	At admission	%	At 24 hours	%	At 72 hours	%
$\geq 150,000/\mu\text{l}$	0	0	2	2.94	9	13.33
100,000 - 149,000/ μl	4	5.88	0	0	19	27.94
80,000 - 99,000/ μl	10	14.7	5	7.35	15	22.05
50,000 - 79,000/ μl	5	7.35	24	35.29	21	30.88
20,000 - 49,000/ μl	47	69.11	33	50	4	5.88
10,000 - 19,000/ μl	1	1.47	4	5.88	0	0
$< 10,000/\mu\text{l}$	1	1.47	0	0	0	0

Analysis of results

12 patients with major bleeding manifestations were in shock at the time of presentation (Table VII). 16 patients with shock had evidence of fluid leak in the third intercostal space in the form of pleural effusion, pericardial effusion and ascites (Table

VIII). Hepatic dysfunction was also observed in patients with shock (n = 24). Liver enzymes, i.e., SGOT (AST) level and SGPT (ALT) level were higher in patients with shock – 890.58 U/L and 303.76 U/L respectively as compared to 25.76 U/L and 104.67 U/L in patients without shock (Table IX). Twenty-eight patients of the study population received platelet transfusion for haemorrhagic manifestations. Twenty-one of these patients improved and seven expired (Table X). 19 patients had major haemorrhagic manifestations (haematemesis, melena, bleeding PR, menorrhagia) (Table II). Out of 68 patients, 40 patients had minor clinical bleeding and platelet transfusion was not done; of these 40 patients, 36 patients improved and 4 patients expired (Table X). This denotes that there is no role of prophylactic platelet transfusion and it should be reserved for major bleeding manifestation with shock. Twenty-four (n = 24) patients developed shock, out of which 13 patients improved while 11 patients died. This revealed that shock had significant correlation with mortality (Table XI).

Table VII: Comparison of the presence of severe bleeding manifestation in patients with shock.

	Bleeding	
	Absent	Present
No Shock (44)	37	7
Shock (24)	12	12
Total (68)	49	19

Table VIII: Comparison of presence of third space fluid accumulation in patients with shock.

	Fluid leak	
	Absent	Present
No shock (44)	32	12
Shock (24)	8	16
Total (68)	40	28

Hepatic dysfunction in patients with shock (24) and without shock (44).

Table IX: Comparison of AST (SGOT) and ALT (SGPT) in patient with shock and those without shock.

	N	Mean (SGOT) (U/L)	Mean (SGPT) (U/L)
Patients with shock	24	890.58	303.79
Patients without shock	44	205.76	104.61

Discussion

Dengue infection has a wide clinical spectrum ranging from a mild, self-limiting presentation to a severe life-threatening situation. In spite of its complex manifestations, the

management is relatively simple and inexpensive but requires a prudent approach. Judicious fluid replacement, good clinical assessment and management decisions at the primary and secondary care levels are critical in determining the clinical outcome. Wali¹² reported higher male to female ratio (2.5:1) as compared to our study.

Table X: Outcome in patients who received platelet transfusion and those who did not receive it.

Group	Outcome	
	Expired	Improved
No platelet transfusion (40)	4	36
Platelet transfusion (28)	7	21
Total (68)	11	57

Table XI: Comparison of mortality with shock.

		Outcome	
		Expired	Improved
Shock	Absent (46)	0	44
	Present (24)	11	13
	Total (68)	11	57

Haemorrhage is one of the major manifestations of DHF/DSS and the cause of severe bleeding is multifactorial rather than thrombocytopenia alone⁷. Lum *et al*⁷ identified duration of shock and low/normal haematocrit as a major risk factor for development of haemorrhage. Prolonged prothrombin time and partial thromboplastin time were not directly responsible for severe bleeding but likely to be prolonged in protracted shock. This in combination with thrombocytopenia, hypoxia, and metabolic acidosis leads to organ failure and advanced DIC. Massive bleeding can also occur in absence of prolonged shock if the patient had taken aspirin, NSAIDs or corticosteroids². We also observed similar significant association between shock and presence of severe bleeding.

Increased capillary permeability results in a parallel rise in haematocrit level and development of fluid leak. A rise of > 20% haematocrit is considered to be significant^{3,11}. In our study, the mean haematocrit was 45.12% and 42% in patients with or without shock respectively. Only 11 patients showed a haematocrit > 50%. No significant association was observed between haematocrit and shock (Table V). This may be because of co-existence of overt bleeding with plasma leak, leading to normal or low haematocrit. In our study there was significant (p = 0.001) association between third space fluid accumulation (pleural/pericardial effusion and ascites) and shock. Therefore pleural/pericardial effusion and ascites should be considered important risk

factors. Organ involvement. (hepatic, myocarditis, ARDS, and renal dysfunction) was observed in our study like other studies^{2,5,10}. Lye *et al*⁷ observed that thrombocytopenia did not correlate with bleeding risk and the efficacy of prophylactic platelet transfusion is also questionable. Lum *et al*¹ also noted that prophylactic platelet transfusion neither reduces the bleeding nor expedites the platelet recovery; instead, causing fluid over load and improvement in platelet was transient (less than five hours)^{6, 9}. We also did not observe significant difference in outcome among patients who received platelet transfusion and who did not receive it. We observed statistically significant association between shock and mortality similar to other studies^{2,5,10}. Patients (n = 7) who succumbed to dengue had severe bleeding except four patients with only petechiae and subconjunctival haemorrhage. Hepatic dysfunction was seen in all patients who died. Among expired patients, two had ARDS, and two had myocarditis and renal failure each.

We did not observe the correlation between the platelet count and severity of bleeding or mortality in the present study. We observed shock, plasma leakage, multiorgan failure, development of DIC and haemorrhage as major risk factors. The presence of plasma leak and shock were significant for development of severe dengue and death. The monocyte- macrophage system involvement is central to the pathogenesis of dengue. During primary infection, neutralising antibodies and cross-reacting antibodies are produced. Subsequent infection and high viral load stimulates the immune system resulting into high level cytokines, complement activation and other soluble mediators leading to endothelial cell activation and damage; thus finally producing plasma leak³. The causes of thrombocytopenia are defect in platelet production, bone marrow depression, platelet activation and aggregation, peripheral sequestration and consumption of platelets³. Therefore all efforts should be done promptly to detect and treat the shock in patients suffering from dengue infection.

Conclusion

The main factors contributing to mortality were presence

of shock, severe haemorrhage, plasma leak, and multi-organ failure. Prompt diagnosis and effective treatment can decrease the mortality. Platelet count has no correlation with severity of haemorrhage and mortality. There is also no role of prophylactic platelet transfusion.

References

1. Cattand P *et al*. Tropical diseases lacking adequate control measure: dengue leishmaniasis and African trypanosomiasis. Diseases Control priorities in developing countries, 2nd Ed. New York, NY, Oxford University Press, 2006.
2. Deen J, Lum L, Martinez E *et al*. Clinical management and delivery of clinical services. Dengue: Guidelines for diagnosis, treatment, prevention and control – New Edition. Geneva: WHO; 2009.
3. Elzinandes Leal de Azeredo, Robsom Q Monterio, Luzia Maria de-Oliveira Pinto: Thrombocytopenia in Dengue: Interrelationship between Virus and the Imbalance between Coagulation and Fibrinolysis and Inflammatory Mediators. (Review Article). 2015; Article ID 313842, 16 pages.
4. Guidelines for Clinical Management of Dengue Fever, Dengue Haemorrhagic Fever and Dengue Shock Syndrome. Government of India. Directorate of National Vector Borne Disease Control Program. Directorate General of Health Services, Ministry of Health and family Welfare, 2008.
5. Gulati S, Maheshwari A. Atypical manifestation of dengue. *Trop Med Int Health* 2007; 12: 1087-95.
6. Guidelines on Management of Dengue Fever and Dengue Haemorrhagic Fever in Adults. Ministry of Health- Sri Lanka. National Guidelines. December 2010.
7. Lye DC, Lee VJ, Yan Sun YS. Lack of Efficacy of Prophylactic platelet Transfusion for severe thrombocytopenia in adults with acute uncomplicated dengue infection. *Clinical Infectious Diseases* 2009; 48: 1262-5.
8. Lum LCS, Goh AYT *et al*. Risk factors for haemorrhage in severe dengue infections. *The Journal of Pediatrics* 2002; 140 (5): 629-31.
9. Lum LCS, Abdel Latif ME, Goh AY *et al*. Preventive transfusion in dengue shock syndrome – is it necessary ? *J Pediatr* 2003; 143: 682-84.
10. Varathraj A. Encephalitis in the Clinical spectrum of dengue infection. *Neurology India* 2010; 58 (issue 4): 586-91.
11. WHO. Dengue Haemorrhagic fever: Diagnosis, treatment, Prevention and Control. 2nd Ed. Geneva. World Health Organisation, 1997.
12. Wali JP, Biswas A, Handa R *et al*. Dengue Haemorrhagic fever in adults: a prospective study of 110 cases. *Trop Doct* 1999; 29: 27-30.

***The root of all health is in the brain.
The trunk of it is in emotion.
The branches and leaves are the body.
The flower of health blooms when all parts work together.***

– KURDISH FOLK WISDOM.

Gastrointestinal profile of corrosive injury in western Rajasthan

Anil Sankhla*, Chandra Prakash Mathur**, Sunil Dadhich***, Kishan Gopal Barupal****, Rhythm Mathur*****, Mukesh Agarwal*****

Abstract

Introduction: Corrosive ingestion is a serious medical problem with a variety of presentations and complicated clinical course and when performed, early endoscopy is considered valuable for diagnosis and management of patients.

Methods and patients: 50 patients (above 14 years) admitted in our hospital from 2009 to 2011 were studied prospectively and their clinical course, endoscopic findings, and outcome were analysed. Most common corrosive taken was diluted alkali (48%) followed by concentrated acid (38%), and concentrated alkali (12%).

Results: We found that clinical features are not reliable for diagnosis and assessing severity and extent of injury. On endoscopy, diluted alkali ingestion causes no or milder grades of injury, whereas concentrated acid and concentrated alkali ingestion causes severe grades of injury. Chances of complications increase as injury grades on endoscopy increase. Patients with injury grades I and IIA developed very few complications and had lesser hospital stay, whereas grade IIB, IIIA to IIIB patients had severe complications and longer hospital stay. Bleeding was the most common gastrointestinal complication followed by strictures and septicaemia. Death occurred in 6% of patients.

Discussion: We found that when performed early, upper gastrointestinal endoscopy is safe and useful in confirming diagnosis and finding out the extent, location, and severity of injury. It has prognostic value and we can plan further management. It is also useful in finding and managing delayed complications.

Introduction

Corrosive ingestion is a serious medical problem with a variety of presentations and a complicated clinical course. Injury to GI tract caused by accidental or intentional ingestion of corrosive agents has become more frequent in recent years; therefore accurate assessment of extent of damage is essential for proper management. When performed within 24-hours of ingestion, endoscopy is considered valuable because there is a close correlation between endoscopy findings and extent of gastrointestinal involvement. Although the spectrum of injury to the upper GI tract due to corrosive substances has been well studied, data from Western Rajasthan is lacking.

Method and materials

50 patients (above 14 years) admitted in hospital from 2009 to 2011 were studied prospectively. Corrosive characteristics (type, amount, concentration, physical state), demographic determinants (name, age, sex, religion, address, occupation), associated intoxication, intention (accidental/suicidal) and clinical features were noted. Local and systemic examination, endoscopy, laryngoscopy, radiological examination, and laboratory investigations were done. Endoscopy was done by flexible video endoscope as early as possible, preferably within 24 hours and repeat

endoscopy was done whenever required. Endoscopy was done without general anaesthesia to decrease the chances of aspiration. Endoscope was negotiated to the farthest extent possible, preferably upto the duodenum until any contraindication was found. In case initial endoscopy was not possible, then barium study or repeat endoscopy was done. Patients were followed up for three months or more and type of feeding, stay in hospital, complications, and outcome were noted. Gastrointestinal injury were graded according to classification proposed by Zargar³ given in Table I.

Table I: Showing grades of injury as described by Zargar³.

Grades	Endoscopic findings
0	Normal
I	Oedema and hyperaemia of mucosa.
Ila	Friability, haemorrhages, erosions, blisters, whitish membrane exudates, and superficial ulcerations.
Ilb	Ila + deep, discrete, or circumferential ulcerations
III	Multiple ulcerations and area of necrosis.
IIIa	Small scattered areas of necrosis.
IIIb	Extensive necrosis (areas of brown-black or growth discoloration were taken as evidence of necrosis)
IV	Perforation

*Senior Resident, **Professor, ***Assistant Professor, ****Intern, *****Junior Resident, Department of Medicine, ***Associate Professor, Department of Gastroenterology, Sarojini Naidu Medical College, Jodhpur, Rajasthan.

Results

The most common corrosive ingested was diluted alkali (cleaning agent) in 24 patients (48%), followed by concentrated acids in 19 patients (38%) and concentrated alkali in 6 patients (12%). A rare case of Copper Sulphate ingestion was seen in one patient. All corrosives were liquid in consistency. It is important because powder adheres to the oral cavity and throat causing more severe injury to these organs whereas liquid agents passed rapidly to oesophagus and stomach causing injury to them³⁰.

Concentrations of corrosives were: concentrated acid (hydrochloric acid, sulphuric acid, nitric acid) – 20 - 30%, concentrated alkali (sodium hydroxide) – 30 - 40% and diluted alkali contains (sodium hypochlorite 1.5%, sodium hydroxide 2%, hydrogen peroxide 3%). Corrosives concentrations are more important in damage production: 1.83% is sufficient for epithelial necrosis, 7.33% causes submucosal necrosis, and 14.66% muscle and adventitia necrosis; 33.66% solutions cause lung and tracheal damage after 10 minutes, and oesophageal perforation after 120 minutes³¹. Average amount of corrosive taken was 84 ml, more alkalis (88.39 ml) than acids (78.95 ml), as acids having pungent odour are spit out early.

Males, younger patients (< 30 yrs) and patients with suicidal tendency were commonly found. 12 patients (24%) were intoxicated, all were males and had taken corrosive accidentally. Details are given in Table II.

Table II: Showing demographic characters, intent, and intoxication.

	Age (in years)		Sex		Intent		Intoxication	
	< 30	> 30	M	F	Suicidal	Accidental	Yes	No
No. of patients	35	15	31	19	32	18	12	38

Most common clinical feature in our patients was mouth ulcer in 92%, followed by oropharyngeal injury in 84%, drooling of saliva in 82%, vomiting and burning sensation in 66%, dysphagia/odynophagia in 68%, abdominal pain in 60%, bleeding in 48%, hoarseness in 24%, dysphonia in 22%, shortness of breath in 20%, laryngeal oedema and stridor in 18%, cough and chest pain in 16%.

On endoscopy, oesophagus was involved in 41 patients (82%) and stomach was involved in 37 patients (74%), both oesophagus and stomach were involved in 33 patients (66%). Duodenum was involved in 5 patients (10%). Details are given in Table III.

Most common complication was bleeding in 24 (48%) patients followed by stricture in 12 (24%), septicemia in 11 (22%), aspiration in 6 (12%) and respiratory obstruction

in 3 (6%). Among the early complications, bleeding was the most common complication occurring in 24 (48%) patients and one patient died due to massive bleeding. Blood transfusion was required in 10 patients. Septicaemia developed in 11 (22%) and aspiration pneumonia developed in 6 (12%) patients. Laryngeal oedema developed in 3 (6%) and required tracheostomy. Details are shown in Table IV.

Hospital stay in grade 0 and 1 injury was 2 days, IIA injury was 4.2 days, IIB injury was 7.78 days, IIIA injury was 12.5 days and IIIB injury was 16.5 days. Oral diet was started on day 2 in grade 0 and I patients and 5.4 days in IIA injury. 2 patients of grade IIB and all patients of grade III injury underwent feeding jejunostomy for nutrition.

On follow-up, 14 (28%) patients developed strictures as a delayed complication. 2 patients had both pyloric and oesophageal stricture, 9 patients had only pyloric stricture, and 3 patients had only oesophageal stricture. Endoscopy and dilatation was done in all. Dilatation was successful in 3 patients, and the remaining 11 patients were referred for reconstructive bypass surgery, out of which 2 patients expired after surgery and 2 were lost on follow-up. We found endoscopy as a safe procedure for treatment of stricture with good results. Mortality occurred in 3 patients (6%), all had grade III injury. One died due to massive gastrointestinal bleeding and the other two due to surgical complications.

Discussion

Diluted alkalis were most common agent in our study where as, other studies in India by Zargar³ and Dilwari² had showed acids as the most common corrosives. This could be because diluted alkali caused minor injury and did not require hospitalisation.

We found clinical features not reliable for assessing severity and extent of injury, as 9 patients having upper gastrointestinal injury did not have oropharyngeal injury and 3 patients of oesophagitis did not present with dysphagia/odynophagia. 5 patients of gastric injury did not have vomiting and abdominal pain. These results are similar to the study of Zargar *et al*³ in which 24 of 28 patients with oropharyngeal burns showed upper gastrointestinal tract involvement, while 7 of 13 with normal pharynx had injury to the upper gastrointestinal tract.

Acids damaged stomach severely; probably because oesophageal epithelium being resistant to acid, it is rapidly cleared to the stomach where it is collected in the pre-pyloric region due to corrosive-induced pylorospasm⁶. Alkali damaged oesophagus more, as being more viscous it tends to adhere to the oesophageal mucosa with only a relatively

Table III: Showing extent and severity of injury on endoscopy.

Types of corrosives with location of injury												
Conc. acid (19 patients)				Conc. alkali (6 patients)			Diluted alkali (24 patients)			Copper sulphate (1 patient)		
Location of injury				Location of injury			Location of injury			Location of injury		
		Oeso.	Stom.	Duod.			Oeso.	Stom.	Duod.			Duod.
Grade I injury		4 patients	1 patient	4 patients	0		1 patient	1 patient	13 patients	11 patients	0	0
Grade II injury	A	7 patients	2 patients	0	0		1 patient	0	2 patients	0	0	1 patient
	B	5 patients	7 patients	0	1 patient		2 patients	0	0	0	0	1 patient
Grade III injury	A	1 patient	2 patients	0	0		0	0	0	0	0	0
	B	2 patients	7 patients	0	5 patients		2 patients	0	0	0	0	0

Table IV: Showing complications according to grades of injury and corrosive type.

Complications according to grades of injury						Complications according to corrosive types				
		Grade I (6 patients)		Grade II (14 patients)		Grade III (14 patients)	Diluted alkali (24 patients)	Concentrated alkali (6 patients)	Concentrated acids (19 patients)	Copper sulphate (1 patient)
		Ila	Ilb	IIla	IIlb					
1	Bleeding	3 patients	3 patients	5 patients	2 patients	11 patients	4 patients	4 patients	15 patients	1 patient
2	Septicaemia	0	0	2 patients	2 patients	7 patients	0	1 patient	10 patients	0
3	Aspiration pneumonia	0	0	0	0	6 patients	0	3 patients	3 patients	0
4	Laryngeal oedema	0	0	0	0	3 patients	0	3 patients	0	0
5	Pyloric stricture	0	0	2 patients	2 patients	7 patients	0	1 patient	10 patients	0
6	Oesophageal stricture	0	0	0	0	5 patients	0	4 patients	1 patient	0

small amount reaching the stomach⁶. Studies by Zargar³ and Dilwari² also found that in acid ingestion stomach was more severely affected. Duodenum was only mildly involved in all cases, probably due to corrosive induced reflex spasm of pylorus³. Both concentrated acid and alkali had higher grades of injury in comparison to diluted alkali. Tohda *et al*²⁹, in their study of 95 patients also found that ingestion of strong acid or strong alkali often produced deep grade III changes while diluted alkalis such as bleach, detergent, ammonia, or other substances usually caused grade I injury.

Bleeding occurred in 24 (48%) patients and chances of bleeding increased according to grades of injury as 50%, 57.14% and 92.86% of patients had bleeding with grades I, II and III respectively. A study by Shiva Kumar *et al*⁷ also showed increased bleeding according to injury grading. Thus, our results matches with their study.

Aspiration pneumonia occurred in 6 patients (12%), all of whom had grade III injury, 3 patients had altered sensorium, 2 patients (33%) had tracheostomy and mean age 40.83 years which was higher than the overall mean age. Yau-Lin *et al*¹⁴ who studied 370 patients for the occurrence of

aspiration pneumonia also found older age nasogastric tube intubation, altered sensorium, and endotracheal intubation as risk factors.

3 patients developed laryngeal oedema and required tracheostomy, all had grade III injury. Septicaemia occurred in 12 patients, out of which 11 patients (91.66%) had grade III injury.

Pyloric stenosis developed in 9 patients. It occurred mostly in patients with higher grades of injury. All of grade III and 22.22% of grade IIB injury patients developed pyloric stenosis. Similar results were found by Zargar¹. 5 patients had oesophageal stricture and all had grade III injury. Oakes¹³ also found that patients with severe oesophageal injury developed oesophageal stricture. A rare case of acid causing oesophageal stricture was also found.

Most of the serious complications occurred with concentrated corrosives whereas diluted corrosives had only few complications. Alkali causes complications more related to oesophagus and surrounding structures, such as oesophageal stricture, hiatus hernia, aspiration pneumonia, septicaemia and respiratory obstruction. Acids, on the other

hand cause complications related to stomach such as pyloric stenosis, bleeding and scarring of stomach. However, in contrary to past belief, concentrated corrosives cause injury to both oesophagus and stomach.

Chances of complications increased as injury grades in endoscopy increased. Patients with injury grades I and IIA developed fewer complications, had lesser duration of hospital stay, and oral diet could be started early in them. As the injury grades of endoscopy increase from IIB, IIIA to IIIB, the number and severity of complications increases, so is the duration of hospital stay, and these patients often required feeding jejunostomy or parenteral nutrition.

We found endoscopy safe and accurate in diagnosis and to find extent, location, and severity of injury. It has prognostic value also and we can plan the further management of these patients. It is also useful in finding and managing delayed complications.

References

1. Zargar SA, Kochhar R, Mehta S *et al.* The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. *Gastrointestinal Endoscopy* 1991; 37 (2): 165-9.
2. Dilwari JB, Singh S, Rao PN *et al.* Corrosive acid ingestion in man a clinical and endoscopic study. *Gut* 1984; 25: 183-7.
3. Zargar SA, Kochhar R, Nagi B *et al.* Ingestion of corrosive acids. Spectrum of injury to upper gastrointestinal tract and natural history. *Gastroenterology* 1989; 97 (3): 702-7.
4. Lahoti D, Broor SL. Corrosive injury to the upper gastrointestinal tract. *Indian J Gastroenterol* 1993; 12 (4): 135-41.
5. Chibishev A, Pereska Z, Simonovska N *et al.* The role of Urgent oesophagogastric-duodenoscopy in prognosis of acute caustic poisonings. *AIM* 2011; 19 (2): 80-84.
6. Ananthakrishnan N, Parthasarathy G, Kate V. Acute Corrosive Injuries of the Stomach: A Single Unit Experience of Thirty Years. *Gastroenterology Hepatology* 2011.
7. Shiva Kumar S, Rajan SK, Jayanthi V *et al.* Corrosive ingestion. A study of acute complications in 35 patients. Government Stanley Medical College and Hospital, Chennai-600001. *JAPI* 2003; 51: 1283.
8. Chiu HM, Lin JT, Huang SP *et al.* Prediction of bleeding and stricture formation after corrosive ingestion by EUS concurrent with upper endoscopy. *Gastrointestinal Endoscopy* 2004; 60 (5): 827-33.
9. Nagi B, Kochhar R, Thapa BR *et al.* Radiological spectrum of late sequelae of corrosive injury to upper gastrointestinal tract. *Acta Radiol* 2004; 45 (1): 7-12.
10. Ramasamy Kovil MD, Gumaste, Vivek V. Corrosive Ingestion in Adults. *Journal of Clinical Gastroenterology* 2003; 37 (2): 119-24.
11. Poley JW, Steyerberg EW, Kuipers EJ *et al.* Ingestion of acid and alkaline agents: outcome and prognostic value of early upper endoscopy. *Gastrointest Endosc* 2004; 60 (3): 372-7.
12. Cheng HT, Cheng CL, Lin CH *et al.* Caustic ingestion in adults: The role of endoscopic classification in predicting outcome. *BMC Gastroenterology* 2008; 8: 31.
13. Oakes DD, Sherck JP, Mark JB. Lye ingestion. Clinical patterns and therapeutic implications. *The Journal of Thoracic and Cardiovascular Surgery* Vol 83: 194-204.
14. Tseng YL, Ho M, Lin WMY *et al.* Outcome of acid ingestion related aspiration pneumonia. *Eur J Cardiothorac Surg* 2002; 21: 638-43.
15. Rafeey M, Shoaran M. Clinical characteristics and complications in oral caustic ingestion in children. *Pakistan Journal Biological Sciences* 2008; 11 (19): 2351-5.
16. Dogan Y, Erka T, Cokugras FC *et al.* Caustic Gastro-oesophageal lesions in childhood: An analysis of 473 cases. *Clinical Pediatrics* 2006; 45: 435.
17. Kochhar R, Poornachandra KS, Dutta U *et al.* Gastrointestinal Bleed as a Predictor of Stricture Formation after Acute Corrosive Ingestion. *Gastrointestinal Endoscopy* 1991; 37: 242-46.
18. Chiu HM, Lin JT, Huang SP *et al.* Prediction of bleeding and stricture formation after corrosive ingestion by EUS concurrent with upper endoscopy. *Gastrointestinal Endoscopy* volume 60, 2004.
19. Kochhar R, Sethy PK, Kochhar S *et al.* Corrosive induced carcinoma of oesophagus: report of three patients and review of literature. *Journal Gastroenterology Hepatology* 2006; 21 (4): 777-80.
20. Franken JR. Caustic damage of the gastrointestinal tract: Roentgen features. *American Journal of Radiology* 1973; 118: 177-85.
21. Cheng HT, Cheng CL, Lin CH *et al.* Caustic ingestion in adults: the role of endoscopic classification in predicting outcome. *BMC Gastroenterol* 2008; 31.
22. Goldman LP, Weigert JM. Corrosive substance ingestion: a review. *American Journal Gastroenterology* 1984; 79: 85-90.
23. Gumaste W, Dave PB. Ingestion of corrosive substance by adults. *American Journal Gastroenterology* 1992; 87 (1): 1-5.
24. Rui Celsom Martins Mamede, Francisco Veríssimo de Mello Filho. Ingestion of caustic substances and its complications. *Sao Paulo Med Journal* 2001; 119.
25. Gorman RL, Khin-Maung-Gyi MT, Klein-Schwartz W *et al.* Initial symptoms as predictors of oesophageal injury in alkaline corrosive ingestions. *American Journal Emergency Medicine* 1992; 10 (3): 189-94.
26. Tseng YL, Wu MH, Lin MY *et al.* Massive upper gastrointestinal bleeding after acid-corrosive injury. *World Journal Surgery* 2004; 50-4.
27. Davis LL, Raffensperger J, Novak GM. Necrosis of the stomach secondary to ingestion of corrosive agents. *Chest* 1972; 62: 48-51.
28. Cabral C, Chirica M, Chaisemarin C *et al.* Caustic injuries of the upper digestive tract: a population observational study. *Surgical Endoscopy* 26: 214-21.
29. Tohda G, Sugawa C, Gayer C *et al.* Clinical evaluation and management of caustic injury in the upper gastrointestinal tract in 95 adult patients in an urban centre. *Surgical Endoscopy* 2008; 22 (4): 1119-25.
30. Christesen HB. Ingestion of caustic agents. Epidemiology, pathogenesis, course, complications and prognosis. *Ugeskr Laeger* 1993; 155 (31): 2379-82.
31. Mattos GM, Lopes DD, Mamede RC *et al.* Effects of time of contact and concentration of caustic agent on generation of injuries. *Laryngoscope* 2006; 116 (3): 456-60.

Spectrum of neurotuberculosis in HIV-infected patients: Clinical and radiological features

Vandana V Ahluwalia*, Shamrendra Narayan**, Prerna S Saharan***, TP Singh****, Dipti Agarwal*****

Abstract

Purpose: To characterise the radiographic findings on neuroimaging of human immunodeficiency virus (HIV)-seropositive patients coinfecting with neurotuberculosis and to correlate those findings with CD4 count.

Method: HIV seropositive patients with clinically suspected neurotuberculosis based on clinical and CSF findings were included in the study. Additional imaging in disseminated disease added the diagnosis possibility (chest and abdominal imaging). CD4 count was collected from the records of all patients.

Result: Twenty-eight seropositive patients underwent CT scan/MRI scan depending on availability. When both CT and MRI studies were available, MRI showed more lesions as compared to CT. Tuberculous meningitis was the most common finding followed by enhancing parenchymal lesion, hydrocephalus and infarcts. CD4 count was correlated with the spectrum of findings.

Conclusion: Clue to neurotuberculosis includes multiloculated abscess, cisternal enhancement, infarction secondary to vasculitis and communicating hydrocephalus. Contrast-enhanced MR is the preferred modality in neurotuberculosis over CT scan in better description of lesion morphology.

Key words: Meningitis, hydrocephalus, tuberculoma, tuberculous abscess, CD4+T-cell count.

Introduction

Tuberculosis is the most common opportunistic infection in HIV-infected patients in developing countries¹. Neurotuberculosis is a fatal form of cerebral infection. Because prompt diagnosis may result in earlier treatment, recognition of this disorder by the radiologist can play a critical role in patient treatment. Thus, the purpose of our study was to examine the findings on neuroimaging of HIV-infected patients with neurotuberculosis and to correlate those findings with CD4 counts.

Computed tomography (CT) remains useful because of short imaging time, widespread availability, ease of access, sensitive in detection of calcification and haemorrhage, and resolution of bony detail. Magnetic resonance imaging (MRI) offers superior soft tissue contrast, excellent visualisation of vascular structures, fewer artifacts, and imaging in any plane³. Cerebral imaging with CT and/or MRI thus allows identification of AIDS (acquired immunodeficiency syndrome) related cerebral changes and may contribute to assessment of prognosis⁴.

Materials and methods

Patients with HIV seropositivity and clinically suspected neurotuberculosis underwent imaging. The presenting complaints included fever, increased intracranial pressure,

vomiting, seizures, paresis, nuchal rigidity, and disturbance of consciousness. These patients were either newly diagnosed or on antiretroviral treatment. CT scan and MRI scan was done in the study subjects according to availability including contrast and non contrast studies. Final diagnosis was made on CSF (cerebrospinal fluid) findings compatible with neurotuberculosis, co-existing tuberculous infection in another organ, the response to antituberculous treatment. Alternative diagnosis was ruled-out by negative cryptococcal antigen and anti toxoplasmosis antibody serology. CD4 count was collected from the records of all patients.

Results

A total number of twenty-eight patients with neurotuberculosis underwent neuroimaging. Age ranged from 23 to 60 years, with a mean age of 33.5 years. Neuroimaging studies for review were available of twenty-six CT and nine MRI scans. Imaging included both contrast and non contrast scans. Neurologic presentations on admission included increased intracranial pressure, headache (85%), fever (67%), vomiting (67%), nuchal rigidity (53%), seizures (33%), and disturbance of consciousness (35%).

Radiological findings included meningeal and parenchymal abnormality as described (Table I). The basal cisterns were a

*Professor, **Assistant Professor, ***Junior Resident, Department of Radio-diagnosis, ****Professor, Department of Medicine, *****Assistant Professor, Department of Paediatrics, Sarojini Naidu Medical College, Agra - 282 002, Uttar Pradesh.

favoured site for meningeal enhancement. More than one-third patients showed hydrocephalus associated with meningitis. However, hydrocephalus was a sole finding also. The focal enhancing parenchymal lesions included cerebral tubercular abscess and granuloma (tuberculomas). Twelve patients showed granulomas and five patients showed abscess. Tuberculous abscess was solitary or with other associated findings. Choroid plexitis was abnormal enhancing choroid plexus in two patients with one of the patient showing hydrocephalus.

Table 1: Imaging findings in neurotuberculosis.

Radiographic finding	No. of patients	Mean CD4 count in relation to radiographic findings
Cisternal/meningeal enhancement	22 (78.5%)	138
Hydrocephalus	15 (53.5%)	164
Enhancing parenchymal lesions	18 (64.2%)	129
Infarction	10 (35.7%)	149
Choroid plexitis	2 (7.1%)	198

When both CT and MRI study was available for the same patient, more lesions were picked up and better delineated the anatomy to explain the clinical features; however, CT was helpful for support of diagnosis especially the immediate attending problems like midline shift and hydrocephalus.

