ANNOUNCING IACMCON-2012

Annual Conference of Indian Association of Clinical Medicine

26th-28th October, 2012 ● Hotel Ashok, New Delhi

E-mail : drmpschawla@gmail.com

Qutub Minar

Delhi Metro

Kindly send your Registration Form alongwith payment to :

Dr. M.P.S. Chawla
Organising Secretary

C/o. INITIALS
E-39, Flatted Factory Complex,
Jhandewalan, New Delhi-110 055

Dear Colleagues,

It is my proud privilege to invite you to the 20th Annual Conference of the Indian Association of Clinical Medicine scheduled to be held from 26th to 28th October, 2012 at Hotel The Ashok, New Delhi. The weather in Delhi is very pleasant and invigorating during this time of the year making it the ideal excuse for visiting the beautiful and amazing capital of India. This time the IACMCON is being organised by the Department of Medicine, PGIMER - Dr. Ram Manohar Lohia Hospital, New Delhi.

This conference will provide an excellent platform to the internists from across the country for scientific and academic exchanges and opportunity to refresh along with cultural and recreational activities in the National Capital Region of Delhi. The theme of the conference is "Skillful integration of scientific knowledge and evidence-based medicine in daily practice".

The Scientific Committee under the chairpersonship of IACM President-Elect Dr. Gursharan Sidhu is leaving no stone unturned in formulating an innovative and interactive programme covering the core knowledge and major advances in the ever-expanding field of internal medicine. A CME session on "HIV – An internist's perspective" is being held on 26th October at PGIMER - Dr. RML Hospital, New Delhi. Outstanding faculty is being selected based on their individual areas of expertise.

Overleaf is the Delegate Registration Form for your convenience. We have kept the Registration Fee to the bare minimum for your benefit. Early registration will ensure minimal registration fees (Members – Rs. 2,000/- and PGs – Rs. 1,000/-) upto 31st May, 2012.

With a warm heart and open arms, New Delhi beckons and welcomes you during this festive season!

Dr. M.P.S. Chawla
Organising Secretary, XXth IACMCON-12
Phones: 011-23404256/0-9868103623

Please use the Registration Form overleaf

IACMCON-2012 REGISTRATION FORM

Annual Conference of Indian Association of Clinical Medicine

26th-28th October, 2012 • Hotel Ashok, New Delhi

Please fill this form in CAPITAL LETTERS Date .....

For extra forms, please use photocopies of this form.

Name: .....
(First) (Middle) (Last)

Mailing Address: .....

.....

City ..... State ..... Pin Code ..... Country .....

Phones: Office ..... Residence ..... Mobile .....

E-mail: .....

IACM Membership/Fellowship No.: ..... Diet : Vegetarian ☐ Non-Vegetarian ☐

Accompanying Persons :

Dr./Ms./Mr.: ..... Diet : Vegetarian ☐ Non-Vegetarian ☐

Ms./Mr.: ..... Diet : Vegetarian ☐ Non-Vegetarian ☐

Ms./Mr.: ..... Diet : Vegetarian ☐ Non-Vegetarian ☐

How would you like us to keep you updated: ☐ E-mail ☐ SMS ☐ Post ☐ None

Delegate Registration Fee:

	Early Bird - Till 31st May, 2012	Till 31st July	From 1st August onwards
IACM Members/Fellows	₹ 2,000/-	₹ 4,000/-	₹ 5,000/-
Non-members	₹ 2,500/-	₹ 4,500/-	₹ 5,500/-
Accompanying Person	₹ 2,000/-	₹ 3,000/-	₹ 4,000/-
Post-graduate Students	₹ 1,000/-	₹ 1,500/-	₹ 2,000/-
Corporate Registration	₹ 5,000/-	₹ 7,000/-	₹ 10,000/-
Spot Registration	–	–	₹ 10,000/-

Mode of payment: ☐ Cash ☐ Cheque ☐ Demand Draft In favour of **IACMCON-2012** payable at New Delhi. Add Rs. 125/- for outstation cheque.

For online registration, please visit our website www.iacm-2012.com

Amount : Rs. ..... Rupees (in words) .....

Drawn on Bank: ..... Branch of Bank .....

Cheque/Bank Draft No:. ..... Dated: .....

For Spot Registration Delegates: Please note that Conference kit is subject to availablity.

Kindly send this Registration Form alongwith payment to

Dr. M.P.S. Chawla, Organising Secretary
C/o. INITIALS, E-39, Flatted Factory Complex, Jhandewalan, New Delhi-110 055
E-mail: drmpschawla@gmail.com • Tel. : 011-23404256 / 0-9868103623

CONTENTS

Journal, Indian Academy of Clinical Medicine • Vol. 13, Number 1, January – March, 2012

Contains 88 pages from 1 to 88 inclusive of all advertisements

CONTENTS

Journal, Indian Academy of Clinical Medicine • Vol. 13, Number 1, January – March, 2012

Contains 88 pages from 1 to 88 inclusive of all advertisements

Journal, Indian Academy of Clinical Medicine

JOURNAL, INDIAN ACADEMY OF CLINICAL MEDICINE

is edited by

Dr. D.G. Jain

for the

Indian Association of Clinical Medicine

Headquarters :

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

Editorial/Mailing Address

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

E-mail: iacmjournal@gmail.com

ISSN 0972-3560

RNI Regn. No. : DELENG/2000/1686

Indexed in Elsevier's Bibliographic Databases

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)."

Indexed Internationally on Elsevier's Bibliographic Databases (a leading indexing service) from January 2005. These databases include EMBASE, Compendex, Geobase and Scopus (Science Direct Navigator).

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

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

Indian Association of Clinical Medicine

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

GOVERNING BODY

President
Ajay Kumar (Patna)

President-Elect
Gursharan Sidhu (Ludhiana)

Immediate Past-President
Madhuchanda Kar (Kolkata)

Vice-Presidents
SK Kalra (Agra)
YS Raju (Hyderabad)

Founder President
(Permanent Invitee)
MC Gupta (Agra)

Hony. General Secretary
Ashok Shiromany (Agra)

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

Associate Editor, *JIACM*
Alladi Mohan (Tirupati)

Hony. Treasurer
Tejpal Singh (Agra)

Members
MP Singh (Agra)
Ramakant Yadav (Saifai)
Siddharth Kumar Das (Lucknow)
Dipanjan Bandyopadhyay (Kolkata)
VN Mishra (Raipur)
UN Gupta (Agra)
Naveen Kumar Soni (Ghaziabad)
Ashish Gautam (Agra)

Zonal Members

North Zone
Santokh Singh (Amritsar)

South Zone
MA Kabeer (Chennai)

East Zone
HS Pathak (Naihati)

West Zone
PK Sinha (Kota)

Central Zone
Parbhat K Agrawal (Agra)

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

Organising Secretary
(IACMCON-2011)
RP Shrivastwa (Patna)

Joint Secretaries
Krishna Kumar (Patna)
Prashant Prakash (Agra)
MPS Chawla (New Delhi)

VIEWPOINT

JIACM 2011; 13(1): 11-4

What is science, anyway?

*BM Hegde**

"It's supposed to be a secret, but I'll tell you anyway. We doctors do nothing. We only help and encourage the doctor within".

– Albert Schweitzer.

Science is only a method. The method – making use of all the human faculties to understand the working of nature – called science, gives mankind greater insight into the working of this enigma called the universe. With better understanding and better technology, naturally newer things come to light in science. Therefore, science is, per force, a constant change. That which does not change does not qualify to be science. With the advent of the magnifying glass and the microscope we could see newer things like germs, etc. With electron microscopic magnification, subtler things came to light. Science has gone to the nano and piko levels of understanding but the Giga problems of the world like poverty, illiteracy, ignorance, and illness still stare us at the face in the 21st century. That is a curse, indeed.

We have no scope yet to fathom the human mind, at the bottom of which are the emotions of greed, anger, pride, jealousy and ego perpetuating suppression, oppression, denial, and power over the lives of others. The last four decide and maintain poverty all over the world. Even in the so-called advanced West, the gap between the poor and the rich is widening by the day. The poor, unfortunately, pay for their poverty with their lives. Poverty is the womb of all diseases. Let us analyse the science of modern medicine in this article. You must have known about the 'Corporate Greed' that is eating into the belly of the whole human race. Interestingly, all those activities in every field are done citing the cover of science and technology!

People like Isaac Newton did not patent their findings. Patenting for monopoly is at the root of the exorbitant drug prices these days. Today less than one per cent of the world population can access those expensive drugs. I once happened to see the budget details of a coronary stent. Its cost to the manufacturer was ten dollars. Five hundred dollars were earmarked for doctor hospitality and the company had a modest profit of 1,490 dollars per stent! How did all these get the scientific tag? One has to go into the origin and the working of two large commissions which will give one an idea as to how these matters are manipulated by big money barons of the greedy business corporates. The Abraham Flexner commission of 1905 was appointed by the US government to investigate medical education in that country in the early part of the 20th century, with the blessings of a cartel formed by John Rockefeller, Andrew Carnegie, and DP Morgan. By then, copying the US model became fashionable and "scientific" for the rest of the world[1].

Abraham Flexner, a retired school principal, who had no inkling into medicine or medical education, was directly and/or indirectly, responsible for giving the "scientific tag" to reductionist chemical molecules made by the present pharmaceutical industry declaring all other healing methods prevalent at that time as unscientific, however effective they were. It was the Flexner Commission that was responsible for making homoeopathy, chiropractic, radio aesthesia, energy medicine, acupuncture, ayurveda, and many other effective healing outcomes declared as unscientific, thus forcing majority of medical schools in the US to close. Only 47 medical colleges working on and using pharmaceutical chemicals and surgical methods, who received "research funds" from the above mentioned

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

cartel remained alive at the end of 1910. Many good and safe systems like homoeopathy and chiropractic died a natural death there. Thanks to the British Royal family, homoeopathy survived in that country and acupuncture did thrive in China, thanks to the Government support there.

Lately I find a concerted effort to kill homoeopathy by the so-called powerful people. One such incident comes to mind. Recently a Nobel Laureate, condemned homoeopathy in no uncertain terms in Chennai where he was brought for a lecture by his "mentors". Of course, he was being faithful to "His Masters'" desire. It was, I think, Lord Churchill who once said that there are three questions in any saying. Who said it? How did he say that? And last, what did he say? Of the three, Churchill opined that the last question is the least important and does not warrant an answer. If a great man says something, that too with big authority behind him, it is usually accepted as gospel truth by society. If I interpret Winston Churchill about this Nobel Laureate's opinion of homoeopathy, as reported by the newspapers, the last part need not be taken seriously by a serious student of human healing. In fact, homoeopathy is a very important part of the healing armamentarium. There is enough and more scientific research base from very authentic scientists and institutions to back homoeopathy as a good holistic science.

A young doctor in London used to write a full page weekly column in *The Guardian*, condemning homoeopathy[2]. Naturally, he does not have enough experience with modern medical hazards to hapless patients and so he documents his theoretical arguments against homoeopathy. In the US, the newly born American Medical Association fought against homoeopathy and destroyed it initially. One of the prominent members of the AMA, Dr. JN McCormack, later in 1903 said that "we must admit that we have *never fought the homoeopaths on matters of principle*. We fought them because they came into our community and got the business". Now one can realise how homoeopathy became *pseudo science* to begin with. The rest is history. The story is still murkier in that arena. The American Homoeopathy Association started about 40 years before the American Medical Association. The homoeopathy association was started by some of the leading lights of mainline American medicine who were fed up and shocked by the results of their medical therapeutics like blood letting and many other procedures that prematurely sent patients to meet their maker in heaven in constant agony as a bonus. Even the first American President, George Washington, was not spared. They let all his blood out to cure him of his typhoid fever until he died of exsanguination.

Maybe Samuel Heinemann started homoeopathy as a 'Placebo' science. He was a regular MD himself who got disillusioned after losing his young son to a simple septicaemia. Curiously, an elaborate study published in 2011 in the four leading universities – of Oxford, Cambridge, Hamburg and Munich – did show modern medical therapeutics also to be predominantly a 'Placebo' effect! To date, nobody seems to say that modern medicine is unscientific, despite what that study showed. Even the higher ups in medicine are now expressing their concern about the evidence base of modern medicine, their benchmark, the Randomised Controlled Trials (RCTs), which seems to be built on very loose sand foundations. Sir Michael Rawlins, the Chief of NICE (National Institute of Clinical Excellence), did say in his recent Harveian Oration at the London Royal College that the RCTs, the benchmark of scientific excellence in medicine, have been put on an undeservedly high pedestal[3]! Who listens, but? This kind of occasional major signal is lost in the cacophony of daily information overload in modern medicine – most of which is pure "noise", or doctored study data, in the scientific sense of the term.

Most of our problems in modern medicine, including the report that the medical establishment as the leading cause of death in the US could be traced to this faulty science base. The RCT type cross-sectional short-term studies with their reports being published even before the ink dries on the report paper, followed by advertisement blitz by the drug cartels, with expensive "conferences" being arranged in major cities all over the globe where doctor hospitality knows no bounds led to our present mess. A few glaring examples will suffice to convince a non-convert. If, instead, we had patience to wait for outcomes studies instead of the surrogate parameters based success stories, we could have avoided a lot of human misery and countless human loss due to death

and disability.

- The long-term risk factor reduction study, called MRFIT, did show that there was *no significant difference* in the outcomes between the groups at the end of 15 years of study which involved screening 500,000 Americans to pick 100,000 subjects for the study which must have cost the tax payers millions of dollars[4]! Roger W Sherwin, Ph.D., who is the JS Copes Professor and Chair of the Department of Epidemiology, TSPHTM writes about the MRFIT thus: "In other words, they found that changing the "risk factors" does not apparently change the risks. This necessarily means that the "risk factors" are not as important as was thought. Indeed, it should be concluded that the "risk factors" were no such thing, at least as far as this trial is concerned.

- All the cholesterol lowering agents, starting from Cholestyramine to statins, did lower blood cholesterol levels (surrogate end-point) but long-term outcomes showed marginally higher death rates in the treated group due to newer diseases. In short, cholesterol lowering did change the lable in the death certificates without reducing total deaths! Statins even have the power to generate diabetes in healthy people to the extent of nearly 10% per year[5]!

- An audit of all the 17 blood pressure lowering drug studies pooled together showed no statistical difference in survival benefit between the groups. From the first drug to the latest, they all had serious side-effects. Sodium thiocyanate, the first drug had cyanide in it[6]!

The founding fathers of the American Constitution knew that this kind of monopoly will be bad for society and healthy science. One of them, Benjamin Rush, MD, a signer of the Declaration of Independence and personal physician to George Washington wrote thus:

"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 freedoms".

The Late Professor Rustum Roy, the man who invented the "Sol-Gel" technique, to extract nano particles way back in 1954 which is being used even today (his paper has been cited 68,000 times to date!) was the leader in this field. His work on the structure of water and the energy signature of water explains the science of homoeopathy, the system he swore by. He was nominated 21 times for the Nobel prize[7]. He had all the awards in the world a scientist could aspire to get and fellowship of all countries Science Academies. He was the Evan Pugh Professor of Material Sciences at Pennsylvania State till his last breath last year. For his innovative and ground breaking work in the healing sciences, Prof Roy was made Professor of Medicine at the Arizona State University. Many of his colleagues in other parts of the world had joined him in his work. Details could be got from authentic scientific literature. This is not the place to give details. Recently one of the IITs in India did show that homoeopathic pills had effective nano particles in them!

A founding member of the IOM, an audit body of medicine started by the American Academy of science, Professor Roy got his pet definition of health and healing accepted by IOM during (his last) the meeting of IOM in February 2010, as Whole Person Healing (WPH), the future definition of healing. Reductionism has NO PLACE in healing sciences. Further, vivisectionist research which goes deeper still has to be useless in the long run. Even human genomics has run into slippery slopes with the discovery of human metagenome showing trillions of germ genes incorporated into the 25,000 human genes[8]! Less said about reductionism the better. The future scientific medicine will have to be holistic, homoeopathy as a part of it, taking the useful methods from many other systems like Ayurveda and modern medicine. Most of us, including scientists who talk about healing methods, would do well to first read The New Biology, so beautifully explained by Nobel Laureate Albert-Szent Gyorgi in his classic, *Sub-molecular Biology*!

Modern medical science uses statistics to survive – it is not pure science but, statistical science. Modern medicine uses the wrong mathematical base of *Euclidean geometry* in a dynamic holistic system where only Mandelbrot's *Fractal Geometry* works[9]. In fact, another American Nobel Laureate Hungarian born scientist, John von Neumann, defined science as "making models, mostly mathematical constructs, which, with verbal jargon, are supposed to work". Modern medicine's mathematical base is faulty; naturally, the building built on that should be very shaky

and dangerous. Recent audits show that the medical establishment, built on this kind of science, is proving to be the leading cause of human mortality and morbidity in the US where records are kept meticulously. *Let us develop a humble respect for the true science, which is nothing but a method to unravel the mysteries of nature who keeps her secrets very close to her bosom.*

However, the Benjamin Fitzgerald Commission in 1953 had unearthed this huge conspiracy; but its report was suppressed as a secret document of fifty years to be in the open now[10]! We need a new science of man for our future research[11].

"It is not... That some people do not know what to do with truth when it is offered to them, but the tragic fate is to reach, after patient search, a condition of mind-blindness, in which the truth is not recognised, though it stares you in the face".

– Sir William Osler (1849-1919).

References

1. Abraham Flexner. www.medicinenet.com/script/main/art.asp?articlekey=8795.
2. Ben Goldacre. www.badscience.net/category/complementary.../homeopathy/
3. Sir Michael Rawlins. Harveian Oration 2008. *bookshop.rcplondon.ac.uk›Bookshop*
4. MRFIT results after 25 years. *jama.ama-assn.org/content/300/11/1343.full*
5. John Carey. Do cholesterol lowering drugs reduce total deaths? Business week January 17, 2008. *www.youtube.com/watch?v=84wbx2qPUzg*
6. Uffe Ravnskov. Chance of survival with or without treatment. *BMJ* 18th June 2002 rapid response.
7. Rustum Roy. www.rustumroy.com/bio2007.html
8. *Human metagenome.* www.human-microbiome.org/fileadmin/.../Paris-recommendations.p.
9. *Benoit Mandelbrot. mathdl.maa.org/images/upload.../07468342.di020711.02p00026.pdf*
10. www.newmediaexplorer.org/.../1953_fitzgerald_report_suppressed_c..
11. BM Hegde. Magical MemBrain-Biology's Holy Grail. *Kuwait Med J* 2011; 43: 173-5.

ORIGINAL ARTICLE

JIACM 2011; 13(1): 15-7

Effect of left nostril breathing in hypertensives

Anshuman Naik, DA Biswas**, Shashikala Patel****

Abstract

Background: Hypertension, a "psychological classical silent killer" is the hallmark of various cardiovascular disorders. Hypertension would become a greater global burden in the next 15 - 20 years. Hypertension is an important and growing public health challenge worldwide. If one believes that 'old is gold', then yoga is quite effective and widely believed to reduce blood pressure. Some varieties of pranayama require the practitioner to inhale and exhale through one nostril selectively. When each respiratory cycle is completed through the left nostril alone, the practice is called Chandra anuloma viloma pranayama, which means a 'heat dissipating or cooling breathing practice'.

Aims of study: The present study has been carried-out to assess the immediate effect of left nostril breathing (LNB) on BP of hypertensive patients.

Material and methods: 30 hypertensive patients who were on regular treatment took part in the study. A baseline record (which served as control) of pulse rate/min, systolic blood pressure (mmHg), diastolic blood pressure (mmHg) were recorded. They carried-out LNB for 5 minutes only and all parameters were recorded again. Student t test was used as the statistical tool to analyse the acquired data.

Results: The mean pulse rate dropped from 84.73 ± 1.89 per minute to 81.80 ± 1.84per minute. Systolic blood pressure dropped from 144.50 ± 3.68 mmHg to 133.83 ± 3.66 mmHg. Diastolic blood pressure dropped from 100.96 ± 2.48 mmHg to 94.83 ± 2.41 mmHg.

Conclusion: This study indicates that BP and pulse rate can be decreased in a non-pharmacological way. Hence this technique can be used as a regular practice for combating the stress and strain of everyday life.

Key words: Chandra anuloma viloma pranayama, hypertension, stress.

Introduction

Hypertension, a "psychological classical silent killer" is the hallmark of various cardiovascular disorders mainly occurring due to increase in the total peripheral resistance because of several aetiological factors – genetic, obesity, glucose intolerance, high salt intake, cigarette smoking, heavy alcohol consumption, increased serum renin levels.

Due to plenty of aetiological factors, hypertension would become a greater global burden in the next 15 - 20 years. The estimated total number of people with hypertension in India and world wide are as follows:

Region	Year	2000	2025
	Worldwide	9.72 billion	15.6 billion
	India	11.82 billion	21.25 billion

It is predicted that the total number of hypertensive patients would increase by about 60%, i.e., a total of 15.6 billion high blood pressure sufferers, by the year 2025. For more than 50% of all stroke deaths and about 25% of coronary heart disease deaths, in which the main cause is hypertension. Hypertension is an important and growing public health challenge worldwide[1]. If we believe in the principle of 'old is gold', then yoga is most effective and widely believed to reduce blood pressure (BP)[2]. Patanjali, the foremost exponent of yoga, described pranayama as the gradual unforced cessation of breathing. Pranayama is derived from two Sanskrit words – prana (life) and yama (control)[3]. Patanjali in his yoga sutra describes yama, niyama, asana, pranayama, pratyahara, dharana, dhyana and samadhi as the eight angas of yoga.

Amongst them, in the present materialistic world, the 3rd and 4th parts – pranayama and asana – are considered very important parts and prescribed by modern medicine too[4].

Some varieties of pranayama require the practitioner to inhale and exhale through one nostril selectively. When

**** Resident, ** Professor and Head, Department of Physiology, *** Resident, Department of Anatomy, Jawaharlal Nehru Medical College, Sawangi (M), Wardha - 442 004, Maharashtra.***

each respiratory cycle is completed through the left nostril alone, the practice is called Chandra anuloma viloma pranayama, which means a 'heat dissipating or cooling breathing practice'[5].

The present study has been carried-out to assess the immediate effect of left nostril breathing (LNB) on BP of hypertensive patients.

Material and methods

30 hypertensive patients who were on regular treatment took part in the study. A baseline record (which served as control) of pulse rate/min, systolic blood pressure (SBP in mmHg), diastolic blood pressure (DBP in mmHg) were recorded. A standard sphygmomanometer of (Diamond, India) of ISI mark was used along with microtone stethoscope to asses blood pressure. They carried-out LNB for 5 minutes only and all parameters were recorded again. Patients were asked to close their right nostril by the thumb and slowly breathe in up to maximum, through left nostril. Student t test was used as the statistical tool to analyse the acquired data. $p < 0.05$ was considered significant.

Table I: Different variables before and after 5 minutes of left nostril breathing (LNB)

Variables	Before (mean ± SEM)	After (mean ± SEM)
Pulse rate (PR/min)	84.73 ± 1.89	81.80 ± 1.84
SBP (mmHg)	144.50 ± 3.68	133.83 ± 3.66
DBP (mmHg)	100.96 ± 2.48	94.83 ± 2.41

P value 0.000, p < 0.05.

Results

The mean pulse rate dropped from 84.73 ± 1.89 per minute to 81.80 ± 1.84 per minute. Systolic blood pressure dropped from 144.50 ± 3.68 mmHg to 133.83 ± 3.66 mmHg. Diastolic blood pressure dropped from 100.96 ± 2.48 mmHg to 94.83 ±2.41 mmHg.