CD4 counts were available on 28 patients. Mean CD4 count was 167 (range 29 - 280). When the CD4 count was correlated with the imaging features, individually meningitis and parenchymal lesions were found at relatively low CD4 count as compared to hydrocephalus which was found at high CD4 count. Most common radiological finding was meningeal enhancement with a mean CD4 count of 138 (range 30 - 250). Hydrocephalus was found at relatively higher CD4 count 164. Lowest of the relative count was associated with abscess which was either solitary or few in

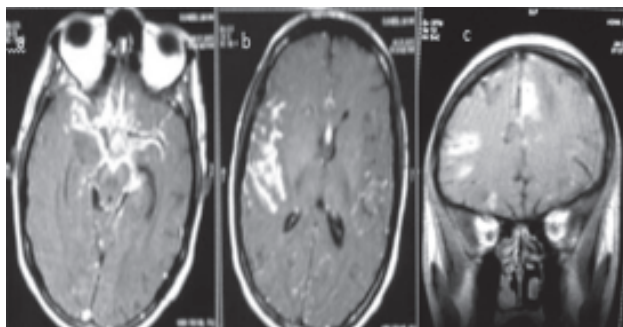


Fig. 1 (a, b, c): Tuberculous meningitis: Axial (a, b) and coronal (c) T1W post-contrast image shows meningeal enhancement in and around basal cisterns and gyromeningeal enhancement.

number and associated with disseminated form of tuberculosis reflecting the advanced immunocompromised state (Fig. 4). Mean CD4 count was low in cases of tuberculous abscess as 54/mm.

Chest X-rays and abdominal ultrasound findings were available for 20 patients in suspected cases of disseminated tuberculosis in which 10 were found positive. Positive chest X-ray findings included infiltrates (Fig. 4b), pleural effusion, and adenopathy. Abdominal positive findings included lymphadenopathy, bowel wall thickening, ascites, and hepatosplenomegaly not explained by other causes.

Discussion

When someone has both HIV and tuberculosis (TB), each

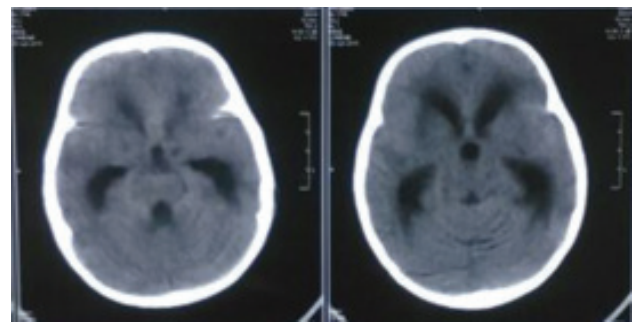


Fig. 2: Nonenhanced CT scan shows communicating hydrocephalus with dilated ventricles.

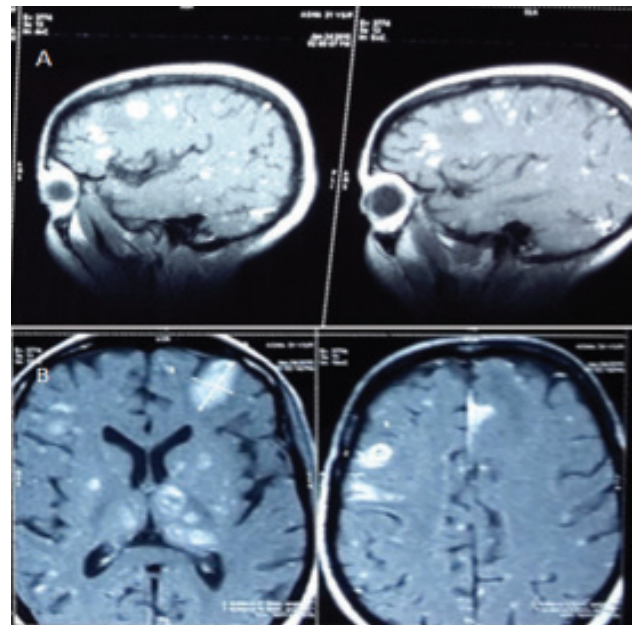


Fig. 3 a, b: Parenchyma tuberculoma – Post-contrast T1 W images coronal (a), Axial (b) in two different patients shows noncaseating granuloma as nodular homogeneously enhancing lesions and caseating granuloma as ring-enhancing lesion respectively. Number of enhancing granulomas are increased in the immunocompromised state.

disease speeds up the progress of the other. In addition to HIV infection speeding up the progression from latent to active TB, TB bacteria also accelerate the progress of HIV infection. The dual infection has been termed "accursed duet"⁵. Research shows that of the opportunistic infections affecting HIV-infected patients, TB is found to be the most common with high-risk for mortality^{6,7} and the risk of co-infection with TB is about 20 - 37 times higher among those infected with HIV. Thus, the importance of concurrent treatment for HIV and TB cannot be emphasised enough. Neurotuberculosis can result from reactivation of a previous infection or from a primary, newly acquired infection. Neurotuberculosis accounts for approximately 0.52% of all cases of TB, carries a high mortality and neurological morbidity, and disproportionately afflicts HIV-infected individuals¹. The great majority of patients with neurotuberculosis are diagnosed and treated early because of characteristic clinical, imaging, and CSF findings.

Although magnetic resonance imaging is superior to CT imaging in the diagnosis of TBM², this modality may not be readily accessible in resource limited settings with high TB burden. Definite diagnosis cannot be made on CT but it can guide to determine the number, location, and extent of lesions. Advanced techniques such as diffusion-weighted imaging (DWI) and MR spectroscopy (MRS) have been used to improve the sensitivity for characterising the type, viability, and burden of the disease and the host tissue response¹³. Additionally, it is possible to demonstrate the complications of the primary infection and those secondary to treatment, in some cases. Specific magnetic resonance techniques are useful in the characterisation and management of diseases. Most of the studies with clinico-radiological correlation of central nervous system infection and HIV are taken in CT correlation because of economical factors and accessibility².

The typical imaging finding in HIV-associated neurotuberculosis differs from immunocompetent patients, looking like tuberculosis "gone wild" with multiple parenchymal granulomas and abscess². The radiological spectrum of neurotuberculosis includes meningitis (TBM), tuberculomas, tuberculous abscess, and cerebral ischaemia and infarction⁸. Most studies on TBM disclose a CD4+ T-cell count between 32 - 200 mm^{14,15}. Tuberculous abscesses are more common in HIV-infected patients, rare finding in immunocompetent patients as well as in the early stages of AIDS but common in severe immunodeficiency states with CD4+ T-cell count under 100 mm¹⁵ which in our study is found 54 mm.

Tuberculous meningitis is the most common manifestation of neurotuberculosis across all age groups and early diagnosis is important to reduce morbidity and mortality⁸. Meningeal enhancement is the typical radiological finding,

frequently of basal cisterns, as well as of the meninges in the convexity sulci and fissures (leptomeningeal compromise) (Fig. 1). There are inflammatory gelatinous exudates at the level of cisterns and subarachnoid spaces enhancing post-gadolinium. Tuberculous meningitis is usually due to haematogenous spread but can also be secondary to rupture of a rich focus or direct extension from cerebrospinal fluid (basal cisterns being the favoured site for meningeal enhancement)⁸. These findings are better seen at gadolinium-enhanced MR imaging than at CT².

Hydrocephalus encountered in TBM can be broadly divided into two types: (1) communicating type, which is common, secondary to an obstruction of the basal cisterns by inflammatory exudates (Fig. 2) and (2) obstructive type, which is less common and either secondary to a focal parenchymal lesion causing mass effect or due to the entrapment of a part of the ventricle by granulomatous ependymitis¹⁰.

Tuberculomas are hypointense on T2-weighted MR images in the early stages; as they mature, they develop a hypointense centre surrounded by an isointense capsule, which corresponds to solid caseation necrosis. They may further progress to abscess formation with a hyperintense centre. However, some tuberculomas have a hyperintense center without abscess formation, an appearance that makes them difficult to distinguish from lesions of toxoplasmosis or lymphoma⁸. On post-contrast images, noncaseating tuberculomas demonstrate nodular homogeneous enhancement. Caseating tuberculomas have ring enhancement (Fig. 3 a, b). On diffusion weighted imaging, tubercular abscesses show central diffusion restriction^{9,13}. Tuberculosis is characterised by lipid peaks on MR spectroscopy¹³. The presence of lipids in the absence of other amino acids, lactate, and succinate is strongly suggestive of tubercular abscess^{9,13}. Among patients with neurotuberculosis, 4% - 8% of those without HIV infection developed abscesses, compared with up to 20% in one group of HIV patients⁸. Abscesses tend to be larger – frequently greater than 3 cm (Fig. 4a) than tuberculomas, which are typically less than 1 cm. Abscess can be solitary and tends to cause mass and parenchymal effect not seen in tuberculoma⁸.

Cerebral infarctions are usually small, affecting primarily the small perforating vessels arising from the middle cerebral artery. These infarcts were often multiple. Cerebral infarction complicates neurotuberculosis and was seen in 36% of the patients⁸. Vasospasm and thrombosis of arteries as they course through the thick basilar exudate result in infarctions of the small perforating arteries that supply the basal ganglia. On CT scan, infarcts appear hypodense, on MRI they appear hyperintense on T2W and FLAIR sequences (Fig. 5 a, b). Diffusion-weighted images are the gold standard

in acute infarction showing diffusion restrictions¹³ (Fig. 5c).

Additional imaging with chest X-rays and abdominal ultrasound was helpful in diagnosis (Fig. 4). Thus, if neuroimaging findings are suggestive of neurotuberculosis, additional imaging can be obtained, because the findings may further support the diagnosis.

Clues to the radiographic diagnosis of neurotuberculosis (in HIV-positive patients) established by our study include a multiloculated abscess, enhancing parenchymal lesions, cisternal enhancement, infarction of the basal ganglia, and communicating hydrocephalus. Meningeal disease and infarction also are commonly seen in neurosyphilis; however, correlation with serum and CSF studies as well as chest X-ray findings should differentiate between these two entities⁸. Toxoplasma encephalitis does not present as a multiloculated mass, and thus the finding of such a lesion in an HIV positive patient should suggest the diagnosis of neurotuberculosis. These well localised lesions in toxoplasmosis have a propensity for the basal ganglia, corticomedullary junction, white matter, and periventricular regions. Calcification in acquired toxoplasmosis is

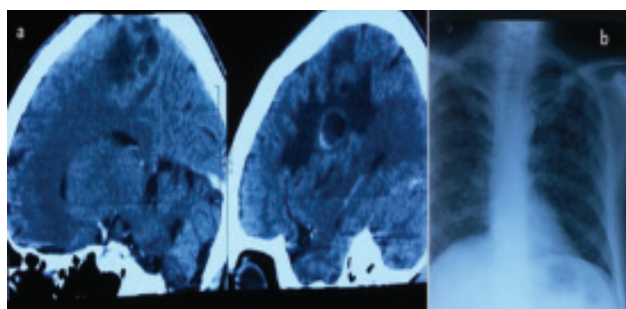


Fig. 4: Tuberculous cerebral abscess: (a) Sagittal contrast-enhanced CT scan shows thin-walled abscess in the right parietal lobe (measuring more than 3 cm) with few lesions adjacent to it. The lesion was surrounded by marked oedema. Patient was a newly diagnosed case of HIV and had CD4 count 29 cu/ml. Supportive diagnosis was made on diffuse infiltrates on X-ray (b) suggestive of tuberculosis.

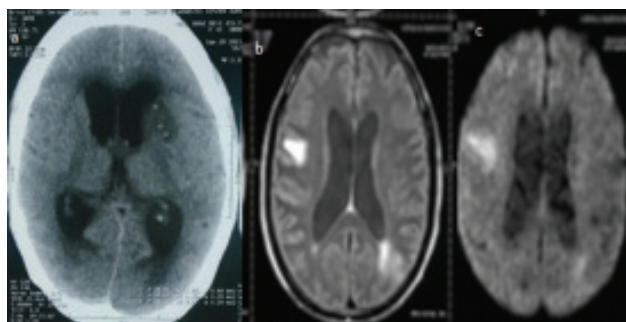


Fig. 5: Infarcts secondary to TB vasculitis: (a) Contrast-enhanced axial CT shows a hypodense area in the left basal ganglia with hydrocephalus. Axial T2W FLAIR (b) shows diffuse hyperintensity in right parietal region with restriction on DWI (c).

uncommon, where as it is common in tuberculosis⁸. Although a multiloculated mass could simulate a necrotic CNS lymphoma, and meningeal enhancement also may be associated with lymphoma, infarction of the basal ganglia and communicating hydrocephalus and radiographic clues are not usually associated with primary CNS lymphoma, a common neoplasm in these patients⁸.

Till date no cure is available for HIV/AIDS. It is only the opportunistic infections emanating from the disease that can be treated. Anti retroviral drugs used to treat HIV/AIDS are effective in slowing down the action of the virus and prolong the life of patients. Earlier, antiretroviral treatment (ART) was started after an intensive phase of antituberculosis treatment due to complication of immune-related inflammatory response, but recent guidelines emphasise to start ART in tuberculosis patient as soon as diagnosed irrespective of CD4 count as better immune response will help cure this coinfection rather than a single infection curing drug regime. CD4 counts for ART initiation were necessary when medications were expensive and had severe side-effects, and when the impact of early ART initiation was unclear. However, current evidence suggests that although CD4 counts may still play a role in guiding clinical care to start prophylaxis for opportunistic infections, CD4 counts should cease to be required for ART initiation¹⁶.

Conclusion

It is imperative that physicians treating HIV-infected patients should aggressively identify those co-infected with tuberculosis in order to reduce the associated comorbidity resulting from the pairing of the infections. Imaging plays a vital role in diagnosis as the lesions are typically inaccessible to tissue sampling. Clues to the radiographic diagnosis of neurotuberculosis (in HIV-positive patients) include a multiloculated abscess, enhancing parenchymal lesions, cisternal enhancement, infarction of the basal ganglia, and communicating hydrocephalus. We concluded that MRI imaging should be performed as a first choice of imaging modality in patients with suspected neurotuberculosis.

References

1. Corbett E, Watt CJ, Walker N *et al*. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; 163: 1009-21.
2. RG, Allison D, Adam A, Dixon AK, eds. *Grainger and Allison's Diagnostic Radiology: A Textbook of Medical Imaging*, 6th ed. New York, NY: Churchill Livingstone, 2013; 1325-36.
3. Laughlin S, Montanera W. Central nervous system imaging. When is CT more appropriate than MRI?. *Postgrad Med* 1998; 104 (5): 736, 814, 878.
4. Munding A, Adam T, Ott D *et al*. CT and MRI: prognostic tools in patients with AIDS and neurological deficits. *Neuroradiology* 1992;

35 (1): 758.

5. Jaiswal RK, Srivastav S, Mahajan H. Socio-demographic profile of TB-HIV co-infected patients in Bundelkhand Region, Uttar-Pradesh. *Natl J Med Res* 2012; 2: 149-51.
6. Corbett EL, Watt CJ, Walker N *et al.* The growing burden of tuberculosis: Global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; 163: 1009-21.
7. Lawn S, Churchyard G. Epidemiology of HIV-associated tuberculosis. *Curr Opin HIV AIDS* 2009; 4: 325-33.
8. Whiteman M, Espinoza L, Post MJ *et al.* Central nervous system tuberculosis in HIV-infected patients: clinical and radiographic findings. *AJNR Am J Neuroradiol* 1995; 16 (6): 1319-27.
9. Gupta RK, Roy R, Dev R *et al.* Finger printing of Mycobacterium tuberculosis in patients with intracranial tuberculomas by using *in vivo*, *ex vivo*, and *in vitro* magnetic resonance spectroscopy. *Magn Reson Med* 1996; 36: 829-33. [PMID:8946348].
10. Villoria MF, de la Torre J, Fortea F *et al.* Intracranial tuberculosis in AIDS: CT and MRI findings. *Neuroradiology* 1992; 34 (1): 11-14.
11. Katrak SM, Shembalkar PK, Bijwe SR *et al.* The clinical, radiological and pathological profile of tuberculous meningitis in patients with and without human immunodeficiency virus infection. *J Neurol Sci* 2000; 181 (1-2): 118-26.
12. Gupta RK, Vatsal DK, Husain N *et al.* Differentiation of tuberculous from pyogenic brain abscesses with *in vivo* proton MR spectroscopy and magnetisation transfer MR imaging. *AJNR Am J Neuroradiol* 2001; 22 (8): 1503-09.
13. Rangarajan K, Das CJ, Kumar A *et al.* MRI in central nervous system infections: A simplified patterned approach. *World J Radiol* 2014; 6 (9): 716-25.
14. Berenguer J, Moreno S, Laguna F *et al.* Tuberculous meningitis in patients infected with the human immunodeficiency virus. *N Engl J Med* 1992; 326: 668-72.
15. Dubé MP, Holtom PD, Larsen RA. Tuberculous meningitis in patients with and without human immunodeficiency virus infection. *Am J Med* 1992; 93 (5): 520-24.
16. Ying R, Granich RM, Gupta S *et al.* CD4 Cell Count: Declining Value for Antiretroviral Therapy Eligibility. *Clin Infect Dis* 2016; pii: civ1224.

**You have brain in your head.
You have feet in your shoes.
You can steer yourself in any direction you choose.
You're on your own ...
You are the guy who'll decide where to go.**

– DR SEUSS.

Knowledge of doctors, interns, and final year medical students on selected parameters of tuberculosis and RNTCP

KB Gupta*, Dinesh Mehta*, Ruchi Sachdeva*, Sandeep Sachdeva*

Introduction

India accounts for nearly one-third of the global burden of tuberculosis and two-third of the total cases in South-East Asia. Nearly 40% of Indians are infected with *Mycobacterium tuberculosis* and everyday about 5,000 people develop TB disease while over 1,000 die of the disease. Every year 1.8 million new cases occur in the country of which 0.8 million are highly infectious sputum positive. Unless properly treated, infectious pulmonary TB patients can infect 10 - 15 persons in a year. Control of TB has come a long way since the initiation of the National Tuberculosis Control Programme (1962) in India. By the end of March 2006, the whole country had been covered under the Revised National Tuberculosis Control Programme (RNTCP) with a focus on Directly Observed Treatment Short-course (DOTS) and annual reports suggest that we are maintaining 85% cure rate and 70% case detection rates; however, with 1,000 TB deaths per day. According to the WHO, around 73,000 of the notified new TB cases in 2010 were already multi-drug resistant. Of these, less than 3,000 were detected¹.

More than half of tuberculosis patients in India seek care initially in the private healthcare sector where diagnostics, treatment, and reporting practices often do not meet national or international standards for tuberculosis and still have remained alienated from DOTS implementation. For national programmers to broaden its reach and to have maximum impact, involvement of private practitioners assumes greater significance and also poses as one of the greatest challenges to ensure their participation which is intimately linked with the success of programme. To maximise the outcome of programme objectives, it is imperative to gauge the knowledge status of human resources at regular intervals so as to fine-tune educational activities and instill good practices. With this background, a study was undertaken to determine the knowledge of doctors (government and private), post-graduate students, interns, and final year medical students about TB and RNTCP on selected parameters.

Materials and methods

A cross-sectional descriptive study was undertaken using pre-designed, pre-tested, semi-structured anonymous, self

administered questionnaire and a total of 504 randomly selected doctors/allied healthcare personnel were contacted which included 115 final year medical students, 115 interns, 164 post-graduate students, 60 Haryana Civil Medical Service (HCMS) doctors and 50 private practitioners (allopathic) from Rohtak after briefing them with the study objectives with 100% response rate. The participants comprised of students, doctors working in various departments at PGIMS, Rohtak, private hospitals/clinics, PHC and CHC in district Rohtak. Available participants were contacted in their respective classrooms, departments, venues of CMEs/seminars/conferences/ monthly meetings and private clinics between August-December 2007 by a single investigator while ensuring non-duplication and no cross-discussion amongst participants. It was followed by multi-media presentation and/or clarification of doubts session. Data management was done using MS excel sheet and analysis carried out by computing descriptive statistics (%).

Results

Overall awareness on DOTS-plus (6.3%) and perception on efficacy of intermittent therapy to daily regime (31.5%) was low (Table I). Still, private practitioners have a high (74%) impression of X-ray being the first modality for diagnosing PTB while only 26% correctly mentioned sputum as first investigation (Table II).

Table III, provides summary findings of incorrect responses. DOTS categories were not correctly enumerated by 58%, 30%, and 17.7% of private practitioners, undergraduate and PG students respectively. Treatment regimen for both adult and paediatric patients was wrongly described by 68.4% and 51.7% of respondents; life prolongation with DOTS in patients with HIV with PTB was wrongly mentioned by 69.6% and stopping ATT criteria was not correctly mentioned by 44% study participants.

Discussion

The present cross-sectional descriptive study was conducted among randomly selected private practitioners, in-service doctors working in the district, final year medical students, interns, post-graduate students associated with PGIMS, Rohtak. Textbooks emerged as the most common

****Departments of Tuberculosis and Respiratory Medicine, and Community Medicine, Pandit B. D. Sharma PGIMS, Rohtak - 124 001, Haryana.***

Table I: Correct knowledge and perception of doctors on selected parameters of tuberculosis and RNTCP.

Study participants (n)	DOTS	RNTCP	DOTS-Plus	Observed treatment of DOTS is more effective than self administered therapy (yes)	Is DOTS the right approach to tuberculosis (yes)	Efficacy of intermittent therapy is similar to daily regime (yes)
Medical students (115)	113 (98.2%)	113 (98.2%)	02 (1.7%)	112 (97.3%)	115 (100%)	29 (25.2%)
Interns (115)	112 (97.5%)	112 (97.5%)	03 (2.6%)	115 (100%)	115 (100%)	06 (5.2%)
PG students (164)	157 (95.7%)	157 (95.7%)	11 (6.8%)	141 (85.9%)	162 (98.8%)	74 (45.2%)
HCMS (60)	59 (98.4%)	59 (98.4%)	06 (10%)	57 (85.2%)	59 (98.4%)	45 (75%)
Pvt. practitioners (50)	09 (18%)	08 (16%)	10 (20%)	13 (26%)	0	05 (10%)
Total (504)	450 (89.2%)	449 (89%)	32 (6.3%)	438 (86.9%)	451 (89.4%)	159 (31.5%)

Table II: First investigation advocated under RNTCP for diagnosing PTB.

Study participants (n)	Sputum for AFB	Chest X-ray	PCR	ELISA	ESR	Tuberculin test
Medical students (115)	110 (95.6%)	02 (1.7%)	03 (2.6%)	0	0	0
Interns (115)	112 (97.3%)	03 (2.7%)	0	0	0	0
PG students (164)	118 (71.9%)	04 (2.4%)	06 (3.6%)	01 (0.6%)	0	0
HCMS (60)	60 (100%)	0	0	0	0	0
Pvt. practitioners (50)	13 (26%)	37 (74%)	0	0	0	0
Total (504)	413 (81.9%)	46 (9.1%)	9 (1.7%)	1 (0.1%)	0	0

Table 3: Incorrect responses (summary table).

Questions	Medical students	Interns	PG students	HCMS	Pvt. practitioners	Total
Current TB programme	0	2.6%	3	0	2	1.5%
DOTS - full form	1.7%	2.5%	4.3%	1.6%	82%	10.7%
DOTS - Plus knowledge	98.3%	97.4%	93.2%	90%	80%	93.6%
DOTS categories	30.1%	2.6%	17.7%	0	58%	19.6%
MC route of TB spread	3.5%	0.86%	3.7%	0	2%	2.3%
MC symptom of PTB	2.5%	2.5%	7.4%	0	8%	4.3%
Adult treatment regimen	93.9%	58.3%	65.2%	68%	54%	68.4%
Paediatric treatment regimen	16.5%	56.5%	65.2%	71.7%	54%	51.7%
Investigation for follow-up	31.3%	6%	42%	11.7%	84%	31.9%
Location of DOTS centre	20%	1.7%	9.2%	0	30	10.9
Stopping ATT criteria	30.4%	8.7%	71.3%	21.7%	94%	44%
ATT given intermittently	6%	0.9%	0	1.6%	44%	6.1%
Emphasis in RNTCP	20.9%	2.5	40.2	23.3	80%	29.1%
DOTS only for adults	2.5%	1.7%	4.9%	1.6%	40%	6.7%
Investigations to diagnose PTB	4.4%	2.5%	28.1%	0	26%	18%
Drug dosage in intermittent therapy	79.1%	66%	70.7%	63.3%	30%	66.6%
Life prolongation with DOTS in patients with HIV + PTB	80.9%	60.9%	67%	68.3%	74%	69.6%

MC= most common

source of information on TB, i.e., undergraduate students (71.3%), interns (91.3%), post-graduates (63.4%), private practitioners (50.0%), HCMS (34.7%). While for HCMS it was journals (25%) and seminars (28.2%) and for private practitioners it was journals (17.5%) and medical representatives also (12.5%). A noteworthy finding was knowledge enhancement through medical representatives amongst 12.5% of private practitioners. The findings were in accordance with a study conducted in Russia where it was found that most doctors used standard textbooks to guide their practice but still a significant number made extensive use of pharmaceutical company information also².

Based on many scientific studies, it is proved that chest radiography may have to be considered for diagnosis but bacteriological confirmation is the gold standard test for diagnosis having good sensitivity and specificity. On assessing knowledge about current diagnostic modalities employed to diagnose PTB, sputum for AFB was the investigation of choice among all the study groups except private practitioners; 74% of them still considered chest X-ray was the investigation of choice. This is in accordance with the various studies conducted in India and international platform wherein the majority of private practitioners relied primarily on chest X-ray for diagnosis – Mumbai (70%), Delhi (89.5%; 49%), Pakistan (62%), Hong-Kong (76%), Korea (50%), etc³⁻⁸.

All the four study groups showed their faith in treatment under RNTCP guidelines whereas 92% private practitioners said that they treat the patients on their own, only 8% said that they will refer the patients to a DOTS centre. Similar findings were observed by Thakur *et al*, where 71% private practitioners dealt TB patients according to their own practice⁹. On being inquired about the DOTS plus, there was very low level of knowledge amongst all sections of participants. Physicians who had been practicing since long relied more on personal experience and were less likely to prescribe recommended RNTCP regime, hence they needed constant training and support.

When asked about the efficacy of intermittent therapy compared with daily regimen, most of the medical students were not aware about any difference between the two, while most of the PG, and interns considered the efficacy of intermittent regimen to be superior than the daily regimen unlike private practitioners, most of whom believed in the superiority of the daily regimen over intermittent regimen thus displaying a lack of faith still persisting in the minds of private practitioners toward the efficacy of DOTS and the dichotomy of thought and speech. On being asked whether they agreed with positive role of private sector in

achieving RNTCP objective, a high percentage of all groups responded in affirmative while a reasonably high percentages of private practitioners were not in agreement with the idea of their involvement in the programme.

The private sector lacked interest in public health aspects of TB treatment and trust in public sector. RNTCP is one of the few DOTS programme in the world to have formally prescribed guidelines for involvement of NGOs and private practitioners (PP) since collaboration between stakeholders has the potential to improve TB control in India. As private sector is the first point of contact for 60% of Indians and with TB being declared as a notifiable disease in the country (2012), the battle to overcome this dreaded diseases appears to have advanced one more step towards control as it would be mandatory for private sector to maintain and transmit record of all TB patients catered by them to RNTCP¹⁰. Various measures are underway for control but still more is required using innovative strategies. Leaders are needed among the medical fraternity to foster stewardship, communication, and collaboration between partners. To conclude, differential but low level of knowledge was ascertained requiring sustained targeted intervention/communication so as to facilitate achievement of RNTCP goals.

References

1. Annual Report. Central TB Division, Ministry of Health and Family Welfare, Government of India, New Delhi; 2011.
2. Balabanova Y, Fedorin I. Antimicrobial prescribing patterns for respiratory diseases including tuberculosis in Russia: a possible role in drug resistance. *J Antimicrob Chemo* 2004; 54: 673-79.
3. Uplekar MW, Juvekar SK. Tuberculosis management in private practice and its implications. *Indian J Tuberc* 1996; 43: 19.
4. Uplekar MW, Rangan S. Private doctors and tuberculosis control in India. *Tubercle and Lung Dis* 1993; 74: 332.
5. Dhingra VK. Dependence on radiology for diagnosing pulmonary tuberculosis: an urban situation. *Indian J Tuberc* 2002; 49: 153-6.
6. Singla N, Sharma PP, Singla R *et al*. Survey of knowledge attitude and practices for tuberculosis among general practitioners in Delhi, India. *Int J Tuberc Lung Dis* 1998; 2 (5): 383-89.
7. Survey of the previous investigations and treatment by the private practitioners of patients with pulmonary tuberculosis attending government chest clinics in Hong Kong. Hong Kong chest services/British Medical Research Council. *Tubercle* 1984; 8 (3): 161-71.
8. Rizvi N. Survey of Knowledge about tuberculosis among family physicians. *Med Assoc* 2001; 51 (9): 333-7.
9. Thakur JS, Kar SS, Sehgal A *et al*. Private sector involvement in tuberculosis control in Chandigarh. *Indian J Tuberc* 2006; 53: 149-53.
10. Sinha K. Finally, tuberculosis declared a notifiable disease. *The Times of India* 9th May, 2012.

Levosimendan: A new calcium sensitiser for inodilator therapy

AS Dabhi*, M Vadivelan**, Molly Mary Thabab**

Abstract

Calcium sensitisers are a new category of drugs that have positive inotropic and vasodilating actions. They increase myocardial contractility and are used in patients with acute decompensation of a pre-existing chronic heart failure (ADCHF). Levosimendan is a drug in this group which has inodilator actions and causes improvement in the haemodynamic status of patients with heart failure not responding to the standard treatment.

Key words: Calcium sensitisers, heart failure, levosimendan.

Introduction

Acute heart failure (AHF) is one of the most common causes of morbidity, hospitalisation, and mortality for patients above the age of 65 years worldwide¹. Acute decompensation of a pre-existing chronic heart failure (ADCHF) is the most common and frequent form of heart failure occurring in 65% of patients and is associated with signs of pulmonary congestion and low cardiac output².

Conventional therapies used in chronic heart failure (CHF) include diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and inotropic agents. Various therapeutic guidelines have been developed for patients with CHF^{2,3}.

In the management of ADCHF, improvement in myocardial contractility can correct cardiovascular dysfunction. This is possible with the use of inotropic agents like dobutamine, dopamine, phosphodiesterase inhibitors, milrinone, and digitalis⁴. However, increase in myocardial oxygen demand and the development of cardiac arrhythmias are frequent undesirable side-effects of these agents that may compromise the utility of inotropic therapy with negative clinical outcomes^{5,6}.

The calcium sensitisers are a new category of cardio-stimulant drugs with combined positive inotropic and vasodilating effects. They enhance myocardial contraction by increasing calcium sensitivity with low intra-cellular calcium. This particular property of calcium sensitisers may avoid some of the undesirable side-effects of other inotropic agents and offer a therapeutic alternative in patients with ADCHF.

Levosimendan

Levosimendan is a new positive inotropic agent having ATP-dependent potassium-channel opening and calcium-

sensitising effects. It has been shown to produce positive inotropic effect without increasing intracellular calcium concentrations. This is in contrast to the currently available inotropic agents, which exert their effects by increasing calcium concentrations that can predispose the patient to arrhythmias.

Levosimendan is a pyridazinone-dinitrile derivative, which is a calcium sensitiser of the heart and is used mainly in the management of ADCHF. It increases myocardial contractility by its positive inotropic effect and causes dilatation of peripheral and coronary arteries. Hence, it is an inodilator.

Levosimendan is the best studied drug in this group and is available for clinical use. The other drug in this class available for clinical use is pimobendan. Drugs which are still under investigation are EMD57033, ORG 30029, CGP 48506 and MCI-154. Levosimendan has been approved for clinical use by the European Society of Cardiology⁷.

Mechanism of action

1. Positive inotropic effect

The positive inotropic effect of levosimendan is due to two mechanisms. One is by calcium sensitisation of myofibrils and the second is due to phosphodiesterase III (PDE III) inhibition.

a) Calcium sensitisation of myofibrils:-

Levosimendan appears to stabilise and prolong the conformational changes that occur when the drug binds to calcium saturated cardiac troponin C (cTnC). The drug gets bound to the N-terminal of cTnC with high affinity and stabilises the calcium bound conformation of this regulatory protein. Hence, systolic interaction of actinomyosin filament is prolonged without any alteration in the rate of

*Associate Professor, Department of Medicine, Government Medical College, Vadodara - 390 001, Gujarat;

**Associate Professor, Department of Medicine, Jawaharlal Institute of Post-Graduate Medical Education and Research (JIPMER), Dhanvantari Nagar, Puducherry - 605 006.

cross-bridge cycling.

Binding of levosimendan to cTnC is dependent on the cytosolic calcium concentration, i.e., it increases during systole but remains relatively unchanged during diastole when the calcium level decreases. This mechanism may be the reason for the parallel enhancement of myocardial contractility and improvement of left ventricular diastolic function without promoting arrhythmogenesis or causing an alteration in myocardial oxygen demand⁸.

b) *Phosphodiesterase III (PDE III) inhibition:-*

This effect is observed at a higher concentration ($> 0.3 \mu\text{M}$) of the drug. The drug does not alter the heart rate, cAMP levels, myocardial relaxation and cytosolic calcium at the therapeutic concentration⁹. Clinically recommended therapeutic range of the drug is $0.1 - 0.3 \mu\text{M}$.

2. Vasodilatation

The mechanism of vasodilatation by levosimendan has been investigated extensively but it has not yet been entirely confirmed. Several pathways are involved in this process.

An important mechanism of vasodilatation in the arterial smooth muscle is opening of potassium (K_z) channels including ATP-sensitive K_z channels (K-ATP). The opening of K-ATP channels in small resistance vessels and calcium activated and voltage dependent potassium channels in large conductance vessels causes hyperpolarisation of the membrane, inhibition of inward calcium current and activation of the sodium-calcium exchanger to extrude calcium. The resultant decrease in intracellular calcium leads to vascular relaxation and vasodilatation¹⁰.

Another mechanism involved in levosimendan induced vasodilatation is reduction of calcium sensitivity of the contractile protein in vascular smooth muscle¹¹. It produces vasodilatation in several vascular beds that includes coronary, pulmonary, renal, splanchnic and cerebral arteries as well as in saphenous, portal, and systemic veins.

Pharmacokinetics

After oral administration, levosimendan is rapidly absorbed with 80% bioavailability. It is 95 - 98% bound to plasma protein. It is mainly eliminated through conjugation. Seventy-five to 80% of the metabolites are conjugated in urine. Major metabolites of the drug are cyclic or N-acetylated cysteinylglycine and cysteine conjugates.

Levosimendan gets metabolised completely. 5% of the drug is metabolised to its active form OR - 1896. This metabolite has pharmacologic effect similar to levosimendan in terms of calcium sensitisation and haemodynamic effects. These effects may last as long as 7 - 9 days after discontinuation of a 24-hour infusion. The metabolite is 40% bound to plasma protein and is formed and eliminated from the body slowly. Peak plasma concentration occurs 2 days after discontinuation of the infusion. In contrast to levosimendan which has an elimination half-life of 1 hour, the metabolite has an elimination half-life of 75 - 80 hours which accounts for its long action even after discontinuation of the initial infusion of levosimendan.

Drug interactions

Levosimendan does not have clinically important pharmacokinetic interactions with captopril, beta-blockers, digoxin, warfarin, isosorbide mononitrate, carvedilol or itraconazole.

Dosing schedule

Treatment is initiated with a loading dose of $6 - 12 \mu\text{g/kg}$ as a slow infusion over a period of 10 minutes followed by a continuous infusion of $0.1 \mu\text{g/kg/minute}$. If the patient is already on concomitant intravenous vasodilators or inotropes or both at the beginning of the infusion, a lower loading dose of $6 \mu\text{g/kg}$ is recommended.

Patient's response should be assessed after the loading dose is given. If the response is excessive (causing hypotension and tachycardia), then the rate of infusion may be reduced to $0.05 \mu\text{g/kg/minute}$ or may be discontinued. If the initial dose is tolerated and an increase in haemodynamic effect is required, then the rate of infusion can be increased to $0.2 \mu\text{g/kg/minute}$.

The recommended duration of levosimendan infusion in patients with ADCHF is 24 hours. No signs of development of tolerance or rebound phenomenon have been observed following discontinuation of the infusion. Haemodynamic effects persist for at least 24 hours and up to 9 days after discontinuation of a 24 hour infusion.

The effect of mild-to-moderate renal involvement on the pharmacokinetics of metabolites of levosimendan (OR - 1855 and OR - 1896) are expected to be less than that in severe renal impairment. Levosimendan is not dialysable, while OR - 1855 and OR - 1896 are dialysable. However, clearance by dialysis is very low and the net effect of a dialysis session on these metabolites is small.

Contraindications

The drug should not be used in the following conditions:-

1. Known hypersensitivity to levosimendan
2. Severe hypotension and tachycardia
3. Significant mechanical obstruction affecting ventricular filling or outflow or both
4. Severe renal and hepatic impairment
5. History of torsades de pointes

Use of levosimendan in special situations

1. **Children:** Levosimendan can be administered to sick children with heart failure not responding to conventional therapy¹². Data indicate that the pharmacokinetics of levosimendan after a single dose in children between the ages of 3 months to 6 years is similar to that in adults. Pharmacokinetics of the active metabolite has not been investigated in children.
2. **Pregnancy:** There is no experience of using levosimendan in pregnant women. Animal models have shown toxic effects on reproduction. Hence, levosimendan should be used in pregnant women only if the benefits for the mother outweigh the possible risks to the foetus.
3. **Lactation:** It is not known whether levosimendan is excreted in human milk. Studies in rats have shown excretion of levosimendan in breast milk, so women receiving the drug should not breastfeed their infants.

Clinical evidence of efficacy and safety

A number of trials have demonstrated the clinical efficacy of levosimendan in the treatment of heart failure.

1. **LIDO Trial:** The levosimendan infusion versus dobutamine in severe low-output heart failure (LIDO) study is a multi-centric, double-blind, randomised study in low-output heart failure patients. This trial compared the effects of levosimendan and dobutamine on haemodynamic performance and clinical outcome in patients with low-output heart failure¹³.

Results of this trial showed that levosimendan treatment had a consistently better effect than dobutamine on the individual haemodynamic variables at the end of the 24-hour treatment period. The haemodynamic advantage of levosimendan over dobutamine was apparently accentuated in the presence of beta-blockade.

The study also showed that the mortality at 180 days was lower in the levosimendan group compared with dobutamine group. Levosimendan had a direct long-lasting protective effect on the myocardium and it did not increase myocardial oxygen requirements in the patients¹⁴.

2. **SURVIVE Trial:** The survival of patients with acute heart failure in need of intravenous inotropic support (SURVIVE) study was a randomised, double-blind trial that compared the efficacy and safety of intravenous levosimendan or dobutamine in patients hospitalised with acute decompensated heart failure requiring inotropic support.

All-cause mortality analysis showed that mortality was lower in the levosimendan group compared with the dobutamine group¹⁵.

3. **REVIVE Trial:** The randomised multicenter evaluation of intravenous levosimendan efficacy versus placebo in the short-term treatment of decompensated heart failure (REVIVE) was a double-blind, placebo-controlled, large-scale study¹⁶.

The results of this study showed that plasma brain natriuretic peptide (BNP) which is a marker of impaired cardiac function was significantly reduced in the levosimendan group compared with the placebo group at 24 hours. Dyspnoea also showed significant improvement in the levosimendan group¹⁷.

The greater level of improvement in the clinical composite on levosimendan was supported by significant reductions in median plasma BNP concentrations compared with placebo at both 24 hours and 5 days.

Comparative analysis

A double-blind study compared levosimendan infusion versus dobutamine infusion in severe low output heart failure. Infusion of levosimendan (24 µg/kg over a period of 10 minutes followed by 0.1 µg/kg/minute over a period of 24 hours) or dobutamine (5 µg/kg/minute) were studied.

At the doses used, levosimendan increased cardiac output and reduced pulmonary capillary wedge pressure (PCWP) to a greater extent than dobutamine. Levosimendan caused greater reduction of systolic blood pressure and more vasodilatation. The haemodynamic effects of dobutamine disappeared six hours after discontinuation of the infusion, but those of levosimendan persisted.

A comparison of the properties of dobutamine, milrinone and levosimendan is given in Table I.

Conclusion

To conclude, levosimendan is one of the first agents in a new class of drugs known as calcium sensitisers. These drugs make myocardial contractile proteins more sensitive to calcium, thereby leading to an increase in contractility. It not only sensitises myofibrils to calcium, but also inhibits

Table I: Comparison between levosimendan, milrinone, and dobutamine.

Feature	Levosimendan	Milrinone	Dobutamine
Class	Calcium channel sensitiser	Phosphodiesterase III inhibitor	Catecholamine (Beta-adrenergic agonist)
Increase in intracellular calcium concentration	Yes	Yes	Yes
Vasodilating action	Coronary and systemic circulations	Peripheral circulation	Mild action on peripheral circulation
Increase in myocardial oxygen demand	No	No	Yes
Arrhythmogenic potential	Rare and maybe due to QTc (corrected QT interval) prolongation	Ventricular and supraventricular arrhythmias	Less ventricular arrhythmogenicity than milrinone
Adverse events	Headache and hypotension	Ventricular arrhythmias	Tachycardia

PDE III enzyme and opens the ATP sensitive potassium channels. All these actions ultimately lead to positive inotropic action and vasodilatation.

The main clinical use of the drug is that it can be used instead of dobutamine in patients with heart failure not responding to the standard therapeutic regimens. It produces a significant reduction in all-cause mortality than dobutamine especially in patients with ADCHF with a known history of congestive heart failure and/or treatment with a beta-blocker¹⁸. Another major advantage is that it improves haemodynamics without much risk of arrhythmias.

References

- Jessup M, Brozena S. Heart failure. *N Engl J Med* 2003; 348: 2007-18.
- McMurray JJ, Adamopoulos S, Anker SD *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology (developed in collaboration with the Heart Failure Association (HFA) of the ESC). *Eur Heart J* 2012; 33 (14): 1787-1847.
- Yancy CW, Jessup M, Bozkurt B *et al.* 2013 ACC/AHA guidelines for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; 62 (16): e147-239.
- Bayram M, De Luca L, Massie MB *et al.* Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. *Am J Cardiol* 2005; 96 (6A): 47G-58G.
- Packer M. The search for the ideal positive inotropic agent. *N Engl J Med* 1993; 329 (3): 201-2.
- O'Connor CM, Gattis WA, Uretsky BF *et al.* Continuous intravenous dobutamine is associated with increased risk of death in patients with advanced heart failure: Insights from the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1999; 138 (1): 78-86.
- Zannad F, McMurray JJV. Clinical outcome endpoints in heart failure trials: A European Society of Cardiology Heart Failure Association consensus document. *Eur J Heart Fail* 2013; 15 (10): 1082-94.
- Haikala H, Nissinen E, Etemadzadeh E *et al.* Troponin C-mediated calcium sensitisation induced by levosimendan does not impair relaxation. *J Cardiovasc Pharmacol* 1995; 25 (5): 794-801.
- Jonsson EN, Antila S, McFadyen L *et al.* Population pharmacokinetics of levosimendan in patients with congestive heart failure. *Br J Clin Pharmacol* 2003; 55 (6): 544-51.
- Pataricza J, Krassoi I, Hohn J *et al.* Functional role of potassium channels in the vasodilating mechanism of levosimendan in porcine isolated coronary artery. *Cardiovasc Drugs Ther* 2003; 17 (2): 115-21.
- Bowman P, Haikala H, Paul RJ. Levosimendan, a calcium sensitiser in cardiac muscle, induces relaxation in coronary smooth muscle through calcium desensitisation. *J Pharmacol Exp Ther* 1999; 288 (1): 316-25.
- Kamath SR, Jaykumar I, Matha S. Levosimendan. *Indian Pediatrics* 2009; 46: 593-6.
- Follath F, Cleland JGF, Just H *et al.* Efficacy and safety of intra-venous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO Study): a randomised double-blind trial. *The Lancet* 2002; 360 (9328): 196-202.
- Lilleberg J, Nieminen MS, Akkila J *et al.* Effects of a new calcium sensitiser, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilisation early after coronary artery bypass grafting. *Eur Heart J* 1998; 19 (4): 660-8.
- Mebazza A, Nieminen MS, Packer M *et al.* Levosimendan vs dobutamine for patients with acute decompensated heart failure-The SURVIVE Randomised Trial. *JAMA* 2007; 297 (17): 1883-91.
- Packer M. REVIVE II and SURVIVE: Use of levosimendan for the treatment of acute decompensated heart failure. *American Heart Association Scientific Sessions* 2005 Nov 14; Dallas, USA.
- Garratt C, Packer M, Colucci W *et al.* Development of a comprehensive new endpoint for the evaluation of new treatments for acute decompensated heart failure: results with levosimendan in the REVIVE 1 study. *Crit Care* 2004; 8 (Suppl 1): 89.
- Mebazza A, Nieminen MS, Filippatos GS *et al.* Levosimendan vs dobutamine: outcomes for acute heart failure patients on beta-blockers in SURVIVE. *Eur J Heart Fail* 2009; 11 (3): 304-11.

Swine flu vaccination

VK Katyal*, Ashima Katyal**, Aman Arora***, Krishna Mohan****, Kiran Bala*****

Abstract

Influenza is a highly infectious viral illness. At least four pandemics of influenza occurred in the 19th century, and three occurred in the 20th century. The first pandemic of the 21st century occurred in 2009 - 2010. Since then, humans have continued to get sick from swine flu. As of February, 2015, despite declines in some key indicators, flu remains widespread across most of the country and severity indicators are still high. Influenza vaccination in India is, therefore, the need of the hour in view of a recent outbreak of swine flu from multiple areas of the country.

Key words: H1N1 influenza, influenza vaccine.

Introduction

Swine influenza (swine flu) is a respiratory disease of pigs caused by type A influenza viruses that regularly cause outbreaks of influenza in pigs. Like human influenza viruses, there are different subtypes and strains of swine influenza viruses. The main swine influenza viruses circulating in the U.S. pigs in recent years are: swine triple reassortant (tr) H1N1 influenza virus, trH3N2 virus, trH1N2 virus¹. It belongs to the family orthomyxoviridae whose members have a segmented negative strand RNA genome. Swine flu viruses do not normally infect humans. However, sporadic human infections with swine influenza viruses have occurred. When this happens, these viruses are called "variant viruses". They also can be denoted by adding the letter "v" to the end of the virus subtype designation. Human infections with H1N1v, H3N2v, and H1N2v viruses have been detected. Several changes occurred, when a new virus emerged that spread among humans who hadn't been near pigs. Swine flu is transmitted from person to person by inhalation or ingestion of droplets containing virus from people sneezing or coughing; it is not transmitted by eating cooked pork products².

In April 2009, the first case of influenza A H1N1 was reported from Mexico. Subsequently, the infection led to spread of disease across 74 countries with 30,000 confirmed cases on June 11, 2009. This prompted the World Health Organisation to raise the warning from phase 5 to phase 6. A total of 214 countries were affected by the pandemic worldwide. In India, the first case of influenza A H1N1 was reported on May 16, 2009 from Hyderabad. The World Health Organisation declared the post-pandemic phase on August 10, 2010. Since then, humans have continued to get sick from swine flu. As of February, 2015, despite declines in some key indicators, flu remains widespread across most of the country and

severity indicators are still high. Swine flu is contagious, and it spreads in the same way as the seasonal flu. When patients who have it, cough or sneeze, they spray tiny droplets of the virus into the air. If one comes in contact with these droplets or touches a surface (such as a door knob or sink) that an infected person has recently touched, one can catch H1N1 swine flu. Like seasonal flu, it can cause more serious health problems for some people. The best protection is to get a flu vaccine, or flu shot, every year. Swine flu is one of the viruses included in the vaccine.

Immune responses

Influenza virus infection induces the production of influenza virus-specific antibodies by naive B cells eliciting primary response. In particular, antibodies directed to the viral haemagglutinin (HA) and neuroaminidase (NA) correlate with protective immunity³. Antibodies directed to the trimeric globular head of HA can afford sterilising immunity to influenza virus infection. By binding to the HA receptor binding site located in this region they can block virus attachment to host cells and/or block receptor-mediated endocytosis. However, most antibodies directed against HA are influenza virus strain-specific and fail to neutralise intrasubtypic drift variants and viruses of other subtypes⁴. This is mainly due to the high variability in the HA globular head. Of interest, humoral immunity elicited after an influenza virus infection does provide long-lasting antibody mediated protection against the strains that resemble the infected strain. Seasonal flu viruses change from year to year, but they are closely related to each other. People who have had prior flu infections usually have some immunity to seasonal flu viruses. The 2009 H1N1 flu virus is a new virus strain. It is very different from seasonal flu viruses. Most people have little or no immunity to 2009 H1N1 flu. Influenza A viruses undergo

*Senior Professor and Head Medicine-III, **Resident, Department of Microbiology, ***Resident, Department of Medicine, ****Professor, Department of Microbiology, Pandit B. D. Sharma Post-Graduate Institute of Medical Sciences (PGIMS), Rohtak - 124 001, Haryana.

antigenic drift and shift, which causes development of newly antigenic strain to which humans do not have past antibodies, hence sparking pandemics. Thus influenza A vaccine should take into account this change in organism every year by tracking dominant variants⁵.

H1N1 vaccination

Vaccination is the major public health measure that can prevent influenza. The seasonal flu vaccine protects against the influenza viruses that research indicates will be most common during the upcoming season⁶. There are several flu vaccine options for the 2015 - 2016 flu season. There are two kind of swine flu vaccines available – trivalent and tertravalent.

1. **Trivalent flu vaccine** protects against two influenza A viruses (an H1N1 and an H3N2) and an influenza B virus⁷. The following trivalent flu vaccines are available:-
 - a) Standard-dose trivalent shots (IIV3) that are manufactured using virus grown in eggs. Different vaccines are approved for people of different ages, but there are vaccines that are approved for use in people as young as 6 months of age and above.
 - b) An intradermal trivalent shot, which is injected into the skin. It is approved for people 18 through 64 years of age.
 - c) A high-dose trivalent shot, approved for people 65 and older.
 - d) A trivalent shot containing virus grown in cell culture, which is approved for people 18 and older.
 - e) A recombinant trivalent shot that is egg-free, approved for people 18 years and older.
2. **Quadrivalent flu vaccine** protects against two influenza A viruses (an H1N1 and an H3N2) and two influenza B viruses. The following quadrivalent flu vaccines are available:
 - a) A quadrivalent flu shot.
 - b) A quadrivalent nasal spray vaccine, approved for humans 2 - 49 years of age

CDC has not expressed a preference for which flu vaccine people should get this season. However, if the child has no contraindications or precautions, s/he should be administered the nasal vaccine. If the nasal spray vaccine is not immediately available and the intramuscular flu shot is, vaccination should not be delayed.

Influenza vaccine for whom?

Vaccination to prevent influenza is particularly important

for people who are at high-risk for serious complications from influenza.

A. People who can get vaccinated:

- i. Different flu shots are approved for people of different ages, but there are vaccines that are approved for use in people as young as 6 months of age and above.
- ii. There are certain flu shots that have different age indications. For example persons younger than 65 years of age should not get the high-dose vaccine and people who are younger than 18-years or older than 64-years, should not get the intradermal vaccine.
- iii. The vaccination is also approved for use in pregnant women and people with chronic health conditions.

B. People who should not be vaccinated:

- i. Children younger than 6 months.
- ii. People with severe, life-threatening allergies to vaccine or any ingredient in the vaccine. This might include gelatin, antibiotics, or other ingredients.
- iii. Person allergic to eggs.
- iv. Patient who had Guillain-Barré Syndrome. Some people with a history of GBS should not get this vaccine.
- v. In people with any other illnesses – if present – vaccine is best avoided.

Nasal spray vaccine

- i. The nasal spray vaccine is recommended for use in humans 2 - 49 years of age.
- ii. Nasal spray vaccine should not be administered in the following:-
 - Children younger than 2 years
 - Adults 50 years and older
 - People with a history of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine
 - People who are allergic to eggs
 - Children or adolescents (2 - 17 years) on long-term aspirin treatment.
 - Pregnant women
 - Immunocompromised individuals
 - Children 2 - 4 years who have asthma or who have had a history of wheezing in the past 12 months.
 - Use of influenza antiviral drugs within the previous

48 hours.

- Severely immunocompromised persons who require a protective environment.

The following group of patients should be cautioned regarding nasal spray vaccine

- i. Asthma: People of any age with asthma might be at an increased risk for wheezing after getting the nasal spray vaccine.
- ii. A chronic condition like lung disease, heart disease, kidney or liver disorders, neurologic/neuromuscular, or metabolic disorders. The safety of the nasal spray vaccine has not been established in people with underlying medical conditions that place them at high-risk of serious flu complications.
- iii. Guillain-Barré syndrome occurrence in the past.
- iv. Other vaccines in the past 4 weeks.

Who should be prioritised during vaccine shortage?

When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to the following people:

- i. Children aged 6 months through 4 years (59 months);
- ii. People aged 50 years and older;
- iii. People with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, haematologic, or metabolic disorders (including diabetes mellitus);
- iv. People who are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus);
- v. Women who are or will be pregnant during the influenza season;
- vi. People who are aged 6 months through 18 years and receiving long-term aspirin therapy and who therefore might be at risk for experiencing Reye's syndrome after influenza virus infection;
- vii. Morbidly obese (BMI score 40 or more);
- viii. Healthcare personnel engaged in providing care to swine flu patients;
- ix. Household contacts and caregivers of children younger than 5 years and adults aged 50 years and older, with particular emphasis on vaccinating contacts of children aged younger than 6 months; and
- x. Household contacts and caregivers of people with medical conditions that put them at higher risk for severe complications from influenza.

Special considerations in egg allergy

People who have ever had a severe allergic reaction to eggs can get recombinant flu vaccine if they are 18 years and older or they should get the regular vaccine given by a clinician with experience in management of severe allergic conditions. People who have had a mild reaction to egg – that is, one which only involved hives – may get the vaccine with additional safety measures. Recombinant flu vaccines also are an option for people if they are 18 years and older and they do not have any contraindications to that vaccine. Most, but not all, types of flu vaccine contain a small amount of egg.

Effectiveness of flu vaccine⁸

It depends on:-

1. Characteristics of the person being vaccinated (such as their age and health).
2. Similarity or “match” between the flu viruses and the flu vaccine is designed to protect against and the flu viruses spreading in the community.

In general, recent studies have supported the conclusion that flu vaccination benefits public health, especially when the flu vaccine is well matched to the circulating flu viruses. Vaccine can reduce the risk of flu illness by about 50 - 60% among the overall population during seasons when most circulating flu viruses are like the viruses the flu vaccine is designed to protect against.

Benefits of flu vaccine

While how well the flu vaccine works can vary, there are a lot of reasons to get a flu vaccine each year:

- Flu vaccination prevents influenza as protecting an individual from flu also protects the people around him who are more vulnerable to serious flu illness.
- Influenza vaccination can help protect people who are at a greater risk of getting seriously ill from swine flu, like older adults, people with chronic health conditions, and young children (especially infants younger than 6 months old who are too young to get vaccinated).
- Prior vaccination also may make swine flu illness milder if a person gets it.
- Influenza vaccination can reduce the risk of more serious flu outcomes, like hospitalisations and deaths.
 - A recent study showed that flu vaccine reduced children's risk of flu-related paediatric intensive care unit (PICU) admission by 74% during flu seasons from 2010 - 2012.

- One study showed that flu vaccination was associated with a 71% reduction in flu-related hospitalisations among adults of all ages and a 77% reduction among adults 50 years of age and older during the 2011 - 2012 flu season.
- It is an important preventive tool for people with chronic health conditions. Vaccination was associated with lower rates of some cardiac events among people with heart disease, especially among those who had had a cardiac event in the past year. Influenza vaccination also has been shown to be associated with reduced hospitalisations among people with diabetes (79%) and chronic lung disease (52%).
- Vaccination helps protect women during pregnancy and their babies for up to 6 months after they are born. One study showed that giving flu vaccine to pregnant women was 92% effective in preventing hospitalisation of infants with influenza.
- Other studies have shown that vaccination can reduce the risk of flu-related hospitalisations in older adults (by 61%).

Adverse effects of vaccination

The CDC expects that any serious side effects following vaccination with the 2014 - 2015 influenza vaccine will be very rare^{9,10}. Mild side-effects that may occur are expected to be similar to those experienced following past seasonal influenza vaccine.

The viruses in the flu shots are either killed (inactivated) or recombinant (don't contain virus particles), so humans cannot get the flu from a flu shot. The quadrivalent vaccines' safety profile in pre-licensure trials have been very similar to the older trivalent flu vaccines.

Most people who receive the vaccine do not experience serious problems from it. Mild problems that may be experienced include soreness, redness, or swelling where the shot was given, fainting (mainly adolescents), headache, muscle aches, fever, and nausea. If these problems occur, they usually begin soon after the shot and last 1 to 2 days. Life-threatening allergic reactions to vaccines are very rare. If they do occur, it is usually within a few minutes to a few hours after the shot is given.

Nasal spray

The viruses in the nasal-spray vaccine are weakened and do not cause the severe symptoms that are often associated with influenza illness. Because the nasal spray vaccine uses live – although weakened – virus, it is possible to transmit

the vaccine virus to close contacts. This has very rarely occurred in clinical studies. This year, all nasal spray vaccines contain four attenuated flu viruses. However, its safety profile has been very similar to the older flu vaccines in pre-licensure trials.

In children, side-effects from nasal vaccine can include: Runny nose, wheezing, headache, vomiting, muscle aches, fever.

In adults, side-effects from nasal vaccine can include: Runny nose, headache, sore throat, cough.

Influenza vaccination in India is, therefore, the need of the hour in view of the recent outbreak of swine flu from multiple areas of the country. However, current recommendations are for vaccination of selected group of individuals, viz., healthcare providers managing swine flu patients, patients with chronic pulmonary conditions (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, haematologic, or metabolic disorders (including diabetes mellitus).

References

1. CDC. Interim Guidance for Clinicians on the Prevention and Treatment of Swine-Origin Influenza Virus Infection in Young Children. Centers for Disease Control and Prevention. <http://www.cdc.gov/swineflu/childrentreatment.htm>.
2. CDC. Interim Guidance on Specimen Collection and Processing for Patients with Suspected Swine Influenza A (H1N1) Virus Infection. Centers for Disease Control and Prevention. <http://www.cdc.gov/swineflu/specimencollection.htm>.
3. WHO. Recommended composition of influenza virus vaccines for use in the 2014 - 2015 northern hemisphere influenza season. World Health Organisation. http://www.who.int/influenza/vaccines/virus/recommendations/2014_15_north/en
4. CDC. Early Data Suggests Potentially Severe Flu Season. Centers for Disease Control and Prevention. www.cdc.gov/media/releases/014/p1204-flu-season.html
5. Owen J, Punt J, Stranford S. USA Macmillan. *Kuby Immunology* 2013; 7: 557-61.
6. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Atkinson W, Hamborsky J, Wolfe S, eds. 12th ed, second printing. Washington DC: Public Health Foundation, 2012.
7. Centers for Disease Control and Prevention. Overview of Influenza Surveillance in the United States. 6 October 2014. <http://www.cdc.gov/flu/pdf/weekly/overview.pdf>
8. Carter NJ, Curran MP. Live attenuated influenza vaccine (FluMist(R); Fluenz): A review of its use in the prevention of seasonal influenza in children and adults. *Drugs* 2011; 71: 1591-1622.
9. Vander Veen RL, Loynachan AT, Mogler MA *et al.* Safety, immunogenicity, and efficacy of an alphavirus replicon-based swine influenza virus hemagglutinin vaccine. *Vaccine* 2012; 30: 1944-50.
10. Monto AS, Ohmit SE, Petrie JG *et al.* Comparative efficacy of inactivated and live attenuated influenza vaccines. *N Engl J Med* 2009; 361: 1260-7.

Management of snakebite In India

Shibendu Ghosh*, Tanmoy Chatterjee*, Prabuddha Mukhopadhyay**

Introduction

The persons or population at risk of snakebite in our country is around 50 million. The estimated death in India is an underestimate because of lack of proper registration of snakebite. The real number of deaths in our country is probably much higher.

There are a large number of conflicting protocols for dealing with first aid and treatment in cases of snakebite. In 2004, the WHO established a snakebite treatment group, whose role was to develop recommendations to reduce mortality according to international norms. A primary recommendation was to establish a single protocol for both first-aid and treatment which contained evidence based procedures and it was relevant to the Indian context. In July 2006, a National Snakebite Conference was convened, which included Indian and international experts. Moreover, publications issued by the WHO Regional Office for South-East Asia, written and edited by David A Warrell in the year 2015, and the enduring efforts of scientists and doctors working in different regions of India is the backbone of the seupdate. We have treated about 10,000 cases of snakebite patients in the Medical College Hospital, Kolkata; Tarakeswer Rural Hospitals and Seba Nursing Home, Tarakeswar, Hooghly, West Bengal; SRI Hospital, Betai, Nadia, West Bengal since 1987.

Early treatment definitely reduces complications. This has been proved by a study done in South India as shown in Table 1.

First Aid treatment protocol

Primary importance is the need to recommend the most effective first aid for victims, to enable them to reach the nearest medical facility in the best possible condition. Much of the first aid currently carried out is ineffective and dangerous (Simpson, 2006). Indian research has agreed on the following recommended method having viewed and considered the available research and concluded that other methods are not appropriate for the conditions in India.

Recommended method for India

The first aid being currently recommended is based around the mnemonic, CARRY N.O.G.H.T.

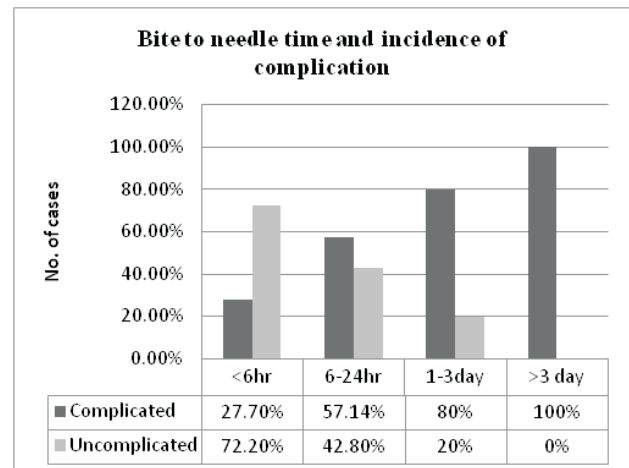


Fig. 1:

It consists of the following:-

CARRY = Do not allow the victim to walk even for a short distance; just carry him in any form, especially when bite is on the leg.

No – Tourniquet

No – Electrotherapy

No – Cutting

No – Pressure immobilisation

Nitric oxide donor (nitrogeseic ointment/nitrate spray)

R = Reassure the patient. 70% of all snake bites are from non-venomous species. Only 50% of bites by venomous species actually envenomate the patient.

I = Immobilise in the same way as a fractured limb. Use bandages or cloth to hold the splints, not to block the blood supply or apply pressure. Do not apply any compression in the form of tight ligatures, they don't work and can be dangerous!

G H = Get to Hospital immediately. Traditional remedies have NO PROVEN benefit in treating snakebite.

T = Tell the doctor of any systemic symptoms that manifest on the way to hospital.

Do not waste time in the first aid management.

This method will get the victim to the hospital quickly,

*Associate Professor, **Assistant Professor, Department of Medicine, Vivekananda Institute of Medical Sciences, Kolkata -700 001, West Bengal.

without recourse to traditional medical approaches which can dangerously delay effective treatment (Sharma *et al*, 2004), and will supply the doctor with the best possible information on arrival.

The snake, if killed, should also be taken to the hospital for identification by the doctor. No time should be wasted in attempting to kill or capture the snake.

Traditional methods to be discarded

Tourniquets – Tourniquet use is contraindicated in India

- Risk of ischaemia and loss of the limb (Warren, 1999).
- Increased risk of necrosis with 4/5 of the medically significant snakes of India. (Fairly, 1929; Pugh *et al*, 1987).
- Increased risk of massive neurotoxic blockade when tourniquet is released (Watt, 1988).
- Risk of embolism if used in viper bites. Pro-coagulant enzymes will cause clotting in distal blood. In addition, the effect of the venom in causing vasodilatation presents the danger of massive hypotension and neuromuscular paralysis when the tourniquet is released.
- They do not work! (Tun Pe 1987; Khin-Ohn Lwin 1984) Venom was not slowed by the tourniquet in several experimental studies, as well as in field conditions. Often this is because they are tied on the lower limb or are incorrectly tied (Watt, 2003; Amaral, 1998; Nishioka, 2000).
- They give patients a false sense of security, which encourages them to delay their journey to hospital.