Discussion

Regarding optimal management of Indian hypertensive population according to CUPS (Chennai Urban Population Study), prevalence of hypertension in men

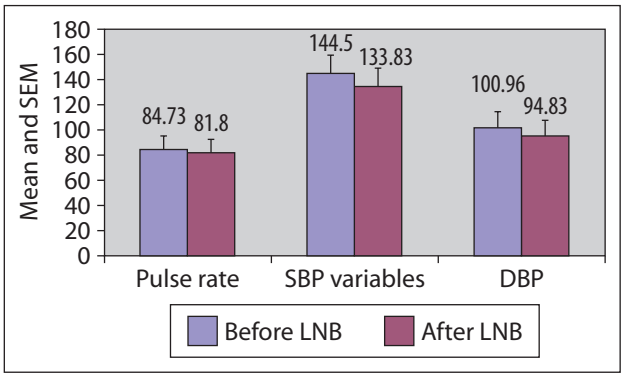


Fig. 1: *Comparison of pulse rate, systolic blood pressure and diastolic blood pressure before and after 5 minutes LNB.*

(22.8%) and in women (19.7%) is still a dream by pharmacological management, because the rule of halves for hypertension states that half the people with high BP are not known, half of those known are not treated, and half of those treated are not controlled. Thus, by this rule, 1 out of 8 patients is optimally treated by pharmacological measurement[2]. Hypertension has been reported to be generally associated with sympathetic overactivity[6]. In our study, the mean pulse rate/min, systolic and diastolic blood pressure decreased significantly just after 5 minutes of left nostril breathing (LNB). It may be due to the fact that in our body the right and left nostrils do not function simultaneously. One of the nostrils is always more congested than the other even when the nasal passages are clean and unobstructed by mucus. In the yogic system of breathing the left nostril dominance corresponds to "Ida" svara with parasympathetic activation[7]. Hence this left nostril dominance corresponding to parasympathetic activation may be the cause for the changes seen. Nidhi Jain *et al* had previously shown that LNB for 15 minutes decreased SBP, DBP, and after 8 week of LNB decrease in SBP and DBP was same[7]. Rai *et al* found that induced LNB produced decreased systolic, diastolic and mean blood pressures. They suggested that LNB could be used as a prophylactic means to combat rises in BP associated with everyday stress and strain of life[8]. Telles *et al* have demonstrated that pranayama breathing through right nostril results in an increase in sympathetic activity, whereas left nostril breathing reduces it. LNB increased oxygen consumption by 24% (LNB practiced as 27 respiratory cycles, repeated 4 times a day for 1 month) and LNB also increased spatial memory scores by 16%

after performing LNB for 45 minutes only[5, 9, 10].

Conclusions

This study indicates that BP and pulse rate can be decreased in a non-pharmacological way. SBP, DBP and pulse rate decrease with short-term practice of LNB, i.e., only 5 minutes. Other studies have shown that there is no further decrease in all theses parameters even after 8 weeks practice; and that practice of LNB increases spatial memory scores. Hence this technique can be used as a regular practice for combating stress and strain of everyday life and also enhancing memory scores.

References

1. Yeligar RR, Shah KA *et al*. The most reliable approach to defeat a silent killer. *IJPSR* 2010; Vol 1, Issue 8.
2. Chaturvedi M, Jindal S, Kumar R *et al*. Lifestyle modification in hypertension in Indian context. *JIACM* 2009; 10 (1 and 2): 46-51.
3. Malhotra V, Tandon OP, Patil R *et al*. Suryanadi anuloma viloma pranayama modifies autonomic activity of heart. *Joy: The Journal of Yoga* 2009; vol 8, No 1.
4. Dhungel KU, Malhotra V, Sarkar D *et al*. Effect of alternate breathing exercise on cardiorespiratory functions. *Nepal Med Coll J* 2008; 10 (1): 25-7.
5. Telles S, Nagarathna R, Nagendra HR *et al*. Breathing through a particular nostril can alter metabolism and autonomic activities. *Indian J Physiol Pharmacol* 1994; 38 (2): 133-7.
6. Rajashekar RK, Niveditha Y, Ghosh S *et al*. Blood pressure response to cold pressor test in siblings of hypertensives. *Indian J Physiol Pharmacol* 2003; 47 (4): 453-8.
7. Jain N, Srivastava RD, Singhal A *et al*. The effects of right and left nostril breathing on cardiorespiratory and autonomic parameters. *Indian J Physiol Pharmacol* 2005; 49 (4): 469-74.
8. Singh S, Singh S, Gautam S *et al*. Pranayama – the yogic science of breathing. *Pak J Physiol* 2009; 5 (1).
9. Udupa K, Madanmohan, Bhavanani AB *et al*. Effect of pranayama training on cardiac function in normal young volunteers. *Indian J Physiol Pharmacol* 2003; 47 (1): 27-33.
10. Telles S, Joshi M *et al*. Immediate effects of right and left nostril breathing on verbal and spatial scores. *Indian J Physiol Pharmacol* 2008; 52 (2): 197-200.

ACKNOWLEDGEMENT

LIST OF *JIACM* REVIEWERS (2011)

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

ORIGINAL ARTICLE

JIACM 2011; 13(1): 18-21

A study on the modulation of adenosine deaminase (ADA) activity in monocytes of type-2 diabetic patients by antioxidants

SS Siddiqi, J Ahmad**, N Islam***, SMK Ashraf****, SP Mishra******

Abstract

Purpose: To access the oxidative stress in type-2 diabetic patients, by measuring the adenosine deaminase (ADA) levels in serum, co-cultured monocytes, monocyte supernatant, and to verify the modularity effect of antioxidant on ADA levels.

Material and methods: Adenosine activity was measured in the serum, 24 hours co-cultured monocytes and cell-free supernatant of the monocytes in 50 type-2 diabetic subjects. 20 age and sex matched healthy subjects were taken as controls. The ADA activity was reassessed after treating the co-cultured monocytes with antioxidants, namely, N-acetyl cysteine and epigallocatechin-3-gallate (EGCG).

Results: Adenosine deaminase levels were found to be raised in monocytes of type-2 diabetic patients. This level decreased after antioxidant therapy.

Conclusion: Adenosine deaminase activity could be regarded as a strong indicator of reactive oxygen species (ROS) production due to oxidative stress in type-2 diabetic subjects, which could be modulated by antioxidants.

Key words: N-acetyl cysteine, epigallocatechin-3-gallate, reactive oxygen species, reactive nitrogen species (ROS), adenosine deaminase (ADA).

Introduction

The increasing prevalence of type-2 diabetes in the Indian subcontinent makes it important to recognise, postpone, or even prevent the serious complications associated with it, if possible. The oxidative stress resulting in free radical production [reactive oxygen species (ROS) and reactive nitrogen species (NOS)] which is considered to be a common pathogenic factor leading to insulin resistance, β-cell dysfunction and ultimately type-2 DM[1], is also considered as an underlying cause of both the macrovascular as well as microvascular complications[2]. Among the well-known effects of adenosine are, selective regulation of pro- and anti-inflammatory cytokines released and free radical production[3,4,5]. Increased levels of adenosine deaminase in diabetic patients could result in increase in hypoxanthine which oxidizes xanthine into uric acid and concomitant generation of O_2. Several studies have found elevated ADA activity in subjects with type-2 DM[6,7,8]. The present study was performed in order to estimate the ADA levels in serum, monocytes, and in monocyte supernatant in type-2 diabetic subjects and also to look for any effect on ADA levels after modulating the same co-cultured monocytes by antioxidants.

Material and methods

The study was conducted at the Endocrine division, Department of Medicine, JN Medical college, AMU, Aligarh. 50 subjects of type-2 diabetes mellitus were included in the study. Their demographic profile with biochemical characteristics was estimated. Peripheral blood monocyte cells (5×10^6 cells/well) were added in 12 wells tissue culture plates in complete RPMI - 1640 medium and subsequently incubated at 37°, 5% CO_2 for 1 - 2 hours. The cells were washed, adhered with 2% autologous serum followed by overnight resting. ADA levels in serum, co-cultured monocytes, monocyte supernatant were evaluated and compared with 20 age and sex matched healthy controls. Statistical analysis was performed using SPSS version 10 statistical package for windows (SPSS, Chisago, IL). Continuous variables were expressed as mean ± SD (Gaussian distribution) or range. Unpaired and paired student t test for independent and dependent samples were used in comparing continuous data between two groups. All P values were two-tailed and values of < 0.05 were considered to indicate statistical significance. All confidence intervals were calculated at 95% level. Pearson's correlation of ADA activity with clinical, and

***** Director, Centre for Diabetes and Metabolism, *** Professor, Department of Biochemistry, **** Junior Resident, Department of Medicine, Aligarh Muslim University, Aligarh, U.P., * Senior Resident, Department of Endocrinology, ***** Assistant Professor, Department of Biochemistry, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221 005, Uttar Pradesh.***

biochemical variables were estimated. Multistage linear regression analysis using ADA activity on dependent variable (HbA_{1C} alone and HbA_{1C} + fasting blood sugar) in same subjects was performed. Thereafter, above adherent monocytes were co-cultured with varying doses of N-acetyl cysteine (10 Mm) and EGCG (5 µg/ml) for 24 hours. Cultures were then harvested after 24 hours and cells were lysed in 0.5 ml of trizol reagent (Invitrogen Inc, Carlsband, CA, USA) and stored at –70°. Finally modularity effect of these antioxidants on the same co-cultured monocytes and their supernatant was evaluated by re-evaluating ADA levels.

Observations and results

Of the 50 type-2 diabetic subjects included in the study, 36 were males while the rest were females. In the control group, out of 20, 14 were males. Age in the study group was 52.19 ± 8.04 while in the control group it was 49.5 ± 7.65. Hb_{AIC} in the study group was 8.55%, while it was 5.02% in the control group. Serum ADA levels in study group reveal values of 31.72 ± 2.80 U/L while in the control group it was 19.13 U/L with t value of -18.53 and p value of < 0.01. Monocyte ADA values in study group were 22.74 ± 2.8 U/L while in control these were 9.26 ± 2.81U/L with a P value of < 0.01. The monocytes supernatant showed the same trends (Table I). Pearson's correlation of ADA activity showed ADA activity significantly correlated with hyperglycaemic parameters like Hb_{A1C} ($p < 0.01$) fasting blood sugar ($p < 0.05$) and post-prandial blood sugar ($p < 0.05$). ADA activity was not significantly correlated with age, BMI, RFT, or serum lipid levels (Table II). On performing multistep regression, Hb_{A1C} entered as the most important significant variable with a regression value of 0.688, indicating appropriate predictability in the relationship between the dependent (ADA activity) and independent (Hb_{A1C}) variables. R^2 value (0.474) indicates the extent to which Hb_{A1C} accounts for the total variance in mean ADA activity. In our case it was 47%. β indicates nature and dynamics of relationship between the two variables. Furthermore, it was seen that each unit increase in the level of Hb_{A1C} increased the level of ADA by 0.688 units (provided that all other independent variables are kept constant). The t-value indicates the significance of regression and the slope of regression line. In our case the regression value is significant, β value is significantly different from zero and the regression line was having a significant slope in comparison to the x-axis. The confidence intervals for β showed that our findings are true to the entire population from which the sample has been taken.

Fasting blood sugar entered as the second most important significant variable. The model 2 contains two variables, Hb_{A1C} and fasting blood sugar. Regression value for model 2 was 0.721 thereby indicating that the variables had a predictive power of 72%. And the R^2 value was 0.520 which denoted that the variables in model 2 (Hb_{A1C} and fasting blood sugar) account for 52% variation in the level of the dependant variable, ADA. β indicated the nature and dynamics of relationship between two variables. Thus, in model 2 the most powerful predictor of ADA value was Hb_{A1C} ($\beta = 0.889, t = 6.426, p < 0.001$), followed by fasting blood sugar ($\beta = -0.294, t = -2.125, p < 0.05$). Regression value was significant, β value was significantly different from zero and the regression line had a significant slope in comparison to the x-axis. Confidence intervals for β showed that our findings are true to the entire population from which the sample has been taken (Table III). Finally after washing with RPMI - 1640 media, the monocytes were co-cultured with 5 µg/ml of EGCG and 10 Mm NAC for 24 hours. The ADA values were compared with those prior to antioxidants addition.

Table I: ADA levels in control and study group.

	Control		Type-2 diabetes		t	p
	Mean	SD	Mean	SD		
ADA (serum)* (U/L)	19.13	1.82	31.72	2.80	-18.53	<0.01
ADA (monocyte)** (U/L)	9.26	1.31	22.74	2.81	-20.56	<0.01
ADA (M. supernatant)*** (U/L)	7.06	1.31	18.84	2.79	-17.97	<0.01

** ADA level in serum; ** ADA level in 24-hour monocytes culture, *** ADA level in cell free supernatant of 24-hour monocyte culture; p - value indicates difference (independent sample t-test). T is the value of student 't' test.*

With EGCG, the p value came out to be < 0.001, while with NAC also, the p value came out to be p < 0.001. Again, on comparing the two antioxidants, p value came out to be < 0.001 (Table IV).

Table II: Pearson's correlation of ADA activity with clinical and biochemical variables in patients of type-2 diabetes mellitus.

	Pearson correlation	Sig. (2-tailed)
Age (years)	0.208	NS
BMI (kg/m2)	.177	NS
BS (f)	.314*	.027
BS (pp)	.310*	.028
Hb A1c (%)	.688**	.000
B. urea (mg%)	.045	NS
S. creatinine (mg%)	.091	NS
Total S. chol (mg%)	.260	NS
HDL (mg%)	-.072	NS
LDL (mg%)	.155	NS
TG (mg%)	.201	NS
VLDL (mg%)	.202	NS
ADA (monocyte)	1.000**	.000
ADA (M. supernatant)	1.000**	.000

*** Correlation is significant at the 0.01 level (2-tailed);*
** Correlation is significant at the 0.05 level (2-tailed);*
NS – not significant.

Discussion

Increased level of adenosine in diabetic cells accompanied by decreased activity of adenosine kinase, diminished efflux, may drive the metabolism of adenosine towards deamination by adenosine deaminase (ADA) to inosine and hypoxanthine; the latter product serves as a substrate for xanthine oxidase which oxidizes xanthine into uric acid with concomitant increased generation of O_2^-. It has been demonstrated that increased purine degradation results in altered free radical formation[9, 10]. ADA is a marker of T-cell activation and is related to the production of ROS by neutrophils[11], the central mechanism of oxidative damage in diabetes. In addition, a link between the ADA gene locus and maturity onset diabetes of the young (MODY) has also been reported[12]. In the present study, we found significantly elevated levels of serum ADA in subjects with type-2 DM with a mean ADA level of 31.72 ± 2.80 U/L. The study also found a Pearson's correlation between the mean ADA activity and hyperglycaemic parameters like Hb_{A1c} (p < 0.01), fasting blood sugar (p < 0.05) and post-prandial blood sugar (p < 0.05).

Among these, Hb_{A1c} has the strongest production power for ADA activity with regression value of 0.68; and when combined with fasting blood sugar, the regression value measured to 0.72. Hb_{A1c} alone is responsible for 47% variance in ADA. Our findings are consistent with two studies Kurtael *et al*[8] who reported that ADA activity was significantly raised in poorly controlled diabetics with

Table III: Multistep regression model.

Model	Variables	R	R^2	β	t	p	95% confidence interval for β	
							Lower	Upper
1	Hb A_1C	0.688	0.474	0.688	6.576	0.000	0.860	1.618
2	Hb A_1C	0.721	0.520	0.889	6.426	0.000	1.100	2.102
	Fasting blood sugar			-0.294	-2.125	0.039	-0.031	-0.001

1 Predictors: (constant), HbA1c (%);
2 Predictors: (constant), HbA1c (%), BS

Table IV: Comparing the model effect of NAC versus a natural antioxidant, ECCG.

	With NAC (10 Mm)		With EGCG (5 G/NK)			Sig. (2-tailed)
	Mean	SD	Mean	SD	t	p
ADA level in monocyte (U/L)	11.88	1.63	10.06	1.17	22.107	< 0.001
ADA level in monocyte supernatant (U/L)	8.98	1.63	6.96	1.17	24.107	< 0.001

HbA1c > 7%. Hoshine *et al*[6] had previously reported that poorly controlled type-2 DM patients had mean HbA1c > 8.5% while in controlled diabetes patients this level was < 7%.

Conclusion

Adenosine deaminase activity is elevated in serum and in monocytes of patients with type-2 diabetes mellitus. Adding antioxidants N-acetyl cysteine or epigallocatechin-3-gallate reduces ADA levels and thereby the oxidative stress, which could delay the complications associated with diabetics.

References

1. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol* 2004; 24: 816-23.
2. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; 414: 813-20.
3. Hasko G, Kuhel DG, Chen JF *et al*. Adenosine inhibits IL-12 and TNF-α production via adenosine A2a receptor dependent and independent mechanisms. *FASEB J* 2000; 14: 2065.
4. Hasko G, Szabo C, Nemeth ZH *et al*. Adenosine receptor agonist differentially regulate IL-10, TNF-α and nitric oxide production in Raw-264.7 macrophages and in endoxemic mice. *J Immunol* 1996; 157: 4634.
5. Cain BS, Harken AH, Meldrum DR. Therapeutic strategies to reduce TNF-α mediated cardiac contractile depression following ischaemia and reperfusion. *J Mol Cell Cardiol* 1999; 31: 931.
6. Hoshino T, Yamada K, Masuoka K *et al*. Elevated adenosine deaminase activity in the serum of patients with DM. *Diabetes Res Clin Pract* 1994; 25: 97-102.
7. Warrier AC, Rao NY, Kulpati DS *et al*. Evaluation of adenosine deaminase activity and lipid peroxidation levels in diabetes mellitus. *Indian J Clin Biochem* 1995; 10 (1): 9-13.
8. Kurtul N, Pence S, Akarsu E *et al*. Adenosine deaminase activity in the serum of type 2 diabetic patients. *Acta Medica (Hradec Kralove)* 2004; 47 (1): 33-5.
9. Siems W, Kowalewski J, Werner A *et al*. Ucleotide degradation and radical formation in ischaemic and reperfused small intestine. *Biomed Biochem Acta* 1989; 48: S16-S19.
10. Jabs CM, Neglen P, Eklof B. Breakdown of adenine nucleotides, formation of oxygen free radicals and early markers of cellular injury in endotoxic shock. *Eur J Surg* 1995; 161: 147-55.
11. Yoneyama Y, Sawa R, Suzuki S *et al*. Relationship between plasma malondialdehyde levels and adenosine deaminase activities in pre-eclampsia. *Clin Chem Acta* 2002; 322: 169-73.
12. Bell GI, Xiang K, Newman MV *et al*. Gene for non-insulin dependent diabetes mellitus (maturity onset diabetes of the young subtype) is linked to DNA polymorphism on human chromosome 20q. *Proc Natl Acad Sci USA* 1991; 88: 1484-8.

FORM IV (See Rule 8)

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

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

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

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

Sd/-
Date: Dr. D. G. Jain
January 15, 2012 Signature of Publisher

ORIGINAL ARTICLE

JIACM 2011; 13(1): 22-6

A study on the prevalence of cardiac autonomic neuropathy in type-2 diabetes in Eastern India

AK Basu, R Bandyopadhyay**, S Chakrabarti***, R Paul****, S Santra*****

Abstract

Neuropathy – especially autonomic neuropathy – is the most common complication of diabetes which is not investigated so frequently. One of the earliest manifestations of diabetic autonomic neuropathy is denervation of the cardiovascular system. Various studies have shown cardiac autonomic neuropathy (CAN) is strongly associated with microvascular complications of diabetes, viz., microalbuminuria and retinopathy. The aim of the present study is to find the prevalence of cardiac autonomic neuropathy in diabetes patients in a sample Eastern Indian population. Cardiac autonomic neuropathy is detected by various cardiac autonomic function tests like Valsalva ratio, heart rate response to standing, BP response to standing, and hand grip and heart rate response to breathing. Dizziness on standing was the most commonly encountered symptom. Bladder symptoms and abnormal sweating were the other symptoms commonly encountered in this study, and CAN was found in 54% of our cases. Parasympathetic neuropathy was found in 52% cases and sympathetic neuropathy in 20% cases. Majority of patients (28%) had two abnormal cardiovascular reflexes. Statistical evaluation revealed that retinopathy is significantly associated with CAN. Statistical evaluation also revealed that microalbuminuria is significantly associated with CAN. Parasympathetic cardiac autonomic function tests are more sensitive for the detection of CAN than sympathetic cardiac autonomic function tests. Evaluation of cardiovascular reflexes constitutes an important feasible and reproducible beside clinical technique.

Key words: Parasympathetic, sympathetic, denervation, microalbuminuria.

Introduction

Diabetes mellitus (DM) is well known for chronic complications particularly the triad of neuropathy, retinopathy, and nephropathy, which have a close correlation with the metabolic abnormalities characteristic of diabetes. Neuropathy – especially autonomic neuropathy – is the most common complication of diabetes which is not investigated so frequently. One of the earliest manifestations of diabetic autonomic neuropathy is denervation of the cardiovascular system[1]. Hence assessment of cardiovascular reflexes affords a satisfactory evaluation. The prevalence of autonomic nervous system dysfunction in diabetes is not precisely known; however, tests of autonomic function have shown impairment in nearly 20 - 30% of diabetic patients. Presence of symptoms along with abnormal cardiovascular function tests suggest poor prognosis and increased incidence of silent myocardial infarction, cardiac arrest, sudden death, and inadequate response to stressful events, e.g., anaesthesia and surgery[2]. There are very few reports about the prevalence of cardiac autonomic neuropathy (CAN) along with correlation with other diabetic complications. To highlight the magnitude of the problem in Eastern India, the present study was undertaken.

Aims and objectives

The aims and objectives of the study were:

1. To determine the prevalence of cardiac autonomic neuropathy in type-2 DM by doing cardiac autonomic function tests.
2. To correlate the cardiac autonomic neuropathy in type-2 diabetes with other complications like retinopathy, microalbuminuria, and glycated haemoglobin (HbA_{1c}).

Materials and methods

The study was conducted in the department of Internal Medicine, with both outdoor and indoor patients and patients attending the Diabetes Clinic, Medical College, Kolkata. We selected 50 documented type-2 diabetes patients as per criteria recommended by the WHO. Patients were selected irrespective of the duration of disease and therapeutic status.

**** Assistant Professor, Department of Endocrinology, ** Assistant Professor, **** Junior Resident, Department of Medicine, Medical College, Kolkata,***
****** Assistant Professor, Department of Pathology, IPGMER and SSKM Hospital, Kolkata, West Bengal.***

Exclusion criteria were:

- Presence of uncontrolled hypertension
- Heart failure
- Urinary tract infection
- Fever
- Cirrhosis of liver
- Prostatitis (All of which could have transient proteinuria).

Written informed consent was obtained from each patient prior to inclusion in the study.

Mercury sphygmomanometer, electrocardiography machine, and modified mouth piece were used for evaluation of cardiac reflexes. Quantitative estimation of microalbuminuria was done by enzyme-linked immunosorbent assay (ELISA), and HbA1c by using HPLC. Ophthalmoscopy was done for the retina.

1. The tests for autonomic cardiovascular function, performed as beside procedures, are described hereunder[3]:-

(A) Tests reflecting cardiac parasympathetic action:

(i) By the patient blowing into a mouth piece connected to a sphygmomanometer and holding it at a pressure of 40 mmHg for 15 seconds while a continuous ECG was recorded. The manoeuvre was performed 3 times with an interval of one minute in-between. The result was expressed as the Valsalva ratio. The mean of three Valsalva ratios was taken as the final value (normal Valsalva ratio is 1.21; borderline is between 1.11 and 1.20; abnormal is < 1.10).

(ii) Heart rate variation during deep breathing: The patient sat quietly and breathed deeply at 6 breaths a minute (5 seconds in and 5 seconds out) for one minute. An ECG was recorded throughout the period of deep breathing with a mark used to indicate the onset of each inspiration and expiration. The maximum and minimum R-R intervals during each breathing cycle were measured and converted to beats/minute. The result was then expressed as the mean of the difference between maximum and minimum heart rates for the 6 measured cycles in beats/minute. The result was then expressed as the mean of the difference between maximum and minimum heart rates for the 6 measured cycles in beats/minute (normal response > 15 beats/minute; borderline response 11 - 14 beats/minute; abnormal response < 10 beats/minute).

(iii) Immediate heart rate response to standing: The test was performed with the patient lying quietly on a couch while the heart rate was recorded continuously on an ECG machine. The patient was asked to stand up unaided and the point at starting to stand was marked on the ECG tracing. The shortest R-R interval at or around the 15th beat, and the largest R-R interval at or around the 30th beat after starting to stand was measured with a ruler. The characteristic heart rate response was expressed by 30: 15 ratio (which is normal if: > 1.04; borderline between 1.01 and 1.03; and abnormal if < 1.00).

(B) Tests reflecting cardiac sympathetic action:

(i) BP response to standing: The test was performed by measuring the patient's BP while he was lying down quietly, and again when he stood up. The postural fall (after 2 minutes) in BP was taken as the difference between systolic BP lying and the systolic BP standing (normal response < 10 mmHg; borderline 11 - 29 mmHg; abnormal response > 30 mmHg).