Snakebite prevention and occupational risk

The normal perception is that rural agricultural workers are most at risk and the bites occur first thing in the morning and last thing at night. However, this is of very little practical use to rural workers in preventing snakebite since it ignores the fact that often snakebites cluster around certain bio-mechanical activities, in certain geographic areas, at certain times of the day.

- Grass-cutting remains a major situational source of bites.
- In rubber, coconut, and arecanut plantations, clearing the base of the tree to place manure causes a significant number of bites.
- Harvesting high growing crops like millet which require attention focussed away from the ground.
- Rubber tapping in the early hours 03:00 - 06:00 am.

- Vegetable harvesting/fruit picking.
- Tea and coffee plantation workers face the risk of arboreal and terrestrial vipers when picking or tending bushes.
- Clearing weeds exposes workers to the same danger as their grass-cutting colleagues.
- Walking at night without a torch barefooted or wearing sandals accounts for a significant number of bites.
- Bathing in ponds, streams, and rivers in the evening. It should not be assumed that because the victim is bitten in water that the species is non-venomous. Cobras and other venomous species are good swimmers and may enter the water to hunt.
- Walking along the edge of waterways.

Preventive measures

- Walk at night with sturdy footwear and a torch and use the torch! When walking, walk with a heavy step as snakes can detect vibration and will move away!
- Carry a stick when grass cutting or picking fruit or vegetables or clearing the base of trees. Use the stick to move the grass or leaves first. Give the snake a chance to move away. If collecting grass that has previously been cut and placed in a pile, disturb the grass with the stick before picking the grass up.
- Keep checking the ground ahead when cutting crops like millet, which are often harvested at head height and concentration is fixed away from the ground.
- Pay close attention to the leaves and sticks on the ground when wood collecting.
- Keep animal feed and rubbish away from your house. They attract rats, and snakes will surely follow.
- Try to avoid sleeping on the ground.
- Keep plants away from your doors and windows. Snakes like cover and plants help them climb up and into windows.

Diagnosis phase

Symptoms

General

There are a great many myths surrounding snake symptoms. The Table below summarises the evidence based situation. Haemostatic abnormalities are *prima facie* evidence of a Viper bite. Cobras and Kraits generally do not cause haemostatic disturbances.

Saw scaled vipers do not cause renal failure whereas Russell's viper and Hump-nosed Pitvipers do.

Russell's viper can also manifest neurotoxic symptoms in a wide area of India. But in our study none of the Russell's viper bite presented with neurotoxic feature.

Table I:

Feature	Cobra	Kraits	Russell's Viper	Saw scaled Viper	Hump-nosed viper
Local pain/tissue damage	Yes	No	Yes	Yes	Yes
Ptosis, neurological sign	Yes	Yes	No*	No	No
Haemostatic abnormality	No	May occur	Yes	Yes	Yes
Renal complication	No	No	Yes	No	Yes
Response to neostigmine	Yes	+/-	No	No	No
Response to ASV	Yes	Yes	Yes	Yes	No

In addition, some of the krait bites (Sochourek) do not respond to ASV of Indian origin.

General signs and symptoms of viperine envenomation

- Swelling and local pain.
- Tender enlargement of local lymph nodes as large molecular weight viper venom molecules enter the system via the lymphatics.
- Bleeding from the gingival sulci and other orifices.
- Epistaxis.
- Vomiting (Kalantri *et al*, 2006).
- Acute abdominal tenderness which may suggest gastro-intestinal or retroperitoneal bleeding.
- Hypotension resulting from hypovolaemia or direct vasodilatation.
- Low back pain, indicative of an early renal failure or retroperitoneal bleeding, although this must be carefully investigated as many rural workers involved in picking activities complain of back pain generally.
- The skin and mucous membranes may show evidence of petechiae, purpura, ecchymosis.
- The passing of reddish or dark-brown urine or declining or no urine output.
- Lateralising neurological symptoms and asymmetrical pupils may be indicative of intra-cranial bleeding.
- Muscle pain indicating rhabdomyolysis.
- Parotid swelling, conjunctival oedema, sub-conjunctival haemorrhage.

General signs and symptoms of Elapid envenomation

- Swelling and local pain (Cobra); may be asymptomatic in case of krait. Patient often can not recognise the bite.
- Local necrosis and/or blistering (Cobra).
- Descending paralysis, initially of muscles innervated by the cranial nerves, commencing with ptosis, diplopia, or ophthalmoplegia. (The patient complains of difficulty in focusing and the eyelids feel heavy. There may be some involvement of the senses of taste and smell, but these need further research).
- Paralysis of jaw and tongue may lead to upper airway obstruction and aspiration of pooled secretions because of the patient's inability to swallow. Numbness around the lips and mouth, progressing to pooling of secretions, bulbar paralysis, and respiratory failure.
- Hypoxia due to inadequate ventilation can cause cyanosis, altered sensorium and coma. This is a life-threatening situation and needs urgent intervention.
- Paradoxical respiration – as a result of the intercostal muscles becoming paralysed – is a frequent sign. Stomach pain which may suggest sub-mucosal haemorrhages in the stomach (Kularatne, 2002) (Krait).
- Krait bites often present in the early morning with paralysis that can be mistaken for a stroke.

Late-onset envenoming

The patient should be kept under close observation for at least 24 hours. Many species, particularly the Krait and the hump-nosed pitviper (Joseph *et al*, 2006) are known for the length of time it can take for symptoms to manifest. Often this can take between 6 to 12 hours. Late onset envenoming is a well documented occurrence (Ho *et al*, 1986; Warren *et al*, 1977; Reitz, 1989).

This is also particularly pertinent at the start of the rainy season when snares generally give birth to their young. Juvenile snakes, 8 - 10 inches long, tend to bite the victim lower down on the foot in the hard tissue area, and thus any signs of envenomation can take much longer to appear.

Diagnosis Phase: investigations

20-minute Whole Blood Clotting Test (20WBCT)

Considered the most reliable test of coagulation and should be carried out at the bedside by the treating physician. It can also be carried out in the most basic settings. It is

significantly superior to the 'capillary tube' method of establishing clotting capability and is the preferred method of choice in snakebite.

A few milliliter of fresh venous blood is placed in a new, clean and dry glass vessel and left at ambient temperature for 20 minutes. The vessel ideally should be a small glass test tube. The use of plastic bottles, tubes, or syringes will give false readings, and should not be used.

The glass vessel should be left undisturbed for 20 minutes and then gently tilted, not shaken. If the blood is still liquid then the patient has incoagulable blood. The must not be washed with detergent as this will inhibit the contact element of the clotting mechanism. The test should be carried out every 30 minutes from admission for three hours and then hourly after that. If incoagulable blood is discovered, the 6 hourly cycle is then adopted to test for the requirement for repeat doses of ASV.

Management of snake bite in general

Pain

Snakebite can often cause severe pain at the bite site. This can be treated with analgesics such as paracetamol.

Aspirin should not be used due to its adverse impact on coagulation. Do not use non steroidal anti-inflammatory drugs (NSAIDs) as they can cause bleeding. This can be particularly dangerous in a patient already having coagulopathy.

If available, mild opiates such as tramadol, 50 mg can be used orally for relief of severe pain. In cases of severe pain at a tertiary centre, tramadol can be given IV.

Handling tourniquets

Care must be taken when removing tight tourniquets which most of the time are used. Sudden removal can lead to a massive surge of venom leading to neurological paralysis, hypotension due to vasodilatation, etc.

- Before removal of the tourniquet, test for the presence of a pulse distal to the tourniquet. If the pulse is absent, ensure a doctor is present before removal.
- Be prepared to handle the complications such as sudden respiratory distress or hypotension. If the tourniquet has occluded the distal pulse, then a blood pressure cuff can be applied to reduce the pressure slowly.

Anti-snake venom (ASV)

After assessing patient whenever decision is taken for giving ASV, start ASV whatever dose is available in hand, do not wait for full dose to be available.

In India, only the polyvalent ASV is available. It is effective against all the four common species; Russell's viper (*Daboia russelii*), Common Cobra (*Raja naja*), Common Krait (*Bungarus caeruleus*) and Saw Scaled viper (*Echis carinatus*). There are no currently available monovalent ASVs primarily because there are no objective means of identifying the snake species, in the absence of the dead snake. And unavailability of ELISA method to detect species specific envenomation for these reason it would be impossible for the physician to determine which type of monovalent ASV to employ in treating the patient.

There are known species such as the Hump-nosed pitviper (*Hypnale hypnale*) where polyvalent ASV is known to be ineffective. In addition, there are regionally specific species such as Sochurek's Saw Scaled Viper (*Echis carinatus sochureki*) in Rajasthan, and Kalach in West Bengal where the effectiveness of polyvalent ASV may be questionable. These species should be detected first and special measures to be taken for these bites.

ASV administration criteria

ASV is a scarce, costly commodity and should only be administered when there are definite signs of envenomation. Unbound, free flowing venom, can only be neutralised when it is in the bloodstream or tissue fluid. In addition, anti-snake venom carries the risk of an anaphylactic reaction and should not therefore be used unnecessarily. The doctor should be prepared for such reactions.

ONLY if a patient develops one or more of the following signs/symptoms will ASV be administered:-

Systemic envenoming

- Evidence of coagulopathy: Primarily detected by 20WBCT or visible spontaneous systemic bleeding, gums, etc. Further laboratory tests for thrombocytopenia, fibrinogen abnormalities, PCV, peripheral smear, etc., provide confirmation, but 20WBCT is of paramount importance.
- Evidence of neurotoxicity: ptosis, external ophthalmoplegia, muscle paralysis, inability to lift the head, etc.

The above two methods of establishing systemic envenomation are the primary determinants. They are simple to carry-out, involving bedside tests or identification of visible neurological signs and symptoms. In the Indian context and in the vast majority of cases, one of these two categories will be the sole determinant of whether ASV is to be administered to a patient:-

- Cardiovascular abnormalities: hypotension, shock,

cardiac arrhythmia, abnormal ECG.

- Persistent and severe vomiting, or abdominal pain.

Severe current local envenoming

- Severe current, local swelling involving more than half of the bitten limb (in the absence of a tourniquet). In the case of severe swelling after bites on the digits (toes and especially fingers) after a bite from a known necrotic species.
- Rapid extension of swelling (for example beyond the waist or ankle within a few hours of a bite on the hands or feet). Swelling which is a number of hours old is not grounds for giving ASV.
- Purely local swelling, even if accompanied by bite mark from an apparently venomous snake, is not grounds for administering ASV.

N.B.

If a tourniquet or tourniquets have been applied, these themselves can cause swelling, once they have been removed for 1 hour and the swelling continues, then it is unlikely to be as a result of the tourniquet, and ASV may be administered.

Prevention of ASV reactions – prophylactic regimes

There is no statistical trial evidence of sufficient statistical power to show that prophylactic regimes are effective in the prevention of ASV reactions in India. Of the three published studies on the efficacy of prophylactic regimens for prevention of reactions to ASV, one (Wen Fan *et al*) showed no benefit and the other two (Prernawardenha *et al*, 1999; Gawarammana *et al*, 2003) showed modest benefit. However, because these studies were under powered to detect the true outcome effect, larger clinical trials are needed to conclude that the prophylactic treatment is beneficial. A recent trial in Sri Lanka using low dose adrenalin (0.25 ml) on a number of patient showed benefit, but a proper study needs to be undertaken in India before making it a routine procedure. Moreover, Indian population are at high risk for premature atherosclerosis and coronary artery disease. Any adverse effect before ASV may be detrimental as a social issue also. However, putting the adrenalin via three way cannula or by puncturing the latex tube may be undertaken and to be injected in emergency. Prophylactic regime should be reserved for children and young adults.

Two regimens are normally recommended

- 100 mg of hydrocortisone and antihistamine (10 mg chlorpheniramine maleate IV or 25 mg promethazine

HCl) 5 minutes before ASV administration.

(The dose for children is 0.1 - 0.3 mg/kg of antihistamine IV and 2 mg/kg of hydrocortisone IV. Antihistamine should be used with caution in paediatric patients.

The conclusion in respect of prophylactic regimens to prevent anaphylactic reactions, is that there is no evidence from good quality randomised clinical trials to support their routine use. If they are used then the decision must rest on other grounds. But the regimes have got an added advantage of decreasing the non-anaphylactic reaction such as febrile, allergic reaction, etc.

If the victim has a known sensitivity to ASV, pre-medication with hydrocortisone and anti-histamine may be advisable, in order to prevent severe reactions. Adrenalin should not be used as a premedication; when it will be required it should be given by IV route without wasting time.

ASV administration

The total required dose will be between 10 vials to 30 vials usually, as each vial neutralises 6 mg of Russell's viper venom. Not all victims will require 10 vials as some may be injected with less than 63 mg. However, starting with 10 vials ensures that there is sufficient neutralising power to neutralise the average amount of venom injected and during the next 12 hours to neutralise any remaining free flowing venom. Even in the large study from south India, the amount of ASV exceeded 50 vials in some patients. So decision of the treating physician is of utmost importance, because the guidelines may not be useful for all patients.

There is no evidence that shows that low dose strategies (Paul *et al*, 2004; Srimanarayana *et al*, 2004; Agraval *et al* 2005) have any validity in India. These studies have serious methodological flaws: the randomisation is not proper, the allocation sequence was not concealed, the evaluators were not blinded to the outcome; there was no prior sample size estimation, and the studies were underpowered to detect the principle outcome.

No ASV test dose must be administered

Test doses have been shown to have no predictive value in detecting anaphylactic or late serum reactions and should not be used (Warren *et al* 1999). These reactions are not IgE mediated but Complement activated. They may also pre-sensitise the patient and thereby create greater risk.

ASV is recommended to be administered in the following initial dose

Neurotoxic/anti-haemostatic: 10 vials

N.B.: Children and pregnant women receive the same ASV

dosage as adults. The ASV is targeted at neutralising the venom. Snakes inject the same amount of venom into adults and children.

ASV can be administered in two ways

Infusion: Liquid or reconstituted ASV in isotonic saline or glucose, may be started without any diluent fluid in volume overload patients.

All ASV is to be administered over 1 hour at constant speed. Local administration of ASV near the bite site has been proven to be ineffective, painful, and raises the intracompartmental pressure, particularly in the digits; it should not be used.

ASV dosage in victims requiring life saving surgery

In very rare cases, symptoms may develop which indicate that life saving surgery is required in order to save the victim, viz. intracranial bleed.

Before surgery can take place, coagulation must be restored in the victim in order to avoid catastrophic bleeding. In such cases a higher initial dose of ASV is justified (up to 25 vials) solely on the basis of guaranteeing a restoration of coagulation after 6 hours.

Snakebite in pregnancy

There is little definitive data published on the effects of snakebite during pregnancy. There have been cases reported when spontaneous abortion of the foetus has been reported although this is not the outcome in the majority of cases. It is not clear if venom can pass the placental barrier.

Pregnant women are treated in exactly the same way as other victims. The same dosage of ASV is given. The victim should be referred to a gynaecologist for assessment of any impact on the foetus.

ASV reactions

Anaphylaxis can be rapid onset and can deteriorate into a life-threatening emergency very rapidly. Adrenaline should always be immediately available.

The patient should be monitored closely (Peshin *et al*, 1997) and at the first sign of any of the following; i.e., urticaria, itching, fever, chills, nausea, vomiting, diarrhoea, abdominal cramps, tachycardia, hypotension, bronchospasm, and angio-oedema,

- ASV is to be discontinued.
- 0.5 mg of 1:1,000 adrenaline should be given IV.
- Children are given 0.01 mg/kg body weight of

adrenaline IV.

- In the elderly, noradrenalin and nitroglycerine infusion when hypotension is corrected can be given to avoid adrenaline-induced arrhythmia which is common in elderly.

If after 10 to 15 minutes the patient's condition has not improved or is worsening,

- A second dose of 0.5 mg of adrenalin 1:1,000 IV is given. This can be repeated for a third and final occasion; but in the vast majority of reactions, 2 doses of adrenaline will be sufficient.
- If there is hypotension or haemodynamic instability, IV fluids should be given.

Once the patient has recovered, the ASV can be restarted slowly for 10 - 15 minutes, keeping the patient under close observation. Then the normal drip rate should be resumed.

Adrenaline should be given IV in case of anaphylactic reaction, because:-

1. Faster action is achieved;
2. Predictable availability;
3. Intramuscular haematoma in patient with coagulopathy can be avoided.

Late serum sickness reactions can be easily treated with an oral steroid such as prednisolone (adults 5 mg 6 hourly, paediatric dose 0.7 mg/kg/day). Oral antihistaminic provides additional symptomatic relief.

Neurotoxic envenomation

Neostigmine is an anticholinesterase that prolongs the life of acetylcholine and can therefore reverse respiratory failure and neurotoxic symptoms. It is particularly effective for post-synaptic neurotoxins such as those of the Cobra (Watt *et al*, 1986).

In the case of neurotoxic envenomation where edrophonium is not available, neostigmine test can be done. The neostigmine dose is 0.04 mg/kg IV and atropine/glycopyrolate may be given by continuous infusion.

The patient should be closely observed for 1 hour to determine if the neostigmine is effective.

The following measures are useful objective methods to assess this:-

- a. Single breath count
- b. Uncovered area of iris measured in mm
- c. Inter-incisor distance (measured distance between the upper and lower incisors)

- d. Length of time upward gaze can be maintained
- e. FEV₁ or FVC (if available)
- f. Water column measurement (Fig. 2). (Length of water column that can be held by blowing through the tube)

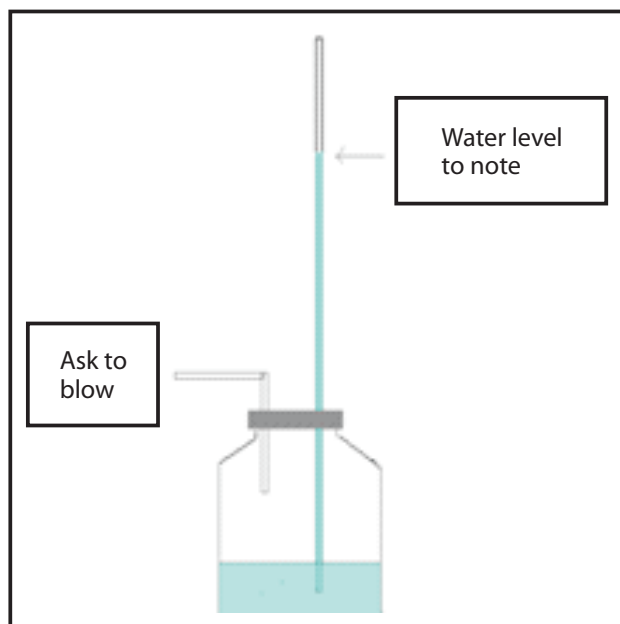


Fig. 2:

For example, if single breath count or inter-incisor distance is selected, the breath count or distance between the upper and lower incisors, and more objective water level measurement that much patient can blow are measured and recorded. Every 10 minutes the measurement is repeated. The average blood plasma time for neostigmine is 20 minutes, so by T+30 minutes any improvement should be visible by an improvement in the measure.

Recovery phase

If an adequate dose of appropriate antivenom has been administered, the following responses may be seen:-

1. Spontaneous systemic bleeding such as gum bleeding usually stops within 15 - 30 minutes.
2. Blood coagulability is usually restored in 6 hours. Principal test is 20WBCT.
3. Post-synaptic neurotoxic envenoming such as the Cobra may begin to improve as early as 30 minutes after antivenom, but can take several hours.
4. Presynaptic neurotoxic envenoming such as the Krait usually takes a considerable time to improve reflecting the need for the body to generate new acetylcholine emitters.

5. Active haemolysis and rhabdomyolysis may cease within a few hours and the urine returns to its normal colour.
6. In patients who are in shock, blood pressure may increase after 30 minutes.

Repeat doses: anti-haemostatic

In case of anti-haemostatic envenomation, the ASV strategy will be based around a six-hour time period. When the initial blood test reveals a coagulation abnormality, the initial ASV amount will be given over 1 hour.

No additional ASV will be given until the next clotting test is carried out. This is due to the inability of the liver to replace clotting factors in under 6 hours.

After 6 hours, a further coagulation test should be performed and a further dose should be administered in the event of continued coagulation defect; and in that case ASV is to be given over 1 hour. CT tests and repeat doses of ASV should continue on a 6-hourly pattern until coagulation is restored or unless a species is identified as one against which polyvalent ASV is not effective.

The repeat dose should be 5 - 10 vials of ASV, i.e., half to one full dose of the original amount. The most logical approach is to administer the same dose again, as was administered initially. Some Indian doctors however, argue that since the amount of unbound venom is declining, due to its continued binding to tissue, and due to the wish to conserve scarce supplies of ASV, there may be a case for administering a smaller second dose. In the absence of good trial evidence to determine the objective position, a range of vials in the second dose has been adopted.

Recurrent envenomation

When coagulation has been restored, no further ASV should be administered unless a proven recurrence of a coagulation abnormality is established. If the patient comes with features of coagulopathy, ASV is to be administered (10 vials). There is no need to give prophylactic ASV to prevent recurrence (Srimannarayana *et al*, 2004). Recurrence has been a mainly US phenomenon, due to the short half-life of Crofab ASV.

Indian ASV is a F(ab)₂ product and has a half-life of over 90 hours and therefore is not required in a prophylactic dose to prevent re-envenomation. But if the patient comes even after a few days reinstitute ASV therapy, because sometime absorption of snake venom depot under skin is erratic. If there is no improvement from the beginning of the whole blood clotting time, and it goes on increasing, then we are dealing with the snake bites which are not amenable to our usual polyvalent ASV.

Anti-haemostatic maximum ASV dosage guidance

Repeat dose: haematotoxic

The normal guidelines are to administer ASV every 6 hours until coagulation has been restored. However, what should the clinician do after, say, 30 vials have been administered and the coagulation abnormality persists?

- It has been established that envenomation by the Hump-nosed pitviper (*Hypnale hypnale*) does not respond to normal ASV. This may be a cause as, in the case of *Hypnale*, coagulopathy can continue for up to 3 weeks.

Surgical intervention

Whilst there is undoubtedly a place for a surgical debridement of necrotic tissue, the use of fasciotomy is highly questionable. The appearance of (Joseph, 2003):

- Pain on passive stretching
- Pain out of proportion
- Pulselessness
- Pallor
- Paraesthesia
- Paralysis

A significant swelling in the limb can lead to the conclusion that the intracompartmental pressure is above 40 mm of mercury and thus requires a fasciotomy. Fasciotomy is required if the intracompartmental pressure is sufficiently high to cause blood vessels to collapse and lead to ischaemia. Now-a-days we are using multiple puncture technique using a large bore needle. Fasciotomy does not remove or reduce any envenomation.

There is little objective evidence that the intracompartmental pressure due to snakebite in India, ever reaches the prescribed limit for a fasciotomy. Very limited trial data has tended to confirm this.

What is important is that the intracompartmental pressure should be measured objectively using saline manometers or newer specialised equipment such as the *Stryker intracompartmental pressure monitoring equipment*. *Visual impression is a highly unreliable guide to estimating intracompartmental pressure.*

The limb can be raised in the initial stages to see if swelling is reduced. However, this is controversial as there is no trial evidence to support its effectiveness.

Renal failure in snakebite

The acute renal failure which occurs due to snakebite is

multifactorial: 1) Severe and persistent hypotension leading to acute tubular necrosis; 2) Hb and other cellular parts of RBC and others (myoglobin and rhabdomyolysis); 3) part of DIC; 4) vasculitis; 5) acute diffuse interstitial nephritis; 6) extra-capillary proliferative glomerulonephritis.

Most of the patients of acute tubular necrosis recover in a few weeks, with the help of an occasional of haemodialysis; but those who develop cortical necrosis require renal replacement therapy on a long term basis. It is the hyperkalaemia rather than elevated urea/creatinine that requires dialysis. The hyperkalaemia of snakebite AKI is a hypermetabolic hyperkalaemia, which may kill the patient within few minutes and calcium gluconate and glucose insulin is mostly ineffective.

Early urgent adequate treatment with ASV can reverse the whole process of deterioration of renal function which is far from our expectation in our country.

Renal failure is a common complication of Russell's Viper and Hump-nosed Pitviper bites (Tin-Nu-Swe *et al*, 1993; Joseph *et al*, 2006). The contributory factors are intravascular haemolysis, DIC, direct nephrotoxicity and hypotension (Chugh *et al*, 1975) and rhabdomyolysis.

Renal damage can develop very early in cases of Russell's Viper bite and even when the patient arrives at hospital soon after the bite, the damage may already have been done. Studies have shown that even when ASV is administered within 1 - 2 hours after the bite, it was incapable of preventing ARF (Myint-lewin *et al*, 1985).

Neurological manifestation in snakebite

Neurological manifestation of snake bite pose an important problem for transportation from the site of bite to the hospital. A well designed study from PGI Chandigarh shows that just putting an airway tube and an AMBU bag decrease the morbidity to a great extent. Mechanical ventilation is to be avoided as far as possible, as because most of the death in ventilated snakebite patients is ventilator associated pneumonia. Early initiation and early weaning from the ventilator is the strategy, noninvasive ventilator with a patent upper air way is a better option.

Heparin and botropase – No role

Snakebite management in primary/community/dispensary health care centres

A key objective of this protocol is to enable doctors in Primary Care Institutions to treat snakebite with confidence. Evidence suggests that even when equipped with anti-snake venom, Primary Care doctors lack the confidence to treat snakebite due to the absence of a protocol tailored to

their needs and outlining how they should proceed within their context and setting (Simpson, 2007).

Patient arrival and assessment

1. Patient should be placed under observation for 24 hours.
2. The snake, if brought, should be carefully examined and compared to the snake identification material.
3. Pain management should be considered.
4. 20WBCT in clean, new, dry, glass test tubes should be carried out every 30 minutes for 1 - 3 hours and then hourly after that. Attention should be paid for any visible neurological symptoms.
5. 20 WBCT must be done in glass tube, never in plastic tube, should be done at bed side, sample must not be sent to laboratory.
6. Severe, current, local swelling should be identified.
7. If no symptoms develop after 24 hours, the patient can be discharged with a TT.

Envenomation; haematotoxic

If the patient has evidence of haematotoxic envenomation, determined by 20WBCT, then 8 - 10 vials of ASV are administered over 1 hour.

Adrenaline to be kept ready in two syringes of 0.5 mg 1:1,000 for IV administration is indicated if symptoms of any adverse reaction appears; it is better to keep ready the adrenalin through a three way cannula.

If symptoms do appear, ASV is temporarily suspended while the reaction is dealt with and then ASV restarted.

Referral criteria

Once the ASV is finished and the adverse reaction dealt with, the patient should be immediately referred to a higher centre with facilities for blood analysis to determine any systemic bleeding or renal impairment.

The 6-hour rule ensures that a six-hour window is now available in which to transport the patient.

Envenomation; neurotoxic

If the patient shows signs of neurotoxic envenomation, 8 - 10 vials are administered over 1 hour.

Adrenaline is made ready in two syringes of 0.5 mg 1:1000 for IV administration if symptoms of any adverse reaction appear. If symptoms do appear, ASV is temporarily suspended while the reaction is dealt with and then recommenced.

A neostigmine (edrophonium if available) test is

administered using 1.5 - 2.0 mg of neostigmine IM plus 0.6 mg of atropine IV. An objective measure such as a single breath count or indigenously made device from oxygen moistening bottle is used as a water level marker for blowing capacity of patient is used to assess the improvement or lack of improvement given by the neostigmine over 1 hour. If there is no improvement in the objective measure, the neostigmine is stopped. If there is improvement 0.5 mg neostigmine is given IM every 30 minutes with atropine until recovery. Usually this recovery is very rapid. IV neostigmine a preferred method now-a-days along with glycopyrolate.

If after 1 hour from the end of the first dose of ASV, the patient's symptoms have worsened, i.e., paralysis has descended further, a second full dose of ASV is given over 1 hour. ASV is then completed for this patient.

If after 2 hours the patient has not shown worsening symptoms, but has not improved, a second dose of ASV is given over 1 hour. Again ASV is now completed for this patient.

Referral criteria

The primary consideration, in the case of neurotoxic bites, is respiratory failure. Capacity of neck lifting is good predictor of requirement of ventilator support. Refer such patients to a centre equipped with invasive ventilation.

Conditions and equipment accompanying neurotoxic referral

The primary consideration is to be well-equipped to provide respiration support to the victim.

Transfer the patient with a face mask, resuscitation bag and a person, other than the driver of the vehicle, who is trained of how to use these devices. If respiration fails, then the victim must be given artificial respiration until arrival at the institution.

Greater success can be achieved with two additional approaches, prior to dispatch.

In the conscious patient, two Nasopharyngeal Tubes (NP) should be inserted before referral. These will enable effective resuscitation with the resuscitation bag by not allowing the tongue to fall back and block the airway, without triggering the gagging reflex. Improvised nasopharyngeal tubes can be made by cutting down size 5 endotracheal tubes to the required length, i.e., from the tragus to the nostril. If necessary allow the patient's relative along with an AMBU bag after proper directions on how to use it.

NP tubes should be prepared and kept with the snakebite kit in the PHC. This is preferable as the patient may well be

unable to perform a neck lift but still remain conscious and breathing. The danger will be that respiratory failure will occur after the patient has left the PHC and before arriving at the eventual institution. In that case the patient will be pre-prepared for the use of a resuscitation bag by the use of NP tubes.

In the unconscious patient, a Laryngeal Mask Airway or preferably a Laryngeal Tube Airway should be inserted before referral which will enable more effective ventilatory support to be provided with a resuscitation bag until the patient reaches an institution with the facility of mechanical ventilation.

References

1. Simpson ID. Management of Snakebite. The National, API WB

branch. *Update in Medicine* 2006; 88-93.

2. Narvencar K. Correlation Between Timing Of ASV Administration And Complication in Snake Bite. *JAPI* 2006; Vol 54.
3. Guidelines for the Clinical Management Of Snake Bites In South-East Asia Region Written and edited by David A Warrell published by WHO, 2005.
4. Srimannaryan J, Dutta TK, Sahai A *et al.* Rational use of Anti-Snake Venom (ASV): Trial of Various Regimens in Hemotoxic snake Envenomation. *JAPI* 2004; 52: 788-92.
5. Bawaskar HS. Snake Venoms and Antivenoms: Critical Supply Issues. *JAPI* 2004; 52: 11-13.
6. Paul V, Pratibha S, Prahaald Jerry Earail KA *et al.* High-Dose Anti-Snake Venom Versus Low-Dose Anti Snake Venom in The treatment of Poisonous Snake Bites: A Critical Study. *JAPI* 2004; Vol 52.
7. Indian National snake bite Protocol 2008.
8. Guideline for management of snake bite in south-east Asian countries by David Warrd.

***The two words 'information' and 'communication' are often used interchangeably,
but they signify quite different things.
Information is giving out;
communication is getting through.***

— SYDNEY J HARRIS.

Tricuspid valve endocarditis in an intravenous drug abuser caused by *Candida guilliermondii*: A rarely implicated fungus

M Narang*, S Prasad**, R Chandel***, R Bandsode****

Abstract

A rare cause of right-sided endocarditis in an intravenous drug abuser with predominantly respiratory presentation is described. The patient, a young male, presented with all features of pneumonic consolidation. He was subsequently found to have vegetations on the tricuspid valve with evidence of embolism to lungs. The causative agent turned out to be Candida guilliermondii, a rarely implicated fungus. Only one case of endocarditis due to this organism has been described earlier.

Key words: *Candida guilliermondii*, tricuspid valve endocarditis.

Key messages: 1. Septic pulmonary embolism from right-sided endocarditis should also be considered in patients with pneumonia, especially in intravenous drug addicts. 2. Candida species other than albicans are becoming important both due to their incidence and propensity for multidrug resistance.

Introduction

Among candida infections, *Candida albicans* is the most common species along with *C. glabrata*, *C. parasilosis* and *C. tropicalis*, while other species are rare¹. According to PubMed search, only one case of *Candida guilliermondii* endocarditis has been reported². We describe here another case of right-sided endocarditis due to this organism in an intravenous drug abuser. This case also illustrates that right-sided endocarditis may have a predominantly respiratory presentation.