(ii) BP response to sustained handgrip: After instructions in using hand grip of an inflated BP cuff, the subject gripped maximally with his dominant arm for a few seconds, this was repeated thrice. Highest of the 3 readings is called maximum voluntary contraction (MVC). Now the subject was instructed to maintain hand grip. The result was expressed

as the difference between the highest DBP during hand grip exercise and mean of 3 DBP readings before hand grip began (normal response > 16 mmHg; borderline 11 - 15 mmHg; abnormal < 10 mmHg). *All borderline tests were interpreted as normal in the present study.*

2. Screening for microalbuminuria:

Morning urine samples were tested for routine and microscopic examination. Urine samples positive for protein by dipstick were first selected. *Patients with urine positive for protein were excluded from the study* and those negative for protein were tested for microalbuminuria with timed urinary collection (24 hrs) by ELISA method. The test for microalbuminuria was repeated for 2 times in the 3 months follow-up period. When at least 2 out of 3 test results were positive for microalbuminuria, patients were considered to have persistent microalbuminuria.

3. Estimation of glycated haemoglobin (by HPLC):

Values more than 7% were taken as elevated.

4. Detection of retinopathy:

By Ophthalmoscopic examination.

Results and analysis

A total 50 cases of type-2 diabetes patient were included in the study group after using proper exclusion criteria.

There was males (56%) predominating over females (44%).

Maximum number of patients (32%) were in the age group of 51 - 60 yrs, followed by the age group 41 - 50 (24%). Younger patients (21 - 30 yrs age group) constituted an insignificant portion (4%) of total patients in the study group.

Symptomatic presentation

Clinical symptoms of autonomic neuropathy were assessed on the basis of presence or absence of various symptoms like dizziness, bladder symptoms, abnormal sweating, impotence, diarrhoea, and dysphagia.

The dizziness on standing was the most frequently occurring symptom (36%), followed by bladder symptoms and abnormal sweating (16 % each). Dizziness on standing was not always associated with documented postural hypotension on format test.

Regarding the various autonomic functions, heart rate responses to deep breathing was the most sensitive test to determine autonomic neuropathy. It was abnormal in 16 (32%) patients, normal in 26 (52%) patients, and borderline in 8 (16%) patients.

This was followed by abnormal heart rate response to standing (30: 15 ratio), which was abnormal in 12 (24%) patients, normal and borderline response were found in 31 (62%) and 7 (14%) patients respectively. Abnormal handgrip test was seen in 8 (16%) patients, normal in 30 (60%) cases, and borderline in 12 (24%) cases. Valsalva ratio was abnormal in 11 (22%) patients, borderline in 20 (40%) cases, and normal in 19 (38%) cases. The least sensitive test to detect autonomic neuropathy was postural hypotension. This was abnormal in 7 (14%) cases, normal and borderline in 32 (64%) cases and11 (22%) cases respectively (Table I).

The results were: parasympathetic neuropathy (defined as: result of at least one of the 3 tests of parasympathetic function was abnormal) is seen in 26 (52%) cases while sympathetic neuropathy (defined as: abnormal result in one of the tests of sympathetic function) was detected in 10 (20%) cases (Table III). Majority of patients (14 patients, i.e., 28%) had two abnormal cardiovascular reflexes (Table II).

Microalbuminuria was detected in 18 (36%) cases. Diabetic retinopathy was detected in 5 patients (10 %). All of them had microalbuminuria and cardiac autonomic neuropathy (CAN). Statistical evaluation revealed retinopathy is significantly associated ($p < 0.05$) with CAN. Of the 18 patients with microalbuminuria, 14 had cardiac neuropathy and microalbuminuria, and 4 had microalbuminuria without any abnormal autonomic cardiovascular function testing. Statistical evaluation revealed that microalbuminuria is significantly associated ($p < 0.05$) with CAN. Out of 50 type 2 DM patients, 38 (76%) patients had raised HbA_{1c} (>7%). Of these patients 20 had cardiac neuropathy and the

remaining 18 patients had no neuropathy.

Table I: Distribution of type-2 DM cases (%) in various cardiovascular tests (n = 50).

Cardiovascular tests	Normal	Borderline	Abnormal
Postural hypotension	32 (64%)	11 (22%)	6 (14%)
Effect of sustained hand grip on BP	30 (60%)	12 (24%	8 (16%)
Effect of deep breathing on heart rate	26 (52%)	8 (16%)	16 (32%)
Effect of Valsalva manoeuvre on heart rate	19 (38%)	20 (40%)	11 (22%)
Heart rate response to standing (30:15 ratio)	31 (62%)	7 (14%)	12 (24%)

Table II: Distribution of cases according to the number of abnormal cardiovascular reflex tests.

Abnormal reflex	No. of cases (%)
One abnormal CV reflex	8 (16%)
Two abnormal CV reflexes	14 (28%)
Three abnormal CV reflexes	5 (10%)
Total no. of patients having abnormal CV reflexes	27 (54%)

Table III: Distribution of type-2 DM cases (%) in abnormal parasympathetic and sympathetic CV reflexes.

Type of autonomic neuropathy	No. of cases	Percentage
Parasympathetic neuropathy	26	52%
Sympathetic neuropathy	10	20%

Discussion

In this study CAN was found in 54% cases. Parasympathetic neuropathy was found in 52% cases, and sympathetic neuropathy in 20% cases. This is in conformity with Ewing *et al*[4]. A recent study in Jaipur done by Mehta *et al* revealed prevalence of CAN in 58% cases – all of them having parasympathetic neuropathy, and sympathetic neuropathy in 20% cases[5]. Heart rate response to deep breathing was the most sensitive test, i.e., 32% in this study. This too is in conformity with reports of Mehta *et at*.

Symptoms of CAN were less commonly encountered in the present study. Dizziness on standing was most commonly encountered in 36% patients. Bladder symptoms and abnormal sweating were the other symptoms commonly encountered in this study. These results are also in conformity with the previous study reports by Mehta *et al*[6].

Microalbuminuria was noted in 36% of patients in our study. Microalbuminuria was also statistically significantly associated with CAN[7]. A study from western India reported a higher incidence, i.e., about 42%[8]. None of the patients in the present study had overt proteinuria. Reports of Mehta *et al* study also showed a similar pattern of microalbuminuria, i.e., 35% of the patients in their study group.

Retinopathy (both background and preproliferative) was detected in 10% of the type-2 DM patients in the present study. Mehta *et al* reported a similar pattern, i.e., around 7.5% of type 2 DM patients had retinopathy. All of the patients with retinopathy had cardiac neuropathy and microalbuminuria in the present study. This is in conformity with previous reports of diabetes with cardiac autonomic neuropathy and microalbuminuria[9].

Raised HbA_{1c} was found in 20 out of 27 patients with CAN, and in 18 out of 23 patients without CAN. There is no statistical difference between these results. This suggests the poor short-term glucose control has no correlation with prevalence of cardiac neuropathy. The probable explanation of this lack of correlation is:–

i) HbA_{1c} reveals glucose control over the past 2 - 3 months. As diabetes – particularly type-2 DM – is a long duration metabolic disease, a single measurement of HbA_{1c} fails to reveal the exact nature of glycaemic control over the past few years, which is important for the development of neuropathy, retinopathy and nephropathy.

ii) Other metabolic parameters may play an important role in the genesis of long-term microvascular complications of diabetes mellitus.

ii) Hypertension is strongly associated with other micro-vascular complications as revealed by various studies.

iv) There is a strong genetic predisposition for the development of microvascular complications, which may be independent of glycaemic control.

Summary and conclusion

The above study result revealed the prevalence of cardiac autonomic neuropathy is 54%. Cardiac autonomic neuropathy is detected by various cardiac autonomic

function tests. Symptoms of autonomic neuropathy are not as sensitive as the autonomic function tests to detect the cardiac neuropathy. As such, assessment of autonomic cardiovascular reflexes affords a satisfactory method of evaluation of CAN.

Parasympathetic cardiac autonomic function tests are more sensitive for the detection of CAN than sympathetic cardiac autonomic function tests.

Heart rate response to deep breathing is the most sensitive parasympathetic cardiac autonomic function test which detects CAN, followed by heart rate response to standing and heart rate response to the Valsalva manoeuvre.

Blood pressure to sustained handgrip is slightly more sensitive in detecting cardiac sympathetic neuropathy than is postural hypotension.

Statistical analysis reveals cardiac autonomic neuropathy is strongly associated with other microvascular complications of diabetes, viz., microalbuminuria and retinopathy.

Statistical analysis failed to reveal any correlation between glycated haemoglobin and cardiac neuropathy.

Evaluation of cardiovascular reflexes in type-2 DM subjects with paucity of related symptoms constitutes an important feasible and reproducible bedside clinical technique and is well correlated with abnormal albumin excretion and retinopathy. It should be included as a routine in the work-up of patients of type-2 diabetes as it often uncovers autonomic neuropathy even in the asymptomatic state. It is of crucial importance to pinpoint some high-risk cases with probability of sudden cardiac death. It is also a pointer to embark upon a search for other complications of diabetes often associated with it.

Acknowledgement: Dr. Anup Roy, M.S.V.P. of Medical College, Kolkata, for allowing us to conduct this study in this institution.

References

1. Maser RE, lenhard MJ. Cardiovascular autonomic neuropathy due to diabetes mellitus: clinical manifestations, consequences and treatment. *Journal of Clinical Endocrinology and Metabolism* 2005; 90 (10): 5896-5903.
2. Maser RE, Pfeifer MA, Dorman JS, Kuller *et al*. Diabetic Autonomic Neuropathy and Cardiovascular Risk: Pittsburgh Epidemiology of Diabetes Complications Study III. *Arch Intern Med* 1990; 150: 1218-22.
3. Spallone V, Menzinger G. Diagnosis of cardiovascular autonomic neuropathy in diabetes. *Diabetes* 1997; 46 (Suppl 2): S67-76.
4. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. *Q J Med* 1980; 49: 95-108.
5. Mehta S, Mathur D, Chaturvedi M, Verma K. Incidence of cardiac autonomic neuropathy and its correlation with retinopathy, micro-albuminuria and glycated haemoglobin in non-insulin dependent diabetes mellitus. *JIMA* 2002; 100: 141-3.
6. Neil HAW, Thompson AV, John S *et al*. Diabetic autonomic neuropathy: the prevalence of impaired heart rate variability in a geographically defined population. *Diabetic Medicine ISSN* 1989; 0742-3071.
7. Andrew Moran, Walter Palmas, Lesley Field *et al*. Cardiovascular autonomic neuropathy is associated with microalbuminuria in older patients with type 2 diabetes. *Diabetes Care* 2004; 27 (4): 972-7.
8. Sheth J, Trivedi B, Shah L, Sheth VS. Prevalence of microalbuminuria in diabetic subjects. *J Assoc Physicians India* 1993; 41 (9): 562-4.
9. Krolewski AS, Barzilay J, Warram JH *et al*. Risk of early-onset proliferative retinopathy in IDDM is closely related to cardiovascular autonomic neuropathy. *Diabetes* 1992; 41 (4): 430-7.

ACKNOWLEDGEMENT

The *Journal, Indian Academy of Clinical Medicine* thanks Dr. R.P. Shrivastwa, Organising Secretary, IACMCON-2011, Patna, for contributing a sum of Rs. 150,000/- from the conference proceeds for the benefit of the *Journal*.

– Editor

ORIGINAL ARTICLE

JIACM 2011; 13(1): 27-32

Clinical profile of systemic lupus erythematosus patients at a tertiary care centre in Western India

Renu Saigal, Amit Kansal **, Manoop Mittal **, Yadvinder Singh**, Hari Ram Maharia**, Manish Juneja***

Abstract

Aim: To determine the clinical profile of systemic lupus erythematosus (SLE) patients at a tertiary care centre in Western India.

Methods: Patients fulfilling the 1982 revised American College of Rheumatology criteria for SLE, seen between August 2007 and July 2008, were included in the study.

Results: Sixty patients of SLE were evaluated over a period of 1 year. Arthritis was the commonest initial manifestation. The patients had varied cutaneous, cardiac, renal, gastrointestinal, and neuropsychiatric manifestations. Haemolytic anaemia was the initial mode of presentation in 6.7% patients in our series. One patient had benign intracranial hypertension as the initial manifestation. This is an uncommon presentation of neuropsychiatric SLE. Antinuclear antibody (ANA) assay and anti-dsDNA was positive in 98.3% and 65% patients respectively.

Conclusion: SLE is a multisystem disorder affecting predominantly young females. Polyarthritis was the most common clinical feature. Incidence of haemolytic anaemia, leucopenia and thrombocytopenia, was much higher in our study as compared with all other Indian series.

Key words: SLE, clinical profile, arthritis, haemolytic anaemia, Western India.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease in which organs, tissues, and cells undergo damage mediated by tissue-binding autoantibodies and immune complexes. SLE primarily occurs in young women in their 20s. Clinical features of systemic lupus erythematosus have been described from different geographical regions in the world, with some clinical differences among different racial groups[1]. An Indian study of 100 patients showed that prolonged fever was the commonest presenting symptom. Other presenting symptoms with decreased frequency were arthralgia, haemolytic anaemia, ITP, malar rash, GTCS, anasarca, splenomegaly, lymphadenopathy, hepatomegaly and goiter[2]. UK studies show that in 85% of patients, the first definitive lupus feature was musculoskeletal and/or cutaneous[3].

A Zimbabwe study showed that renal involvement was more common and photosensitivity and serositis less common than in the United States[4]. A low incidence of Raynaud's phenomenon attributable to the warm climate in Northern Kerala was observed in a series by Binoy *et al*[5]. So, there is a wide variation in the natural history of systemic lupus erythematosus among different ethnic and geographical groups. Severity ranges from a mild disease with rash and arthritis to a devastating illness with renal failure and central nervous system involvement.

The purpose of this study is to delineate the clinical pattern and disease course in patients with SLE at our centre in Western India and to compare it with National data on lupus patients.

Material and methods

All patients satisfying the revised American College of Rheumatology criteria (1982) for SLE were included in the study over a one-year period. The patients were regularly followed-up, the last follow-up being within 2 months of conclusion of the study. Clinical assessment included information on medical history, presenting chief complaints, duration of disease, assessment of various organs involvement like cutaneous, musculoskeletal, nervous, cardiopulmonary, and GIT. Routine investigations including complete blood count, ESR, urine analysis, 24 hr urine protein excretion, renal function tests, liver function tests, random blood glucose, lipid profile, 12-lead

**** Professor and Unit Head, ** Resident, Department of Medicine, Sawai Man Singh Medical College and Hospital, Ajmeri Gate, Sawai Man Singh Road, Tonk Road, Jaipur - 302 018, Rajasthan.***

ECG, chest X-ray, and X-ray of both hands were done in all patients. 2D-Echo was done where required. Immunological investigations like anti-nuclear antibody (ANA), anti-dsDNA, rheumatoid factor (RF) were done in all patients, whereas Coombs' test, lupus anticoagulant and anticardiolipin antibody were done where required. Percutaneous renal biopsy was performed in cases with clinical and biochemical evidence of renal involvement.

Results: (Table I and II)

Age and sex wise distribution of cases

Sixty patients were studied over a one-year period, of which 55 were females and 5 were males. Male to female ratio was 1: 11. The mean age at onset of disease was 28 years (range 13 - 56 years). Mean age of onset in male patients was 33.70 ± 19.13 year and that in female patients was 27.45 ± 10.12 year. Sixty-six per cent of the patients were less than 30 years in age. Mean duration of disease was 24 months.

Musculoskeletal features

Arthritis was the commonest initial manifestation and was seen in 32 patients (53.3%). Symmetrical, non-erosive, non-deforming polyarthritis was noticed in 49 patients. Oligoarthritis was noted in 14 patients and monoarthritis in 4 patients. Generalised myalgia was seen in 38 patients.

Mucocutaneous features

Dermatologic manifestations noted in 55 patients (91.7%) were photosensitivity, malar rash, alopecia, oral ulcers, vasculitic rash, Raynaud's phenomenon, discoid rash and one patient had gangrene of toes (Table I). Subacute cutaneous lupus erythematosus was not seen.

Haematological involvement

Anaemia (Hb < 10 g%) was seen in 32 patients (53.3%). Autoimmune haemolytic anaemia (Coombs' positive) was most common type, seen in 15 patients (25%).

Table I: Clinical profile of 60 patients of SLE.

A)	**Age at onset of disease**	**No. of cases**	**F)**	**Mucocutaneous manifestations**	**No. of cases**
	11 - 20 yrs	15		Photosensitivity	45
	21 - 30 yrs	25		Malar rash	26
	31 - 40	10		Alopecia	39
	41 - 50	08		Oral ulcers	37
	51 - 60	02		Raynaud's phenomenon	13
B)	**Sex distribution**			Vasculitic rash	13
	Male	05	**G)**	**Cardiovascular**	
	Female	55		Pericardial effusion	04
C)	**Haematological**			Valvular involvement	03
	Anaemia	32	**H)**	**Renal**	
	Leucopenia	26		Proteinuria	33
	Thrombocytopenia	20		Active urinary sediment	18
D)	**Musculoskeletal features**			Elevated serum creatinine	08
	Polyarthritis	49	**I)**	**Pleuropulmonary**	
	Oligoarthritis	02		Pleural effusion	04
	Monoarthritis	01		Pleuritic rub	02
	Myalgia	38		Interstitial fibrosis	02
E)	**Neurological**		**J)**	**Gastrointestinal**	
	Seizures	03		Ascites	11
	Neuropathy	02		Hepatomegaly	07
	Psychosis	02		Splenomegaly	05
	CVA	02		Pancreatitis	01

Table II: Clinical profile of 60 patients of SLE.

Immunological profile	No. of cases	Family history of SLE	No. of cases
ANA	59	Male	00
Anti-dsDNA	39	Female	04
RF	11		
Anti-Ro Ab	01		
Menstrual irregularity		**Recurrent abortion**	05
Menarche not attained	45	**APLA +ve**	02
Oligomehorrhoea/amenorrhoea	26		
Menorrhagia	39		
Association to other disorders		**Cause of death**	
Hypothyroidism	05	Sepsis	04
Hyperthyroidism	01	Neuropsychiatric	02
Lymphadenopathy	02	Renal	01
Pulmonary tuberculosis	04	Pancreatitis	01
Survival			
Regular follow-up	50		
Lost to follow-up	02		
Died	08		

10 patients (16.7%) had normocytic normochromic anaemia, 5 (8.3%) had microcytic hypochromic anaemia, and 2 (3.3%) had megaloblastic anaemia. Leucopenia (TLC < 4,000/cu mm) in 26 (43.3%) and thrombocytopenia (< 1,00,000/cu mm) in 20 patients (33.3%).

Renal Involvement

Renal involvement was noted in 34 patients (56.7%). Proteinuria (> 0.2 gm/24 hours) was seen in 33 patients (55%). Abnormal urinary sediment was noted in 18 patients and elevated serum creatinine (> 1.5 mg/dl) was noted in eight. Renal biopsy was performed in 20 patients having indication for biopsy. Diffuse proliferative glomerulonephritis (WHO grade 4) was the most commonly seen histological pattern, seen in 18 patients (90%). One patient had focal and segmental proliferative glomerulonephritis (grade 3) and one had membranous glomerulonephritis (grade 5). These patients were treated with glucocorticoids and cyclophosphamide and responded well.

Neurological features

Neuropsychiatric abnormalities were seen in 8 patients (13.3%), seizures were seen in 3 patients (5%), 2 patients (3.3%) had peripheral neuropathy, 2 (3.3%) had psychosis and 2 (3.3%) suffered from ischaemic stroke. Stroke is clinically evident in 5 - 10% SLE patients in most series and may involve small, medium, or large vessels. Neuropathy in both the patients showed axonal affection on nerve conduction studies. Chorea was not seen in any patient.

Pleuro-pulmonary features

Pleuro-pulmonary involvement was noticed in 7 patients. Pleuritic rub was found in 2 patients. Pleural effusion was present in 4 patients who responded to steroid therapy. 2 patients had interstitial fibrosis, and lupus pneumonitis was not seen in any of the patients.

Cardiovascular features

Cardiac involvement was seen in 4 patients (6.7%). All 4 had pericardial effusion without any sign of tamponade. Two patients had both mitral and aortic regurgitation, whereas one patient had only non-rheumatic mitral regurgitation on 2D-Echo. No patient had significant ECG changes.

GIT involvement

Hepatomegaly was present in 7 patients. 5 patients had splenomegaly. Eleven patients had ascites, 9 were transudative due to proteinuria and hypoproteinaemia, whereas 2 were exudative. Patients with exudative ascites were followed-up weekly by USG, and they responded well to steroids as probably it was due to SLE flare. Ascites occurs in SLE – usually secondary to cardiac, hepatic or renal disorders. Cases have been reported where patients developed ascites due to SLE *per se*. One patient developed pancreatitis which was probably drug-induced as she was on steroid and azathioprine therapy.

Menstrual irregularity and recurrent abortions

Among 55 females, 5 had not attained menarche. Five patients gave history of recurrent abortions of which 2 were positive for antiphospholipid antibodies. These two patients with past history of recurrent abortions were found to have IgG anticardiolipin antibody (aCL) positive at two separate occasions 12 weeks apart. Menstrual irregularity was seen in 19 patients (34.4%) in the present study. Oligomenorrhoea or amenorrhoea was the most common irregularity, seen in 11 patients (20%). No patient with oligomenorrhoea or amenorrhoea was having thyroid disorder. 3 patients experienced menorrhagia (5.4%), among these three, one was having hypothyroidism whereas no one was having thrombocytopenia as a cause of menorrhagia.

Immunological profile

ANA was positive in 59 patients (98.3%) and one ANA negative patient was anti-Ro antibody positive. Anti-dsDNA was positive in 39 patients (65%) and 11 patients (18.3%) were RF positive.

Family history and association to other diseases

4 patients were having family history of SLE or other connective tissue disorders. Out of 60 SLE patients, 5 patients (8.3%) were having hypothyroidism and one patient (1.7%) was having hyperthyroidism. One patient of hypothyroidism was having menorrhagia also. Four patients (6.7%) developed pulmonary tuberculosis during the disease course in the present study, whereas a study of 309 SLE patients from Northern India by Shyam and Malaviya[11] showed 39% patients suffered from pulmonary tuberculosis. 2 patients (3.33%) had cervical and inguinal lymphadenopathy; one showed reactive hyperplasia and the other one was suggestive of 'Kikuchi disease' on histopathological examination.

Follow-up

Out of 60 patients, 8 patients (13.3%) died, 50 patients (83.3%) are on regular follow-up and 2 patients lost to follow-up. Among 8 deaths, sepsis seen in 4 patients, (50%) was the most common cause of death. Of 4 the patients who died of sepsis, all were female patients and were having major organ involvement. 3 of them were on immunosuppressive therapy also. One patient had urinary tract infection, one was suffering from pneumonitis, and two patients were having unknown focus of infection – but all were having leucocytosis and their CRP was positive. They were treated with IV antibiotics according to culture and sensitivity reports but did not survive. 2 patients died of neurological complications during seizures. One patient died of end-stage renal failure and one due to pancreatitis (probably drug-induced as she was on steroid and azathioprine therapy).

Discussion

In our study of 60 patients of SLE, there were 5 males and 55 females in the age range of 13 - 58 years. 23 patients were between 21 - 30 years of age. Mean age was 30 years. The female to male ratio was 11:1. Binoy *et al*[5] reported an average female to male ratio of 19:1. Another Indian series by Malaviya *et al*[6] had a female to male ratio of 8:1. Male patients had similar clinical profile as seen in females, but the increased frequency of SLE among females is thought to be due to hormonal effects. All 5 male patients were ANA positive and showed musculocutaneous features similar to those seen in females. Three male patients had major organ involvement, one was having WHO grade 4 nephritis and 2 were having Coombs' positive anaemia. Two patients were anti-dsDNA positive, and RF was positive in 1 male patient.

Mean duration of disease in 60 patients of SLE was 24 months. In the study of Malaviya *et al*[6], median duration of illness prior to diagnosis was 17 months. In the present study, median age at disease onset was 27.9 years (Table IV). Binoy *et al*[5] observed a median age of disease onset at 21.6 years. Masi *et al* and Hochberg *et al* observed that

median age at disease onset was 31 and 30 years respectively[7]. In India, Malaviya *et al*[6] and Vaidya *et al*[8] noted a median age of onset of 24 and 26 years respectively. The peak incidence of disease onset was seen in the 3rd decade in our study, which is the same in both the Indian series also.