Case report

A 23-year-old male presented to the medicine emergency with a 10-days history of high-grade fever with chills and rigors, body aches, right-sided chest pain, and breathlessness. There was no history of cough, expectoration, diabetes, hypertension, or tuberculosis. The patient had been an intravenous drug abuser (pentazocine) for the past 2 years. On examination, the patient was febrile, had tachycardia of 110/min and blood pressure of 120/80 mmHg. He was pale but there was no icterus, cyanosis, clubbing or pedal oedema. Cardiac examination revealed normal heart sounds and no murmur or rub could be heard. Chest examination revealed crepitations over the right lower zone. Investigations revealed anaemia with haemoglobin level of 7.8 gm/dl and polymorphonuclear leukocytosis (total count of 16,800 per cu mm; P86, L14, M1, E1). Blood urea was 53 mg/dl, serum creatinine 1.9 mg/dl, serum sodium 139 mEq/l and serum potassium 5.3 mEq/l. Liver function tests were normal except an elevated alkaline phosphatase level of 856 IU/l. HIV, HBsAg, and anti-HCV

antibodies were negative. The chest X-ray (Fig. 1) revealed right lower zone consolidation. Ultrasound examination of the abdomen revealed mild hepatomegaly, ascites, and pleural effusion. His arterial blood gas analysis documented hypoxia and hypocapnia while there was only sinus tachycardia on the ECG.

Patient was diagnosed to have pneumonic consolidation with septicaemia. He was started on ceftriaxone and levofloxacin. However, fever persisted and he was switched to piperacillin + tazobactam and vancomycin. Blood and urine cultures failed to isolate any organism. Initial Gram's and Ziehl-Neelsen stain as well as culture of the sputum were also unrevealing. A repeat chest X-ray (Fig. 2) showed that the infiltrates had become bilateral with areas of cavitation. Pleural effusion had also appeared. Broncho-alveolar lavage (BAL) was performed and microscopic examination of BAL aspirate provided diagnostic visualisation of candida yeast along with non-specific inflammation. Contrast-enhanced CT showed bilateral lung field consolidation with cavitation (suggestive of septic pulmonary embolism), right-sided pleural effusion and right paratracheal lymphadenopathy (Fig. 3). As the patient was an intravenous drug abuser and had developed bilateral lung infiltrates, right-sided infective endocarditis was suspected. Echocardiography was performed which showed a vegetation over the tricuspid valve, thus confirming the diagnosis of infective endocarditis. There was also tricuspid regurgitation.

Blood for fungal culture was collected and patient was empirically initiated on fluconazole (amphotericin B was avoided in view of deranged renal function). Within 48 hours

Senior Specialist and Associate Professor, **Consultant and Associate Professor, ***Senior Resident, *Resident, Department of Medicine, Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital, New Delhi - 110 029.**

of starting fluconazole, he became afebrile. His chest X-ray also showed improvement (Fig. 5). Repeat sputum culture for fungus also isolated *Candida* species (sensitive to fluconazole and amphotericin B). Though the fever subsided, the patient had intermittent episodes of tachypnoea and palpitations, which would subside spontaneously. These were thought to be episodes of recurrent pulmonary embolisation. A repeat echocardiogram showed a large tricuspid vegetation for which opinion of cardiothoracic surgeons was sought. However, surgery was deferred in view of high operative risk.



Fig. 1: Initial X-ray chest showing right lower zone consolidation.



Fig. 2: Chest X-ray showing worsening of lung lesions with development of pleural effusion.

About 3 weeks after admission, the patient had a severe persistent episode of dyspnoea and palpitations. Arterial blood gas analysis revealed type I respiratory failure. He was shifted to the intensive care unit and was ventilated non-invasively. During his stay in the ICU, he suddenly developed bradycardia with unrecordable blood pressure and required cardiopulmonary resuscitation. He was successfully resuscitated, mechanically ventilated, and put on vasopressor support. Later in the day, the patient again had a cardiac arrest and despite all efforts could not be revived.

Two blood fungal culture reports became available later which had isolated *Candida guilliermondii* (sensitive to amphotericin B and fluconazole). Sputum for fungal examination also isolated *Candida guilliermondii* with

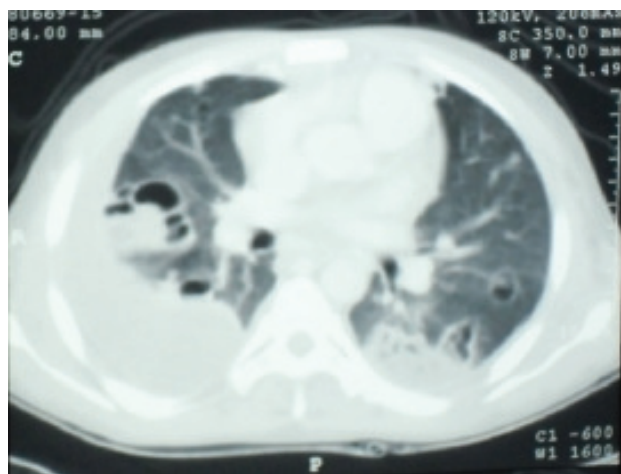


Fig. 3: CT scan of chest showing cavities in lungs and pleural effusion.



Fig. 4: Chest X-ray showing some improvement with treatment including ventilation.

similar antifungal sensitivity profile.

Discussion

Candida infections have become important causes of life-threatening conditions over recent years³. Intravenous drug abuse, cardiovascular surgery and long-term intravenous catheters predispose to candidal endocarditis. Common species of Candida include *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. guilliermondii* and *C. lusitaniae*⁴. *Candida guilliermondii*, however, is less pathogenic and has only once been implicated for endocarditis². In a comparative study, *C. guilliermondii* was found to be amongst the least pathogenic of 8 medically important species⁵.

There are a number of recent reports on *C. guilliermondii* infections^{3,6-9}. Savini *et al* have noted the emergence of Candida non-albicans species all over the world³. These account for 35 - 65% of all candidaemias³. *Candida guilliermondii* is found on normal human skin and mucosal surfaces, but has been implicated in chronic onychomycosis, device-related periodontitis, cellulitis, acute osteomyelitis, septic arthritis, endocarditis, fungaemia, and disseminated invasive infections. *C. guilliermondii* is also known to have a greater ability to develop multidrug resistance than other Candida species. Some have reported very low sensitivity to itraconazole, fluconazole, and echinocandins like caspofungin^{3,7}. Most reports have however found good sensitivity to amphotericin B¹⁰.

Reports from India also indicate a growing concern about this organism^{9,10}. Chakrabarti *et al* (2009) reported that of 140 cases of fungaemia, 73% were in the paediatric population⁹. *Candida tropicalis* was the most common isolate, but in 30% cases *C. guilliermondii* was isolated. In an earlier study (2002) from the same centre, the *C. guilliermondii* had accounted for 14% of cases¹⁰. These values are much higher than those reported from ARTEMIS DISK Antifungal Surveillance Program (3.7% in Latin America, 1.1% in Asia-Pacific, 1.0% in Europe and only 0.6% in North America)⁷. Overall mortality was about 50% in the Indian study⁹.

Conclusion

Patients with respiratory symptoms as well as history of drug abuse should be evaluated early for possible septic pulmonary embolisation from right-sided endocarditis and echocardiography should be performed early. Fungal endocarditis should also be ruled out in such cases by appropriate investigations. Increased prevalence of Candida non-albicans species should be kept in mind, especially in view of their propensity for resistance to antifungals.

References

1. Hazen KC. New and emerging yeasts pathogens. *Clin Microbiol Rev* 1995; 8: 462-78.
2. João I1, Duarte J, Cotrim C *et al*. Native valve endocarditis due to *Pichia ohmeri*. *Heart Vessels* 2002; 16 (6): 260-3.
3. Savini V, Catavittello C, Onofrillo D *et al*. What do we know about *Candida guilliermondii*? A voyage throughout past and current literature about this emerging yeast. *Mycoses* 2011; 54 (5): 434-41.
4. Colombo AL1, Guimarães T, Camargo LF *et al*. Brazilian guidelines for the management of candidiasis - a joint meeting report of three medical societies: Sociedade Brasileira de Infectologia, Sociedade Paulista de Infectologia and Sociedade Brasileira de Medicina Tropical. *Braz J Infect Dis* 2013; 17 (3): 283-312.
5. Arendrup M1, Horn T, Frimodt-Møller N. *In vivo* pathogenicity of eight medically relevant Candida species in an animal model. *Infection* 2002; 30 (5): 286-91.
6. Pasqualotto AC1, Antunes AG, Severo LC. *Candida guilliermondii* as the aetiology of candidosis. *Rev Inst Med Trop Sao Paulo* 2006; 48 (3): 123-7.
7. Pfaller MA1, Diekema DJ, Mendez M *et al*. *Candida guilliermondii*, an opportunistic fungal pathogen with decreased susceptibility to fluconazole: geographic and temporal trends from the ARTEMIS DISK antifungal surveillance program. *J Clin Microbiol* 2006; 44 (10): 3551-6.
8. Cantón E1, Pemán J, Sastre M *et al*. Killing kinetics of caspofungin, micafungin, and amphotericin B against *Candida guilliermondii*. *Antimicrob Agents Chemother* 2006; 50 (8): 2829-32.
9. Chakrabarti A1, Chatterjee SS, Rao KL *et al*. Recent experience with fungaemia: change in species distribution and azole resistance. *Scand J Infect Dis* 2009; 41 (4): 275-84.
10. Chakrabarti A1, Mohan B, Shrivastava SK *et al*. Change in distribution and antifungal susceptibility of Candida species isolated from candidaemia cases in a tertiary care centre during 1996 - 2000. *Indian J Med Res* 2002; 116: 5-12.

**No armies, weapons, nations, no religions are needed.
All that is needed is a little meditateness, silence, love, a little more humanity ...
and existence will become fragrant with something so totally unique and new ...**

– OSHO.

Marfan syndrome

Kavita Paul*, Narendra Kumar Bairwa**, Harbans Lal Kazal***

Abstract

Marfan syndrome is an autosomal dominant multisystem disease with a worldwide incidence of 1:3,000 - 5,000. This may present with a wide variety of symptoms and signs and mainly affects the skeleton, cardiovascular system and eyes^{2,3}.

Mutation in the gene FBN1 that encodes extra-cellular matrix protein Fibrillin -1, causes classic Marfan syndrome. But 30% cases may present denovo. The patient's prognosis mainly depends on cardiovascular involvement and its severity. It is important to identify this potentially life-threatening condition early and initiating immediate medical and surgical intervention by referring the patient to the concerned healthcare professionals^{2,3,4}.

Keywords: Marfan syndrome, Ghent criteria, aortic regurgitation.

Introduction

Marfan syndrome was first describe by Marfan in 1896. It is a multisystem connective tissue disorder and mainly has autosomal dominant pattern, but in 25% of cases this may be sporadic. The molecular defect FBN-1 mutation is found in 90% of patients. FBN-1 gene is associated with decoding of Fibrillin-1^{4,5}. The patients are classified by Ghent criteria, depending on family history, FBN-1 mutation, aortic root dilatation, skeletal and ocular abnormalities. Some patients may have mutation in gene for TGF1 β receptor-2 (TGF1BR-2). Overall 550 different mutations are found in FBN-1 gene, scattered throughout its 65 coding exons².

Diagnosis of Marfan syndrome is based on at least two of four features, i.e., family history and ocular, cardiovascular, and skeletal manifestations.

In ocular features, ectopic lentis, myopia, retinal detachment, formation of cataract are present. The main cardiovascular features are aortic root dilatation and aortic regurgitation, mitral valve prolapse with mitral regurgitation. Aortic aneurysm may also present with above-mentioned features. Aortic root dilatation is increased by physical and emotional stress.

In musculoskeletal abnormalities, long bone overgrowth compared to other family members, kyphosis, scoliosis, pectus excavatum, pectus carinatum, arachnodactyly, and joint hypermobility are present.

CNS features are dural ectasia, enlargement of neural canal^{2,3}.

Spontaneous pneumothorax and increased risk of aortic dilatation and dissection are other complications of Marfan syndrome^{2,3,6}.

Case report

A 25-years very tall male patient was admitted in Guru Gobind Singh Medical College, Faridkot, Punjab (India) with dyspnoea and decreased vision for last 6 months. Symptoms were gradual in onset and progressive. At presentation he was having class III NYHA dyspnoea. Diminishing vision was also compromising the quality of life of this patient. No similar history was present in any other family member. He was the only family member with 1.93 m height. Patient took consultancy from various health professionals but did not benefit. Physical examination revealed him to be a tall, thin man with long tapering fingers. His arm span was more than his height. Blood pressure in his right upper limb was 120/80 mm Hg. Pulse was 92/min in right radial artery. Patient was tachypnoeic with respiratory rate 26/minute.

Skeletal abnormalities are shown in pictures:-

Patient was not suffering from any dental abnormalities.

CVS examination revealed diffused apex, most prominent in the left 7th intercostal space 2 cm away from mid clavicular line. S1 was normal and A2 was soft. Early diastolic murmur of aortic regurgitation was present in neo-aortic and aortic area. In addition, he was having peripheral signs of aortic regurgitation.

In skeletal abnormalities, pectus excavatum, arachnodactyly, dolichocephalia and high-arched palate were present.

On chest examination, basal crepitations were present. No other abnormality was found. Breathing pattern was vesicular bilaterally.

Routine investigations were almost in normal range; Hb 13.3 gm%, BUN 31 mg/dl, S. creatinine 1.0 mg/dl, S. uric acid 10 mg/dl, S. bilirubin 2.8 mg/dl, SGOT 44 IU/L, SGPT 91

*Assistant Professor, **PG Resident, ***Professor, Department of Medicine, Guru Gobind Singh Medical College, Sadiq Road, Kotakpura, Faridkot - 151 203, Punjab.



Fig. 1: Height 1.93 m.



Fig. 2: Arm span 1.95 m. Arm span is more than height.



Fig. 3: Pectus excavatum.



Fig. 4: Wrist sign. Showing long length of middle finger.



Fig. 5: Thumb sign. Length of thumb exceeds over median margin of palm.

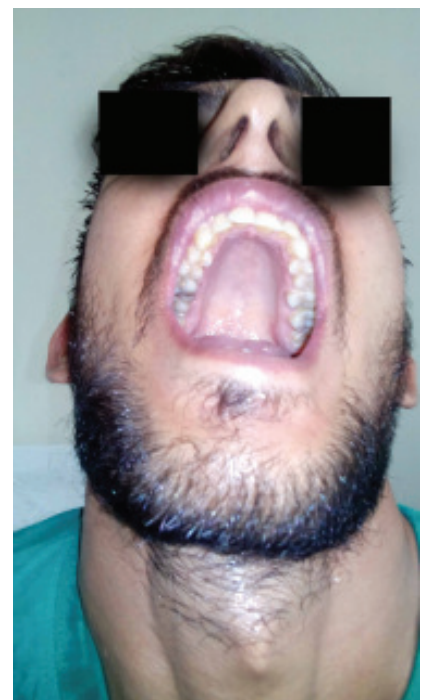


Fig. 6: High-arched palate.

IU/L, alkaline phosphatase 80 IU/L, urine routine – NAD.

His 2-D echo showed severe AR, left ventricular dilatation, global hypokinesia, LV ejection fraction – 35%

Eye examination revealed ectopia lentis.

He was treated symptomatically with diuretics, β -blockers, and was referred to cardiothoracic surgeon for Bentall's procedure (aortic root surgery).

Conclusion

A physician should have a suspicious eye; when a patient presents with tall stature, long fingers, along with cardiovascular abnormality, ocular feature, i.e., ectopia lentis, and high-arched palate, malocclusion of teeth. These are important in diagnosis. Therefore, such a patient should be referred to cardiothoracic surgeon in time to avoid further complications.

References

1. Mulla FMA. Marfan Syndrome – a case study. *International Journal of Scientific Study* 2013; 1 (1).
2. Bagirzaden L. Anesthesia recommendations for patients suffering for Marfan Syndrome. July 2013.
3. Prockop DJ, Bateman JF. Heritable disorder of connective tissue: Marfan Syndrome, Harrison; Principal of Internal Medicine edi. 18 (2): 3212-12.
4. Randhawa AK et al. Marfan Synfrome: Report of two cases with review of literature. *Nigerian Journal of Clinical Practice* 2012; 15 (3).
5. Tuna N. Some unusual features of Marfan Syndrome: report of four cases: Journal of Americal Heart Association. *Circulation* 1961; 24: 1154-63.
6. Dennison AD. Exercise for individual with Marfan Syndrome. *Cardiopulmonary Physical Therapy Journal* 2006; 17 (3).

FLAVIDONE MR

Rosai-Dorfman disease mimicking meningioma– a diagnostic dilemma

Gaurav Jain, Anshul Gupta**, Satnam S Chhabra****

Abstract

Rosai-Dorfman disease (RDD) is a rare benign histiocytic proliferative disorder featuring massive painless cervical lymphadenopathy, fever, and polyclonal hypergammaglobulinaemia. CNS involvement particularly in absence of nodal disease is rare and has to be differentiated from meningioma, meningiosarcoma, and meningeal carcinomatosis. Surgical excision of the lesion is the treatment of choice though adjuvant treatments like radiotherapy, steroid therapy, and cytotoxic drugs have led to remission in subtotal excisions. Prognosis of CNS disease is good in absence of nodal disease, and follow-up of patient, with serial brain imaging is recommended.

Introduction

Rosai-Dorfman disease (RDD) is a rare benign histiocytic proliferative disorder also known as SHML (sinus histiocytosis with massive lymphadenopathy), first described in 1969¹. Cardinal features include massive, painless, cervical lymphadenopathy, fever, and polyclonal hypergammaglobulinaemia presenting usually in the first two decades. Although extranodal involvement has been reported in diverse sites in about 23% to 43% cases¹, CNS involvement particularly in absence of nodal disease is rare. Isolated intracranial RDD is rare, and only a few cases have been reported – to the best of our knowledge around 40 cases – in the literature². We hereby present a case who was operated for meningioma excision, but later proved to be RDD.

Case report

A 64-years-old female presented with history of low-grade fever off and on along with headache for 6 months. She had one episode of generalised tonic clonic seizure and underwent MRI brain which was suggestive of meningioma at left frontal convexity region with oedema and mass effect. She was evaluated for fever and on examination had no lymphadenopathy or organomegaly, and her blood profile was unremarkable and was neurologically intact. She underwent left craniotomy with total excision of the lesion which was found attached to the duramater and good pial plane between tumour and brain, intraoperative impression was also meningioma. On histopathological examination, the processed tissue had few histiocytes, lymphocytes, and plasma cells. Histiocytes were showing emperipolesis (lymphophagocytosis) and immunohistochemistry staining was positive for S-100 and CD68. All these histopathological features confirmed the diagnosis of Rosai-Dorfman disease. The post-operative period was uneventful, and after 3 months follow-up the patient is

doing well, and MRI brain reveals no recurrence.

Discussion

Rosai-Dorfman disease is a benign histoproliferative disease of unknown aetiology. Isolated intracranial RDD with no systemic involvement is extremely rare with only a few cases reported in the literature². The ratio of 1.5:1 shows a slight male predominance and usually presents itself in the fourth-fifth decade commonly with headache, seizures, numbness, and paraplegia, as evident in the largest series³. It is adherent to duramater and resembles meningioma in both clinical and radiological findings. Histopathological and immunohistochemical confirmation is essential for definitive diagnosis. In addition to emperipolesis (lymphophagocytosis), reactivity for S-100 protein and CD68, but nonreactivity for CD1 a immunostaining are characteristic features⁴⁻⁶. Differentials include meningioma, meningiosarcoma, and meningeal carcinomatosis. There are no definitive treatment guidelines for RDD. Surgical excision of the lesion is the treatment of choice, preferably total excision³. Adjuvant treatments like radiotherapy, steroid therapy, and cytotoxic drugs have led to remission in subtotal excisions. Intracranial recurrence with symptoms is about 14% in the largest series, mostly following subtotal resections by Petzold *et al*³. Radiosurgery, steroid therapy, and chemotherapeutic agents without surgical resection, have also led to remission; and low-dose radiation is advocated for subtotal resection and recurrence⁷. Cytotoxic drugs like methotrexate, 5-mercaptopurine and vinca alkaloids have shown good results for remission⁷. Prognosis of CNS disease is good in absence of nodal disease and follow-up of patient with serial brain imaging until 5 years is recommended³.

Conclusion

RDD being a rare benign disease mimicking meningioma stands a good chance for a wrong diagnosis both clinically

***Senior Resident, Department of Neurosurgery, All India Institute of Medical Sciences (AIIMS), Ansari Nagar, New Delhi - 110 029; **Consultant, ***Chairman and Consultant, Department of Neurosurgery, Sir Ganga Ram Hospital, New Rajinder Nagar, New Delhi - 110 060.**

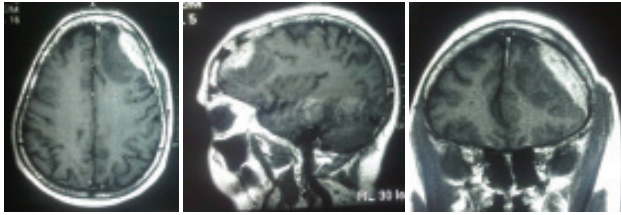


Fig. 1, 2 and 3: MRI images showing axial T1 with hypointense lesion and Gadolinium-enhanced axial, coronal and sagittal T1 weighted images showing homogenously enhancing mass lesion in the left frontal region.

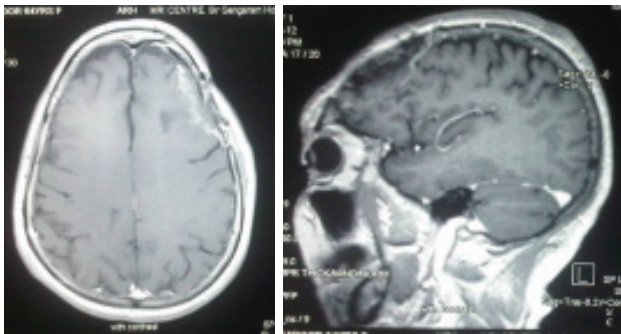


Fig. 4 and 5: Follow-up MRI done at 3 months post-surgery showing no evidence of recurrence-T1 contrast axial and sagittal images.

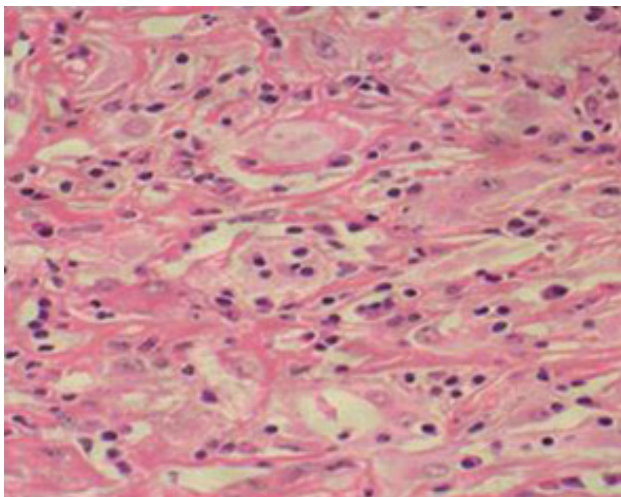


Fig. 6: Paraffin section showing (a) histiocytes with emperipolesis (Haematoxylin and Eosin, 6400).

and radiologically. Pathologist should be well aware of the mimickers of meningioma for accurate diagnosis. Correct diagnosis is important as surgical excision gives a good response and is curative; and corticosteroid therapy or radiation may have to be given after diagnosis in subtotal resected lesions. Steroid therapy with cytotoxic drugs or radiosurgery alone can also lead to remission in few. Follow-up brain imaging for recurrence is essential.

References

1. Foucar E, Rosai J, Dorfman R. Sinus histiocytosis with massive

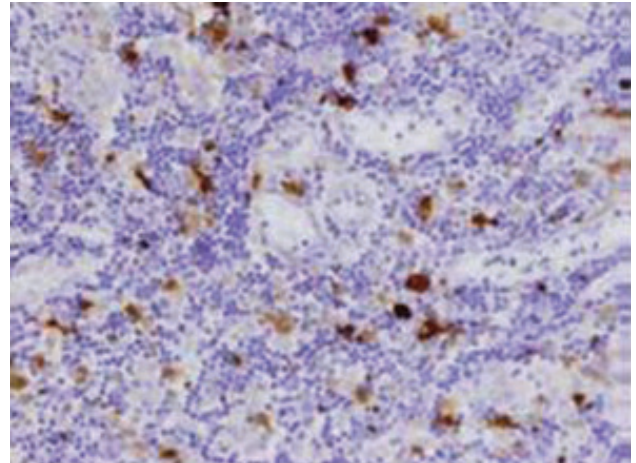


Fig. 7: The histiocytes are stained for S-100 protein.

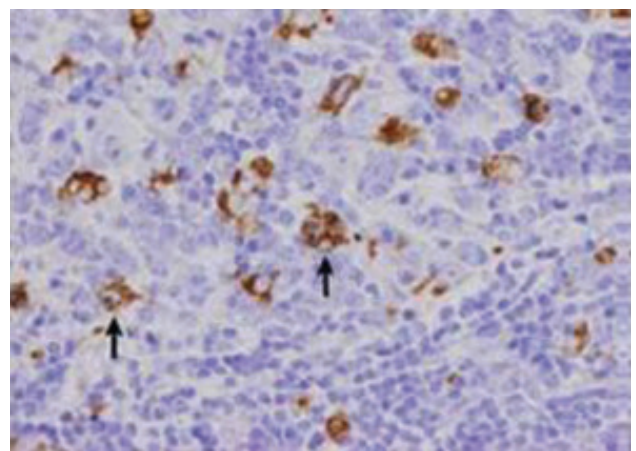


Fig. 8: The histiocytes are positive for CD68, demonstrating emperipolesis (lymphophagocytosis) (arrows).

- lymphadenopathy (Rosai-Dorfman disease): Review of the entity. *Semin Diagn Pathol* 1990; 7: 19-73.
2. Sameshima T, Morita A, Tanikawa R *et al.* Isolated Intracranial Rosai-Dorfman Disease Mimicking Convexity Meningioma: A Case Report. *J Clin Exp Pathol* 2012; 2: 118.
3. Petzold A, Thom M, Powell M *et al.* Relapsing intracranial Rosai Dorfman disease. *J Neurol Neurosurg Psychiatry* 2001; 71: 538-41.
4. Eisen RN, Busque L, Griffith BB *et al.* Langerhans' cell histiocytosis (histiocytosisX) a clonal proliferative disease. *N Engl J Med* 1994; 331: 154-6.
5. Warke RA, Weiss LM, Chan JK *et al.* Sinus histiocytosis with massive lymphadenopathy (Rosai Dorfman disease). In: Rosai J, editors. *Atlas of tumour Pathology, 3rd Series: Tumours of the Lymph Nodes and Spleen*. Washington: Armed Forces Institute of Pathology: 1995; p. 349-6.
6. Andriko JA, Morrison A, Colegial CH *et al.* Rosai-Dorfman disease isolated to the central nervous system: A report of 11 cases. *Mod Pathol* 2001; 14: 172-8.
7. Horneff G, Jurgens H, Hort W *et al.* Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): Response to methotrexate and mercaptopurine. *Med Pediatr Oncol* 1996; 27: 187-92.

Kikuchi's disease with pleural effusion

Kripa Shanker Jhirwal*, Hemant Mahur**, DP Singh***

Abstract

We report here an unusual case of a 26-year-old female patient presenting with clinical features of moderate to high grade fever with chills and rigors, bilateral cervical and submandibular lymphadenopathy, and left-sided exudative pleural effusion. On lymph node biopsy, the patient was diagnosed as Kikuchi's disease. Our case of Kikuchi's disease is unusual because this patient had exudative pleural effusion which is not reported earlier in the literature.

Introduction

Kikuchi's disease, also known as Kikuchi-Fujimoto disease, is an uncommon, idiopathic, generally self-limiting, disease with very rare recurrence and mortality. The cause of Kikuchi's disease is unknown. It is three times more common in females and typically affects young adults.

Kikuchi's disease most frequently manifests as relatively acute onset of cervical adenopathy associated with fever and flu-like prodrome. Other less common symptoms include headache, nausea, vomiting, malaise, fatigue, weight loss, arthralgia, myalgia, night sweats, rash, and abdominal pain.

Besides lymphadenopathy, hepatosplenomegaly is not uncommon. Neurological involvement – though rare – can include conditions such as aseptic meningitis, acute cerebellar ataxia, and encephalitis. Patients with aseptic meningitis may report headache, but they do not exhibit neck rigidity or positive Kernig's or Brudzinski's sign. CSF findings are similar to those noted in patients with aseptic meningitis of viral aetiology. In patients with Kikuchi's disease, laboratory and radiological findings are nonspecific. Although result of FNAC of lymph node may be suggestive, the diagnosis of Kikuchi's disease is confirmed only by excisional lymph node biopsy.

Case report

A 26-year-old female home maker who was apparently well until three months back, was admitted with complaints of fever of three month duration and cervical lymph node swelling since one month. Her complaints started as moderate to high grade fever which was continuous, associated with chills and rigors, occurring during any time of the day and relieved by antipyretics. There was no history suggestive of weight loss, cough with haemoptysis, arthralgia, bone pains, rashes, pain abdomen, high risk sexual behaviour, occupational exposure to animals, urinary

symptom, etc. Since the last one month she noticed a painless swelling over both sides of the neck, which was gradually increasing in size. Swelling was not associated with pain except when pressed hard. No past history of DM, pulmonary tuberculosis, or any other major chronic illness was elicited.

On clinical examination, she was moderately built and nourished. Her vitals were normal except for raised temperature in the range of 102°F to 103.8°F. No pallor was present. There was bilateral cervical lymphadenopathy, multiple (both anterior and posterior cervical and submandibular), approximately 1.5 x 2.0 cm in size, round-to-oval, smooth surface, mobile, firm in consistency, few were matted, non tender and the overlying skin was normal and free from the underlying structures. On systemic examination, the respiratory system revealed stony dullness and absent air entry over the left infraxillary and infrascapular areas. This finding was consistent with left pleural effusion. Alimentary system revealed hepatomegaly which was four cm below the right costal margin with a leafy margin, smooth surface, moving with respiration, nontender, with a liver span of 19 cm. There was moderate splenomegaly which was non-tender. Cardiac and neurological

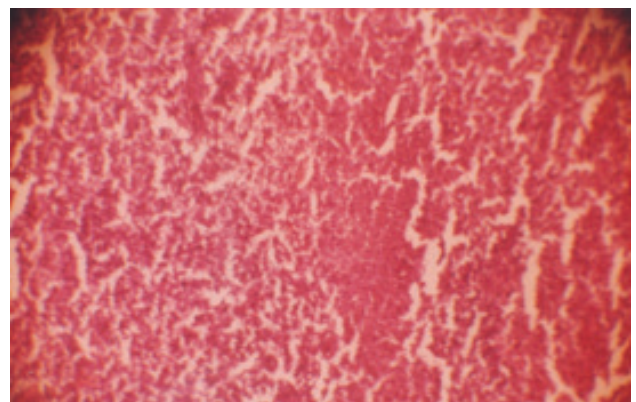


Fig. 1: Histopathology slide from FNAC of cervical lymph node.

*Final Year Resident, **Associate Professor, ***Senior Professor and Head, Department of Medicine, RNT Medical College, Udaipur - 313 001, Rajasthan.

examinations were within normal limits.

On laboratory examination: Hb - 12.4 mg%, TLC - 7,100/cu mm, DLC - P - 76%, L - 24%, ESR by Westergren was 30 mm in one hour. Malarial parasite was negative by both QBC and peripheral blood-film. IgG and IgM for typhoid fever was negative. Peripheral blood film showed normocytic and normochromic red blood cells, no immature cells, and platelets were adequate in number and no haemoparasite was seen. Urine analysis was normal. Renal function and liver functions were normal. HIV, Hbs Ag, VDRL, LE Cell, LDH, ANA, anti ds DNA, RA factor, ASO, CRP, and TB IgM and IgG were negative. Blood culture for pyogenic bacteria was negative.

Chest X-ray PA view showed pleural effusion on the left side. Pleurocentesis was done. Pleural fluid was yellowish in colour and was exudative type (total protein 3.9 gm%, cell count 900 cells/cu mm which was predominantly lymphocytic). Pleural fluid AFB culture was negative and ADA level was normal, Gram's stain was negative and pyogenic culture was sterile.

USG abdomen revealed hepatosplenomegaly. FNAC from cervical lymphadenopathy showed presence of sheets of lymphocytes, macrophages, neutrophils against a background of RBCs with no atypical cells suggestive of

reactive hyperplasia. Lymph node biopsy was done which on serial section showing patchy area of necrosis with focal collection of neutrophils. Rest of the lymph node appeared normal. Capsules of lymph nodes also did not show any infiltration. This whole biopsy picture is suggestive of Kikuchi's disease.

Our case of Kikuchi's disease had the following manifestation:-

1. Moderate to high grade fever with chills and rigors.
2. Cervical and submandibular lymphadenopathy.
3. Left-sided exudative pleural effusion.

The patient was treated conservatively. Left-sided pleurocentesis was done and the patient was given symptomatic treatment in the form of antipyretics and anxiolytics. Patient was followed over a period of three months. After one-and-half-a-months of follow-up, the patient became afebrile and there was no lymphadenopathy. Patient became symptom free after three months, i.e., afebrile with no lymphadenopathy, gained weight of 5 kilograms and his X-ray chest PA view was normal.

Discussion

Kikuchi's disease is generally a self-limiting disease with a favourable prognosis. In various literatures, the male female



Fig. 2: X-ray chest PA view before treatment.



Fig. 3: X-ray chest PA view after treatment.

ratio is 1:3 and the age is 4 - 75 years. About lymphadenopathy, cervical nodes are affected in about 80% of cases of which posterior cervical nodes are frequently involved (65 - 70%), lymphadenopathy is isolated to a single location in 83% of cases but multiple chains may be involved. Nodes are usually described as painless or mildly tender, usually firm and mobile.

Various extranodal findings

1. Skin: The incidence of skin involvement varies from 5 - 30%. Findings are varied and non specific and include maculopapular lesions, morbilliform rash, urticaria, and malar rash which may resemble that of SLE. Skin lesions resolve in a few weeks to months.
2. Hepatosplenomegaly is not uncommon.
3. Neurological involvement is rare.

Kikuchi's disease is misdiagnosed as lymphoma, SLE, infectious mononucleosis, sarcoidosis, tuberculosis, etc.

Management of Kikuchi's disease

Treatment is generally supportive. NSAIDs may be used to alleviate lymph node tenderness and fever. The use of prednisolone has been recommended in severe extranodal

or generalised Kikuchi's disease. Indications for corticosteroid use include the following:-

- A. Neurological involvement: Aseptic meningitis and cerebellar ataxia
- B. Hepatic involvement with elevated LDH level
- C. Severe lupus like syndrome

Conclusion

This was a rare case of Kikuchi's disease with unilateral pleural effusion. The occurrence of pleural effusion in Kikuchi's disease is not yet reported in the literature.

References

1. Baumgotner BJ, Helling ER. Kikuchi's disease: A case report and review of the literature. *Ear, Nose, Throat J* 2002; 81(5): 331-35.
2. Bosch X, Guilbest A, Miquel R *et al.* Engimetic Kikuchi. Fujimoto disease, a comprehensive review. *Am J Clin Pathol* 2004; 122 (I): 141-52.
3. Jang YJ, Park KH, Seok HJ. Management of Kikuchi's disease using glucocorticoid. *J Laryngol Otol* 2000; 114 (9): 709-11.
4. Soto Y, Kuno H, Oizumi K. Kikuchi's disease with aseptic meningitis. *J Neurol SC* 1999; 163 (2): 187-91.
5. Yasukaw K, Matsumara T, Sato Matsumara KC *et al.* Kikuchi's disease and the skin: case report and review of the literature. *British J Dermat* 2001; 144 (4): 885-89.

***All around us is the cosmic game, the cosmic play.
The universe is full of joy, inner and outer.
When realisation takes place,
we have to feel the necessity of manifesting this constant delight in our heart.***

— SRI CHINMOY.

Enteric duplication cyst presenting as stridor in a 2-month old infant

Aparajita Shukla*, Alpa Gupta**, Pramod Sharma***, Manju Saini****

Abstract

The purpose of this case report is to highlight the fact that congenital masses such as the enteric duplication cyst can be a cause of stridor in an infant and is often missed or misdiagnosed as happened in this case. A plain chest radiograph alongwith a CT scan of the chest, helped establish the diagnosis, following which the cyst was excised and the infant's stridor was cured.

Key words: Neonatal stridor, enteric duplication cyst, mediastinal masses, cystic lesion of chest.

Introduction

Stridor in a child is a feature of upper respiratory tract obstruction. The causes of stridor can be extra-luminal and intra-luminal. Important extra-luminal causes are mediastinal masses, vascular rings, bronchogenic cysts and thyroid enlargement, etc. Important intra-luminal causes are foreign body, papilloma, laryngomalacia, etc. Amongst the extra-luminal causes, congenital mass lesions in the thorax may sometimes present as stridor in the early neonatal period or infancy, especially if they are present in the upper part of the thorax. The stridor, if mild, many-a-times is misdiagnosed as noisy breathing/pneumonias. Here, we are presenting the case of a 2 months old child who had an enteric duplication cyst but continued to be misdiagnosed as a case of pneumonia till a chest radiograph was done.

Case report

A 2 months old male baby was brought in a sick state to the emergency with noisy breathing. The child was full term, vaginal delivered at home, was low birth weight (according to the parents) and had no history of birth asphyxia. He was exclusively breastfed. At 1 month of age, the child was noticed to have noisy breathing with fever and mild cough, for which he was treated empirically as having pneumonia by a local practitioner (no radiograph done). There was only mild improvement in the symptoms and the fever subsided but the noisy breathing persisted. Fifteen days later, the noisy breathing increased but there was no fever. The child was again treated as pneumonia but this time the patient had no improvement in the symptoms. The noisy breathing continued to increase and since 2 days prior to admission, he also developed respiratory distress. On examination, the patient was found to have biphasic stridor and decreased air entry bilaterally. Chest X-ray was done, which revealed a rounded, homogeneous opacity in the right upper zone,

with the deviation of the trachea to the opposite side, suggesting a space occupying lesion. CECT thorax was done, which revealed a cystic lesion in the right para-tracheal region, producing mass effect on the right main bronchus. The patient was taken up for surgery under general anaesthesia. A right postero-lateral thoracotomy was done, the cyst was identified, which was found to be compressing the trachea and superior vena cava. Complete cyst removal was done, following which the lung expanded. In the post-op period, the child did not have any respiratory distress. On histopathological examination, the cyst was diagnosed to be an enteric duplication cyst. The patient became stable and gradually improved, hence was discharged on the 7th post-operative day.



Fig. 1: Plain radiograph of the chest showing a homogeneous opacity in the right upper and middle zone.

*Junior Resident, **Professor, Department of Paediatrics, ***Surgeon, Department Paediatric Surgery, ****Professor, Department of Radio-diagnosis, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Jolly Grant, Dehradun - 248 140, Uttarakhand.

On regular monthly follow-up, the child was found to have gained weight, did not have any stridor and had normal respiratory system examination.

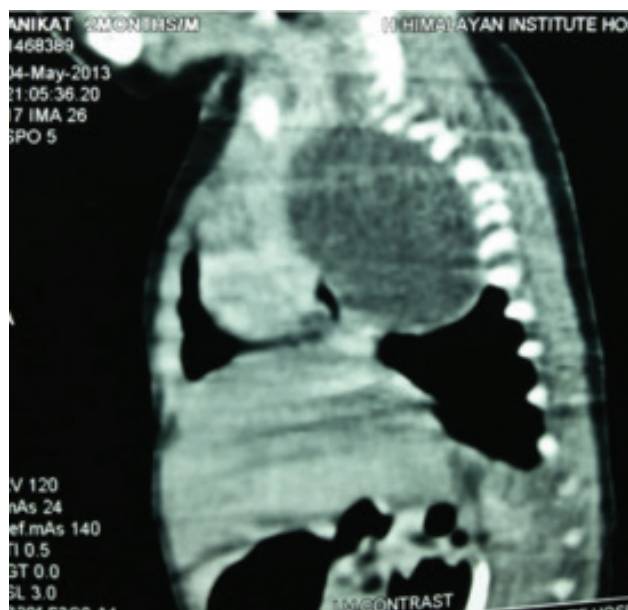


Fig. 2: CECT chest (lateral view) showing a large homogeneous opacity.

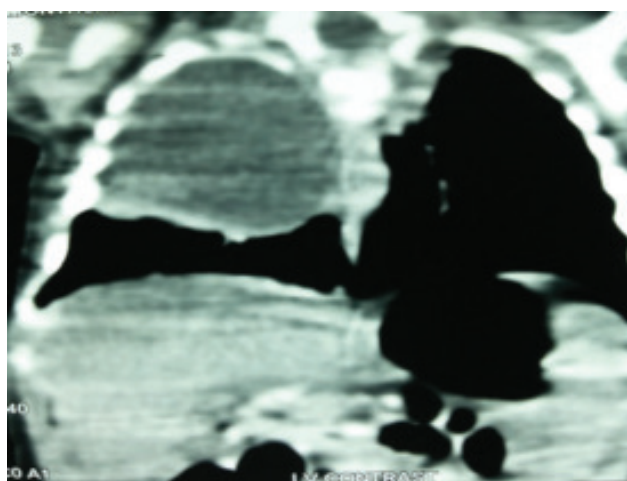


Fig. 3: CECT chest showing a large homogeneous opacity in the right upper zone.

Discussion

The term 'duplications of the alimentary tract' encompasses a wide variety of congenital mass lesions throughout the course of the gastrointestinal tract that are either tubular or cystic¹. Oesophageal duplication cysts are rare anomalies of the foregut. They are derived from the posterior part of the primitive foregut and may contain gastric, intestinal mucosal, or neural tissue².

Multiple theories exist explaining the possible causes of

these duplications. According to the theory postulated by Bentley and Smith³, in the 3rd week of gestation (stage 8), the notochord appears growing cephalad in close association with the endoderm. It normally separates from the endodermal cells. During this separation, a gap sometimes appears in the notochord through which a diverticulum from the foregut (endoderm) can herniate by incomplete detachment. These endodermal cells from the developing foregut then attach to the ectoderm and can form a cyst⁴.

Enteric duplication cysts (EDCs) are uncommon lesions, accounting for approximately 15% of foregut cysts⁵. Of these, jejunal and ileal cysts are the commonest with 53% incidence and cervical oesophageal cysts are the rarest at 1%⁶.

They are generally cystic or tubular masses. They present in a variety of ways depending on their size and location. The majority of duplications are diagnosed in the first 2 years of life. If the mass is in the chest, it may present as wheezing, pneumonia, or dysphagia. Other potential symptoms include failure to thrive, respiratory distress, and vomiting. Chest pain is a rare symptom unless the mass acutely enlarges from haemorrhage or infection⁷.

CT is the best diagnostic modality⁷. EDC manifests as a smooth, rounded, fluid-filled, round or tubular cyst structure with thin, slightly enhancing wall on contrast CT scan⁸.

Surgical excision is the standard treatment and for thoracic EDC traditionally the resection is done via thoracotomy. However, less invasive approaches such as video-assisted thoracoscopy can also be the first-line approach to these patients. The outcome of surgery for these patients is favourable².

With proper treatment, children born with enteric duplications should do well and have excellent long-term outcomes and quality of life⁷.

Message

1. Enteric duplication cyst in thorax is one of the causes of the stridor and respiratory distress in infants.
2. In infant presenting for the first time with stridor (or noisy breathing) or respiratory distress, chest radiograph (a cheap and easily available investigation) should always be done to timely diagnose any congenital thoracic mass.

References

1. Calder J. *Medical Essays Obser* 1733; 1: 205.
2. Dr Phillip Silberberg, Kosair Children's Hospital Hospital, Radiologist, Kosair Children's Hospital, Kentucky, USA; <http://>

www.mypacs.net/cases/ESOPHAGEAL-DUPLICATION-CYST-5463005.html.

3. Bentley JFR, Smith JR. Developmental posterior remnants and spinal malformations. *Arch Dis Child* 1960; 35: 76.
4. Skandalakis JE, Gray SW (eds): Embryology for Surgeons: The Embryologic Basis for the Treatment of Congenital Anomalies, 2nd ed. Baltimore, Williams and Wilkins, 1994.
5. Lakhkar BN, Ghosh MK, Patil UD *et al*. Enteric cyst. *Indian J Chest Dis Allied Sci* 1990; 32: 225-8.
6. Oldham KT, Colombani PM, Foglia RP (eds): Surgery of infants and children: Scientific principles and practice. Philadelphia, Lippincott-Raven, 1997.
7. Grosfeld Jay L, O'Neill Jr James A, Fonkalsrud Eric W, Coran Arnold G. *Paediatric Surgery* 2006; 6: 1403.
8. Correia-Pinto J, Tavares ML, Monteiro J *et al*. Prenatal diagnosis of abdominal enteric duplications. *Prenat Diagn* 2000; 20: 163-67.

***You have to work out your own problems,
work hard every day;
you have got to hold on to the real thing;
believe me, there's no other way!***

– GERTRUDE T BUCKINGHAM.

Hypothyroidism masking myotonic dystrophy

Neera Chaudhry*, Vinod Puri**, Yogesh Patidar***, Geeta A Khwaja****

Abstract

A patient with marked clinical hypothyroidism with an underlying myotonic dystrophy is described. Dystrophia myotonica and hypothyroidism have many common presenting symptoms, which may lead to a masking of either disorder. The disease process is discussed in relation to the muscle and metabolic changes. EMG findings and the muscle histopathology are commented on and compared with the changes described in hypothyroidism and dystrophia myotonica.

Key words: Hypothyroidism, dystrophia myotonica, myotonia.

Introduction

The neurologic manifestations of hypothyroidism are protean, affecting both the central and peripheral nervous system. The common neuromuscular symptoms are carpal/tarsal tunnel syndrome, mononeuropathy, peripheral neuropathy, and myopathy^{1,2}. Its association with myasthenia gravis, polymyositis, familial periodic paralysis and myotonic dystrophy have also been reported. Hypothyroidism may be associated with pseudomyotonia characterised by slow contraction and relaxation of the muscles; however, true myotonia is not a feature of hypothyroidism^{3,4}. Here we report a patient in whom hypothyroidism significantly masked the underlying myotonic disorder.

Case report

A 39-year-old female presented with a two-years history of difficulty in releasing grip along with stiffness in limbs, a gradually progressive weakness of lower limbs from 1.5 years and that of upper limbs from 1.2 years. She had initially developed difficulty in releasing objects while working in the kitchen and also noticed stiffness in her limbs. Six months later she developed progressive weakness in her lower limbs in the form of difficulty in getting up from squatting position, climbing stairs, buckling of knees with no distal weakness; and a similar involvement in upper limbs two months later in the form of difficulty in taking her arms above shoulder level, wearing sleeves of clothes and lifting bucket of water and only a mild weakness of grip. However, there was no sensory diminution. There was no history of motor incoordination, twitching, cramps, thinning of limbs, or increase in size of calves, nor any complaints of weakness in distribution of any of the cranial nerves or any bladder or bowel involvement.

Around one year into the illness she developed hair fall to the extent of baldness, along with coarsening of skin, hoarseness of voice, facial puffiness and also developed amenorrhoea; however, there was no history of weight gain, cold intolerance, constipation, nor was there a history of exposure to any chemicals. Over another six months she also developed change in behaviour, became irritable, abusive, and there was a decrease in social interactions. There was no forgetfulness, hallucinations, or delusions.

On general physical examination she was conscious, oriented to time, place, and person. There was periorbital oedema, malar rash, coarse skin (without any hyper/hypo pigmentation), generalised wasting, and alopecia (Fig. 1a). Detailed nervous system examination revealed normal higher mental functions; visual acuity was diminished bilaterally, visual fields were normal. On fundus examination, she had bilateral anterior subcapsular opacities, pale discs, macular oedema, and macular hole. Bilateral mild ptosis, facial weakness, as well as neck flexor weakness were also present. Motor examination revealed generalised thinning. Percussion myotonia and myotonia on asking the patient to release a fist was elicitable, which improved on exercise. The power on MRC grading was 3/5 at the hip, 4/5 at the knee, and 5/5 at the ankle with normal power of small



Fig. 1a: Patient at presentation: Facial puffiness and alopecia (Telogen effluvium). **Fig. 1b:** Patient after achieving euthyroid state.

*Associate Professor, **Director-Professor and Head, ***Senior Resident, ****Director-Professor, Department of Neurology, G.B. Pant Hospital, New Delhi 110 002.

muscles of foot, bilaterally. In the upper limbs the power was 2/5 at the shoulder, 4/5 at the elbow and a mildly weak grip bilaterally. The deep tendon reflexes were well elicitable and the Woltman sign was positive. Plantars were bilaterally flexor. Cerebellar signs could not be commented upon. Sensory system examination did not reveal any abnormality. The likelihood of a metabolic myopathy associated with myotonia, most probably hypothyroid myopathy was entertained and the patient investigated.

On routine investigations she had a haemoglobin of 9 gm% (13.5 - 15.5 g/dl), ESR of 54 mm in the 1st hour (0 - 12 mm in the 1st hour). The biochemical profile for blood sugar, blood urea, serum creatine, liver function tests, serum electrolytes was normal. Lipid profile (chemical method) revealed, serum cholesterol 344 mg% (normal range 130 - 230 mg%), triglycerides 159 mg% (normal range 80 - 160 mg%), LDL cholesterol 190 mg% (normal range 80 - 180 mg%) and HDL cholesterol 41 mg% (normal range 40 - 70 mg%). Her serum CPK was 1,216 (0 - 40 IU/L), TSH was 137.01 (0.1 - 5 IU/ml), FT3 was 1.6 (normal range 2.0 - 4.4 pg/ml), and FT4 was 0.84 (normal range 0.93 - 1.7 ng/dl). Thyroid antibodies, ANA, RA factor, ELISA for HIV were negative. ECG was a low voltage graph, but 2D-echo was normal without any evidence of pericardial effusion. Fluorescent fundus angiography revealed a right macular hole and sub-retinal exudation and left subretinal changes. Electromyography revealed normal insertional activity, myotonic discharges from abductor pollicis brevis (Fig. 2), and not from deltoid. The recruitment pattern was incomplete but there was a poor effort from the patient. Muscle biopsy done from the quadriceps revealed relatively maintained lobular architecture, marked variation of fibre size, type-1 fibre atrophy, hypertrophic fibres, marked internal nucleation, longitudinal fibres showing tandem chain of nuclei, more than 15 in number, intrafascicular increased fibrous tissue, cluster of myonuclei, no accumulation of glycogen (Fig. 3a, b).

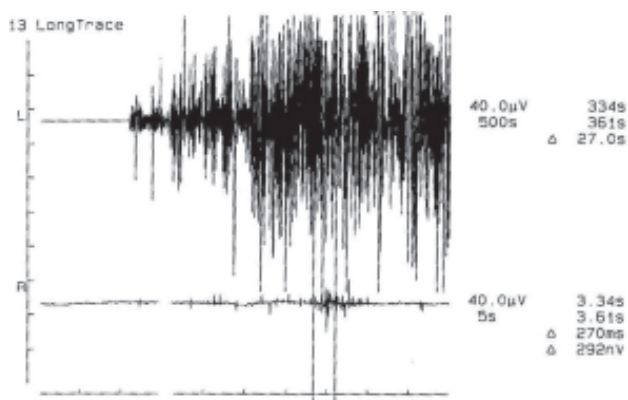


Fig. 2: Needle EMG from APB showing myotonic discharges.

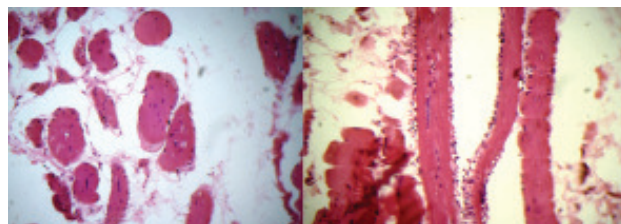


Fig. 3a, b: Muscle biopsy H and E stain: showing maintained lobular architecture, marked variation of fibre size, marked internal nucleation, intra-fascicular increased fibrous tissue, cluster of myonuclei, no accumulation of glycogen. Longitudinal fibres were showing tandem chain of nuclei more than 15 in number.

In view of severe hypothyroidism she was started on tablet eltroxin 100 µgm/day. Her sequential thyroid profiles showed normalisation of serum TSH levels [31.3 uIU/ml (6 month), 13.10 uIU/ml (9 month), and 0.35 uIU/ml (12 month)]. She had a marked improvement in her symptoms including facial puffiness, coarse skin, hoarse voice, malar rash, alopecia (Fig. 1b) and menstrual abnormality. However, there was only moderate improvement in muscle power with persistent grip weakness even when the thyroid functions normalised. Facial and neck flexor weakness improved minimally and the myotonia decreased but persisted (both percussion and electrical).

With the patient having been in our follow-up for almost four years, her son aged sixteen developed difficulty in releasing grip. There was no history of weakness of any limb or any other systemic illness. They then remembered that the patient's mother also had developed similar complaints around the age of 50, however no other family member was affected. Son's examination revealed mild bilateral ptosis and facial weakness. There was no cataract, retinal abnormality, or any weakness of sternocleidomastoid or distribution of any of the cranial nerves, nor was there any limb weakness, or muscle hypertrophy. Clinical and electrophysiological myotonia was elicitable. His thyroid profile was normal. A genetic analysis for myotonic disorder, (CTG)_n trinucleotide repeat expansion in the 3-prime-untranslated region of a protein kinase-encoding gene, DMPK (160900), which maps to 19q13.3, revealed a CTG repeat size of 165 (normal range 5 - 34). She was started on tab phenytoin 100 mg twice a day leading to a decrease in myotonia.

Discussion

The salient features of hypothyroid myopathy are muscle aches, cramps, slow movements, slow relaxation which is worse in cold⁵. There is a slowness of contraction, and it worsens with exercise as the muscles become more contracted with exercise. Hypertrophy of muscles occurs because of this prolongation of activity, sometimes even

giving rise to a classical muscle bound appearance, Hoffman and Kocher-Debri-Semelaigne syndrome. Myoedema is a feature of hypothyroid myopathy and a slow prolonged local moulding of muscle, also known as pseudomyotonia, occurs on percussing the muscle, but it is electrically silent^{3,4}. True myotonia which is characterised by a warm-up phenomenon (improvement on exercise), percussion myotonia, electrophysiological elicibility, is however, not a feature of hypothyroidism. CPK is usually elevated⁵. Muscle biopsy shows only a few changes like type II fibres atrophy, and excessive glycogen accumulation^{1,2}.

Other neurological manifestations of hypothyroidism include disturbed visual acuity, optic atrophy with central scotoma and uveitis. Primary hypothyroidism with pituitary enlargement may lead to compression of optic chiasma, pseudotumour cerebri and papilloedema may be present. Facial pain, Bell's palsy, diminished hearing, diminished taste sensation and vocal changes are known to occur, but rarely.

Our patient had proximal muscle weakness, a positive Woltman sign, along with severe hair fall, coarsening of skin, hoarseness of voice, and facial puffiness, raised TSH and CPK levels, all of which are attributable to hypothyroidism. However, subcapsular opacities, pale discs, macular oedema, macular hole, bilateral ptosis, bifacial, neck flexure and distal upper limb weakness; percussion myotonia, myotonia improving on exercise with an EMG evidence of myotonia, a muscle biopsy showing type-1 fibre atrophy, increase in number of central nuclei but no excess glycogen, were features not explainable by hypothyroidism. These were pointers towards an underlying myotonic disorder.

Myotonic disorders can be inherited or acquired. Inherited myotonic disorders include myotonic dystrophy, myotonia congenita (Thomsen's disease, Becker's disease), paramyotonia congenita, periodic paralysis (hypokalaemic, normal/hyperkalaemic) and chondrodystrophic myotonia (Schwartz-Jampel syndrome), while acquired myotonia can be caused by hypothyroidism, malignancy and certain drugs⁶.

Dystrophica myotonica (DM 1) typically presents in the 20s and 30s (and less commonly after age 40 years), though it may be evident in childhood, when subtle signs such as myotonic facies and myotonia are observed as was evident in her son. It usually presents with ptosis, facial weakness, weakness of sternocleidomastoids, jaw muscles and that of distal limb muscles. Proximal limb weakness occurs late with involvement of shoulder and pelvic girdle⁷⁻⁹. Myotonia is clinically elicitable but patients do not complain of myotonia per se. Pseudohypertrophy of muscles can occur. Peripheral nerve involvement is variable; rarely, clinically

significant minor sensory loss may occur. Mild mental deterioration, hypersomnia are also known. Premature balding, calcifying epithelioma, cataract, retinal degeneration, ocular hypotonia, ptosis, extra-ocular weakness, corneal lesions are well described. Endocrinopathies including hyperinsulinism, diabetes mellitus, testicular atrophy, and possible abnormalities in growth hormone secretion can be observed, although they are rarely clinically significant⁷⁻⁹. Occurrence of hypothyroidism is extremely rare¹⁰⁻¹⁷.

In view of a marked and early proximal weakness it was debated whether the patient had proximal myotonic myopathy (PROMM) (DM2). The presence of cataract, bilateral ptosis, bifacial, neck flexures and distal upper limb weakness; and above all, a strong history of anticipation in the family favored type 1 myotonic dystrophy¹⁸. The genetic analysis also showed an increased CTG and not CCTG repeats which cleared our query.

The proximal weakness in our patients was probably due to both myotonic disorder and hypothyroidism and it did show improvement on correction of the metabolic abnormality. Clearly hypothyroidism very prominently masked the underlying myotonic disorder in our case. The case teaches us that even in the era of advanced investigative tools, a good clinical evaluation stands its ground and should always be adhered to.

References

1. Duyff RF, Bosch JV, Laman MD *et al.* Neuromuscular findings in thyroid dysfunction: a prospective clinical and electrodiagnostic study. *J Neurol Neurosurg Psychiatry* 2000; 68: 750-55.
2. Monzani F, Caraccio N, Guerra PD *et al.* Neuromuscular symptoms and dysfunction in subclinical hypothyroid patients: beneficial effect of L-T4 replacement therapy. *Clinical Endocrinology* 1999; 51 (2): 237-42.
3. Cruz MW, Tendrich M, Vaisman M *et al.* P. Novis. Electroneuromyography and Neuromuscular findings in 16 Primary Hypothyroidism patients. *Arq Neuropsiquiatr* 1996; 54 (1): 12-18.
4. Eslamian F, Bahrami A, Aghamohammadzadeh N *et al.* Electrophysiologic changes in patients with untreated primary hypothyroidism. *J Clin Neurophysiol* 2011; 28 (3): 323-28.
5. Scott KR, Simmons Z, Boyer PJ. Hypothyroid myopathy with a strikingly elevated serum creatinine kinase levels. *Muscle Nerve* 2002; 26: 141-44.
6. Mankodi A. Myotonic disorders. *Neurology India* 2010; 56 (3): 298-304.
7. Turner C, Hilton-Jones D. The myotonic dystrophies: diagnosis and management. *J Neurol Neurosurg Psychiatry* 2010; 81: 358-67.
8. Conravey A, Santana-Gould L. Myotonia Congenita and Myotonic Dystrophy: Surveillance and Management. *Current Treatment Options in Neurology* 2010; 12: 16-28.
9. Schoser B, Timchenko L. Myotonic Dystrophies 1 and 2: Complex Diseases with Complex Mechanisms. *Current Genomics* 2010; 11:

77-90.

10. Rioperez E, Botella JM, Palacio A *et al.* Myotonic dystrophy associated with thyroid disease. *J Neurol Sci* 1979; 43 (3): 357-66.
11. Steinbeck KS, Carter JN. Thyroid abnormalities in patients with myotonic dystrophy. *Clin Endocrinol (Oxf)* 1982; 17 (5): 449-56.
12. Fukazawa H, Sakurada T, Yoshida K *et al.* Thyroid function in patients with myotonic dystrophy. *Clin Endocrinol (Oxf)* 1990; 32 (4): 485-90.
13. Margolis J, Freitas WJ, Margolis LS. Hypothyroidism mimicking myotonic dystrophy. *J Am Geriatr Soc* 1973; 21 (1): 31-32.
14. Konagaya Y, Honda H, Konagaya M *et al.* Myotonic dystrophy associated with hyperthyroidism. *Nihon Naika Gakkai Zasshi* 1983; 72 (10): 1391-97.
15. Sansone V, Griggs RC, Moxley RT. Hypothyroidism unmasking proximal myotonic myopathy. *Neuromuscular Disorders* 2000; 10 (3): 165-72.
16. Tredici G, Coletti A. Dystrophia Myotonica and hypothyroidism. *J Neurol* 1978; 218 (3): 215-18.
17. Brumlik J, Maier RJ. Myxoedema and Myotonic Dystrophy. *Arch Intern Med* 1972; 129 (1): 120-22.
18. Finsterer J. Myotonic dystrophy type 2. *European Journal of Neurology* 2002; 9: 441-47.

DIAMICRON XR 60

Coeliac disease presenting in association with rare transfusion reaction due to MNS mismatch

Nitya Nand, Parveen Malhotra**, Dhananjay Kumar***, Dipesh Dhoot****

Abstract

Coeliac disease is an immune disorder that is triggered by an environmental agent (gliadin) in genetically predisposed persons. It has been reported previously to be associated with "secretor status" which determines the ability to secrete the blood group antigens into saliva and other body fluids. But no association of coeliac disease has ever been reported with any blood group or rare blood group incompatibility due to any "atypical" or "unexpected" antibodies. We report here a case of a 20-year-old female presenting with severe anaemia. Her blood group was O Rh positive but she could not be given blood transfusion due to cross-reaction with blood units of same group. Patient was diagnosed as a case of atypical coeliac disease with rare transfusion incompatibility due to fairly common but rarely cross reacting anti-M antibody.

Key words: Coeliac disease, blood group incompatibility, anti-M antibody.

Introduction

Coeliac disease is a common cause of intestinal malabsorption syndrome presenting in a wide range of intestinal and extra-intestinal manifestations. It is an immune disorder that is triggered by an environmental agent (gliadin) in genetically predisposed persons. IgA antibodies against endomysium, a connective tissue structure surrounding intestinal smooth muscle, are virtually pathognomonic for coeliac disease and are found only rarely in the absence of disease. Its association with non-secretor status¹, CTLA4 gene polymorphism, and TNF-alpha gene promoter polymorphism has been reported. But till date there has been no report of association of coeliac disease with any blood group or rare blood group incompatibility due to any "atypical" or "unexpected" antibodies. Here we present a case of coeliac disease who presented with severe iron deficiency anaemia with rare transfusion reaction due to MNS mismatch.

Case summary

A 20-year-old female presented to our emergency department with a 6-month history of generalised weakness and fatigue with a 15-days history of dyspnoea associated with orthopnoea, palpitations, and generalised swelling over the body. Her menstrual history was notable for late onset menarche at age of 16 years and complaints of amenorrhoea since the last 6 months. She had no history of any blood transfusion in past life. On examination, she was severely anaemic and having pedal oedema, facial puffiness, and raised jugular pressure, suggestive of heart failure. Vitals were stable, pulse rate being 94 per minute and blood

pressure was 120/60 mm Hg with a respiratory rate of 18 per minute. Chest auscultation was normal but flow murmurs were appreciated on cardiac auscultation. Apex was localised in 5th intercostal space, 1 cm lateral to mid-clavicular line but a huge cardiomegaly was seen on a chest radiogram signifying presence of pericardial effusion. Abdomen was soft and non-tender but liver was palpable 5 cm below the costal margin. Spleen was not appreciated on palpation as well as percussion of Traube's space. Her neurological examination was unremarkable.

Routine investigations showed severe anaemia (Hb - 2.0 gm%) with microcytic hypochromic picture. White blood cell count was 5,400/cumm with 78% neutrophils and platelet count of 430,000/cumm. RBC indices showed markedly decreased mean corpuscular volume (44.7 fl), mean corpuscular haemoglobin (11.4 pg), mean corpuscular haemoglobin concentration (25.5 g/dl) and haematocrit (14.1%). With reticulocyte count of 9%, corrected reticulocyte index came out to be 1.2% signifying it as hypoproliferative anaemia. Serum ferritin was 45 ug/l and levels of vit. B12 and folate were within normal limit. Her total iron binding capacity was 564 ug/dl and transferrin saturation was 10%. Routine liver and kidney function tests were normal except for raised transaminases (AST - 150 U/L and ALT - 60 U/L). Blood transfusion was planned and a sample was sent for cross match but failed due to incompatibility with all donor units of the same blood group (O positive), tested multiple times.