In the present study, arthritis was the initial presentation in 53.3% (Table III). Binoy *et al*[5], Malaviya *et al*[3] and Madhavan *et al*[9] noted arthritis as the initial manifestation in 66.7%, 57% and 68.5% respectively.

13.3% patients presented initially with cutaneous manifestations and this incidence was comparable with

Table III: Initial manifestations of SLE (percentage).

Symptoms	Malaviya: 101 pts 1985, N. India	Madhavan: 54 pts 1983, Madras	Binoy: 75 pts 2003, S. India, N. Kerala	Present study: 60 pts 2003, West India
Arthritis	57	68.5	66.7	53.3
Cutaneous	36	48.1	14.7	13.3
Renal	8	7.4	6.7	13.3
Fever	44	11.1	4.0	6.7
Anaemia	-	-	1.3	6.7
Thrombocytopenia	2	5.5	1.3	3.3
Pericardial effusion	-	5.5	2.7	-
Neuropsychiatric	-	3.7	2.7	3.3

Table IV: Cumulative incidence of clinical and immunological manifestations of SLE in Western India as compared to other series.

Clinical manifestations	Malaviya[10] (1985) n = 101 (N. India)	Vaidya[8] (1997) n = 220 (W. India)	Madhavan[9] (1983) n = 54 (Madras)	Binoy[5] (2003) n= 75 (N. Kerla)	Present study n = 60
Arthritis	66%	70.91%	81.4%	89.3%	86.7% (n = 52)
Dermatologic	85%	NA	62.9%	64%	91.7% (n = 55)
Malar rash	68%	53.18%	NA	40%	43.3% (n = 26)
Discoid lupus	5%	NA	NA	5.3%	1.7% (n = 01)
Photosensitivity	67%	9.55%	NA	32%	75% (n = 45)
Oral ulcers	64%	NA	48.1%	64%	61.7% (n = 37)
Alopecia	82%	NA	57.4%	60%	65% (n = 39)
Raynaud's phenonmenon	32%	15.5%	1.8%	2.7%	21.7% (n = 13)
Haemolytic anaemia	9%	NA	NA	0.01%	25% (n = 15)
Leucopenia	16%	NA	3.7%	14.7%	43.3% (n = 26)
Thrombocytopenia	11%	NA	7.4%	12%	33.3% (n = 20)
Renal	73%	35%	38.8%	33.3%	56.7% (n = 34)
Pulmonary	17%	15.5%	16.6%	8%	11.7% (n = 07)
Cardiovascular	5%	11.8%	9.2%	5.3%	6.7% (n = 04)
Neuropsychiatric	15%	25.5%	20.3%	13.3%	13.3% (n = 08)
ANA	98%	NA	NA	93.3%	98.3% (n = 59)
Anti-dsDNA	55%	NA	NA	76%	65% (n = 39)
+ve RF	21%	NA	NA	20%	18.3% (n = 11)

the Binoy *et al*[5] series but was lower than other series.

The incidence of renal involvement as the initial manifestation was 13.3% in the present study and is higher than in other Indian series.

Fever was the initial manifestation in 6.7% cases in the present study, which is less than that seen in the study by Malaviya *et al* (44%) and Madhavan *et al* (11.1%), but it is higher than that reported by Binoy *et al* (4.0%) (Table III).

Haemolytic anaemia was the initial mode of presentation in 6.7% patients in our series as compared to 1.3% in the Binoy *et al* series. This was not an initial feature in other Indian series.

One patient in the present study had benign intracranial hypertension as the initial manifestation. This is an uncommon presentation of neuropsychiatric SLE.

Table IV compares the cumulative incidence of clinical manifestations of SLE in our study as compared to other studies. Arthritis was the commonest clinical feature (86.7%) and the incidence is comparable to the Binoy *et al* series, but higher as compared to other Indian series.

Incidence of cutaneous manifestation in our study (91.7%) is higher as compared to the studies from South and Western India. Incidence of photosensitivity (75%) in our study is higher, whereas that of alopecia and oral ulcers is comparable to other Indian series. Incidence of Raynaud's phenomenon is higher as compared to the series from South India, probably due to warm climate in South India. Incidence of cardiac and pleuro-pulmonary features was similar to other Indian series. During recent years, it has become clear that the risk of cardiovascular disease (CVD) is very high in a prototypic autoimmune disease, systemic lupus erythematosus (SLE). SLE-related CVD and atherosclerosis are important clinical problems. A combination of traditional and nontraditional risk factors, including dyslipidaemia (and to a varying degree hypertension, diabetes, and smoking), inflammation, antiphospholipid antibodies (aPL), and lipid oxidation are related to CVD in SLE. Premature atherosclerosis in some form leading to atherothrombosis is likely to be a major underlying mechanism[12].

Incidence of haemolytic anaemia (25%), leucopenia (43.3%), and thrombocytopenia (33.3%) was much higher in our study as compared to all other Indian series. Genetic susceptibility for autoimmune haematological involvement may explain this higher incidence.

References

1. Rabbani MA, Siddiqui BK, Tahir MH *et al*. Systemic lupus erythematosus in Pakistan. *Lupus* 2004; 13 (10): 820-5.
2. Prasad AK, Srinivasan VR, Rao VMM, Narendra AMVR. Clinical profile of SLE – 100 cases. *J Assoc Phys India* 2003; 51: 1204-5.
3. Hopkinson ND, Doherty M, Powell RJ. Clinical features and race – specific incidence/prevalance rates of Systemic lupus erythematosus in a geographically complete cohort of patients. *Annals of the Rheumatic Disease* 1994; 53: 675-80.
4. Taylor HG, Stein CM. Systemic lupus erythematosus in Zimbabwe. *Annals of the Rheumatic Disease* 1986; 45: 645-8.
5. Paul BJ, Muhammed Fassaludeen, Nandakumar, Razia MV. Clinical profile of Systemic Lupus Erythematosus in Northern Kerala. *J Indian Rheumatol Assoc* 2003; 11: 94-7.
6. Malaviya AN, Singh RR, Kumar A *et al*. SLE in Northern India. A review of 329 cases. *J Assoc Phys India* 1988; 36: 476-80.
7. Masi AT, Kaslow RA. Sex effects in SLE – a clue to pathogenesis. *Arthritis Rheum* 1978; 21: 480.
8. Vaidya S, Samant RS, Nadkar MY, Borges NE. SLE- review of two hundred and twenty patients. *JIRA* 1997; 5: 14-8.
9. Madhavan *R et al*. Systemic Lupus Erythematosus: The Madras Experience. *J Assoc Phys India* 1988; 36: 481-4.
10. Malaviya AN, Misra R, Banerjee S *et al*. Systemic Lupus Erythematosus in North Indian Asians: A prospective analysis of clinical and immunological features. *Rheumatology International* 1986; 6: 97-101.
11. Shyam C, Malaviya AN. Infection-related morbidity in systemic lupus erythematosus: a clinico-epidemiological study from northern India. *Rheumatol Int* 1996; 16: 1-3.
12. Frostegård J. SLE, atherosclerosis and cardiovascular disease. *J Intern Med* 2005; 257 (6): 485-95.

ORIGINAL ARTICLE

JIACM 2011; 13(1): 33-6

Human chorionic gonadotrophin and thyroid hormones status during normotensive pregnancy

Shahid A Mujawar, Vinayak W Patil**, Rekha G Daver****

Abstract

Hormonal changes during pregnancy result in profound changes in thyroid functions. The present study was designed to determine human chorionic gonadotrophin and thyroid hormones in normotensive pregnancy. 50 normotensive pregnant subjects with mean age 26.4 ± 4.48 years who attended the gynaecology OPD were inducted in the study. Their mean ± SD gestational age at time of study was 23.8 ± 10.2 weeks. Age matched 50 non-pregnant subjects, not having any acute illness, thyroid, liver, and renal diseases were taken as control. Serum human chorionic gonadotrophin (hCG), total circulating triiodothyronine (total T3), total circulating thyroxine (total T4) and thyroid stimulating hormone (TSH) were estimated by using fully automated enzyme amplified chemiluminescent immunoassay based Immulite 1000 analyser. The alterations of serum hCG and thyroid hormones level in normotensive pregnant subjects were found as compared to those of control group. We, therefore, conclude that these investigations should be performed routinely in pregnancy. In addition, thyroid function tests should be interpreted against gestational age in pregnancy.

Key words: Human chorionic gonadotrophin, triiodothyronine, thyroxine, thyroid stimulating hormone, normotensive pregnancy.

Introduction

Human placenta synthesises glycoprotein, steroids, and protein hormones during pregnancy[1]. The production of human chorionic gonadotrophin (hCG) by placenta in the first trimester of pregnancy is critical for implantation and maintenance of the blastocyst[2]. hCG can stimulate the thyroid gland during first trimester of pregnancy because of its structural resemblance with TSH[3]. During pregnancy, thyroid hormones have an important role in embryogenesis and foetal brain development[4]. Therefore, thyroid function is frequently assessed during pregnancy, both to evaluate suspected thyroid abnormalities, and to monitor the status of pre-existing thyroid disease[5].

Aim of study

The present study was undertaken:

1. To determine human chorionic gonadotrophin in women with normotensive pregnancy.
2. To determine serum total circulating triiodothyronine, total circulating thyroxine, and thyroid stimulating hormone in women with normotensive pregnancy.
3. To correlate the serum human chorionic gonadotrophin and thyroid hormones in women with normotensive pregnancy.

Material and methods

This study was carried-out at the Department of Biochemistry, Grant Medical College and Sir J. J. Group of Government Hospitals, Mumbai, over the period from October 2007 to June 2010. All participants completed a medical history form and provided informed consent in writing. All the participants were also subjected to a questionnaire which included family income, maternal education and occupation, living conditions, personal history like age, height, weight, dietary history, religion, caste, sub-caste, addictions and medications, history of lactation, gravidity, gestation period and previous laboratory investigation if any.

Inclusion criteria

50 normotensive pregnant subjects with mean age 26.4 ± 4.48 years who attended the gynaecology OPD. Their mean ± SD gestational age at time of study was 23.8 ± 10.2 weeks.

Exclusion criteria

Study subjects with hypertension, proteinuria, and

**** Assistant Professor, ** Professor and Head, Department of Biochemistry, *** Professor and Head, Department of Obstetrics and Gynaecology, Grant Medical College and Sir J. J. Group of Government Hospitals, Byculla, Mumbai - 400 008, Maharashtra.***

oedema. None of the subjects had history of polycystic ovary syndrome, liver disease, renal disease, human immune deficiency virus (HIV) infection.

Withdrawal criteria

Insufficient quantity of sample, specimen collected in inappropriate container, lipaemic or haemolysed sample, and lack of adequate information. Insufficient quantity of sample, were the criteria forwithdrawal from the study.

Control group

Age matched 50 non-pregnant subjects, not having any acute illness, thyroid, liver, and renal diseases were taken as control.

Ethical aspect

The Institutional Ethical Committee at the Grant Medical College and Sir J. J. Group of Government Hospitals, Mumbai, India, approved the study.

Sample collection and analysis

Venous blood sample of each subject was collected in a test tube with aseptic precautions. After 2 hours of collection, the sample was centrifuged at 3,000 rpm for 5 minutes. Serum was separated and collected in a polythene tube with cork. Serum was immediately stored at -20° C until assayed.The sera with no sign of haemolysis was used for the analysis of hCG, total T3, total T4, and TSH.

Total T3 and T4 estimation was done by solid-phase, competitive chemiluminescent enzyme immunoassay[6,7]. Third generation TSH and hCG concentrations were measured by solid-phase, two-site chemiluminescent immunometric assay[8,9]. We used fully automated enzyme amplified chemiluminescent immunoassay based Immulite 1,000 analyser.

Statistical analysis

Numerical variables were reported in terms of mean and standard deviation. Statistical analysis of results was done by normal distribution 'z' test. In this analysis, variables showing'p'value less than 0.05 and 0.001 were considered to be statistically significant and highly significant respectively. Pearson correlation test was used to test correlation.

Results

Fifty subjects with normotensive pregnancy and 50 healthy non-pregnant subjects were compared in this study.

Table I: Age-wise distribution of normotensive pregnant subjects.

Age	No. of subjects (n)	Percentage (%)
18 - 20 years	09	18
21 - 25 years	17	34
26 - 30 years	18	36
31 - 35 years	06	12

Table I showed the age of subjects ranged from 18 - 35 years. Majority of the normotensive subjects were 21 - 30 years (70%). Out of 50 subjects in the study group, 10 came from the tribal areas of Thane and Raigad district of Maharashtra, and the remaining 40 were from the urban and suburban areas of Mumbai.

Table II: Thyroid status-wise distribution of normotensive pregnant subjects.

Characteristics	Distribution of subjects n = 50 (100%)		
	Clinical	Subclinical	Total
Hypothyroidism	03 (06)	09 (18)	12 (24)
Hyperthyroidism	None	02 (04)	02 (04)
Euthyroidism	None	None	36 (72)

In the study group, 12 subjects gave biochemical evidence of hypothyroidism (3 clinical, 9 subclinical) and 2 subjects had subclinical hyperthyroidism. Remaining 36 subjects were euthyroid in normotensive pregnant group (Table II).

Table III: Biochemical profile in controls and normotensive pregnant subjects.

Parameters	Non-pregnant (n = 50)	Normotensive pregnant (n = 50)	'p' value
hCG (mIU/mL)	1.29 ± 1.54	17533 ± 8919	0.0001 **
Total T3 (ng/dL)	125 ± 17.1	162 ± 51.7	0.0001**
Total T4 (µg/dL)	7.30 ± 1.55	11.5 ± 3.83	0.0001**
TSH (µIU/mL)	3.29 ± 0.54	5.99 ± 7.54	0.0058 *

*** P < 0.001; * P < 0.05.*

Table III shows levels of serum hCG, total T3, total T4 and

TSH in healthy non-pregnant subjects and normotensive pregnant group. Study group showed a significantly higher ($p < 0.001$) increase in serum hCG, total T3 and total T4, whereas significant ($p < 0.05$) increase in serum TSH as compared to those of control subjects.

Table IV: Correlation between serum hCG and thyroid hormones in normotensive pregnant subjects.

Parameters	95% CI of 'r'	DF	'r' value	'p' value
Total T3	-0.136 to 0.409	1.035	0.148	0.3057 ^{NS}
Total T4	-0.182 to 0.369	0.709	0.102	0.4819 ^{NS}
TSH	0.231 to 0.668	3.769	0.478	0.0004**

*CI = Confidence interval; DF = Degree of freedom; r = Correlation coefficient; ** P < 0.001; NS = Not significant.*

Positive and significant ($p < 0.001$) correlation was observed between levels of hCG and TSH, whereas statistically insignificant correlations were seen between the levels of hCG and total T3, total T4 in normotensive pregnant subjects (Table IV).

Discussion

The diagnosis of thyroid abnormalities in pregnancy is difficult, and the choice of therapy for thyroid dysfunction is also difficult because of the foetus. We studied fifty pregnant women who gave a history of normotensive pregnancy. Of these, 24% gave biochemical evidence of hypothyroidism (6% clinical, 18% subclinical) and 4% had subclinical hyperthyroidism. Remaining 72% subjects were euthyroid in normotensive pregnant group.

In this study, serum hCG levels in normotensive pregnant subjects showed highly significant increase ($p < 0.001$) when compared with that of non-pregnant group. Serum hCG is a glycoprotein hormone produced by the developing placenta shortly after fertilisation. In normal pregnancy, hCG concentration increased in both urine and serum as early as days after conception[10-13].

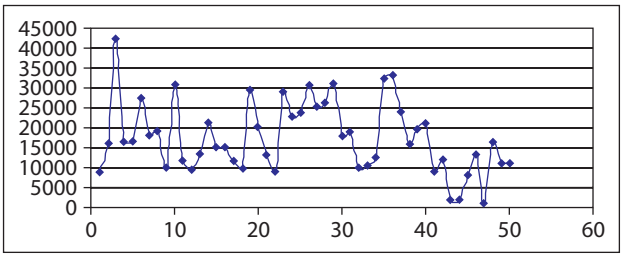


Fig. 1: *Line diagram showing the levels of serum hCG in normotensive pregnant group.*

In normal normotensive pregnant subjects, serum total T3 levels were significantly elevated ($p < 0.001$). Zarghami *et al* found alterations in thyroid function tests in each trimester in normal pregnant women as compared to non-pregnant women in Tabriz, Iran[14]. Their study showed that serum total T3 levels of non-pregnant women was normal, but in pregnant women rose stepwise and significantly increased in each trimester when compared to that of non-pregnant women. These findings are fairly in agreement with those of ours.

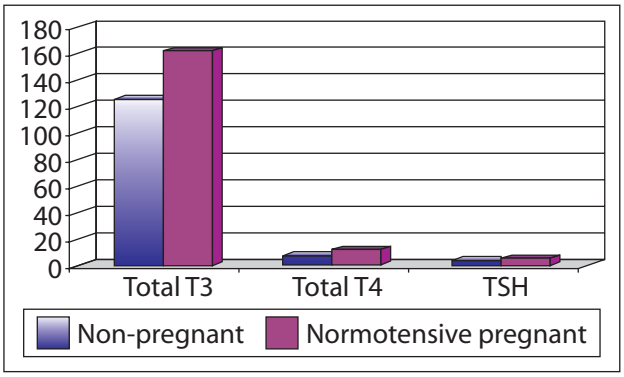


Fig. 2: *Bar diagram showing the levels of serum thyroid hormones in control and in normotensive pregnant group.*

Serum total T4 levels were significantly elevated ($p < 0.001$) in normotensive pregnant group. Khandakar *et al* studied alteration in serum thyroid hormone levels in normal pregnant women as compared those of non-pregnant women[15]. Their study showed that serum total T4 level of non-pregnant women was normal, but in pregnant women during third trimester, it was significantly higher as compared to that of non-pregnant. This finding in our study is striking.

In the present study, serum TSH level in normotensive pregnant group showed significant increase ($p < 0.05$) when compared with that of non-pregnant group. Kumar *et al* also showed progressive rise in mean TSH level through the trimesters of pregnancy especially in the second trimester and third trimester. In our study also, TSH showed increased levels in both the second and the third trimester. The study of Kumar *et al* corroborates with our findings in pregnancy[16]. The above-mentioned correlations found between serum hCG and thyroid hormones may be due to physiological

changes during pregnancy.

We, therefore, conclude that these investigations should be performed routinely during pregnancy. Otherwise, lack of appropriate and early diagnosis and treatment can lead to neurological impairment of foetal brain as well as increases risk of maternal hypertensive pregnancy.

References

1. Harrington K, Campbells S. Fetal size and growth. *Curr Opin Obstet Gynecol* 1993; 5: 184-94.
2. Petraglia F, Volpe A, Gennazani AR *et al*. Neuroendocrinology of human placenta. *Front Neuroendocrinol* 1990; 11: 6-37.
3. Fantz CR, Dagogo-Jack S, Ladenson JH, Gronowski AM. Thyroid function during pregnancy. *Clin Chem* 1999; 45: 2250-8.
4. Haddow JE, Palomaki GE, Allan WC *et al*. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999; 341: 549-55.
5. Zarghami N, Rohbani-Noubar M, Khosrowbeygi A. Thyroid hormones status during pregnancy in normal Iranian women. *Ind J Clin Biochem* 2005; 20 (2): 182-5.
6. Utiger RD. Serum triiodothyronine in man. *Ann Rev Med* 1974; 25: 289-302.
7. Refetoff S. Thyroid function tests. In: DeGroot LJ, ed. Endocrinology, Philadelphia: Grune and Stratton, 1979.
8. Spencer CA, Takeuchi M. Inter-laboratory/inter-method differences in functional sensitivity of immunometric assay of thyrotropin and impact on reliability of measurement of subnormal concentrations of thyrotropin. *Clin Chem* 1995; 41: 367-74.
9. Babson AL. The Immulite automated immunoassay system. *Immunoassay* 1991; 14: 83-8.
10. Batzer FR. Hormonal evaluation of early pregnancy. *Fertil Steril* 1980; 34 (1): 1-13.
11. Catt KJ, Dufau ML, Vaitukaitis JL. Appearance of hCG in pregnancy plasma following the initiation of implantation of the blastocyte. *J Clin Endocrinol Metab* 1975; 40 (3): 537-40.
12. Braunstein GD, Rasor J, Danzer H *et al*. Serum human chorionic gonadotrophin levels throughout normal pregnancy. *Am J Obstet Gynecol* 1976; 126 (6): 678-81.
13. Lenton EA, Neal LM, Sulaiman R. Plasma concentration of human chorionic gonadotrophin from the time of implantation until the second week of pregnancy. *Fertil Steril* 1982; 37 (6): 773-8.
14. Zarghami N, Rohbani-Noubar M, Khosrowbeygi A. Thyroid hormones status during pregnancy in normal Iranian women. *Ind J Clin Biochem* 2005; 20 (2): 182-5.
15. Khandakar MA, Ali MS, Kahtun M. Thyroid status of normal pregnant women in Dhaka City. *Mymensingh Med J* 2002; 1: 1-5.
16. Kumar A, Gupta N, Nath T *et al*. Thyroid function tests in pregnancy. *Ind J Med Sci* 2003; 57: 252-8.

ORIGINAL ARTICLE

JIACM 2011; 13(1): 37-42

Profile of poisoning in children and adolescents at a North Indian tertiary care centre

Nowneet Kumar Bhat, Minakshi Dhar**, Sohaib Ahmad***, Vipan Chandar*****

Abstract

***Objectives:** Poisoning in children and adolescents – a common worldwide problem – is a preventable cause of morbidity and mortality. It has not been extensively studied in India. The aim of this study was to determe the profile and outcome of children presenting with acute poisoning at a North Indian tertiary care centre.*

***Methods:** We retrospectively reviewed the hospital records of all children and adolescents aged less than 18 years with definite history of poisoning during the 3-years period from December 2008 to November 2011. We profiled all cases and noted their outcome.*

***Results:** 117 patients presented with acute poisoning during the study period. Median age of our patients was 4 years (range 0.75 - 17.75). The majority of our patients (60.68%) were in the 1 - 6 year age group. Male to female ratio was 1.4:1. The majority of our patients resided in rural areas. Insecticides (37.61%), drugs (25.64%), and Kerosene oil (18.8%) were the agents most frequently implicated. Almost all (97.2%) cases in 1 - 6 year age group were accidental in nature, whereas in the 12 - 18 year group, the majority (80.9%) were suicidal. Thirty-six patients (30.7%) remained asymptomatic, the rest developed symptoms related to toxic ingestion and required symptomatic or definitive treatment. Thirteen patients required ICU care and 7 required intubation and mechanical ventilation. Gastric lavage was done in 34% patients and specific antidote was given to 28 (23.9%) patients. Four patients (3 adolescents and 1 preschool child) died.*

***Conclusion:** The profile of paediatric poisoning noted at our centre was not very different from that observed in other hospital-based studies. Most of our patients were symptomatic and required hospitalisation because of the inherent toxicity of the substances implicated. This is in sharp contrast to developed countries, where common non-toxic household products are commonly implicated. Patient management is improved by consultation with national poison information centre.*

***Key words:** Poisoning, accidental, suicidal, profile, children and adolescents.*

Introduction

Poisoning in children is an important paediatric emergency and is a worldwide problem. It is a common and preventable cause of morbidity and mortality in children. Profile and outcome of poisoned paediatric patients varies in different parts of the world and in a given region is influenced by the prevalent social, occupational, economic, and cultural practices, and also by the availability and the quality of the medical facilities. Thus, epidemiological surveillance specific for each country and region is necessary to determine the extent and characteristics of the problem, according to which related preventive measures can be taken.

Studies from the developed countries show that common nontoxic household products are now implicated in the majority of paediatric poisonings and most of their paediatric patients are discharged after a brief period of observation in the emergency room[1,2,3]. Decrease in cases of paediatric poisoning related to toxic drugs and chemicals in these countries is due to introduction of child proof packs and bottles[4], measures which are yet to be implemented in many of the developing countries.

There are a few studies from India that describe the profile of poisoned paediatric patients from various regions, most of them are now a decade old and none from this part of India[5,6,7]. With increasing urbanisation and rapid socio-economic development in India during the last two decades, some change in paediatric poisoning profile and outcome is to be expected. We carried-out this study in the department of paediatrics of a tertiary care centre located in the rural outskirts of Dehradun, Uttarakhand, with the aim of determining the profile and outcome (discharge after observation, admission and treatment or death) of children presenting with acute poisoning.