In the view of signs of congestive heart failure and huge cardiomegaly on chest skiagram, 2-D echocardiography was done which revealed pericardial effusion of 7mm in the posterior sac. The cause for iron deficiency anaemia was

***Senior Professor and Unit Head, **Associate Professor, ***Resident, Department of Medicine, Pandit B. D. Sharma Post-Graduate Institute of Medical Sciences (PGIMS), Rohtak - 124 001, Haryana.**

investigated and endoscopy-guided duodenal biopsy was done which revealed histopathological findings suggestive of coeliac disease, Marsh class – III (Fig. 1). Anti-endomysial antibodies were found to be present. Injectable iron therapy was started for anaemia with diuretics for congestive heart failure and gluten restricted diet was started and patient started improving slowly. Immunohaematology revealed the blood incompatibility due to anti-M antibody (Table I) and for that reason, blood transfusion could not be given but patient improved symptomatically as well as biochemically. Her reticulocyte count raised to 18% within 3 days and haemoglobin level started improving in 7 - 8 days. Pericardial effusion decreased spontaneously without aspiration and signs of congestive heart failure disappeared and patient was discharged 3 weeks after admission.

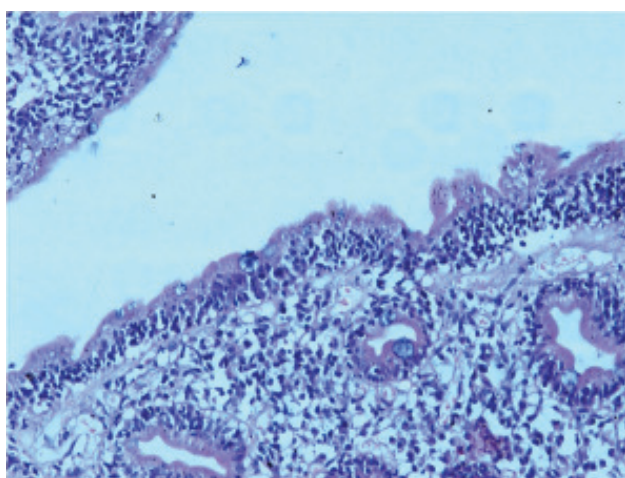


Fig. 1: Histopathologic findings suggestive of coeliac disease, Marsh class-III.

Discussion

Coeliac disease is an immune mediated disease with the target autoantigen identified as the enzyme contained within the endomysium called tTG-2 (tissue transglutaminase). tTG deamidates neutral glutamine residues in gliadin and converts them into negatively charged glutamic acid residues, causing conformational change in gliadin facilitating its binding with HLA-DQ2 heterodimer over surface of APC (Antigen Presenting Cells) thereby facilitating antigen presentation to T-helper lymphocytes and subsequent antibodies formation and cytokines production. Thus immune factors (anti-tTG, anti-gliadin), environmental factors (gliadin exposure) and genetic factors (HLA-DQ2/DQ8) all play their role in its pathogenesis. But only a minority of persons who express DQ2/DQ8 actually develop coeliac disease. Hence, the search for other genes and factors that confer susceptibility to coeliac disease has revealed numerous loci of interest on several different chromosomes including CTLA4 gene polymorphism, TNF-alpha gene promoter polymorphism and "non secretor" status¹.

Secretor or non-secretor status of a person is determined by single gene locus at chromosome 19q13.3 which encodes for Fucosyltransferase-2 (FUT2) enzyme which is responsible for secretion of ABO and Lewis blood group antigens into the body secretions. This is the same locus of gene encoding FUT1 enzyme responsible for fucosylation of oligosaccharide antigen in the formation of H antigen which is precursor for ABO blood group antigens. Hence, Bombay phenotype is also associated with non-secretor status and therefore indirectly to celiac disease. In our case,

Table I:

Antigen Panel

	Rh-hr					Kell					Duffy					Kidd		Lewis		P				MNS				Lut		Xg		Spec. Ag	Result
	D	C	E	c	e	C ^w	K	k	Kp ^a	Kp ^b	Js ^a	Js ^b	Fy ^a	Fy ^b	Jk ^a	Jk ^b	Le ^a	Le ^b	P	M	N	S	s	Lu ^a	Lu ^b	Xg ^a			Coombs				
034233	+	+	0	0	+	+	0	+	0	+	nt	+	+	0	0	+	0	0	+	+	0	+	0	0	+	+				2+			
454054	+	+	0	0	+	0	+	+	0	+	nt	+	0	+	+	0	+	0	+	+	+	+	+	0	+	+				1+			
154050	+	0	+	+	0	0	0	+	0	+	nt	+	0	+	0	+	0	+	+	+	+	+	0	+	0	+	+				1+		
339142	0	+	0	+	+	0	0	+	0	+	nt	+	+	0	0	+	0	+	0	0	0	+	0	+	0	+	+				-		
472508	0	0	+	+	+	0	0	+	0	+	nt	+	0	+	+	0	0	+	+	+	+	+	+	0	0	+	+				1+		
293387	0	0	0	+	+	0	+	+	0	+	nt	+	+	0	0	+	0	+	+	+	+	+	0	+	+	+	0	Bg ^a +			1+		
405566	0	0	0	+	+	0	0	+	0	+	nt	+	0	+	+	0	+	0	vw+	+	+	0	+	0	0	+	+				2+		
160569	+	0	0	+	+	0	0	+	0	+	0	+	0	0	+	+	+	0	0	+	+	0	+	0	0	+	+				1+		
556728	0	0	0	+	+	0	0	+	0	+	nt	+	0	+	0	+	0	+	+	0	+	0	+	0	+	+					-		
433797	0	0	0	+	+	0	0	+	+	+	nt	+	+	0	+	0	0	0	0	+	+	+	+	0	+	+					2+		
160036	0	0	0	+	+	0	0	+	0	+	nt	+	+	+	+	0	0	+	+	0	+	0	+	+	+	+	nt				-		

the patient was found to be O positive and reacting with all blood units of same group, so Bombay phenotype was thought to be the most probable explanation of this incompatibility in this case and further tested for the same by anti-H lectin test which showed the presence of H antigen; hence Bombay phenotype was ruled out. A thorough antibody screening was done with a panel consisting of 26 probable antigens and the panel suggested the incompatibility to be due to anti-M antibody (Table I).

Anti-M is a fairly common antibody and is thought to mostly be naturally occurring because it is frequently found in children who have never received a blood transfusion. Anti-M antibody is usually of IgM type and is a cold antibody, i.e., it does not react at body temperature so it is generally not considered to be a cause of transfusion reactions or haemolytic disease of newborn (HDFN), although rare cases of reaction have been reported^{2,3} as a result of anti-M due to IgG antibody reacting at 37°C. These rare cases have not been reported to be associated with any immune disease and this case is the first of its kind as it is the first ever report of association of an immune disease with a rare blood group incompatibility due to one of the most common naturally occurring antibodies. Whether this association is significant or merely a coincidence may be a topic of further debate.

References

1. Dickey W, Wylie JDC, Collins JSA *et al.* Lewis phenotype, secretor status, and coeliac disease. *Gut* 1994; 35: 769-770
2. Tondon R, Kataria R, Chaudhry R. Anti-M: Report of two cases and

review of literature. *Asian J Transfus Sci* 2008; 2: 81-3.

3. Duguid J, Bromilow I, Entwistle G *et al.* Haemolytic Disease of the Newborn due to Anti-M. *Vox Sanguinis* 1995; 68: 195-96.

ADVERTISEMENT TARIFF

Journal, Indian Academy of Clinical Medicine

Advertisement Tariff effective January, 2016

Position	Single Issue	Consecutive Four Issues
(a) Back cover	₹ 20,000/-	₹ 60,000/-
(b) Inside back and inside front cover	₹ 15,000/-	₹ 45,000/-
(c) Full page	₹ 10,000/-	₹ 30,000/-
(d) Half page	₹ 6,000/-	₹ 18,000/-

Note: Artworks/positives (processing)/art pulls of advertisements for Back cover, Inside front cover, Inside back cover and Full page should not exceed 28 cm (H) x 21 cm (W) – (for bleed); and 25 cm (H) x 18 cm (W) – (for non-bleed). For half page advertisements the artwork should not exceed 12 cm (H) x 18 cm (W).

Size of the Journal is 28 cm x 21 cm.

For advertisement assistance & queries, contact:

Dr. Sumeet Singla, Secretary, JIACM
Mobile: +91-9810104431

The only thing that will redeem mankind is cooperation.

– BERTRAND RUSSELL.

Unaccustomed exertion, opiate consumption, and dehydration leading to acute renal failure in a healthy male

Monica Gupta, Mandip Bhatia**, Sanjay D Cruz****

Abstract

A 38-year-old male presented with stupor and acute renal failure (ARF) following opium consumption and a protracted excursion on foot to a holy shrine situated at altitude of 4,329 m above sea level. The finding of dark-coloured urine, myoglobinuria, and a markedly elevated serum creatine phosphokinase level supported the diagnosis of rhabdomyolysis. The patient had a rapid and complete recovery following fluid resuscitation and haemodialysis.

Key words: Rhabdomyolysis, acute renal failure, opium consumption.

Introduction

Rhabdomyolysis is a clinical syndrome wherein contents of injured muscle cells escape into circulation resulting in electrolyte imbalance, acidosis, clotting disorders, hypovolaemia, ARF. This may result in visible myoglobinuria, i.e., red or brown urine. Incidence is higher in males, adults, inherited enzyme deficiencies of carbohydrate or lipid metabolism, and myopathies. In the US, rhabdomyolysis accounts for an estimated 8 - 15% cases of acute renal failure. No Indian data is available. Mortality in rhabdomyolysis is roughly 5%.

Rhabdomyolysis following severe physical exertion with or without heat stress resulting in ARF is rare. We report a rare case of exertional rhabdomyolysis under the effect of dehydration, opium overdose, complicated by acute renal failure (ARF) in a previously healthy individual.

Case presentation

A 38-year-old male, previously in good health went on excursion to a holy shrine situated at an altitude of 4,329 m above sea level in Uttarakhand, India. After continuous walking for 21 kilometres in the hot, humid, hilly terrain, he collapsed. He had illicitly consumed opium (as raw opium) before starting the trek and also during the trek in significant amount along with tablets of proxyvon (paracetamol 400 mg, dextropropoxyphene napsylate 100 mg). On admission, he was drowsy (GCS 9/15) and dehydrated. There was no pallor, icterus, cyanosis, or oedema. The pupils were small and sluggishly reactive, blood pressure was 98 mmHg systolic, pulse 98/min and respiration was laboured. Chest, cardiovascular, and abdominal examinations were unremarkable. Plantars were flexor bilaterally and there were no meningeal signs. Catheterisation yielded 100 ml of reddish-brown urine.

Investigations at admission revealed haemoglobin of 13 gm/dl, haematocrit 42 (normal range 38.8 - 46), total leucocyte count 10,700/cumm and platelet count of 150,000/cumm. Prothrombin time was 13 sec (normal range 12.7 - 15.4 s), urine analysis showed pH 5.0, albumin 1+, 5 - 6 red blood cells/HPF and muddy casts. Urine for haemoglobin (by multistix) tested positive (normally undetectable). Urine spot Na⁺ was 88 mEq/l (normal range 100 - 260 meq/l) and urine myoglobin was 157 IU (normally undetectable). Toxicology screen for opioids tested positive.

The renal function tests showed blood urea to be 206 mg/dl and serum creatinine to be 7.5 mg/dl which increased to 9.5 mg/dl on the second day. Other lab parameters were serum calcium 7.45 meq/l, serum phosphate 6.35 meq/l, serum albumin 4.2, uric acid 7.85/ml, serum sodium 143 meq/l, serum potassium 5.5 meq/l, serum chloride 100 meq/l. ABG (on supplemental oxygen) analysis revealed pH - 7.21, pCO₂ - 45, pO₂ - 89, HCO₃ - 16.7, O₂ saturation 96% (acute respiratory and metabolic acidosis). The creatine phosphokinase showed a value of 867 U/L (normal range 51 - 294 U/L), lactate dehydrogenase 980 U/L (normal range 115 - 221 U/L), alanine aminotransferase 85 IU/l (normal range 7 - 41 U/L) and aspartate aminotransferase 77 IU/l (normal range 12 - 38 U/L). ECG showed no hyperkalaemic changes. Ultrasound abdomen showed normal sized kidneys.

He was resuscitated with intravenous fluids under central venous pressure (CVP) monitoring. After a bolus dose of 0.4 mg, 6 mg of naloxone was given as a slow infusion over 3 hours, during which his pupillary reaction and GCS improved. He was infused with saline containing sodium bicarbonate followed by intravenous diuretics. However, his overnight urine output was only 600 ml. Due to worsening of azotaemia, he was haemodialysed the next day and subsequently required two more sessions of haemodialysis. After three sessions of haemodialysis, the

***Assistant Professor, **Ex-Senior Resident, ***Associate Professor, Department of Medicine, Government Medical College and Hospital, Sector 32, Chandigarh - 160 030.**

patient started showing improvement, entered the diuretic phase and his renal functions improved with serum creatinine falling to 2.1 mg/dl after one week. Subsequently, the patient was reviewed in the out-patient clinic after two weeks; his urine output was normal and serum creatinine had come down to 1.1 mg/dl, transaminases had normalised and he had no myalgias.

Discussion

Rhabdomyolysis is caused by injury to skeletal muscles resulting in release of intracellular muscle constituents. It was first described in the victims of crush injury during the Second World War in 1940 - 1941 and was known as "crush injury syndrome"¹. Since then, several non-traumatic conditions leading to rhabdomyolysis and myoglobinuric renal failure have been described^{2,3}.

Excessive muscular activity especially in unconditioned men (so called white collar rhabdomyolysis), physical injury from compression, ischaemia, hyperthermia, electrical injury, all can result in hyperkalaemia, metabolic acidosis, and rhabdomyolysis⁴. Non-traumatic rhabdomyolysis is usually caused by toxic reaction to drugs; common compounds associated with it being opium, alcohol, cocaine, amphetamines, and ecstasy. Prolonged hypoxic coma following opiate overdose can lead to intracapillary myohypoxia causing rhabdomyolysis⁵. A positive orthotolidine test (less sensitive) or preferably spectrophotometry in the supernatant urine, an elevated CPK and myoglobin in serum helps clinch the diagnosis of rhabdomyolysis.

Ramamoorthy *et al* described myoglobinuria with ARF in a nineteen-year-old boy who performed three hours of continuous dance programme on a hot humid summer afternoon⁶. Uberoi *et al* reported seven cases over a period of six years with ARF due to exercise-induced myoglobinuria in the absence of heat stress⁷. Similarly another series of eight cases was reported from a naval officers training institute⁸.

In a retrospective study of 181 patients of rhabdomyolysis from poisoning centre of Loghman-Hakim hospital in Tehran during September 2004 to September 2005, opium overdose was found to be most commonly associated with rhabdomyolysis with ARF⁹. Melandri *et al* reported a case of myocardial damage along with rhabdomyolysis due to prolonged hypoxic coma following opiate overdose⁵.

The major life threatening complication of myoglobinuria is acute tubular necrosis, as occurred in our case. The exact mechanism of ARF is not well understood. It is postulated that direct tubulo-toxic effect of ferrihaemate or myoglobin, obstruction to tubular lumen by myoglobin casts, back diffusion of glomerular filtrate through a break in the epithelium and decreased glomerular filtration rate, leads

to ARF. Dehydration, heat stress, hypovolaemia and acidification of urine are crucial precipitating factors. Renal involvement is characterised by oliguria, exceptionally high creatinine levels, hyperkalaemia, hyperphosphataemia and hyperuricaemia. Serum calcium may be low in the oliguric phase; and later in diuretic phase, patients may develop hypercalcaemia. Our patient had hypocalcaemia, hyperphosphataemia, hyperkalaemia and hyperuricaemia. Predictors for development of renal failure are CPK levels more than 6,000 IU/L, dehydration, haematocrit > 50, serum sodium > 150 meq/l, orthostasis and Pulmonary Capillary Wedge Pressure (PCWP) < 5 mmHg.

Treatment of ARF due to myoglobinuria is by volume replacement, forced diuresis, haemodialysis, and supportive measures. ARF should be suspected in patients with CPK levels in excess of 2 - 3 times the reference range, in the presence of risk factors for rhabdomyolysis. Vigorous hydration with isotonic crystalloid supports the intravascular volume, increases the glomerular filtration rate (GFR) and oxygen delivery, and dilutes myoglobin and other renal tubular toxins. If initiated early, alkaline solute diuresis and infusion of mannitol or sodium bicarbonate can improve renal function.

Conclusion

Unintentional or intentional overdose with illicit drugs like opium or cocaine should always be investigated in cases of unexplained rhabdomyolysis and acute renal failure. Sporadic strenuous and prolonged exercise along with poor intake of fluids and heat stress can be potentially life-threatening.

References

1. Bywaters EQL, Beall D. Crush injuries with impairment of renal function. *Br Med J* 1941; 1: 427-32.
2. Black C, Jick H. Aetiology and frequency of rhabdomyolysis. *Pharmacotherapy* 2002; 22: 1524-6.
3. Singh S, Sharma A, Sharma S *et al*. Acute alcoholic myopathy, rhabdomyolysis and acute renal failure: a case report. *Neurol India* 2000; 48: 83-5.
4. Knochel JP. Catastrophic medical events with exhaustive exercise: "White collar rhabdomyolysis". *Kidney Int* 1990; 38: 709-19.
5. Melandri R, Re G, Lanzarini C *et al*. Myocardial damage and rhabdomyolysis associated with prolonged hypoxic coma following opiate overdose. *J Toxicol Clin Toxicol* 1996; 34 (2): 199-203.
6. Ramamoorthy KP, Varghese AM, Ravikumar P *et al*. Myoglobinuria after exercise – a rare presentation. *Ind J Nephrol* 2002; 12: 61-2.
7. Uberoi HS, Dugal JS, Kasthuri AS *et al*. Acute Renal Failure in Severe Exertional Rhabdomyolysis. *J Assoc Physicians India* 1991; 39: 677-9.
8. Smith RF. Exertional rhabdomyolysis in naval officer candidates. *Arch Intern Med* 1968; 121: 313-9.
9. Talaie H, Emam-Hadi M, Panahandeh R *et al*. On the mechanisms underlying poisoning-induced rhabdomyolysis and acute renal failure. *Toxicol Mech Methods* 2008; 18 (7): 585-8.

Disseminated tuberculosis with immune thrombocytopenia

Bimal K Agrawal, Gaurav Aggarwal**, Charu Batra Atreja***, Aruna Bhagat Dubey***

Abstract

Thrombocytopenia as a manifestation of tuberculosis is very rare. We report a 22-year-old male who presented with fever of about two months duration, cough with sputum since 15 days and an abnormal chest X-ray findings with thrombocytopenia. There was no lymphadenopathy, hepatosplenomegaly. Bone marrow examination revealed normal maturation of myeloid and erythroid series with megakaryocytic thrombocytopenia. There was granulomatous infiltration of bone marrow. Chest X-ray showed miliary shadows and contrast-enhanced CT of the chest was suggestive of tuberculosis, and MRI brain showed features suggestive of tuberculoma. A diagnosis of disseminated tuberculosis with immune thrombocytopenia was made. High-dose steroid therapy along with antitubercular treatment corrected the thrombocytopenia.

Key words: Tuberculosis, thrombocytopenia, steroid therapy.

Introduction

Tuberculosis (TB) keeps on challenging the advances in medicine and surging ahead. The WHO (World Health Organisation) gave a call to 'Unite to End Tuberculosis' (theme for World TB Day, 2016) to fight this menace. Though we seem to know so much about this 'great mimic', it can still challenge our clinical acumen and ability. We are presenting here a case of disseminated tuberculosis with immune thrombocytopenia as one of its initial manifestations. The patient had responded well to antitubercular drugs supported by steroid therapy.

Case report

A 22-year-old male presented to our institute in January 2016 with the chief complaints of fever of two months duration and cough with sputum for 15 days. There was significant loss of appetite and weight loss. Before coming to us, the patient had received antipyretics, analgesics, and antitubercular drugs (ATT) probably based on the miliary shadows in the chest X-ray. Patient continued to have all the symptoms. ATT had been stopped after 10 days for unknown reasons. About two weeks later, the patient attended our out-patient department and was admitted for further evaluation.

The investigations done elsewhere before starting ATT showed haemoglobin (Hb) - 13.6 gm%, total leukocyte count (TLC) - 8,900/cmm, platelet count of 65,000/cmm. All the routine investigations were done again with haemogram showing thrombocytopenia (platelets - 40,000/cumm) with normal haemoglobin and leukocyte counts. Chest X-ray was done which showed miliary shadows with minimal left-sided pleural effusion. Contrast-

enhanced computed tomography (CECT) chest also supported the diagnosis of military tuberculosis. Serological tests for HIV, dengue, HBsAg, anti HCV antibody and antinuclear antibodies were negative. The peripheral blood smear examination was negative for the malarial parasite. Bone marrow biopsy was done which showed granulomatous infiltration of bone marrow suggestive of tuberculosis (Fig. 1) with normal megakaryocytes (Fig. 2). The patient was diagnosed as a case of disseminated tuberculosis with thrombocytopenia. Patient was started on daily regimen of first line antitubercular drugs (isoniazid, rifampicin, pyrazinamide, ethambutol).

After a few days, the patient started developing headache with alteration in sensorium. Repeated platelet count was hovering around 40,000 - 50,000/cumm. Urgent magnetic resonance imaging (MRI) was done to rule-out the possibility of intracerebral bleed in view of accompanying thrombocytopenia. MRI showed tiny lesions suggestive of granulomas in right high frontal region, right insular cortex, and left basifrontal regions, with minimal perilesional oedema consistent with tuberculosis. Prednisolone was started, at a dose of 1 mg/kg body weight per day after breakfast, in view of the imaging findings and literature search suggested thrombocytopenia to be an indication for steroid therapy. There was improvement in the sensorium and the patient became afebrile. Two weeks after ATT and steroid therapy, platelet count showed improving trends. Patient was discharged with a diagnosis of disseminated tuberculosis with immune thrombocytopenia. On subsequent follow-up, steroid was tapered and stopped. Three months after starting ATT and five weeks after stopping steroids, the patient's platelet count remains normal. Appetite had improved and weight gain was noted.

***Professor and Head, Department of Medicine, **Department of Medicine, ***Department of Pathology, MM Institute of Medical Sciences and Research, MM University, Mullana - 133 207, Haryana.**

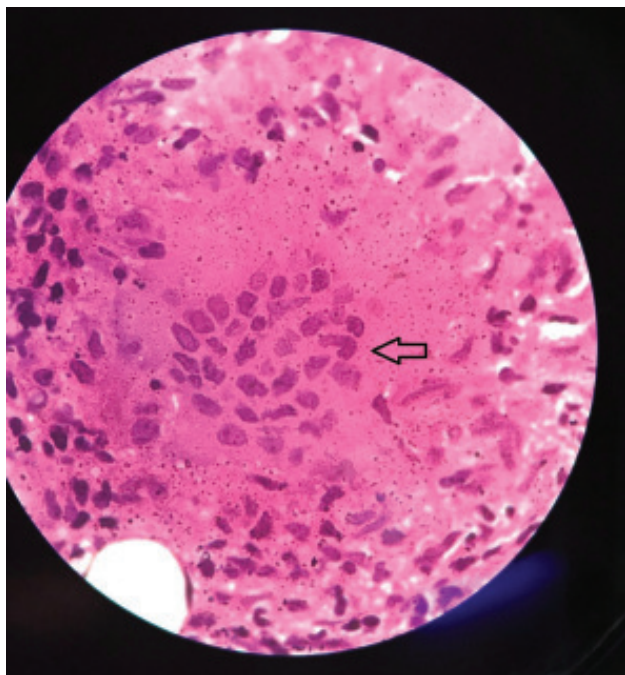


Fig. 1: Showing granuloma formation.

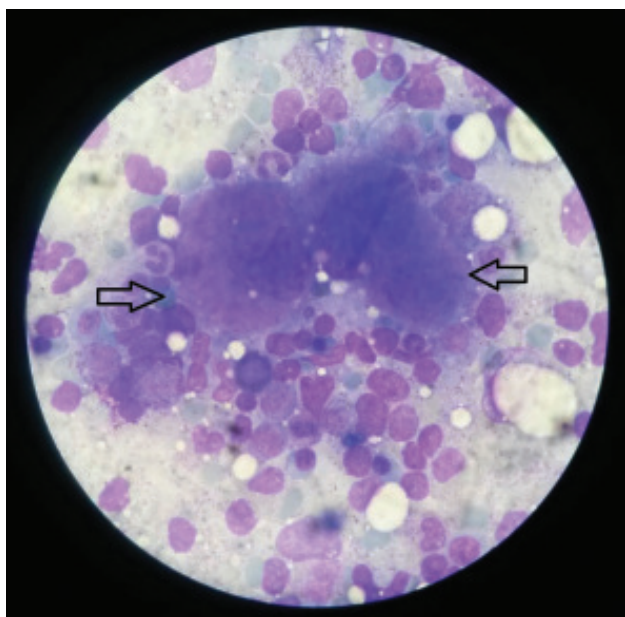


Fig. 2: Showing normal megakaryocytes.

Discussion

Tuberculosis differs from many other infectious maladies in having particular social and geographic distributions. The disease was under control in developed nations and getting under control in developing nations, until the emergence of HIV infection and the advent of multidrug resistant strains of mycobacteria¹⁻³. India is the country

with the highest burden of TB.

The World Health Organisation (WHO) statistics for 2014 gave an estimated incidence of 2.2 million cases of TB in India out of a global incidence of 9 million. Various haematologic abnormalities such as anaemia, leucocytosis, monocytosis, lymphopenia, leukopenia, thrombocytopenia, thrombocytosis, leukemoid reactions and pancytopenia have been seen in tuberculosis^{4,5}. Severe thrombocytopenia as one of the presenting features of tuberculosis is extremely rare. There are a few reports about tuberculosis associated immune thrombocytopenia published in the world literature⁶⁻¹⁰.

There are only a few clinical situations where tuberculosis may be associated with thrombocytopenia. Patients under steroid therapy for immune thrombocytopenia may develop tuberculosis. In other cases, thrombocytopenia was induced by haemophagocytic syndrome or invasion of the bone marrow because of disseminated tuberculosis^{11,12}. On the other hand, thrombocytopenia as a side-effect of anti-tubercular drugs has also been reported, with rifampicin inducing thrombocytopenia at a relatively high frequency compared to other drugs¹³. It seems intermittent dosing schedule of rifampicin is more likely to cause thrombocytopenia. We chose to give daily regimen of antitubercular drugs for the patient.

Immune thrombocytopenia may occur secondary to viral infections like hepatitis C, dengue, HIV. These possibilities were ruled out in the present case. Autoimmune disorders and lympho-proliferative disorders may have immune thrombocytopenia, and being immune-suppressed condition may have associated tuberculosis. But the patient did not have any such condition. Recently association of *H. pylori* infection with immune thrombocytopenia has been reported. Eradication of *H. pylori* infection may lead to remission of thrombocytopenia¹⁴. Because of lack of facility, possibility of associated *H. pylori* infection could not be ruled-out. However, the patient had responded to ATT and steroid treatment. The platelet count had remained normal even after the stoppage of corticosteroid. Low platelet counts were clearly associated with the activity of disseminated tuberculosis in the present case. In a study by al-Majed *et al*, out of 846 patients with tuberculosis, only 9 were accompanied by immune thrombocytopenia¹⁵. There is a consistently positive response to steroid therapy^{16,17}. Intravenous immunoglobulin can be used in case of side-effects or nonresponsiveness to steroid treatment. The exact mechanism of immune thrombocytopenia in tuberculosis is not known. However, the possibility of the molecular mimicry between an unknown tuberculosis-specific protein and platelet membrane could be considered.

To conclude, thrombocytopenia may be associated with

tuberculosis due to various reasons. If the patient has immune suppressed status, due to underlying disease or due to steroid therapy as in case of ITP, he may develop tuberculosis. ATT – rifampicin in particular – may lead to thrombocytopenia. Tuberculosis may be disseminated to bone marrow and cause thrombocytopenia. Though underlying immune mechanism of thrombocytopenia is not known, a gratifying response to steroid administration has been observed. Intravenous immunoglobulin is an alternative option for treatment of immune thrombocytopenia.

Reference

1. Enarson DA, Murray JF. Global epidemiology of tuberculosis. In: Tuberculosis Edited by: Rom WN, Garay S. New York, Little, Brown and Comp; 1996; 57-76.
2. Aaron L, Saadoun D, Calatroni I *et al.* Tuberculosis in HIV-infected patients: a comprehensive review. *Clin Microbiol Infect* 2004; 388-98.
3. Paolo WF Jr, Nosanchuk JD. Tuberculosis in New York city: recent lessons and a look ahead. *Lancet Infect Dis* 2004; 4: 287-93.
4. Goldenberg AS. Hematologic abnormalities and mycobacterial infections. In: Tuberculosis Edited by: Rom WN, Garay S. New York, Little, Brown and Comp; 1996; 645-55.
5. Mert A, Bilir M, Tabak F *et al.* Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. *Respirology* 2001; 6: 217-24.
6. Ghobrial MW, Albornoz MA. Immune thrombocytopenia: a rare presenting manifestation of tuberculosis. *Am J Hematol* 2001; 67: 139-43.
7. Spedini P. Tuberculosis presenting as immune thrombocytopenic purpura. *Haematologica* 2002; 87 (2): ELT09.
8. Madkaikar M, Ghosh K, Jijina F *et al.* Tuberculosis and immune thrombocytopenia. *Haematologica* 2002; 87 (8): ELT38.
9. Tongyoo S, Vilaichone W, Sukpanichnant S *et al.* Thrombocytopenic purpura associated with military tuberculosis. *J Med Assoc Thai* 2003; 86: 976-80.
10. Bakhshi S, Kabra M, Iyer VK *et al.* Thrombocytopenic purpura as a presenting manifestation of tubercular lymphadenitis. *Indian J Pediatr* 2003; 70: 993-94.
11. Browett PJ, Varcoe AR, Fraser AG *et al.* Disseminated tuberculosis complicated by the hemophagocytic syndrome. *Aust N Z J Med* 1988; 18: 79-80.
12. Mert A, Bilir M, Tabak F *et al.* Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. *Respirology* 2001; 6: 217-24.
13. Mehta YS, Jijina FF, Badakere SS *et al.* Rifampicin-induced immune thrombocytopenia. *Tubercle and Lung Disease* 1996; 77 (6): 558-62.
14. Emilia G, Longo G, Luppi M *et al.* *Helicobacter pylori* eradication can induce platelet recovery in idiopathic thrombocytopenic purpura. *Blood* 2001; 97: 812-4.
15. al-Majed SA, al-Momen AK, al-Kassimi FA *et al.* Tuberculosis presenting as immune thrombocytopenic purpura. *Acta Haematol* 1995; 94: 135-8.
16. Ghobrial MW, Albornoz MA. Immune thrombocytopenia: a rare presenting manifestation of tuberculosis. *Am J Hematol* 2001; 67: 139-43.
17. Tsuru K, Kojima H, Mitoro A *et al.* Immune thrombocytopenic purpura associated with pulmonary tuberculosis. *Intern Med* 2006; 45: 739-42.

***The most important kind of freedom
is to be what you really are.***

– JIM MORRISON.

An unusual presentation of rib caries without pleuro-pulmonary tuberculosis in an old male mimicking rib secondaries

Pashaura Singh*, Riputapan Singh, Saurabh Agarwal***, Khushvinder Sherry***, NS Neki******

Abstract

Introduction: Rib caries is an extremely rare condition with the incidence not exceeding 3% of all skeletal tuberculosis. We report an unusual presentation of rib caries without pleuropulmonary tuberculosis in an old male mimicking rib secondaries.

Case presentation: A 74-year-old man presented with complaints of pain in the right parasternal area along with swelling which increased gradually since 1 month. Chest X-ray along with ultrasound of the abdomen showed a fracture and destruction of the rib on the right side with surrounding collection. Fine needle aspiration cytology (FNAC) of the swelling along with the culture revealed the mass to be caries of the rib with growth of *Mycobacterium tuberculosis* from the pus aspirated. Chest X-ray and CT scan of the chest revealed no abnormality of the lung parenchyma. The patient was put on antitubercular drugs for a period of 1 year. No rib resection was performed. A follow-up CT of the chest revealed caries rib with slight sclerosis with cortical break in the anterior end of the 8th rib without any pulmonary involvement. The patient has improved and has been on regular follow-up since then.

Conclusion: This case report highlights the fact that primary or secondary tuberculosis should be considered as one of the aetiological factors in the causation of localised rib destruction which is very uncommon and also underlines the importance of CT Chest and FNAC along with pus culture as important imaging modalities in the diagnosis of caries ribs. This case also highlights the fact that not all patients require surgical intervention and can be managed conservatively on antitubercular therapy.

Key words: Fine needle aspiration cytology (FNAC), CT chest, *mycobacterium tuberculosis*, antitubercular drugs.

Introduction

Tuberculosis (TB) is an ancient disease that has long been a major public health challenge. The disease is now increasing in frequency in the developed world due to increased world migration and the AIDS epidemic. In addition to classical pulmonary TB, atypical presentation is becoming more common. Skeletal tuberculosis accounts for 1 - 5% of all tuberculosis infections. Of these infections, 50% involve the vertebral column and only 0 - 5% involve ribs¹. Rib tuberculosis is seen in only 0.1% of all tuberculosis infections. The rarity of rib tuberculosis may be attributed to its insidious onset, which often occurs up to 18 months after infection, and to the lack of other organ involvement while < 50% of patients have active pulmonary disease. Chest radiography may be insensitive in detecting early skeletal disease. The diagnosis is often delayed until osseous destruction is seen or palpable chest wall masses develop². Here, we report a case of an unusual presentation of rib caries without pleuropulmonary tuberculosis in an old male mimicking rib secondaries.

Case report

A 74-year-old military personnel, non-smoker, non-alcoholic, and non-diabetic, non-hypertensive, non-obese, with moderate daily activity and no significant past medical

history, presented to the medical out-patient department of Guru Nanak Dev Hospital attached to the Government Medical College, Amritsar, with the chief complaint of a small swelling in the right hypochondrium since 1 month duration, which increased gradually, associated with dull aching pain which aggravated on deep inspiration. There were no complaints of any breathlessness, or palpitation. There was history of significant weight loss and myalgias. But he did not complain of any fatigue, exertional dyspnoea, fever, dizziness, cough with sputum production, joint pains or back pains. There was no history suggestive of malignancy of any part of the body or drug abuse. There was no past history or family history of tuberculosis or any antitubercular drug intake. The patient's blood pressure at presentation was 124/60 mm Hg, pulse was 94/min, regular, and good volume. All the peripheral pulses were equally palpable. There was no tachypnoea, pallor or postural hypotension. Local examination of the swelling revealed a slightly tender non fluctuant mass of about 3 x 3 x 3 cms with no evidence of inflammation. The swelling was not attached to the skin. Examination of the respiratory system revealed no abnormality. The breath sounds were vesicular in both the lung fields, and there was no evidence of pleural effusion. No cardiac abnormality was detected on the ECG. Routine investigations revealed haemoglobin - 11.6 gm/dl, total leukocyte count was - 6,400 cells/mm³, differential

Assistant Professor, ***Post-Graduate Student, *Professor, Department of Medicine, Government Medical College and Guru Nanak Dev Hospital, Amritsar, Punjab; **Medical Officer, Modern Hospital Jalandhar, Punjab.**

leukocyte count: neutrophil 69%, lymphocyte 28%, monocyte 1%, eosinophil 2%; erythrocyte sedimentation rate 40 mm at first hour; total red blood cell count 4.25 million/mm³; platelet count 190,000/mm³. Peripheral blood film examination showed normocytic, normochromic blood picture. Serum sodium 128 mEq/l, serum potassium 4.1 mEq/l, blood urea 25 mg/dl, serum creatinine 0.8 mg/dl, serum calcium 8.7 mg/dl, serum phosphorous 3.4 mg/dl. The liver function tests were within normal limits. Urine examination was unremarkable. Sputum for AFB was negative. A chest roentgenogram showed evidence of erosion of right 8th rib. Lung parenchyma and the heart were normal on X-ray and no evidence of any mass was seen (Fig. 1).

The abdominal and chest ultrasonogram revealed an echo-poor collection measuring approximately 46 x 33 mm in size along one of the lower anterior rib on the right side. There was no evidence of intra-abdominal malignancy (Fig. 2).

X-ray of the dorso-lumbar spine revealed no abnormality and the levels of prostate specific antigen and anti-nuclear antibodies were normal. CT scan of the chest showed caries rib with slight sclerosis with cortical break in the anterior end of the 8th rib without any pulmonary involvement (Fig. 3 and 4).

Fine needle aspiration cytology of the swelling was performed where yellowish pus-like fluid was aspirated which showed granulomatous reaction. Mycobacterium tuberculosis was grown from the pus aspirated in the third week which was found to be sensitive to all first-line antitubercular drugs along with 2nd-line drugs such as aminoglycosides, ethionamide, and PAS.

The patient was put on category I antitubercular therapy



Fig. 1: Chest X-ray showing erosion of right 8th rib.



Fig. 2: USG showing destruction of lower anterior rib on the right side with surrounding collection.

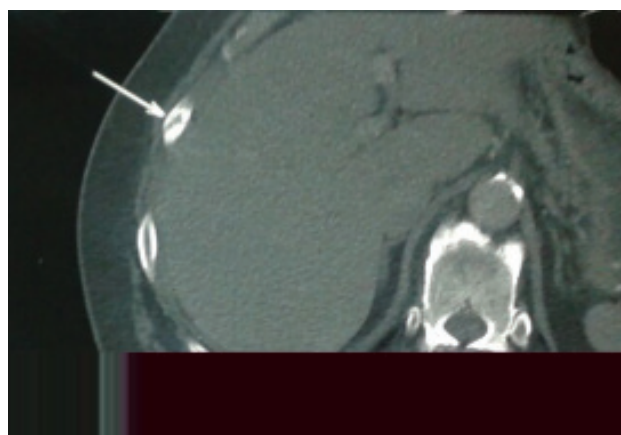


Fig. 3: CECT chest showing slight sclerosis with cortical break of the anterior end of 8th rib on the right side.



Fig. 4: CECT chest showing mediastinal lymphadenopathy.

consisting of isoniazid (300 mg/day), rifampicin (600 mg/day), pyrazinamide (1,500 mg/day), ethambutol (900 mg/day) as intensive phase for a period of two months and then was switched to continuation phase consisting of the same dosage of Isoniazid and rifampicin for a period of 10 months. The patient has been asymptomatic since then.

Discussion

Tuberculosis (TB) has been a major cause of morbidity and mortality, especially in the developing parts of the world. After an initial dramatic response to antitubercular therapy (ATT), the disease has started to resurge. The problem is still more alarming due to the emergence of multi-drug resistant cases and association of TB with AIDS³. Tuberculosis of the ribs usually presents with rib destruction and extrapulmonary soft tissue mass. Rib involvement may occur by direct extension from lungs or haematogenous spread from a distant focus. Parenchymal lung lesion was not found adjacent to the involved rib in our case. Studies by Davies *et al*⁴ and Kalley⁵ failed to find any parenchymal lung lesion. The dominant clinical presentation in our patient was presence of a dull aching superficial mass which was in harmony with studies done by Halsey *et al*⁶. Radiologically, presence of an osteolytic lesion, widening of the rib with periosteal reaction, and presence of sequestrum indicate TB rib⁷. X-ray chest and ultrasound of the patient showed a localised rib destruction with a superficial collection (Fig. 1). CT scan showed osteolytic expansile lesions with varying degrees of rib destruction. Also typically found are well-defined juxta-costal soft tissue masses of low attenuation on both sides or on the inner aspect of ribs, with peripheral rim enhancement, the so-called cold abscess (Fig. 3)⁸. In our patient CT scan of the chest was useful in demonstrating the skeletal lesion and delineating the extent of the disease. FNAC of the swelling along with culture and antibiotic sensitivity testing confirmed the lesion to be a caries of the ribs. Chang *et al*⁹ confirmed TB in all of their twelve cases only following rib resection. Faure *et al*¹⁰ reported FNAC as an inaccurate diagnostic tool. The patient in our case was put on antitubercular therapy for a period of 1 year which showed complete resolution of his symptoms. The patient was not subjected to any surgical intervention. Studies done by Mathlouthi *et al*¹¹ also suggested that surgery is rarely indicated and ATT is all that is necessary once the diagnosis is established by histology.

Conclusion

This is a case of unusual presentation of rib caries without pleuro-pulmonary tuberculosis in an old male mimicking rib secondaries. This case report highlights the fact that primary or secondary tuberculosis should be considered as one of the aetiological factors in the causation of localised rib destruction which is very uncommon and also underlines the importance of CT chest and FNAC along with pus culture as important imaging modalities in the diagnosis of caries ribs. This case also highlights the fact that not all patients require surgical intervention and can be managed conservatively on antitubercular therapy.

References

1. Ip M, Chen NK, So SY *et al*. Unusual rib destruction in pleuropulmonary tuberculosis. *Chest* 1989; 95: 242-44.
2. Lee SH, Abramson SB. Infections of the musculoskeletal system by M. tuberculosis. In: Rom WN, Garay SM, eds. *Tuberculosis*. New York: Little Brown, 1996; 635-44.
3. Trombati N, Afif H, El Farouki Z *et al*. Parietal thoracic tuberculosis in the absence of immunosuppression by HIV infection. *Rev Mal Respir* 2001; 18: 301-4.
4. Davies PDO, Humphries MJ, Byfield SP *et al*. Bone and joint tuberculosis - a survey of notification in England and Wales. *J Bone Joint Surg* 1984; 66: 326-30.
5. Kalley MA, Micozzi MS. Rib lesions in chronic pulmonary tuberculosis. *Am J Phys Anthropol* 1984; 65: 381-86.
6. Halsey JP, Reeback JS, Barnes CG. A decade of skeletal tuberculosis. *Ann Rheum Dis* 1982; 41: 7-10.
7. Khalil A, Le Breton C, Tassart M *et al*. Utility of CT-scan for the diagnosis of chest wall tuberculosis. *Eur Radiol* 1999; 9: 1638-42.
8. Lee G, Im JG, Kim JS *et al*. Tuberculosis of the ribs: CT appearance. *J Comput Assist Tomogr* 1993; 17: 363-66.
9. Chang DS, Rafii M, McGuinness G *et al*. Primary multifocal tuberculous osteomyelitis with involvement of the ribs. *Skeletal Radiol* 1998; 27: 641-45.
10. Faure E, Souilamas R, Riquet M *et al*. Cold abscess of the chest wall: a surgical entity? *Ann Thorac Surg* 1998; 66: 1174-78.
11. Mathlouthi A, Ben M, Rad S *et al*. Tuberculosis of the thoracic wall. Presentation of four personal cases and review of the literature. *Rev Pneumol Clin* 1998; 54: 182-86.

***The only way to save a rhinoceros is to save the environment in which it lives,
because there's a mutual dependency between it and
millions of other species of both animals and plants.***

— DAVID ATTENBOROUGH.

Levels of vitamin D in patients with HIV infection and its correlation with CD4 cell counts

RS Taneja*, Pulin Kumar Gupta, Afroz Jamal***, Ashok Kumar****, BB Rewari*****, Anubhuti*****, Jyoti Aggarwal*****

Introduction

Since the first detection of acquired immunodeficiency syndrome (AIDS) case in 1981 among homosexuals in the USA, the numbers of human immunodeficiency virus (HIV) positive individuals and AIDS cases have increased tremendously¹. The estimated adult HIV prevalence in India was 0.32 per cent (0.26% - 0.41%) in 2008 and 0.31 per cent (0.25% - 0.39%) in 2009. Analysis of epidemic projections revealed that the number of new annual HIV infections has declined by more than 50 per cent during the last decade². More than 90% of HIV-infected people live in areas of the world where nutritional deficiencies are also highly prevalent, and the interactions between HIV and nutritional status have been widely documented. Deficiencies of several micronutrients have been associated with increased rates of progression to AIDS and HIV-related mortality, and selected nutritional interventions including supplementation with vitamins B, C, D and E have been found to decrease the risk of HIV disease progression and AIDS-related deaths. The beneficial effect of vitamin supplements on health and survival outcomes among HIV-infected persons is likely to be mediated by enhancements in specific aspects of immunity that include increases in CD4+ cell counts and reduced viral loads³.

Although the incidence of new HIV infections is decreasing but because of universal availability of ART, people are living longer with HIV/AIDS and thus are experiencing more side-effects of long-term ART. Cardiovascular diseases, osteoporosis, peripheral neuropathy, depression, dementia, stroke and many other chronic disorder are now being seen more frequently in HIV/AIDS patients as compared to general populations. Amongst these disorders hypovitaminosis D is now a common accompaniment of patients with HIV/AIDS and is associated with increase occurrence most of above mentioned chronic disorders along with certain cancers.

Vitamin D is an essential fat-soluble steroid hormone. Humans get vitamin D from exposure to sunlight and from their diet or dietary supplements. Both endogenously

synthesised vitamin D3 and dietary vitamin D are transported to the liver, where they are metabolised to 25-hydroxyvitamin D, major circulating metabolite and a marker for determination of a patient's vitamin D status. Bone and skeletal muscle, brain, prostate, breast, and colon tissues as well as immune cells have vitamin D receptors. Vitamin D has been associated with bone growth, regulation of cellular proliferation of both normal cells and cancer cells, differentiation, apoptosis, and angiogenesis⁴.

Advanced age, lack of sun exposure, residence at higher altitude, dark skin pigmentation, malnutrition, obesity, and certain medications leading to increased catabolism of vitamin D such as anticonvulsants, glucocorticoids and many others are associated with vitamin D deficiency. Vitamin D has a significant role in decreasing the risk of chronic illness, including osteoporosis, common cancers, and cardiovascular diseases⁴. These disorders are now being increasingly recognised in HIV-infected patients because as previously discussed these patients are living longer in the era of highly active antiretroviral therapy (HAART)⁵. Vitamin D is a potent immunomodulator of both innate and adaptive immunity with receptors found on monocytes, macrophages, as well as T lymphocytes and B lymphocytes⁶. Low levels of 25-hydroxycholecalciferol have been associated with an inability of macrophages to initiate innate immune response and so increased propensity to develop AIDS and severe OI (i.e., faster progression to higher stage of HIV infection)⁷.

Vitamin D inadequacy has been reported in approximately 36% of otherwise healthy young adults and up to 57% of general medicine inpatients in the United States⁸ and in even higher percentages in India. Studies have shown that every 1 microgram of vitamin D in the diet was associated with a significant increase of 34 CD4+ cells⁹. Low vitamin D status (serum 25-hydroxyvitamin D < 32 ng/ml) was significantly associated with progression to WHO HIV disease stage III or greater in multivariate models. Vitamin D status had a protective association with HIV disease progression, all-cause mortality, and development of anaemia during follow-up in HIV-infected women¹⁰.

Professor and Head, **Associate Professor, ***Senior Resident, *Ex-Professor, *****Associate Professor, Department of Medicine, *****Assistant Professor, Department of Biochemistry, PGIMER, Dr. Ram Manohar Lohia Hospital, Baba Khark Singh Marg, New Delhi - 110 001.**

Materials and methods

After clearance from institutional ethical committee this cross sectional observational study was conducted at ART centre, department of medicine, PGIMER, Dr RML hospital. A total of 170 diagnosed patients of HIV/AIDS with or without ART were included in this study. Patient taking any medication which affects bone/calcium metabolism or on Vitamin D supplementation were excluded. Patients who had diabetes mellitus or liver or kidney dysfunction were similarly excluded from this study.

All the patients were evaluated as per the standard protocol of history, physical examination and underwent routine baseline investigations viz CBC, KFT, LFT, plasma glucose (both fasting and post-prandial), lipid profile, serum proteins, VDRL, anti-HCV, HBsAg, CD4 counts and 25-hydroxy vitamin D levels after an overnight fasting. Vitamin D deficiency was defined as fasting serum 25 (OH) D levels below 20 ng/ml and vitamin D insufficiency was defined as fasting serum 25 (OH) D levels of 21 - 29 ng/ml¹¹, and levels > 30 ng/ml were taken as normal. Proposed objective was to study the vitamin D levels in HIV-infected individuals and to assess its correlation with CD4-cells counts (a direct marker of immune status).

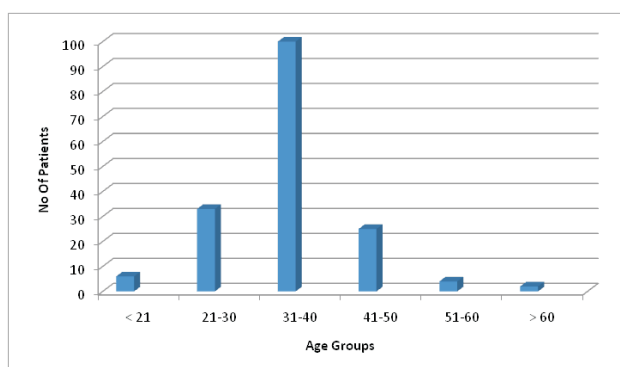


Fig. 1: Distribution of patients in age groups.

Observations and results

Amongst the study group of 170 patients 134 were males (78.8%) and 36 females (21.2%). The mean age of patients was 35.54 ± 8.05 years ranging between 19 and 70 years. Maximum patients were in 31 to 40 years of age group.

97% of our patients acquired HIV infection through sexual route of transmission. The mean duration of disease was 3.28 ± 2.08 years, ranging between zero to thirteen years. Out of 170 patients 127 (74.7%) patients were on ART and 43 (25.3%) were not taking ART, 162 (95.3%) were non vegetarians and 8 (4.7%) were pure vegetarians. Among 170 HIV-infected individuals, 10 (5.88%) were reactive for HBsAg, 1 (.6 %) was reactive for anti HCV and 7 (4.12%) were reactive for VDRL.

The mean CD4 counts in the study was $249.30 \pm 18.67/\mu\text{l}$, ranging between 3 and 1,141/ μl . On the basis of CD4 counts patients were divided into three groups as described in the Table.

Table I:

CD4 counts ¹²	Hiv associated immunodeficiency	Group	Frequency
< 200/mm ³	Severe	A	81 (47.65%)
200 - 349/mm ³	Advanced	B	53 (31.18%)
$\geq 350/\text{mm}^3$	Mild	C	36 (21.18%)
Total	Total	Total	170

The mean vitamin D levels in the study group was 11.26 ± 5.49 ng/ml ranging between 3.44 ng/ml to 31.20 ng/ml. The prevalence of vitamin D deficiency [25 (OH) D < 20 ng/ml] among all patients was 93.53% (159/170) and vitamin D insufficiency [25 (OH) D 21 - 29 ng/ml] was 5.30% (9/170). Almost 99% of patients had hypovitaminosis-D. There was no significant difference between the mean vitamin D levels in males and females, the mean values being 11.47 ± 5.37 ng/ml and 10.48 ± 5.89 ng/ml respectively (p - value = 0.388). There was no statistically significant correlation between vitamin D levels and CD4 cells counts although the mean vitamin D levels in group A, B and C was 10.43 ± 4.98 ng/ml, 11.89 ± 6.01 ng/ml, 12.21 ± 5.64 ng/ml respectively which was shown to increase with increasing CD4 counts. However, the difference in mean vitamin D levels in group A, B and C was not statistically significant (p - value = 0.161).

Table II: Distribution of patients according to vitamin D levels and CD4 cells counts in different groups.

Groups	Vit D < 20 ng/ml	Vit D - 21 - 29 ng/ml	Vit D > 30 ng/ml	Mean Vitamin D (ng/ml)	Mean CD4 counts (mm ³)
A	77	4	0	10.43 ± 4.98	109.78 ± 51.40
B	49	3	1	11.89 ± 6.01	269.98 ± 45.24
C	33	2	1	12.21 ± 5.64	532.78 ± 175.90
Total	159	9	2	11.26 ± 5.49	249.30 ± 186.74

The mean value of vitamin D in males of group A, B and C was 10.82 ± 5.19 , 11.83 ± 4.94 and 12.31 ± 5.96 respectively and in female it was 8.72 ± 3.55 , 10.72 ± 6.25 , 13.79 ± 8.25 respectively. As we can see that males had higher vitamin D levels as compared to females in group A and B although the difference was not statistically significant.

Serum calcium levels and vitamin D levels in non vegetarians were more but this difference as compared to vegetarians was not statistically significant.

Amongst 127 patients taking ART mean vitamin D levels were 11.54 ± 5.97 ng/ml and in patients not taking ART mean vitamin D levels were 10.45 ± 3.63 ng/ml. No specific group of drugs used as part of 1st-line ART in NACO Indian guidelines was shown to correlate with high or low values of vitamin D. Although the vitamin D levels were more in patients on ART; however, the difference in mean vitamin D levels was not statistically significant (p -value = 0.263). Patients who were on ART had higher levels of serum cholesterol and LDL ($p < 0.05$) as compared to those not on ART. Similarly, patients who had higher CD4 counts and vit D levels had higher haemoglobin levels ($p < 0.05$).

Discussion

Vitamin D is an essential vitamin which also acts as a hormone and has role in regulating the proliferation and functions of macrophages, dendritic cells, and activated T and B lymphocytes. CD4+ T-helper cells are white blood cells that are an essential part of the human immune system. CD4-cells send the signal and CD8-cells destroy and kill the infection or virus. If CD4-cells become depleted, for example in untreated HIV infection the body is left vulnerable to a wide range of infections and is not able to fight with invading organism. HIV infection causes a progressive decrease in the number of T-cells expressing CD4-cells. CD4 count is used to assess the immune status of a patient and also used to determine the efficacy of HAART. Vitamin D is known to have direct impact on immune cells (CD4- and CD8-cells) and is indirectly associated with inhibition of viruses and bacteria by this function.

Amongst our 170 HIV positive patients a total of 93.53% individuals had vitamin D deficiency and vitamin D insufficiency was noted in 5.30% of patients, where as only 1.17% of patients were noted to have sufficient vitamin D levels. The results of present study corresponds to previous studies, which reported a high prevalence of low vitamin D levels in HIV-infected individuals. Borderi M *et al* reported 61% prevalence of hypovitaminosis D in HIV positive patients living in western countries¹³. Poudel-Tandukar *et al* (2013) did a cross-section survey in Kathmandu valley, Nepal and found that the prevalence of 25 (OH) D serum levels less than 20 ng/ml was 83.2%¹⁴. This was similar to study by Crutchley *et al* who found that, two-thirds (64%) of HIV-infected patients had vitamin D insufficiency and 20.5% had severe vitamin D deficiency (a total of 84% patients had hypovitaminosis D)¹⁵. In our study we found that hypovitaminosis D is present in approximately 99% which is much more than previous studies. High prevalence of hypovitaminosis D in our study may be due to the dark skin colour of Indian that corresponds to the previous study described by Kim *et al* who stated that the presence of dark

skin was significantly associated with vitamin D deficiency¹⁶. Adeyemi *et al* found that 63% HIV-infected woman had vitamin D deficiency and African American women had the highest rates of vitamin D deficiency¹⁷. Stein *et al* found that the levels of 25 (OH)D was significantly lower in African American subjects as compared to Hispanic subjects¹⁸. All of the above studies showed that the dark skin coloured individuals had lower vitamin D levels as compared to fair skinned individuals. Our study was conducted on Indian people who are ethnically black and have dark skin colour and exposure to sun is limited. Limited outdoor activities and increasing sedentary lifestyle further compounds this problem in a metropolitan city population. Also with increasing pollution cover in Delhi the sun rays are not able to penetrate and reach ground level in Delhi, further limiting synthesis of vit D (cutaneous route).

In general population, the prevalence of hypovitaminosis D is approximately 80% as shown by the previous studies, but in our study, the prevalence of hypovitaminosis D is approximately 99% and this shows that in HIV-infected patients, prevalence of hypovitaminosis D is higher than general population. This may be due to HIV infection per se which may have some role in hypovitaminosis D. HIV-infected patients share common risk factors for vitamin D deficiency with general population, i.e., ageing, low sunlight exposure, dark coloured skin, low consumption of fortified foods, malnutrition, etc. A probable explanation to this increased risk is HIV virus itself or accompanying opportunistic infections or malnutrition or inflammation in various tissues which are universal in HIV/AIDS patients. Virus produces pro-inflammatory cytokines such as TNF-alpha and interferon gamma which can interfere with the enzymes of vitamin D pathway. Interferon gamma induces the enzyme 1-alpha-hydroxylase in macrophages directly or indirectly via toll like receptors (TLRs) which leads to a decrease in levels of vitamin D 25 (OH). In our study most of the patients were on ART and it has been reported that ART itself interferes with the metabolism of vitamin D, mainly 1-alpha-hydroxylase although we could not find any statistical difference.

In our study the mean vitamin D levels in group A, B and C was 10.43 ± 4.98 ng/dl, 11.89 ± 6.01 ng/dl and 12.21 ± 5.64 ng/dl respectively. This shows that vitamin D levels increase with increasing CD4 counts (and so proportionately with better immune status). This linear escalatory effect is seen throughout; however, the difference in mean vitamin D levels in group A, B and C was not statistically significant (p -value = 0.161). In our study there was statistically no significant difference in vitamin D level in the groups, hence level of immunity and immunodeficiency does not seem to influence vitamin D levels (and so vice versa). Though we have found

that a significant proportion of the patients enrolled in our study had vitamin D deficiency and the prevalence of vitamin D deficiency was the highest in patients with severe immunodeficiency, but we could not find out a significant correlation or association between CD4 counts and vitamin D levels – the reason may be, most of the study population was on ART and also most of the study population belongs to the city where vitamin D deficiency is highly prevalent and the common multiple causative factors are present in all patients. Since hypovitaminosis D is multifactorial and most of these factors were present in Indian patients so it is difficult to directly correlate CD4 levels with vitamin D levels. In the current study a correlation was observed between CD4 counts and haemoglobin level in the sense that as CD4 counts decrease, haemoglobin level decreases, this fall in haemoglobin is probably due to increase in the viral load leading to cytokine mediated myelosuppression. In our study we could not find any relationship between vitamin D levels and ART. Those patients who were on ART, the mean vitamin D level was 11.54 ± 5.97 ng/ml and in patients who were not on ART mean vitamin D levels was 10.45 ± 3.63 ng/ml. Difference in vitamin D levels was not statistically significant (p - value = 0.263). Van Den Bout-Van Den Beukel *et al* found that vitamin D status did not affect CD4-cell recovery after initiation of HAART¹⁹. De Luis *et al* found that the, every 1 microgram rise of vitamin D levels in the diet was associated with a significant increase of 34 CD4+ cells⁹. Mueller *et al* found that the vitamin D levels remained unchanged regardless of ART exposure²⁰. Stein *et al* found that no association was observed between vitamin D levels and type of ART¹⁸. In contrary to our finding, Paul *et al* found that significant proportion of patients on ART (74%) had vitamin D deficiency as compared to ART naïve (37%) patients²¹. Wasserman *et al* concluded that highly active antiretroviral therapy (NNRTI) recipient may be associated with lower vitamin D levels²².

The difference in our opinion may be because of the low number of ART naïve patients as compare to patients on ART. In addition to that since most of our patients are from Delhi which itself has high prevalence of vitamin D deficiency so a difference due to a single factor could not be brought about. Further prospective studies with large number of patients are required to confirm the effect of ART on vitamin D.

Conclusion

Increasing prevalence of vitamin D deficiency in HIV positive patients has been reported by various authors. The current study also consolidates the fact that the prevalence of

hypovitaminosis D in the HIV positive patients is approximately 99%. The study also revealed that there is no correlation of CD4 count and vitamin D levels and also there is no correlation of vitamin D levels and ART although there is a linear increase in CD4-cells counts with increasing vitamin D levels. But in view of the high prevalence of vitamin D deficiency and other data suggesting high incidence of osteoporosis, cardiovascular diseases and mental diseases in HIV-infected individuals (with or without ART), we advocate vitamin D supplementation to all HIV patients. This after corroboration with other medical studies may be recommended by health authorities and NACO (National AIDS control organisation).

References

1. CDC. Pneumocystis pneumonia - Los Angeles. *MMWR* 1981; 30: 250-52.
2. NACO annual report 2010-2011. Available at: <http://nacoonline.org>. Accessed on 15 April, 2016.
3. Fawzi WW, Msamanga GI, Spiegelman D *et al*. A randomised trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004; 351: 23-32.
4. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357: 266-81.
5. Harrison KM, Song R, Zhang X. Life expectancy after HIV diagnosis based on national HIV surveillance data from 25 states, United States. *J Acquir Immune Defic Syndr* 2010; 53: 124-30.
6. Adams JS, Hewison M. Unexpected actions of vitamin D: New perspectives on the regulation of innate and adaptive immunity. *Nat Clin Pract Endocrinol Metab* 2008; 4: 80-90.
7. Liu PT, Stenger S, Li H *et al*. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006; 311: 1770-73.
8. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; 81: 353-73.
9. de Luis DA, Bachiller P, Aller R *et al*. Relation among micronutrient intakes with CD4 count in HIV-infected patients. *Nutr Hosp* 2002; 17: 285-89.
10. Mehta S, Giovannucci E, Mugusi FM *et al*. Vitamin D status of HIV-infected women and its association with HIV disease progression, anaemia, and mortality. *PLoS One* 2010; 5: e8770.
11. Holick MF, Binkley NC, Heike A *et al*. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2011; 96: 1911-30.
12. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Available at <http://www.who.int/hiv/pub/vct/hivstaging/en/>. Accessed on 15 April, 2016.
13. Borderi M, Vescini F, Cozzi-Lepri A *et al*. prevalence of hypovitaminosis D and factors associated with vitamin D deficiency and morbidity among HIV-infected patients enrolled in a large Italian cohort. *J Acquir Immune Defic Syndr* 2011; 58: 163-72.
14. Poudel-Tandukar K, Poudel KC, Jimba M *et al*. Serum 25-hydroxyvitamin D levels and C-reactive protein in persons with human immunodeficiency virus infection. *AIDS Res Hum Retroviruses* 2013; 29: 528-34.
15. Crutchley RD, Gathe J Jr, Mayberry C *et al*. Risk factors for vitamin D deficiency in HIV-infected patients in the south central United

- States. *AIDS Res Hum Retroviruses* 2012; 28: 454-9.
16. Gandhi V, Kim JH, Psevdos G Jr *et al.* Evaluation of Vitamin D Levels among HIV-Infected Patients in New York City. *AIDS Res Hum Retroviruses* 2012; 28: 235-41.
 17. Adeyemi OM, Agniel D, French AL *et al.* Vitamin D deficiency in HIV-infected and HIV-uninfected women in the United States. *J Acquir Immune Defic Syndr* 2011; 57: 197-204.
 18. Stein EM, Yin MT, McMahon DJ *et al.* Vitamin D deficiency in HIV-infected post-menopausal Hispanic and African-American women. *Osteoporos Int* 2011; 22: 477-87.
 19. Van Den Bout-Van Den Beukel CJ, Fievez L, Michels M *et al.* Vitamin D deficiency among HIV type 1-infected individuals in the Netherlands: effects of antiretroviral therapy. *AIDS Res Hum Retroviruses* 2008; 24: 1375-82.
 20. Mueller NJ, Fux CA, Ledergerber B *et al.* High prevalence of severe vitamin D deficiency in combined antiretroviral therapy-naïve and successfully treated Swiss HIV patients. *AIDS* 2010; 24: 1127-34.
 21. Paul TV, Asha HS, Thomas N *et al.* Hypovitaminosis D and bone mineral density in human immunodeficiency virus-infected men from India, with or without antiretroviral therapy. *Endocrine Practice* 2010; 16: 547-53.
 22. Wasserman P, Rubin DS *et al.* Highly prevalent vitamin D deficiency and insufficiency in an urban cohort of HIV-infected men under care. *AIDS Patient Care STDS* 2010; 24: 223-7.

***If all mankind were to disappear,
the world would regenerate back to the rich state of equilibrium
that existed ten thousand years ago.
If insects were to vanish,
the environment would collapse into chaos.***

– E.O. WILSON.



Indian Association of Clinical Medicine

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

MEMBERSHIP / FELLOWSHIP FORM

No.

Date

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

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): E-mail:

Photograph

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. 9,000/-
(Minimum 10 Years Standing after Post-graduate Qualification or 5 years after membership).
- Life Membership Subscription: Rs. 3,000/-
(Minimum Qualification: Post-graduate Qualification as specified in the Constitution of IACM).
- Associate-Life Membership Subscription: Rs. 3,000/-
(Diploma, or Post-graduate Qualification not covered as per Constitution of IACM).
- Please attach attested photocopy of Post-graduate 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. T. P. Singh, Hony. Gen. Secretary, IACM, P.G. Department of Medicine, Sarojini Naidu Medical College, Mahatma Gandhi Road, Agra-282 002, U.P.

In Asthma and COPD

Formonide

Formonide 100 mg/200 mcg, Formonide 200 mg/400 mcg, Formonide 400 mg/800 mcg, Formonide 800 mg/1600 mcg

The Single Inhaler Therapy



MAGNEX

BORINGHER