***** Assistant Professor, *** Associate Professor, Department of Medicine, * Assistant Professor, **** Professor and Head, Department of Paediatrics, Himalayan Institute of Medical Sciences, Jolly Grant, Doiwala, Dehradun - 248 140, Uttarakhand.***

Material and methods

We retrospectively reviewed the hospital records of all the paediatric patients who presented with acute poisoning during the 3-years period from December 2008 to November 2011. We profiled all cases of paediatric poisoning and noted their outcome. All children and adolescents aged less than 18 years with a definite history of poisoning were included. Children who had food poisoning, toxic or idiosyncratic reaction to prescribed drugs, snake bites and scorpion stings were excluded from the study. Data regarding age, sex, type of residence, type and quantity of substance consumed, time of ingestion, nature of ingestion, time of symptom onset, time of presentation to hospital, symptoms and signs, investigations, diagnostic and therapeutic interventions, and outcome was noted on a predesigned proforma. All the data from the duly filled proforma was transferred to a Microsoft Excel spreadsheet. We analysed the data using SPSS 10. For statistical analysis, Fisher's exact $\chi 2$ test was used where appropriate and a p value less than 0.05 was taken to be significant.

Results

During the 3-year study period from December 2008 to November 2011, 117 children (68 males, 49 females) presented to the paediatric department with acute poisoning, accounting for 1.4% of admissions. Median age of these children was 4 years with a range of 9 months to17 years 9 months. The majority of our children, i.e., 71 (60.68%) were in the 0 - 6 year age group, while 6 - 12 year and 12 - 18-year-old comprised 4 (3.42%) and 42 (35.9%) of our patients respectively (Table I). The boys outnumbered girls with a male to female ratio of 1.4:1. The majority, i.e., 74 (63.2%) of our patients resided in rural areas, whereas 43 (36.8%) patients resided in urban areas. In most of the children, i.e., 80 (68.38%) the poisoning was accidental in nature whereas it was suicidal in 35 (29.91%) and homicidal in 2 (1.71%) (Table I). Of the 71 children aged 1 - 6 years, 97.2% had accidental poisoning, as compared to homicidal (2.8%), and none with suicidal poisoning. However, among the 42 children aged 12 - 18 years, 80.9% had intentionally ingested the poison when compared to 19.1% with accidental poisoning. These differences were statistically significant ($\chi 2 = 82.729$, p value < .05). In this age group, female to male ratio (2.2:1) was significantly higher when compared with the other age group ($\chi 2 = 11.442$, $p = 0.003$). Among the 35 children with suicidal poisoning, an immediate precipitating factor was found in 26 (77.1%). It included argument with family members – especially father – in 19, death of a parent in 5, and psychiatric illness in 2.

Insecticides (37.61%), drugs (25.64%) and kerosene oil (18.8%) were the substances most frequently implicated in our patients. The exact nature of consumed substance could not be determined in 8 (6.83%) of our patients. Among the insecticides, organophosphorous compounds (OPC) were the most common agents implicated accounting for 27.35% of poisoning episodes. The drugs that were ingested included: carbamazepine, phenytoin, valproic acid, triclofos, paracetamol, enalapril, metoclopramide, dapsone, glimepiride, metformin, and atomoxitine (Table II).

Median time of presentation to the paediatric emergency for our patients was 3 hours (range = 30 minutes - 7 days). The median time of presentation was larger for rural patients (5 hrs) when compared to urban ones (2 hrs) ($p < 0.05$).

Thirty-six patients (30.7%) were asymptomatic after 8 - 12 hours of observation; 81 patients (69.3%) had symptoms of poisoning at presentation or developed so during the observation period. Although majority of our patients who were symptomatic had only a single symptom, more than half developed serious symptoms like altered sensorium, respiratory distress, seizures, ataxia, hypotension, cyanosis, burns, renal or liver failure (Table III).

Routine investigations (haemogram, electrolytes) were available in the case of 53 (45.3%) patients. Chest radiograph was advised for 36 (30.7%) patients including 22 with kerosene oil poisoning; and one patient with corrosive ingestion required endoscopy. Gastric lavage was done in 40 (34%) patients. A telephonic consultation with the National Poison Information Centre (NPIC) was obtained for most patients. This standard practice avoids inappropriate intervention or therapy. No patient with kerosene poisoning underwent gastric lavage. Specific antidote was required in 28 (23.9%) patients: for organophosphate (24), metoclopramide (3), and paracetamol (1) poisoning.

Table I: Distribution of 117 children depending on age and type of poisoning.

Age in years	Accidental		Suicidal		Homicidal		Total		Total (M+F)
	M	F	M	F	M	F	M	F	
1 - 6	48	21	0	0	2	0	50	21	71 (60.68)
6 - 12	2	1	0	1	0	0	2	2	4 (3.42)
12 - 18	5	3	11	23	0	0	16	26	42 (35.90)
Total	55	25	11	24	2	0	68	49	117 (100.00)
Total (M + F)	80 (68.38)		35 (29.91)		2 (1.71)		117 (100.00)		

Table II: Major toxic agents involved according to the mode of poisoning.

Poison	Accidental	Suicidal	Homicidal	Total (%)
Insecticides and pesticides	19	24	1	44 (37.61)
Organophosphorous compounds	16	15	1	32
Aluminiun phosphide	0	5	0	5
Zinc sulphide	2	1	0	3
Ethylene dibromide	0	2	0	2
Prallethrin	1	1	0	2
Drugs	27	3	0	30 (25.64)
Carbamazepine	5	0	0	5
Antitussives	4	0	0	4
Paracetamol	2	2	0	4
Metoclopramide	3	0	0	3
Phenytoin	2	0	0	2
Valproic acid	2	0	0	2
Enalapril	2	0	0	2
Triclofos	2	0	0	2
Glimepiride	2	0	0	2
Metformin	2	0	0	2
Dapsone	1	0	0	1
Atomoxitine	0	1	0	1
Kerosene oil	17	5	0	22 (18.80)
Phenyl	3	2	0	5 (4.27)
Corrosives	4	0	0	4 (3.42)
Naphthalene	2	0	0	2 (1.71)
GBHC (gama/benzene/hexachloride)	1	0	0	1 (0.86)
Mercury	1	0	0	1 (0.86)
Unknown	6	1	1	8 (6.83)
Total (%)	80 (68.38)	35 (29.91)	2 (1.71)	117 (100.00)

Table 3 - Common symptoms in patients with poisoning.

Symptom	No of patients (%)
Vomiting	58 (49.6)
Altered sensorium	28 (23.9)
Diarrhoea	19 (16.2)
Respiratory distress	16 (13.6)
Lacrimation/rhinorrhea/salivation	13 (11.1)
Pain abdomen	11 (9.4)
Pneumonitis	10 (8.5)
Fever	9 (7.7)
Seizures	9 (7.7)
Hypotension	8 (6.8)
Facial flushing	6 (5.1)
Oliguria	6 (5.1)
Oral burns	4 (3.4)
Ataxia	3 (2.5)
Headache	3 (2.5)
Dystonia	3 (2.5)
Gastrointestinal bleeding	2 (1.7)
Psychosis	2 (1.7)
Skin rash	2 (1.7)
Dysphagia	2 (1.7)
ARDS	2 (1.7)
Jaundice	2 (1.7)
Cyanosis	1 (0.8)
Acute liver failure	1 (0.8)
ICU care	13 (11.1)
Mechanical ventilation	7 (5.9)
No symptoms	36 (30.7)
Death	4 (3.4)

Outcome

Thirty six (30.7%) patients remained asymptomatic and were discharged after 8 - 12 hours of observation, while 81 (69.3%) required symptomatic or definitive treatment. ICU care and mechanical ventilation was required in 13 (11.1%) and 7 (5.9%) patients respectively. Four patients (3 adolescents and 1 preschool child) died, one each due to zinc sulphide, ethylene dibromide, OPC and paracetamol poisoning.

Discussion

Childhood poisoning is a significant cause of morbidity and mortality in paediatric patients in our country. It is responsible for 0.33% to 7.6% (1.4% in present study) of total admissions in paediatric wards at various hospitals across India[8]. It is very likely that this reporting is an underestimate of the actual magnitude of this problem as many cases go unreported[8]. Various studies from India and abroad show that childhood poisoning is more common in males and a similar pattern was observed in the present study[5-15]. Children between 1 - 6 year were most commonly involved in the present study, a pattern consistent with most of the other studies[2,5-8,14]. Rapid neurological development, leading to increased exploratory activity, and a natural oral curiosity to mouth objects, could be the reasons for frequent involvement of preschool children in poisoning accidents.

Most cases of poisoning in children < 6-year-old are accidental in nature in contrast to adolescents in which it is more often deliberate self-poisoning (suicidal)[2,12-18]. This fact was reaffirmed by our data which showed that 96.9% and 68.5% of our poisoning cases in these age groups were accidental and suicidal in nature respectively. Poisoning can also occur following accidental administration of overdoses of therapeutic drugs (therapeutic error) by parents or pharmacists[19]. Rarely it can be caused by deliberate administration of poison (homicidal) by others or by caregivers as a form of child abuse[20]. The majority of our patients were from a rural background as our hospital caters to a large rural area. The median time to presentation after consumption of the poison was 5 hours for rural patients who presented later than urban patients (2 hrs). This was significantly longer than reported by Kohli *et al*[5]. This could be explained by the longer distance that these rural patients travelled to reach our centre and also by the fact that most of these patients received initial treatment at other health care facilities, before being referred to our hospital.

Insecticides, drugs, and kerosene in decreasing order of frequency, were commonly implicated in our poisoned patients. Previous studies from India and adjoining regions have shown that kerosene is the major culprit in majority

of childhood poisonings accounting for 25 - 50% of cases[5,6,8,14,16,21]. Kerosene is mostly used in our country as a cooking fuel by low income families, and is frequently stored in empty soft drink bottles that are kept on the floor, within easy reach of the children. However, our results show kerosene to be the third leading cause (18.8%) after insecticides (37.61%) and drugs (25.64%). This decline could be explained by wider coverage of LPG services during the last two decades.

Toxicity due to drugs is also fairly common in our country[8], as well as in certain developed countries[22,23] because of lack of availability of child-proof containers and packaging, and also on account of their being stored within easy reach of children. A broad group of agents including anti-epileptics, anti-hypertensives, anti-diabetics, anti-emetics, anti-tussives, and anti-pyretics were implicated in our patients; anti-epileptics being the commonest.

In developed countries, majority of poisonings are due to common non-toxic household products. 40% patients do not develop symptoms, and up to three-fourths of the symptomatic patients are discharged after a brief period of observation in the emergency ward[2,3,24]. In contrast, 69.3% of our patients developed symptoms after poisoning, that ranged from trivial to severe and life-threatening. Common symptoms noted in decreasing order of frequency were vomiting, altered sensorium, diarrhoea, respiratory distress, abdominal pain, fever, and seizures. While 4 of our patients died, 13 required ICU care and 7 required intubation and mechanical ventilation. Inherent toxicity of substances commonly consumed by our patients could possibly explain these findings. Only 30.7% were asymptomatic and could be discharged after 8 - 12 hours of observation.

Singh *et al*[7] studied the pattern of paediatric poisoning in a large north-Indian tertiary care centre and observed a significant decline in kerosene poisoning in the decade 1980 - 89 compared to 1970 - 79. Their data showed a mortality rate of 12.5%[7]. While kerosene still remains an important cause of poisoning in our patients, it was the third most common cause after insecticides and drugs. No deaths were reported due to it. A retrospective analysis of National Poison Centre data (1999 - 2002) published in 2003 showed 1 - 6-year-old to be the commonest group involved in paediatric poisoning[12]. Our findings are in conformity with the findings reported in this study, with approximately 61% of our patients in this age group. Household products were most commonly implicated (approximately in 50% cases) in this report. Mortality data was not reported[12]. Data from another large north-Indian centre published in 1998 suggested kerosene poisoning to be responsible for more than half of the paediatric poisonings[21]. This data also showed insecticides and pesticides to be important contributors[21]. Our results suggest that insecticides (especially OPCs) are the most common cause of childhood poisoning followed by drugs. Kerosene poisoning although decreasing, still remains the third most common cause in our population. A large rural catchment area of our hospital, with agriculture as predominant occupation, along with wider penetration of LPG services right up to rural areas may explain these findings. In contrast to previous reports, our results show a worrisome increase in poisoning due to drugs.

The retrospective nature of the present study is a limitation. This may be responsible for non-availability of data on some of the aspects.

Conclusion

The trends for paediatric poisoning noted at our centre are not very different from those observed in hospital-based studies conducted in other parts of our country. However, the rapid socioeconomic development that our country has seen during the last couple of decades, and with wider availability of LPG as a cooking fuel, kerosene has decreased to the third most common cause of childhood poisoning after insecticides and drugs. In sharp contrast to developed countries, where the majority of poisonings are due to common non-toxic household products and up to three-fourths of patients are discharged after a brief period of observation in the emergency ward[3], most of our patients required hospitalisation because of severe symptoms related to inherent toxicity of the substance ingested. Most of our patients improved with conservative management with only one-fifth requiring a specific antidote, highlighting the important role of good supportive care in the management of poisoned patients.

Although adequate evidence regarding effectiveness of community-based childhood poisoning prevention

programmes is lacking at present[25], simple measures like parental education, safe storage and use of child-proof packaging and containers for drugs and insecticides, could go a long way in preventing a large proportion of morbidity and mortality related to childhood poisoning[26].

Acknowledgements

The authors thank Dr. Prakash Keshaviah, Chairman, Research Committee of the HIMS and his team for permission to publish this manuscript.

Authors contributions: NKB: concept and study design, generation and interpretation of data, drafting, and critical intellectual inputs.

MD, SA: generation and interpretation of data, drafting

VC: concept and study design, critical intellectual inputs.

References

1. Marchi AG, Renier S, Messi G, Barbone F. Childhood poisoning: a population study in Trieste, Italy, 1975 - 1994. *J Clin Epidemiol* 1998; 51: 687-95.
2. Rodgers GC, Matyunas NJ. Poisonong: Drugs, Chemicals and Plants. In: Kleigman RM *et al*, Nelson's Textbook of Pediatrics. Philadelphia: Elsevier: 19th ed. 2010; 2362-6.
3. Lamireau T, Llanas B, Kennedy A *et al*. Epidemiology of poisoning in children: a 7-year survey in a paediatric emergency care unit. *Eur J Emerg Med* 2002; 9: 9-14.
4. Lawson GR, Craft AW, Jackson RH. Changing Pattern of poisoning in children in Newcastle, 1974 - 81. *BMJ* 1983; 287: 15-7.
5. Kohli U, Kuttait VS, Lodha R, Kabra SK. Profile of Childhood Poisoning at a Tertiary Care Centre in North India. *Indian J Pediatr* 2008; 75: 791-4.
6. Sitaram S, Sharma U, Saxena S. Accidental Poisoning in children. *Indian Pediatr* 1985; 22: 757-60.
7. Singh S, Singhi S, Sood NK *et al*. Changing pattern of childhood poisoning (1970 - 1989): Experience of large North Indian hospital. *Indian Pediatr* 1995; 32: 333-6.
8. Dutta AK, Seth A, Goyal PK *et al*. Poisoning in children: Indian scenario. *Indian J Pediatr* 1998; 65: 365-70.
9. Fernando R, Fernando DN. Childhood poisoning in Sri Lanka. *Indian J Pediatr* 1997; 64: 457-60.
10. Goto K, Endoh Y, Kuroki Y, Yoshioka T. Poisoning in children in Japan. *Indian J Pediatr* 1997; 64: 461-8.
11. Yang CC, Wu JF, Ong HC *et al*. Children poisoning in Taiwan. *Indian J Pediatr* 1997; 64: 468-83.
12. Gupta SK, Peshin SS, Srivastava A, Kaleekal T. A study of childhood poisoning at National Poisons Information Centre, All India Institute of Medical Sciences, New Delhi. *J Occup Health* 2003; 45: 191-6.
13. Gauvin F, Bailey B, Bratton SL. Hospitalisations for pediatric intoxication in Washington state, 1987 - 1997. *Arch Pediatr Adolesc Med* 2001; 155: 1105-10.
14. Akhtar S, Rani GR, Anezi FA. Risk factors in acute poisoning in children: a retrospective study. *Kuwait Med J* 2006; 38: 33-6.
15. Shotar AM. Drug poisoning in childhood. *Saudi Med J* 2005; 26: 1948-50.
16. Paudyal BP. Poisoning: pattern and profile of admitted cases in a hospital in central Nepal. *J Nepal Med Assoc* 2005; 44: 92-6.
17. Andiran N, Sarikayalar F. Pattern of acute poisoning in childhood in Ankara: what has changed in twenty years? *Turkish Journal of Pediatrics* 2004; 46: 147-52.
18. Christo KK, Mareus D, Sagerman S, Bennet S. Adolescent suicide and suicide attempts: A population study. *Pediatr Emerg Care* 1988, 4: 32-40.
19. Wiseman HM, Guest K, Murray VSG, Volans GN. Accidental poisoning in childhood: A multicentre survey. I. General epidemiology. *Hum Exp Toxicol* 1987; 6: 293-301.
20. World Health Statistics Annual 1988. Geneva, World Health Organization, 1988.
21. Gupta S, Govil YC, Misra PK *et al*. Trends in poisoning in children: experience at a large referral teaching hospital. *Natl Med J India* 1998; 11: 166-8.
22. Chan TYK, Critchley JAJ. Childhood poisoning in Hong Kong. *HKMJ* 1996; 2: 191-5.
23. Buffoni L, Reboa E, Galletti A *et al*. Epidemiological aspects of poisoning in children observed over a 10-year period. *Clin Toxicol* 1981; 18: 1149-56.
24. McGuigan MA. Common culprits in childhood poisoning: epidemiology, treatment and parental advice for prevention. *Paediatr Drugs* 1999; 1: 313-24.
25. Nixon J, Spinks A, Turner C, McClure R. Community based programs to prevent poisoning in children 0 - 15 years. *Inj Prev* 2004; 10: 2-3.
26. Chan TY. Childhood poisoning: the scope for prevention. *Vet Hum Toxicol* 1998; 40: 361-3.

REVIEW ARTICLE

JIACM 2011; 13(1): 43-7

Coronary artery disease in women: How does it differ from men?

Adarsh Kumar, Harharpreet Kaur**, Pushpa Devi****

Abstract

It is not generally known that coronary artery disease (CAD) is quite common in women and that more women than men die of ischaemic heart disease every year. Also it has become clear in the past few years that CAD in women has many unique features which are not present in men. Obesity, metabolic syndrome, and diabetes disproportionately affect women. They demonstrate more symptoms and/or non-invasive findings suggestive of ischaemic heart disease, yet they have a lower prevalence of significant luminal obstruction compared to men. Women, especially the younger ones, have poorer outcomes. There are substantial delays in healthcare seeking behavior and less use of treatment resources in case of women as compared with men. The timely diagnosis of CAD and assessment of potential risk of coronary artery disease in women are crucial steps toward improving outcomes. The physicians/cardiologists need to be made aware of the differences in the pattern of CAD in the two sexes so that complications can be prevented and optimal management strategies can be outlined.

Key words: Coronary artery disease, women.

Introduction

It is a myth that coronary artery disease (CAD) is less common and less severe in women. During the fertile age they do have a lower incidence of CAD, but after menopause the incidence is the same or higher. They tend to be 10-year-older than men when they first experience ischaemic episode. A 50-year-old woman's risk of dying from coronary artery disease is 10 times greater than her mortality risk from hip fracture and breast cancer combined. Although mortality from ischaemic heart disease (IHD) has declined in the recent years, the decline observed is of lesser magnitude in women as compared to men of a similar age[1]. It is generally not appreciated that the CAD follows a somewhat different pattern in women. The gender based differences in the age of manifestation, risk factors, pathophysiology, clinical manifestations, and diagnosis of CAD need to be understood by the treating physician so that appropriate and timely treatment can be given.

Social factors and gender bias in treatment

Women tend to minimise their symptoms and have poorer psychosocial adjustment following a CAD event. Since research studies have included very few women, the knowledge regarding heart disease in them is poor. Although substantial medical advances have improved outcomes following cardiac ischaemic events, they generally receive suboptimal and less-aggressive therapy. India and many other countries of the world are male dominated societies where females have lesser treatment resources, hence their treatment is delayed and incomplete. Women are less likely to have an ECG when they have an episode of ischaemic heart disease or chest pain. They are less likely to receive aspirin, beta-blockers, statins , antiarrhythmic treatment, thrombolytic therapy, cardiac resynchronisation therapy (CRT), an implantable cardioverter defibrillator (AICD) and cardiac transplant strategies[2]. However, the situation has improved somewhat in the recent years in the developed countries. Earlier, after abnormal noninvasive test results (USA data) women were less likely to be referred for coronary angiography. Now, once angiography has been undertaken, there is currently comparable referral for myocardial revascularisation for both genders in the USA and the UK[3]. In fact, the major contributor to the increased survival among women since 2000 appears to be improved care of established cardiovascular disease rather than a decrease in the occurrence of new cases of cardiovascular disease in women, emphasising the need for preventive interventions. However, the situation is not the same in developing countries like India.

Gender differences in risk factors

In general, women consume an excess of fat and carbohydrates, do not exercise regularly and have less time to rest. Those presenting with CAD are more likely to

**** Professor and Head, Department of Cardiology, ** Associate Professor, Department of Medicine, *** Professor, Department of Microbiology, Government Medical College and Guru Nanak Dev Hospital, Circular Road, Amritsar GPO, Amritsar - 143 001, Punjab.***

have a history of diabetes mellitus, hypertension, and hyperlipidaemia than the male counterparts. While the risk factors for CAD are virtually the same in men and women, the impact of these risk factors is different for both sexes. Elderly hypertensive women and young female smokers are prominent at risk subsets. Diabetes is a more powerful risk factor for women than for men[3]. Diabetic females have significantly greater rates of ischaemic heart disease (IHD) mortality compared with diabetic men[4]. Diabetic women with myocardial infarction (MI) have a doubled risk of re-infarction, and a four-fold greater likelihood of developing heart failure[3]. Diabetes is an independent risk factor for poor outcome of percutaneous interventions (PCI) in women more than men. Apple type obesity and metabolic syndrome are independent risk factors for CAD mortality, more in women than men. According to some studies, low (high-density lipoprotein cholesterol) HDL levels, elevated triglyceride and (Lipoprotein A) Lp(a) levels are a stronger predictor of CAD risk in the fair sex[5].

Importance of cardiac biomarkers

In patients with acute coronary syndromes (ACS), men are more likely to have elevated creatine kinase MB and troponins, whereas women are more likely to have raised C-reactive protein (hs CRP) and brain natriuretic peptide (BNP)[6]. Inflammation is believed to have a role in the pathogenesis of cardiovascular events. Therefore, the measurement of inflammatory markers has been proposed as a method to improve the prediction of the risk of these events, particularly in females. Newer markers like Apolipoprotein E polymorphism and serum amyloid a levels are more important in women[6].

Differences in the pathophysiologic mechanisms

The exact pathophysiology of ischaemic heart disease in women is not known but many theories have been put forward. They develop a different form of vascular disease than men. Structurally, their coronary vessels appear to contain more diffuse atherosclerosis with involvement of the entire circumference of the artery and not localised plaques. These women, in response to atherosclerosis, "remodel" the entire artery so that the lining of the artery becomes thickened throughout, making the plaques flush with the wall of the artery ("Female-pattern" coronary artery disease). On cardiac catheterisation, their coronary arteries appear smooth-walled and normal. Nearly 50% of women undergoing invasive evaluation do not have any flow-limiting coronary stenoses at angiography[7]. However, in such cases the intravascular ultrasound (IVUS) examination revealed that > 80% of women with so-called "normal angiograms" have plaque lesions.

Whereas atherosclerotic plaque rupture, platelet-rich thrombus, and microembolisation may be operative more often in men, small-vessel disease and vascular inflammation may be operative more often in women[6]. Findings from the WISE study[8] have highlighted the pathophysiologic role of microvascular and endothelial dysfunction in CAD in females. On an average, they have coronary vessels 10% smaller than those in men. Functionally, their vessels frequently show impaired vasodilator responses[9]. In such women, an area of ischaemic injury may not be limited because the usual vasorelaxation required for collateral function is abnormal. This theory could help explain why they tolerate acute coronary syndromes (ACS) poorly compared with men and why subsequent heart failure, for example, is not only more frequent but also more lethal in women than men. However, objections have been raised to the above theories as convincing evidence is lacking.

Differences in symptoms

The syndrome of chest pain without obstructive coronary artery disease (CAD) is distinctly more common in women than in men. They are more prone to have atypical symptoms. Almost half of myocardial infarctions in women present with shortness of breath (SOB), nausea, indigestion, a burning sensation in the chest or upper abdomen, dizziness, sweating, vague fullness or fatigue. They are more likely to have neck, arms, back, and shoulder pain. They also tend to experience anxiety and sleep disturbances, as initial cardiac symptoms. A recent study has observed that women reporting frequent angina were more likely to exhibit ischaemia. and this may characterise a female-specific typical angina pattern[10].

Myocardial infarction in women

For women, the initial manifestation of CAD is usually stable angina (47% in women compared to 26% in men) or unstable angina rather than enzyme or ECG-documented acute MI[11]. Among those with MI, fewer women than men had ECG-ST elevation MI, the subset appropriate for coronary thrombolysis.

Pathologic evidence of MI may exist in the absence of

obstructive CAD[12]. Women, in particular young ones (< 55 years), have a worse prognosis from acute MI than their male counterparts, with a greater recurrence of MI[13]. For a woman under 50 years of age, who has a myocardial infarction (MI), the mortality rate is approximately twice that for men. After MI they have greater prevalence of tachycardia and heart block. They also have higher rates of in-hospital complications from myocardial infarction, including strokes, bleeding, shock, and cardiac rupture. The difference does not occur in older women with MI. It is not clear why sex differences in the outcome of MI are seen in young and middle-aged patients but not older patients. Strikingly increased incidence of sudden cardiac death before reaching the hospital have been reported in younger women aged 35 to 44 years[14]. An effective diagnostic strategy is critical in women at risk because up to 40% of initial cardiac events are fatal. Triple-vessel or left main CAD is more common in men, even though more women than men die from CAD. In contrast to these patients with STEMI (ST elevation MI), no sex differences are usually found among the patients with nonST-segment elevation MI after adjustment for risk factors. Women with unstable angina actually did better than men[15].

Coronary artery disease in younger women

Younger women who die suddenly of coronary thrombosis are often cigarette smokers although other risk factors may also contribute. They may have a hypercoagulable state, coronary spasms, or microvascular disease. They tend to have plaque erosion. The younger women have relatively little coronary arterial narrowing and less plaque calcium. Older women who die suddenly of coronary thrombosis are typically hypercholesterolaemic, have plaque rupture in contrast to plaque erosion, and have severe coronary arterial narrowing and far more plaque calcium[16].

Heart Failure (HF) in women

HF most often occurs after ACS, longstanding hypertension, and diabetes. Post-MI heart failure has also increased more in women (46% as compared to 22% in men). Diastolic dysfunction is more common in women as compared to men (43% vs 23%)[17]. A new study found that women receiving cardiac resynchronisation therapy defibrillator (CRT-D) therapy to prevent heart failure progression had significantly better outcomes than men receiving the therapy. Reduction of heart failure in females was twice that of males – 70 per cent versus 35 per cent[18].

Gender-specific optimised diagnostic strategies

In symptomatic women, non-invasive diagnostic studies (exercise ECG and cardiac imaging studies) are recommended for those who are at an intermediate to high pre-test likelihood of coronary artery disease[19]. These include women older than 50 years with risk factors like diabetes and metabolic syndrome.

The exercise ECG has a lower sensitivity for women (with more false positives) than for men, which is compounded by the inability of many women to exercise to adequate intensity. Nonetheless, a true negative exercise ECG has high predictive accuracy for the absence of clinically significant CHD in women. On the whole, treadmill testing has lesser diagnostic value in women as compared to men.

Myocardial perfusion imaging improves the diagnostic accuracy of exercise testing, with particular benefit of technetium 99m sestamibi SPECT imaging. Stress echocardiography in women shows comparable sensitivity and specificity to studies in men and is a valuable test as long as an adequate echocardiographic image can be obtained. It is advisable to follow a sequential approach to testing as it would be a more cost-effective diagnostic strategy[3].

Medical treatment and prevention of CAD in women

Timely and accurate diagnosis can significantly reduce CAD mortality for women; Her risk for developing CAD should be determined before starting the treatment. The latest classification of cardiovascular disease (CVD) risk determination in women proposed by the American Heart Association (2011) is as follows[20].

The criteria for high-risk women (≥ 1 high-risk state) include clinically manifest (coronary heart disease) CHD, clinically manifest cerebrovascular disease, clinically manifest peripheral arterial disease, abdominal aortic aneurysm, end-stage or chronic kidney disease, and diabetes mellitus.

The criteria for at risk women (≥ 1 major risk factor[s]) are cigarette smoking, systolic blood pressure (SBP) ≥

120 mmHg, diastolic blood pressure (DBP) ≥ 80 mmHg, or treated hypertension, total cholesterol ≥ 200 mg/dl, HDL-C < 50 mg/dl, or treated for dyslipidaemia, obesity, particularly central adiposity, poor diet, physical inactivity, family history of premature cardiovascular disease occurring in first-degree relatives in men < 55 year of age or in women < 65 year of age, metabolic syndrome, evidence of advanced subclinical atherosclerosis, [e.g., coronary calcification, carotid plaque, or thickened intima media thickness (IMT)], poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise, systemic autoimmune collagen-vascular disease (e.g., lupus or rheumatoid arthritis), history of pre-eclampsia, gestational diabetes, or pregnancy-induced hypertension.

Ideal cardiovascular health criteria are total cholesterol < 200 mg/dl (untreated), BP < 120/< 80 mmHg (untreated), body mass index < 25 kg/m^2, abstinence from smoking, physical activity at goal for adults > 20 years of age: ≥ 150 min/week moderate intensity, ≥ 75 min/week vigorous intensity, or combination and healthy Dietary Approaches to Stop Hypertension (DASH-like) diet.

Guidelines for the prevention of cardiovascular disease in women published by the Journal of the American College Cardiology (2011 update)[20] recommend that intervention intensity and treatment goals should be tailored to overall risk, with those at highest risk receiving the most intense risk-lowering interventions. Women at high-risk for CVD and without contraindications should receive aspirin, beta-blockers, and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, omega-3 fatty acids in addition to pharmacologic therapy for hyperlipidaemia, hypertension, and diabetes. Aspirin appears to be cost-effective in women ≥ 65 years of age with moderate-to-severe CVD risk. Cardiac rehabilitation is recommended in case of a recent cardiovascular event or procedure or symptoms of heart failure. Women who are at optimal or low-risk for CVD should be encouraged to maintain or further improve their healthy lifestyle practices. They should be advised to consume a diet rich in fruits and vegetables; to choose whole-grain, high-fibre foods; to consume fish, especially oily fish, at least twice a week; to limit intake of saturated fat, cholesterol, alcohol, sodium, and sugar; and avoid trans-fatty acids and to exercise regularly. Women should maintain or lose weight through an appropriate balance of physical activity, caloric intake, and formal behavioural programmes when indicated to maintain or achieve an appropriate body weight (e.g., BMI < 25 kg/m^2 in USA women), waist size (e.g., < 35 inches), or other target metric of obesity. Optimal application of these preventive practices significantly reduces the burden of death and disability caused by CAD in women. A thorough non-invasive assessment should be made for deciding specialised PCI/ CABG procedures keeping in mind the other co-morbid conditions. More and more females should be submitted to post-MI and post-CABG rehabilitation programmes. Dosage of unfractionated heparin, enoxaparin and glycoprotein IIb/IIIa inhibitors (like eptifibatide) have to be given less according to body weight, advanced age, and creatinine clearance, etc., because women are significantly more likely to be overdosed than men.

Results of myocardial revascularisation procedures in women

In-hospital mortality after CABG has been reported to be twice as high in women relative to men. They have more post-operative depression and relatively lower quality of life at 1-year after CABG. In-hospital mortality of both primary PCI as well as elective PCI are also more in women than in men probably because they are older, have smaller arteries and more concomitant diseases[3].

Why the gender differences?

The complete explanation of the unfavourable prognosis of younger women with myocardial infarction is far from elucidated. Is it a bias in patient-care patterns? Or is it a different disease with a more prominent microvascular/ inflammatory component that provokes symptoms of ischaemia without obstructive coronary artery disease. It is possible that unaccounted co-morbidities and risk factors are responsible for the outcome differences. Alternatively, other unknown factors may be involved; among these, social and psychological factors have rarely been considered. A recent study, for example, documented a remarkable decrease in mortality in women with coronary heart disease randomly assigned to a stress-reduction intervention specifically tailored to women[21].

Role of hormone replacement therapy (HRT)

Oestrogen helps in cardioprotection by improving

endothelial function and by decreasing inflammation in the vessel wall. Oestrogen deficiency increases the progression of atherosclerosis. Initial observational studies in the late eighties and early ninieties had shown the role of HRT in women for protection against CAD and its complications. However, the subsequent randomised controlled trials like WHI have shown that instead of cardioprotection, HRT may be causing more CAD and its sequelae on long-term use especially in late-onset cases. The suggestion from the Women's health initiative study that oestrogen intervention at or shortly after the menopause may be protective[22] now known as the "critical timing" hypothesis warrants further investigation. At present, HRT cannot be routinely recommended for cardioprotection against CAD in women.

Conclusions

CAD in women represents an important problem that is difficult to identify early owing to our incomplete understanding of the disease mechanisms. There is a need for recognising CAD as a major public health issue in women so that outcomes can be improved in future with timely medical management. The atypical presentations, the unique risk factors, and more frequent normal coronaries on angiography should be kept in mind. More research is needed to explore these sex-related differences so that optimal gender-specific diagnostic and management strategies can be developed.

References

1. Heron MP, Hoyert DL, Xu J *et al*. Deaths: preliminary data for 2006. *Natl Vital Stat Rep* 2008; 56: 1-52.
2. Enriquez JR, Pratap P, Zbilut JP *et al*. Women tolerate drug therapy for coronary artery disease as well as men do, but are treated less frequently with aspirin, beta-blockers, or statins. *Gend Med* 2008; 5 (1): 53-61.
3. Wenger NK. Clinical characteristics of coronary heart disease in women: emphasis on gender differences. *Cardiovascular Research* 2002; 53: 558-67.
4. Spencer EA, Pirie KL, Stevens RJ *et al*. For the Million Women Study Collaborators. Diabetes and modifiable risk factors for cardiovascular disease: the prospective Million Women Study. *Eur J Epidemiol* 2008; 23: 793-9.
5. Bass KM, Newschaffer CJ, Klag MJ, Bush TL. Plasma lipoprotein levels as predictors of cardiovascular death in women. *Arch Intern Med* 1993; 153: 2209-16.
6. Wiviott SD, Cannon CP, Morrow DA *et al*. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non-ST elevation myocardial infarction. A TACTICS-TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18) substudy. *Circulation* 2004; 109: 580-86.
7. Chokshi NP, Iqbal SN, Berger RL *et al*. Sex and race are associated with the absence of epicardial coronary artery obstructive disease at angiography in patients with acute coronary syndromes. *Clin Cardiol* 2008; 33: 495-501.
8. Bairey Merz, Shaw Leslee, Reis Steven E *et al*. Insights From the NHLBI Sponsored Women's Ischaemia Syndrome Evaluation (WISE) Study. *J Am Coll Cardiol* 2006; 47: 21-9.
9. Pepine CJ, Kerensky RA, Lambert CR *et al*. Some thoughts on the vasculopathy of women with ischemic heart disease. *J Am Coll Cardiol* 2006; 47 (3 Suppl): S30-5.
10. Mieres JH, Heller GV, Hendel RC *et al*. Signs and symptoms of suspected myocardial ischaemia in women: results from the What is the Optimal Method for Ischaemia Evaluation in Women? *Trial M J Womens Health (Larchmt)* 2011; 20 (9): 1261-8. Epub 2011 Jul 8.
11. Rosengren A, Wallentin L, Gitt AK *et al*. Sex, age, and clinical presentation of acute coronary syndromes. *Eur Heart J* 2004; 25: 663-70.
12. Nathaniel RS, Barbara AS, Christopher RA *et al*. Women Have Less Severe and Extensive Coronary Atherosclerosis in Fatal Cases of Ischemic Heart Disease. *American Heart Journal* 2011; 161 (4): 681-8.
13. Alter DA, Naylor CD, Austin PC *et al*. Biology or bias: practice patterns and long-term outcomes for men and women with acute myocardial infarction. *J Am Coll Cardiol* 2002; 39: 1909-16.
14. Gerber Y, Jacobsen SJ, Frye RL *et al*. Secular trends in deaths from cardiovascular diseases: a 25-year community study. *Circulation* 2006; 113: 228-592.
15. Berger JS, Elliott L, Gallup D *et al*. Sex differences in mortality following acute coronary syndromes. *JAMA* 2009; 302: 874-82.
16. Burke AP, Farb A, Malcom GT *et al*. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. *Circulation* 1998; 97: 2110-16.
17. Vasan RS, Larson MG, Benjamin EJ *et al*. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999; 33: 1948-55.
18. Arshad A, Moss AJ, Foster E *et al*. Cardiac resynchronisation therapy is more effective in women than in men. *J Am Coll Cardiol* 2011; 57: 813-20.
19. Mieres JH, Shaw LJ, Arai A *et al*. Role of Non-invasive Testing in the Clinical Evaluation of Women With Suspected Coronary Artery Disease. *Circulation* 2005; 111: 682-96.
20. Mosca L, Benjamin EJ, Berra K *et al*. Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women2011 Update. *J Am Coll Cardiol* 2011; 57: 1404-23.
21. Orth-Gomer K, Schneiderman N, Wang H-X *et al*. Stress reduction prolongs life in Women with coronary disease: the Stockholm Women's Intervention Trial for Coronary Heart Disease (SWITCHD). *Circ Cardiovasc Qual Outcomes* 2009; 2: 25-32.
22. Hsia J, Langer RD, Manson JE *et al*. Conjugated equine oestrogens and coronary heart disease: The Women's Health Initiative. *Archives of Internal Medicine* 2006; 166 (3): 357-65.

REVIEW ARTICLE

JIACM 2011; 13(1): 48-54

Probiotics – the nano soldiers of oral health

Harpreet Singh Grover, Shailly Luthra***

Abstract

The term "probiotic" was first used in 1965 by Lilly and Stillwell, to describe substances secreted by one organism which stimulate the growth of another. FAO (Food and Agriculture Organisation) and the WHO defined probiotics as "live micro-organisms", which, when administered in adequate amounts confer a health benefit on the host. Probiotics utilise naturally occurring bacteria to confer a health benefit when administered in adequate amounts. Most of the probiotics are products of two groups of bacteria, lactobacillus or bifidobacterium. Probiotics have been extensively studied for their health promoting effects. During the last decade they have also been studied for their role in promoting oral health. Even though these studies are yielding positive results, they need to be further evaluated and more studies need to be conducted.

Key words: Probiotics, oral health, lactobacillus, bifidobacterium.

The term 'probiotics' was derived from the Greek word, meaning "for life". The concept of probiotics dates back to 1908, when the Nobel Prize winner, Ukrainian bacteriologist Ilya Metchnikoff suggested that the long-life of Bulgarian peasants resulted from their consumption of fermented milk products[1]. The term "probiotic" was first used in 1965, by Lilly and Stillwell for describing substances secreted by one organism which stimulate the growth of another[2].

Mann and Spoering in 1974 discovered that the fermented yogurt reduced blood serum cholesterol. In 1984 Hull identified the first probiotic species, the *Lactobacillus acidophilus*. Later in 1991, Holcombh identified *Bifidobacterium bifidum*. In 1994, the WHO reckoned probiotics as the next most important in immune defense system following antibiotic resistance. These incidences paved the way for a new concept of probiotics in medicine and dentistry[3].

Probiotics can be defined as living microbes, or as food ingredients containing living microbes, that beneficially influence the health of the host when used in adequate numbers[4]. Marteau *et al*, in 2002, defined them as "microbial preparations or components of microbial cells that have a beneficial effect on health and well-being"[5].

FAO (Food and Agriculture Organisation) of the United Nation and the WHO defined probiotics as "live micro-organisms", which, when administered in adequate amounts confer a health benefit on the host.

Composition of probiotics

Probiotics, which are regulated as dietary supplements and foods, consist of yeast or bacteria. They are available as capsules, gels, pastes, tablets, packets, liquids, or powders, and are contained in various fermented foods, most commonly yogurt or dairy drinks. Probiotic products may contain a single microorganism or a mixture of several species. Probiotics can be bacteria, moulds, yeast. But most probiotics are bacteria. Among bacteria, lactic acid bacteria are more popular[6].

Microorganisms used as probiotics[7,8,9]

Bacteria	
Lactic acid producing bacteria	**Non-lactic acid producing bacteria**
Lactobacillus species	*Bacillus cereus*
L. acidophilus	*Propionibacterium*
L. bulgaricus	*Enterococcus faecalisa*
L. casei	*Enterococcus faeciuma*
L. crispatus	*Escherichia coli Nissle*
L. fermentum	*Streptococcus thermophiles*
L. gasseri	
L. johnsonii	
L. lactis	
L. plantarum	**Non-pathogenic Yeast**
L. reuteri	*Saccharomyces boulardii*
L. rhamnosus GG	
Bifidobacterium species	**Non spore forming and non-flagellated rods or coccobacillus**
B. adolescentis	
B. animalis	
B. bifidum	
B. breve	
B. infantis	
B. lactis	
B. longum	

**** Professor and Head, ** Post-graduate Student, Department of Periodontics and Oral Implantology, SGT Dental College, Hospital and Research Institute, Gurgaon, Haryana.***

Health benefits of different species

The *Lactobacillus species* help in production of enzymes which digest and metabolise proteins and carbohydrates. They also aid in the synthesis of vitamin B and vitamin K and facilitate the breakdown of bile salts. More than 100 species of *L. acidophilus, L. salivarius , L. rhamnous, L. brevis, L. casei,* have been identified. They help enhance innate and acquired immunity as well as cause inhibition of pro-inflammatory mediators. More recently, a study demonstrated that long-term consumption of milk caused a significant reduction in caries risk [10].

Bifidobacterium species are strictly anaerobic and preponderate the large intestines. Over 30 species have been identified. Their assistances include metabolisation of lactose, generation of lactic ions from lactic acid and vitamin synthesis. They also ferment indigestible carbohydrates and produce beneficial short-chain fatty acids. They are believed to be beneficial in reducing antibiotic associated diarrhoea and traveller's diarrhoea. They relieve constipation, alleviate inflammatory bowel disease and prevent DNA damage. Finally, they may prevent or delay the onset of cancers[11,12].

Streptococcus thermophillus and Lactobacillus bulgaricus are the chief cultures used in yogurt production. Most distinguished benefits are to metabolisation of lactose, improvement in lactose intolerance, and antimicrobial activity[15].

Saccharomyces boulardii is a non-colonising lactic acid producing yeast. It checks or treats antibiotic-associated diarrhoea, *C. difficile* related disorders, acute diarrhoea, traveller's diarrhoea in tube-fed patients. They are also beneficial in AIDS-associated diarrhoea and in preventing relapse of Crohn's disease. Most eminent feature is that they secrete proteases and other substances that breakdown bacterial enterotoxins and hinder their binding to intestinal receptors. They also help in enhancement of immune function. Most of the beneficial species enhance vitamin production and decrease serum cholesterol levels and have a role in anticarcinogenic activity[11,12].

Features of a good probiotic[13]

1. It should be a strain which is capable of exerting a beneficial effect on the host animal, e.g., increased growth or resistance to disease.
2. It should be non-pathogenic and non-toxic.
3. It should be present as viable cells, preferably in large numbers.
4. It should be capable of surviving and metabolising in the gut environment, e.g., resistance to low pH and organic acids, and should be able to maintain genetic stability in oral microflora.
5. It should be stable and capable of remaining viable for periods under storage and field conditions.

Probiotics and prebiotics could affect the host in combination by synergistic action. The term probiotics is connected with functional food whereas the term prebiotics is generally used to define non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already established in the colon, and thus in effect improve the host health[9]. These prebiotics include inuline, fructooligosaccharides, galactooligosaccharides and lactulose.

The theory of prebiotics essentially has the same goal as probiotics, which is to improve host health via modulation of the intestinal flora, although by an altered mechanism. However, there are some cases in which probiotics may be beneficial for the probiotic, especially with regard to *Bifidobacteria*. This is known as the symbiotic concept.

Synbiotics are defined as mixtures of probiotics and prebiotics that beneficially affect the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract of the host.

The use of probiotics in antibiotic resistance is termed microbial interference therapy/replacement therapy or bacteriotherapy, and is sometimes used interchangeably along with probiotics.

Although both methods use live bacteria for the inhibition or management of infectious disease, there are a few differences.

Table II: Differences between probiotic therapy and replacement therapy[14].

Replacement therapy	Probiotic therapy
1. Effector strain is not ingested, rather is applied directly on the site of infection.	1. Probiotics are generally dispensed as dietary supplements.
2. Involves dramatic and long-term change in the indigenous microbiota.	2. Hardly a dramatic and long-term change in the microbiota.
3. Colonisation of the site by the effector strain is crucial.	3. Probiotics are able to exert a beneficial effect even without permanently colonising the site.
4. Has a minimal immunological impact.	4. Exerts beneficial effects by influencing the immune system

Probiotics and general health[9]

Probiotics have traditionally been used to treat diseases related to the gastrointestinal tract. Studies suggest that probiotics may be useful in treatment of patients with hypertension, urogenital infections, lactose intolerance, and elevated levels of cholesterol. Other areas of application include probiotic effects against *Helicobacter pylori* infections in the stomach, alcoholic liver disease, small bowel bacterial overgrowth, ulcerative colitis, allergy to milk protein, juvenile chronic arthritis, antioxidative effects, asthma, hepatic encephalopathy and their use as vaccine delivery vehicles.

Mechanism of action of probiotics in the oral cavity

Some of the hypothetical mechanism of probiotics action in the oral cavity is by[8,10,16,17]:

Direct interaction in dental plaque

- Involvement in binding of oral micro-organisms to proteins.
- Action on plaque formation and on its complex ecosystem by competing and intervening with bacterial attachments.
- Involvement in metabolism of substrate and production of chemicals that inhibit oral bacteria.

Indirect probiotic actions are also featured such as:

- Modulating systemic immune function.
- Effect on local immunity.
- Effect on non-immunologic defence mechanisms.
- Regulation of mucosal permeability.
- Probiotics function as antioxidants and also produce antioxidants.
- Prevent plaque formation by neutralising the free electrons.

The mechanisms of probiotic action in the oral cavity could be analogous to those described for the intestine. Possible mechanisms through which probiotics might affect oral health are summarised in Figure 1. Thus far, oral colonisation by probiotic bacteria has often been considered essential for them to exert oral effects; however, the possibility of systemic effects cannot be excluded.

Effect of probiotic strains in the oral health

An essential requirement for a microorganism to be an oral probiotic is its ability to adhere to and colonise surfaces in the oral cavity in long-term[18].

Among the different assays available to study the adhesion phenomenon, two model systems predominate: systems using saliva-coated hydroxyapatite, and hydroxyapatite coated with buffers, proteins, and other substances[19].

Various experiments of adhesion of probiotic strains in the oral cavity have been carried-out using different strains of microorganisms. A comparatively new strain and a prospective candidate for a probiotic, *Weissella cibaria (W. cibaria),* has been isolated from humans and animals globally, as well as from fermented foods, was verified for co-aggregation ability with *Fusobacterium nucleatum (F. nucleatum)* and their attachment to epithelial cells[20].

F. nucleatum plays an important role as a bridge-organism that enables the colonisation of other bacteria by co-aggregation[21]. It has also been suggested that the co-aggregation abilities of *Lactobacilli* species might aid them in forming a barrier that prevents colonisation of pathogenic bacteria, due to the production of a micro-environment around these pathogens in which inhibiting substances were generated by *Lactobacillus* species[22].

There has been successful reporting of co-aggregation between the species of *Weissella cibaria* and *Fusobacterium nucleatum*. The interspecies interaction between the two has also been documented as pronase treatment and led to additional reduction in co-aggregation between both species, thus indicating the proteinaceous character of the interspecies interaction.

In another study, Haukioja *et al* tested the colonisation potential of different commercially available probiotics and *Lactobacillus* and *Bifidobacterium* strains obtained from the dairy production[23]. The results cast light on several controversial points reflecting mechanisms of colonisation in the oral cavity. All test strains demonstrated 24-hour survival rates in saliva but with great variations among the strains in their binding capacity to the saliva-coated surfaces.

Lactobacilli showed better adherence than *Bifidobacteria*. Thus, *Lactobacilli* may compete for the same binding sites on saliva coated hydroxylapatite with *F. nucleatum* which explains their lower colonisation capacity. This phenomenon indicates that probiotics might affect the formation of oral biofilms and modify resident microflora[23].

Probiotics and periodontal disease

Periodontal disease could also benefit from oral probiotic administration. The presence of periodontal pathogens could be regulated by the means of antagonistic interactions. Krasse *et al* observed a decrease in gingival bleeding and reduced gingivitis with the application of *L. reuteri*[24]. In another report by Koll-Klais it was stated that resident population of lactobacillus flora inhibits the growth of *Porphyromonas gingivalis* and *Prevotella intermedia* in 82% and 65% respectively[25].

Probiotic strains included in periodontal dressings at optimal concentration of 108 CFU/ml have been shown to diminish the number of most frequently isolated periodontal pathogens: *Bacteroides* sp., *Actinomyces* sp. and *S. intermedius*, and also *C. albicans*[26].

These authors registered a 10- to 12-month remission period after periodontal treatment by application of the periodontal dressing that comprised collagen and *L. casei*. Grudianov *et al* reported that probiotics were effective in normalisation of microbiota in periodontitis and gingivitis patients when compared with a control group[27].

In a study, Al-Zahrani[28] has shown an inverse association between the intake of dairy products and prevalence of periodontitis. Shimazaki[29] concluded that the routine intake of lactic acid foods may have a beneficial effect on periodontal disease.

In a double-blind, randomised, placebo controlled clinical trial in healthy volunteers without severe periodontitis conducted to evaluate whether the oral administration of probiotic tablets containing *L. salivarius* WB21 could change the clinical parameters of periodontal tissues and the expression of salivary inflammatory markers, it was found that probiotics could be used in the improvement of oral health in subjects at risk of periodontal disease[30]. However, further longitudinal studies are required to confirm these findings.

In another study, Teughels *et al* reported that the subgingival application of a bacterial mixture including *Streptococcus sanguinis, Streptococcus salivarius (S. salivarius)*, and *Streptococcus mitis* after scaling and root planing significantly suppressed the re-colonisation of *Porphyromonas gulae (canine P. gingivalis)* and *P. intermedia* in a beagle dog model[31].

Probiotics and imbalanced oral ecosystem

Halitosis is not a disease but a discomfort normally ascribed to disturbed commensal microflora equilibrium, probiotics are marketed for the treatment of both mouth- and gut-associated halitosis. Kang *et al* have shown a definite inhibitory effect on the production of volatile sulphur compounds (VSC) by *F. nucleatum* after ingestion of *W. cibaria* both *in vitro* and *in vivo*[20]. In children, a marked reduction in the levels of H2S and CH3SH by approximately 48.2% ($p < 0.01$) and 59.4% (p

< 0.05), respectively, was registered after gargling with *W. cibaria* containing rinse. The possible mechanism in the VSC reduction is the hydrogen peroxide generated by *W. cibaria* that inhibits the proliferation of *F. nucleatum*. *S. salivarius,* also a possible candidate for an oral probiotic, has demonstrated inhibitory effect on VSC by competing for colonisation sites with species causing an increase in levels of VSC[27]. Burton *et al* further reported that *S. salivarius* strain K12 produced two antibiotic bacteriocins, i.e., compounds that are inhibitory to strains of several species of Gram-positive bacteria implicated in halitosis[32].

Candida albicans is among the most common infectious agents in the oral cavity. The incidence of yeast infections is higher at older age and under conditions of impaired immunity. Testing the pattern of colonisation of *L. acidophilus* and *L. fermentum*, Elahi *et al* showed a rapid decline in *C. albicans* in mice after the intake of probiotic strains. Continuous consumption of probiotics led to almost undetectable numbers of fungi in the oral cavity, maintaining the protective effect for a prolonged period after cessation of application. The capacity of different *lactobacilli* to stimulate cellular and humoral factors of mucosal protection varies particularly in terms of salivary nitrous oxide and c-interferon levels. Elahi *et al* have observed a correlation between the highest peak of interleukin-4 secretion and complete eradication of *C. albicans*[33].

Probiotics and dental caries[18]

The impact of oral administration of probiotics on dental caries has been studied in several experiments utilising different test strains. *Lactobacillus rhamnosus* GG and *L. casei* have proved their potential to impede growth of these oral streptococci. Aglar *et al* registered a definitive *S. mutans* count reduction after a 2-week consumption of yoghurt containing *L. reuteri*. A temporary reduction in *S. mutans* was observed during the period of yogurt intake and few days after completion of consumption, indicating the requisite of continual administration of the probiotic in order to achieve an effect.

Considering the emerging evidence about the role of probiotics on caries pathogens, however, it has been suggested that the operative approach in caries treatment might be challenged by probiotic implementation with subsequent less invasive intervention in clinical dentistry.

However, more studies are definitely needed before this goal could be achieved.

Safety aspects[18,34]

The issue of safety is of special concern during the past few years due to the increased probiotic supplementation in different food products.

Probiotics are often regulated as dietary supplements rather than as pharmaceuticals or biological products. From the safety point of view, the putative probiotic microorganisms should not be pathogenic, should not have any growth stimulating effects on bacteria causing diarrhoea, and should not have an ability to transfer antibiotic resistance genes. The probiotics should rather be able to maintain genetic stability in oral microflora. The most important area of concern with probiotic use is the risk of sepsis. One theoretical concern with the safety of probiotics is that some have been designed or chosen to have good adherence to the intestinal mucosa, and this is considered important for their mechanism of action. Adherence to the intestinal mucosa may also increase bacterial translocation and virulence. The most potent probiotics, therefore, may have increased pathogenicity.

Lactobacillus bacteraemia is a rare entity, and data on its clinical significance are mainly found through case reports. For the last 30 years there have been approximately 180 reported cases[35]. Clinical characteristics of *Lactobacillus* bacteraemia are highly variable, ranging from asymptomatic to septic shock-like symptoms. Any viable microorganism is capable of causing bacteraemia, especially in patients with severe underlying diseases or in those in an immunocompromised state. Nevertheless, the present literature supports the conclusion that the incidence of *Lactobacillus* bacteraemia is unsubstantial, and that all the cases where it has been registered are individuals with other systemic diseases such as diabetes, cardiovascular diseases, gastrointestinal disorders, malignancies, or organ transplant patients[36]. However, it is evident that careful monitoring is needed in this regard in the future.

Conclusion

Probiotic agents are living microorganisms belonging to the normal flora, with low or no pathogenicity and a positive effect on the health and well-being of the host. Probiotic therapy uses bacterial interference and immunomodulation in the control of several infectious, inflammatory, and immunologic conditions. The use of probiotics in general clinical practice is not far away. The critical step in wider application will be to make products available that are safe and clinically proven in a specific formulation easily accessible to physicians and consumers. Efforts are needed to advance the scientific knowledge of probiotics and determine their mechanisms of action, as well as describe when and why they fail in certain situations. Data on oral probiotics are yet insufficient and it is not known whether the putative probiotic strains could modulate, for example, immune response in the oral cavity as has been suggested to take place in the gut mucosa.

In conclusion, it remains to be seen, however, whether Metchnikoff's ideas are applicable to promoting oral health. Probiotics have made their way into oral healthcare and are more likely to be our friend than our foe. Despite our rapidly increasing knowledge of pathogen-host interactions, the role of beneficial bacteria in preventing the emergence of pathogenic species and oral health remains ambiguous. There is a great need to illuminate the role of the oral beneficial microbiota, to identify beneficial bacteria, and to conduct proper large-scale studies on the usefulness of probiotics to preserve or improve oral health.

References

1. Metchnikoff E. The prolongation of life. Optimistic studies New York: Putman's Sons; 1908; p. 161-83.
2. Lilly DM, Stillwell RH. Probiotics: growth-promoting factors produced by microorganisms. *Science* 1965; 147: 747-8.
3. Elisa KB, Scott BS. Regulatory T-cells in inflammatory bowel disease. *Curr Opin Gastroenterol* 2008; 24 (6): 733-41.
4. Ashwell M. Concept of functional foods 2002. ILSI; (International Life Sciences Institute) Europe: B-1200 Brussels, Belgium ISBN 1-57881-145-7.
5. Marteau P, Cuillerier E, Meance S *et al*. *Bifidobacterium animalis* strain DN-173 010 shortens the colonic transit time in healthy women: a double-blind, randomised, controlled study. *Aliment Pharmacol Ther* 2002; 16 (3): 587-93.
6. Suvarna VC, Boby VG. Probiotics in human health. A current assessment. *Current Science* 2005; 88: 1744-8.
7. Senok AC, Ismaeel AY, Botta GA. Probiotics: facts and myths. *Clin Microbiol Infect* 2005; 11 (12): 958-66.
8. Santosa S, Farnworth E, Jones PJ. Probiotics and their potential health claims. *Nutr Rev* 2006; 64 (6): 265-74.
9. Doron S, Gorbach SL. Probiotics: their role in the treatment and prevention of disease. *Expert Rev Anti Infect Ther* 2006; 4 (2): 261-75.
10. Meurman JH. Probiotics: do they have a role in oral medicine and dentistry? *Eur J Oral Sci* 2005; 113 (3): 188-96.
11. Galdeano CM, de Moreno de Le Blanc A, Vinderola G *et al*. Proposed model: mechanisms of immunomodulation induced by probiotic bacteria. *Clin Vaccine Immunol* 2007; 14 (5): 485-92.
12. deRoos NM, Katan MB. Effects of probiotic bacteria on diarrhoea, lipid metabolism, and carcinogenesis: a review of papers published between 1988 and 1998. *Am J Clin Nutr* 2000; 71 (2): 405-11.
13. Oyetayo VO, Oyetayo FL. Potential of probiotics as biotherapeutic agents targeting the innate immune system. *African Journal of Biotechnology* 2005; 4 (2): 123-7.
14. Agarwal E, Bajaj P, Guruprasad CN *et al*. Probiotics: A Novel Step Towards Oral Health. *AOSR* 2011; 1 (2): 108-15.
15. Sanders ME. Considerations for Use of Probiotic Bacteria to Modulate Human. *Health J Nutr* 2000; 130 (2S Suppl): 384S-390S.
16. Huovinen P. Bacteriotherapy, the time has come. *BMJ* 2001; 323 (7309): 353-4.
17. Salminen MK, Tynkkynen S, Rautelin H *et al*. Lactobacillus bacteraemia during a rapid increase in probiotic use of *Lactobacillus rhamnosus* GG in Finland. *Clin Infect Dis* 2002; 35 (10): 1155-60. Epub 2002 Oct 21.
18. Meurman JH, Stamatova I. Probiotics: contributions to oral health. *Oral Dis* 2007; 13 (5): 443-51.
19. Ostengo Mdel C, Elena Nader-Macías M. Hydroxylapatite beads as an experimental model to study the adhesion of lactic acid bacteria from the oral cavity to hard tissues. *Methods Mol Biol* 2004; 268: 447-52.
20. Kang MS, Na HS, Oh JS. Coaggregation ability of *Weissella cibaria* isolates with *Fusobacterium nucleatum* and their adhesiveness to epithelial cells. *FEMS Microbiol Lett* 2005; 253 (2): 323-9. Epub 2005 Oct 21.
21. Kolenbrander PE. Oral microbial communities: biofilms, interactions, and genetic systems. *Annu Rev Microbiol* 2000; 54: 413-37.
22. Boris S, Suárez JE, Barbés C. Characterisation of the aggregation promoting factor from *Lactobacillus gasseri*, a vaginal isolate. *J Appl Microbiol* 1997; 83 (4): 413-20.
23. Haukioja A, Yli-Knuuttila H, Loimaranta V *et al*. Oral adhesion and survival of probiotic and other lactobacilli and bifidobacteria *in vitro*. *Oral Microbiol Immunol* 2006; 21 (5): 326-32.
24. Krasse P, Carlsson B, Dahl C *et al*. Decreased gum bleeding and reduced gingivitis by the probiotic *Lactobacillus reuteri*. *Swed Dent J* 2006; 30 (2): 55-60.
25. Köll-Klais P, Mändar R, Leibur E *et al*. Oral lactobacilli in chronic periodontitis and periodontal health: species composition and antimicrobial activity. *Oral Microbiol Immunol* 2005; 20 (6): 354-61.
26. Volozhin AI, Il'in VK, Maksimovski-Iu M *et al*. [Development and use of periodontal dressing of collagen and *Lactobacillus casei* 37 cell suspension in combined treatment of periodontal disease of inflammatory origin (a microbiological study)]. *Stomatologiia (Mosk)* 2004; 83 (6): 6-8.
27. Grudianov AI, Dmitrieva NA, Fomenko EV. Use of probiotics Bifidumbacterin and Acilact in tablets in therapy of periodontal

inflammations. *Stomatologiia (Mosk)* 2002; 81 (1): 39-43.

28. Al-Zahrani MS. Increased intake of dairy products is related to lower periodontitis prevalence. *J Periodontol* 2006; 77 (2): 289-94.
29. Shimazaki Y, Shirota T, Uchida K *et al*. Intake of dairy products and periodontal disease: the Hisayama Study. *J Periodontol* 2008; 79 (1): 131-7.
30. Shimauchi H, Mayanagi G, Nakaya S *et al*. Improvement of periodontal condition by probiotics with *Lactobacillus salivarius* WB21: a randomised, double-blind, placebo-controlled study. *J Clin Periodontol* 2008; 35 (10): 897-905. Epub 2008 Aug 24.
31. Teughels W, Newman MG, Coucke W *et al*. Guiding periodontal pocket recolonisation: a proof of concept. *J Dent Res* 2007; 86 (11): 1078-82.
32. Burton JP, Chilcott CN, Moore CJ *et al*. A preliminary study of the effect of probiotic *Streptococcus salivarius* K12 on oral malodour parameters. *J Appl Microbiol* 2006; 100 (4): 754-64.
33. Elahi S, Pang G, Ashman R, Clancy R. Enhanced clearance of *Candida albicans* from the oral cavities of mice following oral administration of Lactobacillus. *Acidophilus* 2005; 141 (1): 29-36.
34. Boyle RJ, Robins-Browne RM, Tang ML. Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr* 2006; 83 (6): 1256-64; quiz 1446-7.
35. Borriello SP, Hammes WP, Holzapfel W *et al*. Safety of probiotics that contain lactobacilli or bifidobacteria. *Clin Infect Dis* 2003; 36 (6): 775-80. Epub 2003 Mar 5.
36. Cannon JP, Lee TA, Bolanos JT, Danziger LH. Pathogenic relevance of Lactobacillus: a retrospective review of over 200 cases. *Eur J Clin Microbiol Infect Dis* 2005; 24 (1): 31-40.

Rozavel F

REVIEW ARTICLE

JIACM 2011; 13(1): 55-59

Asymptomatic bacteriuria in diabetics

BD Sharma, Rohit Bansal**, B Gupta****

Abstract

Asymptomatic bacteriuria (ASB) defined as the presence of at least 10^5 colony-forming units (CFU) per ml of 1 or 2 bacterial species in clean-voided midstream urine sample from an individual without symptoms of a urinary tract infection (UTI)[7], like dysuria, frequency, urgency, strangury, abdominal distention or fever has been reported to occur with two to three times increased frequency in women with diabetes mellitus[1,2]. ASB may lead to symptomatic urinary infection, as well as increase in the frequency of renal dysfunction as one of the long-term adverse effects[3]. Infections with Klebseilla and fungi like Candida and Torulopsis glabrata species are more common and more likely to lead to upper urinary tract infections, though E. coli still remains the most common infecting organism. Diabetes mellitus appears to be an independent risk factor for infection with a multidrug-resistant organism by causing several abnormalities of the host defense mechanisms that might result in a higher risk of certain infections, including UTI. Some other patient related factors like duration of DM, poor metabolic control, sexual activity, UTI during the preceding year and use of certain contraceptive devices have been associated with higher incidence of ASB though no association with micralbuminuria and renal dysfunction has been demonstrated. At present, no consensus exists regarding the treatment of ASB in diabetic patients[37]. However, pregnant women irrespective of whether they are diabetic or not, must be treated with a reasonably long course of antibiotics, that are safe in pregnancy, and as dictated by culture and sensitivity results. The duration of such therapy predictably would be longer in diabetics. Other medical conditions requiring treatment of ASB incude renal transplant recipients, immune-compromised patients, and those with impaired renal functions or single kidney. Some patients with persistent pyuria and sterile urine culture, may be subjected to multiple AFB and fungal cultures in appropriate media and treated accordingly.

Introduction

Asymptomatic bacteriuria (ASB) is defined as the presence of at least 10^5 colony-forming units (CFU) per ml of 1 or 2 bacterial species in clean-voided midstream urine sample from an individual without symptoms of a urinary tract infection (UTI)[7], like dysuria, frequency, urgency, strangury, abdominal distention or fever. The urinary tract is usually sterile. The risk of infection is higher and urinary tract infections are serious clinical problem in patients with diabetes mellitus[5,6]. Besides, the rate of upper urinary tract involvement is much higher than in the general population. Emphysematous cystitis, pyelonephritis, renal and perinephric abscess, bacteraemia, and renal papillary necrosis are more commonly seen in diabetic patients. Infections also cause considerable morbidity and mortality in patients with diabetes mellitus. They may precipitate metabolic derangements and, conversely, the metabolic derangements of diabetes mellitus may facilitate infection. This review aims at having a look at the clinical significance and consequences of ASB in diabetics.

Prevalence

The prevalence of ASB is about 3 times higher in diabetic women (ranging from 15% to 30%) than in non-diabetic women (less than 10%)[7]. Hale Turan and co-workers found ASB in 22 of 123 (17.8%) type 2 diabetes mellitus patients. Zamanzad *et al* reported ASB in 20% of the total study group with type 2 diabetes mellitus. In three of the largest studies, however, the reported prevalence of asymptomatic bacteriuria in diabetic women has been 10% or less[8, 9, 10]. These findings suggest that the prevalence of ASB in diabetic women may be only about twice that in non-diabetic women.

Table I shows the prevalence of ASB in selected populations.

Aetiopathogenesis of ASB

Escherichia coli is the most common organism isolated from patients with ASB. The infecting organisms however are diverse and include Enterobacteriaceae (including *Proteus, Klebsiella, Enterobacter,* and

**** Consultant and Associate Professor, *** Professor and Head, Department of Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi - 110 029,***
***** Senior Resident, Department of Medicine, AIIMS (Main), Ansari Nagar, New Delhi - 110 029.***

Citrobacter species), *Pseudomonas aeruginosa, Enterococcus* species, *Gardnerella vaginalis,* streptococci, staphylococci, *Candida albicans* and other fungi. The percentage of infections with *Klebsiella* species is higher in diabetic persons than in those without diabetes mellitus[12]. Fungal UTIs caused by *Candida* or *Torulopsis glabrata*, are also more common in persons with diabetes mellitus[14]. The normally sterile urinary tract has both non-specific and specific defence mechanisms against infections. The non-specific defence mechanisms of urinary tract include normal commensal flora, flushing effect of voiding, bladder glycocalyx, Tamm-Horsfall glycoprotein, endotoxin induced shedding of bladder epithelial cells, and phagocytosis; and the specific ones are secretory IgA and circulating IgG and IgM antibodies.

Table I: Prevalence of asymptomatic bacteriuria in selected populations.

Population	Prevalence (%)
Healthy premenopausal women	1.0 to 5.0
Pregnant women	1.9 to 9.5
Post-menopausal women (50 to 70 years)	2.8 to 8.6
Patients with diabetes mellitus	
Women	9.0 to 27.0
Men	0.7 to 1.0
Older community-dwelling patients	
Women (older than 70 years)	> 15.0
Men	3.6 to 19.0
Older long-term care residents	
Women	25.0 to 50.0
Men	15.0 to 40.0
Patients with spinal cord injuries	
Intermittent catheter	23.0 to 89.0
Sphincterotomy and condom catheter	57.0
Patients undergoing haemodialysis	28.0
Patients with an indwelling catheter	
Short-term	9.0 to 23.0
Long-term	100

In a retrospective analysis of data on 435 patients with UTIs treated in the emergency department setting, after excluding those with an indwelling urinary catheter, Wright and associates[13] found diabetes mellitus to be an independent risk factor for infection with a multidrug-resistant organism. Diabetes mellitus causes several abnormalities of the host defense system that might result in a higher risk of certain infections, including UTI. Possible underlying mechanisms include:

- Impaired granulocyte function.
- Increased adherence of uro-pathogens to bladder epithelial cells.
- The effects of glucosuria on the growth of uro-pathogens in diabetic persons ("sweet urine" theory).
- Neuropathic bladder, leading to impaired bladder emptying.

Kaneshige and associates[15] found normal phagocytosis but impaired intracellular killing in insulin-treated diabetic patients. However, Balasoiu and colleagues[16] found no differences in the results of granulocyte function tests (chemotaxis, opsonisation, oxidative burst, phagocytosis, and killing capacity) among diabetic women with asymptomatic bacteriuria, nonbacteriuric women, and healthy control subjects. They concluded that granulocyte function impairment is not present in women with diabetes mellitus and bacteriuria and therefore cannot account for the increased prevalence of bacteriuria in this population. Other researchers have sought to determine whether the increased adherence of bacteria to uroepithelial cells in diabetic women is to blame for the increased prevalence of UTIs and asymptomatic bacteriuria in this population. *Escherichia coli* has been reported to adhere more tightly *in vitro* to the vaginal and buccal cells of women with recurrent UTIs than to those of healthy control subjects[17]. Role of blood-group antigens found on uroepithelial cells on bacterial adherence to uroepithelial cells has been studied by Lichodziejewska-Niemierko and colleagues[18] who determined P1 phenotype, Lewis-blood-group phenotype, and secretor status in diabetic patients with and without bacteriuria. They found no difference in these variables between the two groups.

High levels of glucose in the urine of persons with diabetes mellitus might create a culture medium for pathogenic microorganisms. Geerlings and associates[19] found that moderate and severe glucosuria (glucose concentrations between 100 and 1,000 mg/dl) enhanced

bacterial growth *in vivo* concluding thereby that glucosuria may be one factor contributing to the increased prevalence of bacteriuria in diabetic persons.

In both type 1 and type 2 diabetic patients, the presence of cardiovascular autonomic dysfunction, and post-void urinary bladder residue did not increase the odds of developing ASB. However, an earlier study[20] showed that women with diabetes mellitus (type 1 and 2) with ASB had significantly more cardiovascular autonomic function disturbances than non-bacteriuric women. Furthermore, those disturbances did not correlate with the presence of a post-void urinary bladder residue. This lack of association between the presence of diabetic cystopathy and bacteriuria has been shown previously[21].

Predisposing factors

The prevalence of ASB might be influenced by the various patient related factors. Vejlsgaard[26] and Keane *et al*[23] found a correlation between duration of the diabetes mellitus and the presence of ASB in type 1 and 2 diabetic patients. When women with type 2 diabetes were studied separately, some studies showed that a longer duration of the diabetes mellitus[22] increased the risk of developing ASB. These findings however could not be confirmed by other studies[24,25].

Many investigators have scrutinised the possible impact of metabolic control, as evidenced by glycosylated haemoglobin levels (HbA_{1c}), on the prevalence of bacteriuria. While Geerlings *et al*[27], Boroumand *et al*[29], and Ishay *et al*[30] did not find a significant relation, Bonadio *et al*[28] and Kelestirnur *et al*[1] argued that a high HbA_{1c} level may be a risk factor for ASB.

Another risk factor for ASB in type 2 diabetic patients is at least one episode of UTI during the previous year. It has been proposed that, the colonisation of uropathogens in the urinary tract of diabetics after episodes of UTI and also local secretion of cytokines, can lead to the prolonged release of bacteria from urinary tract which may cause bacteriuria. Stamm *et al*[31] studied the natural history of uncomplicated UTI in 51 non-diabetic women who had recurrent UTI (UTI-prone) during a mean follow-up period of 9.3 years. They diagnosed 770 episodes of bacteriuria. 205 (27%) of these episodes were asymptomatic.

It has been found that diabetic women with ASB have lower urinary cytokine concentrations and therefore decreased urinary leukocyte numbers compared with non-diabetic women with ASB[32]. It has previously been shown that no differences in granulocyte functions are present among bacteriuric diabetics, non-bacteriuric diabetics, and non-diabetic control subjects[16]. The increased prevalence of ASB in diabetic patients is probably partly the result of a lower leukocyte number and not the result of a dysfunction of granulocytes.

Some studies have demonstrated in women with and without diabetes mellitus that recent sexual intercourse, the use of a diaphragm[33], or the use of spermicide-coated condoms[34] increases the risk of developing bacteriuria. However, it has been demonstrated in other studies that recent sexual intercourse was not a risk factor[4] with no differences between the different contraceptive methods. Higher age and the lower frequency of sexual intercourse of the patients in these studies (compared with the studies mentioned above) were probably the reasons for the absence of an association between sexual intercourse and bacteriuria.

Advanced age has been proposed as a risk factor for ASB in patients with type 2 diabetes mellitus[27]. Earlier studies, however, have reported contradictory results, with most not showing an increased incidence of ASB in elderly women with diabetes mellitus. Similarly, microalbuminuria and renal dysfunction has not demonstrated any correlation with ASB in recent studies[27,28].

Whether ASB leads to symptomatic UTI is not very clear. Geerlings[35] showed that 23% of patients with diabetes mellitus type 2 and ASB developed symptomatic UTI within 2 months and postulated that ASB was the most important risk factor for developing UTI in diabetic women. Similarly, the role of ASB in the progression of renal disease is unclear. Some studies have reported that declining renal functions is a consequence of ASB in diabetic patients[36].

Management of ASB

Clinical trials dealing with the treatment of ASB in diabetics are limited. In these trials, patients have been

treated for periods ranging from 2 weeks to long-term suppression lasting 67 weeks. At present, no consensus exists regarding the treatment of ASB in diabetic patients[37]. Many experts in the US recommend treating ASB in diabetic patients because of the frequency and severity of upper UTIs[3]. On the other hand, European experts believe that the benefit of treatment is doubtful[38].

At this time, whether diabetic patients with ASB should be treated is not known because whether treatment of ASB prevents the development of symptomatic UTI or a decline in renal function is not clear. Long-term follow-up studies are required to show whether ASB becomes symptomatic and affects renal function in diabetic patients and whether treatment of ASB is warranted.

However, pregnant women irrespective of whether they are diabetic or not, must be treated with a reasonably long course of antibiotics that are safe in pregnancy, as dictated by culture and sensitivity results. The duration of such therapy predictably would be longer in diabetics, with mandatory follow-up cultures to document eradication of infection as first aim and at least three negative monthly cultures for cure.

Figure 2 shows the algorithm for therapeutic approach to ASB. Other medical conditions requiring treatment of ASB incude renal transplant recipients, immuno-compromised patients, and those with impaired renal functions or single kidney. Some patients with persistent pyuria and sterile urine culture, may be subjected to multiple AFB and fungal cultures in appropriate media. The duration of therapy shall also vary as per the isolated microbe. Changing the urinary pH with the use of alkylating or acidifying agents, appropriate to the antibiotic used, along with liberal use of oral fluids are other useful measures, though less frequently recommended these days because of the easy availabilty of potent antibiotics.

Imaging of the urinary system with ultrasound or other appropriate imaging modalities to screen for any evidence of covert or overt obstruction of urinary tract is mandatory especially in patients who have persistent pyuria even after rendering the urine sterile with antibiotics. Such patients may have urinary tract stones.

The proper metabolic control of diabetes mellitus must be ensured and short-term addition of insulin therapy may be considered, if need be. Use of radiographic contrast agents should be avoided especially in patients with poorly controlled diabetes and with even mild renal failure. Only nonionic contrast should be used if such procedures are absolutely essential in the management of such patients. Due precautions must taken to adequately hydrate these patients prior to and after the imaging procedure atleast for 24 - 48 hours, with a close watch on renal functions.

In the end, it must be borne in mind that the presence of urinary infection renders the control of diabetes mellitus difficult, at times necessitating an increase in the dose of oral hypoglycaemic agents/insulin. Eradication of the urinary infection may restore the insulin sensitivity, rendering the patients at risk of hypoglycaemia. Hence, close monitoring of diabetic status is required.

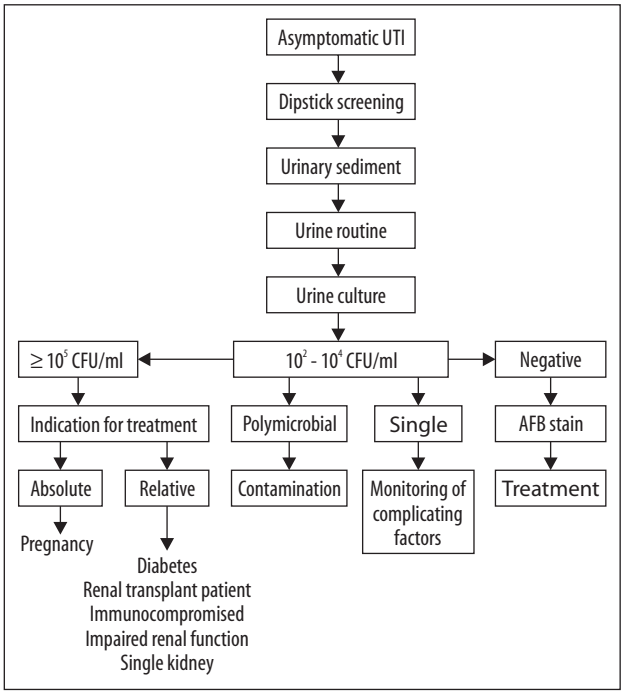


Fig. 1: *Algorithm for therapeutic approach to asymptomatic bacteriuria (ABS).*

References

1. Zhanel GG, Harding GK, Nicolle Lii. Asymptomatic bacteriuria in patients with diabetes mellitus. *Rev Infect Dis* 1991; 13: 150-4.
2. Nicolle LE, Zhanel GG, Harding GK. Microbiological outcomes in women with diabetes and untreated asymptomatic bacteriuria.

World J Urol 2006; 24: 61-5.

3. Patterson 1b, Andriole VT. Bacterial urinary tract infections in diabetes. *Infect Dis Clin North Am* 1997; 11: 735-50.
4. Suzanne E Geerlings *et al*. Asymptomatic bacteriuria may be considered a complication in women with diabetes. *Diabetes Care* 2000; 23: 744-9.
5. Pozzilli P, Leslie RD. Infections and diabetes: mechanisms and prospects for prevention. *Diabet Med* 1994; 11: 935-41.
6. Joshi N, Caputo GM, Weitekamp MR *et al*. Infections in patients with diabetes mellitus. *N Eng J Med* 1999; 341: 1906-12.
7. Harding GK, Zhanel GG, Nicolle LE, Cheang M. Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. *N Engle J Med* 2003; 348 (10): 957-8.
8. Zhanel GG, Nicolle LE, Harding GKM, and the Manitoba Diabetic Urinary Infec Study Group. Prevalence of asymptomatic bacteriuria and associated host factors in women with diabetes mellitus. *Clin Infect Dis* 1995; 21: 316-22.
9. Schmitt JK, Fawcett CJ, Gullickson G. Asymptomatic bacteriuria and haemoglobin A1. *Diabetes Care* 1986; 9: 518-20.
10. Sawers JS, Todd WA, Kellett HA *et al*. Bacteriuria and autonomic nerve function in diabetic women. *Diabetes Care* 1986; 9: 450-64.
11. Cogan R, Nicolle LE, Andrew M, Hootan TM. Asymptomatic bacteriuria in adults. *American Family Physician* 2006; 74: 985-90.
12. Lye WC, Chan RKT, Lee EJ, Kumarasinghe G. Urinary tract infections in patients with diabetes mellitus. *J Infect* 1992; 24: 169-74.
13. Wright SW, Wrenn KD, Haynes M, Haas DW. Prevalence and risk factors for multidrug resistant uropathogens in ED patients. *Am J Emerg Med* 2000; 18: 143-6.
14. Wheat LJ *et al*. Infection and diabetes mellitus. *Diabetes Care* 1980; 3: 187-97.
15. Kaneshige H, Endoh M, Tomino Y *et al*. Impaired granulocyte function in patients with diabetes mellitus. *Tokai J Exp Clin Med* 1982; 7: 77-80.
16. Balasoiu D, van Kessel KC, van Kats-Renaud HJ *et al*. Granulocyte function in women with diabetes and asymptomatic bacteriuria. *Diabetes Care* 1997; 20: 392-5.
17. Schaeffer AJ, Jones JM, Dunn JK. Association of *in vitro Escherichia coli* adherence to vaginal and buccal epithelial cells with susceptibility of women to recurrent urinary-tract infections. *N Engl J Med* 1981; 304: 1062-6.
18. Lichodziejewska-Niemierko M, Niemierko JM, Malinowska A *et al*. P1 blood group, secretion status and susceptibility to asymptomatic bacteriuria in diabetes. *Pol Arch Med Wewn* 1994; 92: 223-7.
19. Geerlings SE, Brouwer EC, Gaastra W *et al*. Effect of glucose and pH on uropathogenic and non-uropathogenic *Escherichia coli:* studies with urine from diabetic and non-diabetic individuals. *J Med Microbiol* 1999; 48: 535-9.
20. Sawers JS, Todd WA, Kellett HA *et al*. Bacteriuria and autonomic nerve function in diabetic women. *Diabetes Care* 1986; 9: 450-64.
21. Frimodt-Moller C *et al*. Diabetic cystopathy: epidemiology and related disorders. *Ann Intern Med* 1980; 92: 318-21.
22. Schmitt JK, Fawcett CJ, Gullickson G. Asymptomatic bacteriuria and haemoglobin A1. *Diabetes Care* 1986; 9: 518-20.
23. Keane EM, Boyko EJ, Barth Reller L, Hamman RF. Prevalence of asymptomatic bacteriuria in subjects with NIDDM in San Luis Valley of Colorado. *Diabetes Care* 1988; 11: 708-12.
24. Brauner A, Flodin U, Hylander B, Ostenson CG. Bacteriuria, bacterial virulence and host factors in diabetic patients. *Diabet Med* 1993; 10: 550-54.
25. Perez Luque EL, de la Luz Villalpando M, Malacara JM. Association of sexual activity and bacteriuria in women with noninsulin-dependent diabetes mellitus. *J Diabete Complications* 1992; 6: 254-7.
26. Vejlsgaard R *et al*. Studies on urinary infection in diabetics. II. Significant bacteriuria in relation to long-term diabetic manifestations. *Acta Med Scand* 1966; 179: 183-8.
27. Geerlings 5F, Stolk RR, Camps MJ *et al*. Asymptomatic bacteriuria may be considered a complication in women with diabetes. *Diabet Care* 2000; 23: 744-9.
28. Bonadio M, Boldrini E, Forotti G *et al*. Asymptomatic bacteriuria in women with diabetes: influence of metabolic control. *Clin Infect Dis* 2004; 38: 41-5.
29. Boroumand MA, Sam L, Abbasi 5H *et al*. Asymptomatic bacteriuria in type 2 Iranian diabetic women: a cross sectional study. *BMC Women's Health* 2006; 6: 4.
30. Ishay A, Lavi I, Luboshitzky R. Prevalence and risk factors for asymptomatic bacteriuria in women with type 2 diabetes mellitus. *Diabet Med* 2006; 23: 185-8.
31. Stamm WE, McKevitt M, Roberts PL, White NJ. Natural history of recurrent urinary tract infections in women. *Rev Infect Dis* 1991; 13: 77-84.
32. Geerlings SE, Brouwer EC, van Kessel CPM *et al*. Cytokine secretion is impaired in women with diabetes mellitus (Abstract). In *Proceedings from the 39th Interscience Conference of Antimicrobial Agents and Chemostherapy.* San Francisco, CA, 1999; 388.
33. Strom BL, Collins M, West SL *et al*. Sexual activity, contraceptive use, and other risk factors for symptomatic and asymptomatic bacteriuria. *Ann Intern Med* 1987; 107: 816-23.
34. Fihn SD, Boyko EJ, Chen CL *et al*: Use of spermicidecoated condoms and other risk factors for urinary tract infection caused by *Staphylococcus saprophyticus*. *Arch Intern Med* 1998; 158: 281-7.
35. Geerlings SE. Consequences of asymptomatic bacteriuria in women with diabetes mellitus. *Arch Intern Med* 2001; 161 (11): 1421-7.
36. Meiland R. Asymptomatic bacteriuria management choices in different patient groups. *Ned Tigdschr Geneeskd* 2002; 146 (14): 659-62.

CASE REPORT

JIACM 2011; 13(1): 60-1

Hypoglycaemia in systemic lupus erythematosus

N Nand, T Gupta***

Abstract

A case of hypoglycaemia due to unusual aetiology (systemic lupus erythematosus) is described.

Key words: Hypoglycaemia, systemic lupus erythematosus.

Introduction

Hypoglycaemia is common in diabetics, when they present in the medical emergency with unconsciousness. However, hypoglycaemia in a non-diabetic young person who had been on normal diet raises eyebrows and is a brainstorming exercise for the treating physician. We report here one such case that had been a known case of systemic lupus erythematosus (SLE) and presented with unconsciousness.

Case summary

A 22-year-old female patient, who was a known case of systemic lupus erythematosus, presented with the complaint of altered sensorium of one day duration followed by one episode of generalised tonic-clonic convulsion associated with frothing from the mouth, up-rolling of eyeballs, and incontinence of urine. On admission, her vitals were stable. On general physical examination, our patient had mucocutaneous lesions. CNS examination was unremarkable. Blood investigations revealed blood sugar < 30 mg%, normal haemogram, and normal liver and kidney function tests. The patient was diagnosed as a case of hypoglycaemia and given 25% dextrose intravenously; and she regained consciousness subsequently. The patient was a known case of lupus nephritis with alopecia and mucocutaneous lesions. She had a positive ANA level with ds-DNA level. She was receiving hydroxychloroquine and prednisolone for lupus. Patient was advised further investigations, i.e., serum insulin, C-peptide and insulin receptor autoantibody to establish that hypoglycaemia was secondary to her basic lupus disease. However, she could not afford these expensive tests. As patient has improvement in her clinical symptoms after giving IV dextrose, so a diagnosis of hypoglycaemia in SLE due to most probably insulin receptor antibody was kept.

Discussion

Hypoglycaemia is basically diagnosed by Whipple's triad, which constitutes 3 findings: blood glucose level < 50 mg/dl, symptoms of hypoglycaemia, and improvement of symptoms by giving glucose. Causes of hypoglycaemia may be high insulin levels as in insulinoma, drugs like sulphonylureas and insulin therapy, and many others[2]. The other causes may include autoantibodies against insulin receptors which are most commonly found in autoimmune disorders like SLE, Sjögren's syndrome, progressive systemic sclerosis, Hashimoto's thyroiditis, and primary biliary cirrhosis[1,3].

Autoantibodies are actually directed towards insulin receptors and have three biological effects which include inhibiting the binding of insulin to the receptor, simulating the effect of insulin, and stimulating the receptor and desensitising the receptor to the effect of insulin[1].

Corticosteroids are the drugs used for suppressing the autoantibody levels and helping in neoglucogenesis. In our case, probably low-dose corticosteroids were not able to control autoantibody titre[4].

Our patient had hypoglycaemia which improved after giving dextrose and it was mostly due to insulin receptor antibodies. The patient's economical status was very low, so we could not perform the tests for insulin and C-peptide levels due to financial constraints. Insulin receptor antibodies test is not done in India and the sample is sent to the USA by some selective laboratories. But as our

**** Senior Professor and Head, Department of Medicine and Nephrology, ** Assistant Professor, Department of Medicine, Pandit B. D. Sharma Post-Graduate Institute of Medical Sciences, Rohtak - 124 001, Haryana.***

patient was receiving low-dose prednisolone, probably the antibody levels were not controlled and the patient had hypoglycaemic symptoms. Therefore we increased the dose of prednisolone, following which the symptoms – including those of mucocutaneous lesions – abated on follow-up.

Therefore SLE should be considered in the differential diagnosis of hypoglycaemia, especially if the patient is young and non-diabetic and having signs/symptoms of multisystem involvement.

References

1. Howard RL, Beck LK, Schneebaum A. Systemic lupus erythematosus presenting as hypoglycaemia with insulin receptor antibodies. *West J Med* 1989; 151 (3): 324-5.
2. Cryer PE. Glucose Homeostasis and Hypoglycaemia. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR (eds). William's Textbook of Endocrinology. Philadelphia: Saunders-Elsevier 2008; 11: 1503-33.
3. Moller D, Ratner R, Borenstein D. Autoantibodies to the insulin receptor as a cause of autoimmune hypoglycaemia in systemic lupus erythematosus. *Am J Med* 2009; 84 (2): 334-8.
4. Kato Y, Ichiki Y, Kitajimar Y. A case of systemic lupus erythematosus presenting as hypoglycaemia due to anti-insulin receptor antibodies. *Rheumatol Inter* 2008; 29: 103-5.

CASE REPORT

JIACM 2011; 13(1): 62-3

Congenital rubella syndrome presenting in the gastroenterology clinic

Rajeev Gupta, Nishant Gangil**, Yogesh Varma***, BS Yadav****, VK Sharma******

Abstract

There are very few cases of congenital rubella syndrome these days reported worldwide. We present one such case in Central India. A 35-year-old female presented with major complaints of progressive abdominal distention along with dyspnoea on exertion. Examination revealed signs of left ventricular failure along with a continous murmur in the pulmonary area. Echocardiography confirmed supravalvular pulmonary stenosis with no evidence of patent ductus arteriosus. Though she never complained, on examination she was found to have sensori-neural hearing loss in the right ear and presenile cataract in her left eye. Her mother had not been vaccinated with the measles, mumps and rubella (MMR) vaccine. With the classic triad of signs along with IgG rubella titre twice the normal range along with no history of her getting vaccinated for rubella, the diagnosis of congenital rubella syndrome was established.

Key words: Pulmonary stenosis, sensorineural deafness, cataract, togavirus.

Introduction

Rubella is an exanthematous illness characterised by nonspecific signs and symptoms, including transient erythematous and sometimes pruritic rash, post-auricular or suboccipital lymphadenopathy, arthralgia, and low grade fever. Clinically similar exanthematous illnesses are caused by parvovirus, adenovirus, and enteroviruses[1]. Moreover, 25 - 50 per cent of rubella infections are subclinical. Rubella is typically a mild disease with minor morbidity and a few complications, unless it is contracted by a pregnant woman (particularly during the first trimester). In such cases, rubella often leads to foetal death or severe congenital defects including blindness, deafness, cardiovascular anomalies and mental retardation[2].

Case report

A 35-year-old female presented with complaints of progressively increasing abdominal distention over the last 3 years along with dyspnoea progressing from New York Heart Association (NYHA) grade 2 to grade 4. The patient had previous records of treatment at a tertiary medical centre where she was treated as chronic liver disease due to altered echotexture of liver, ascites, and splenomegaly.

On examination, our patient had grade 1 clubbing with increased jugular venous pressure (JVP) and pedal oedema. Her left eye showed lenticular opacity which was proven to be presenile cataract on ophthalmologic examination along with very slight haziness in her right eye lens.

Abdominal examination showed tender hepatomegaly with mild splenomegaly with moderate ascites. Respiratory examination was normal. Cardiac examination showed a continous murmur grade IV/VI in pulmonary area radiating to peripheral lung fields, more so on the right side. There was a pansystolic murmur in the tricuspid area as well. Nervous system examination was normal except for 8th cranial nerve. Rinne's test was normal (air conduction > bone conduction) but Weber's test showed lateralisation of sound to the left ear. Audiometry confirmed the finding of severe right-sided hearing loss which ws predominantly sensori-neural.

Her chest X-ray showed cardiomegaly with slight cut-off of right pulmonary artery. Electrocardiogram showed presence of positive 'R' wave in V1 with R:S ratio < 1 in lead I suggestive of right ventricular hypertrophy. Ascitic fluid examination gave transudative picture. Her echocardiogram revealed supravalvular pulmonary stenosis with annular narrowing with peak systolic gradient of 98 mmHg and tricuspid regurgitation with

** Associate Professor, **** Professor, Department of Cardiology,*
*** Post-Graduate Student, ***** Professor and Head, Department of Medicine,*
**** Dean, Gandhi Medical College, Bhopal - 462 016, Madhya Pradesh.*

estimated right ventricular systolic pressure 90 mmHg + estimated right atrial pressure. There was no evidence of patent ductus arteriosus. Her IgG rubella titre was 2.05 units (considered significant over 1.1).

Discussion

With widespread immunisation against rubella, incidence of foetal exposure to rubella has dramatically decreased. Congenital rubella syndrome, caused by rubella virus – a togavirus – is characterised classically by the triad of cataract, deafness, and heart disease – especially patent ductus arteriosus or peripheral pulmonary stenosis. It has been postulated that systolic expansion of the high pressure proximal pulmonary trunk sets the stage for brisk diastolic flow across the stenotic segment as the expanded proximal segment relaxes[3], so small gradients persist into diastole[3]. A modest diastolic gradient following a large systolic gradient explains the occasional occurrence of a prominent systolic murmur followed by a soft, low-pitched diastolic murmur[4]. The foregoing comments are made on the assumption that continous murmurs originate at the sites of stenosis, an assumption that is not necessarily true. Pulmonary arterial obstruction may lead to an increase in the amount of blood flow through bronchial collateral arteries[5]. In one study of pulmonary artery stenosis, a continous murmur was believed to originate in bronchial arteries that were demonstrated by selective angiocardiography[5].

Maternal infection in the first trimester is more serious and affects approximately 50 per cent of foetuses. In offspring of mothers who had rubella during the first trimester, the overall incidence of congenital heart diseases is approximately 65 per cent[6]. Defects resulting from rubella, especially congenital heart disease and deafness, consistently occur in infants infected before the 11th week of pregnancy. Patent ductus arteriosus is present in the majority[6], followed closely by stenosis of the pulmonary arterial branches[7]. Infection after the 16th week of gestation are usually less severe with deafness being the only manifestation. It has other features such as autism, diabetes mellitus, glaucoma, retinopathy, thyroid disorders, spastic diplegia, mental retardation, microcephaly, myopia. There are certain transient features which may be present at birth but resolve later on such as hepatosplenomegaly, lymphadenopathy, cloudy cornea, haemolytic anaemia, meningoencephalitis.

When to suspect maternal rubella infection?

If a pregnant woman has classical rubella rash with or without arthralgia, serum IgG rubella titres should be done. If positive within 7 days of exposure, it suggests mother is immune. If maternal IgG is negative, serum IgM for rubella is done and repeat serum IgG after 3 - 4 weeks to look for a four-fold rise in IgG titres[8].

Post-natal diagnosis of congenital rubella syndrome

As per CDC (Centers for Disease Control and Prevention, USA) guidelines, diagnosis is made by one of the following:

1. Isolation of rubella virus from oropharynx or urine.
2. Detection of rubella specific IgM in cord or neonatal blood.
3. Persistent rubella IgG titres over time, i.e., there is no decline in titre as expected for transplacentally derived maternal IgG. In addition, if there are congenital defects, diagnosis of congenital rubella syndrome is made.

References

1. Burchett SK. Viral Infections. Manual of Neonatal Care, 5th edition: Cloherty JP, Eichenwald EC, Stark AR. Lippincott Williams and Wilkins, Philadelphia, 2004; 282-5.
2. Robertson SE, Featherstone DA, Gacic-Dobo M, Hersh BS. Rubella and Congenital Rubella Syndrome: Global Update. *Rev Pam Salud Publica* 2003; 14 (5): 306-15.
3. Eldridge F, Selzer A, Hultgren H. Stenosis of a branch of the pulmonary artery. An additional cause of continous murmurs over the chest. *Circulation* 1957; 15: 865.
4. Rios JC, Walsh BJ, Massumi RA *et al*. Congenital pulmonary artey branch stenosis. *Am J Cardiol* 1969; 24: 318.
5. Liebow AA, hales MR, Bloomer WE *et al*. Studies on the lung after ligation of the pulmonary artery. II. Anatomical changes. *Am J Pathol* 1950; 26: 177.
6. Gittenberg-de Groot AC, Moulaert AJM, Hitchcock JF. Histology of the persistent ductus arteriosus in cases of congenital rubella. *Circulation* 1980; 62: 183.
7. Hastreiter AR, Joorabchi B, Pujatti G *et al*. Cardiovascular lesions associated with congenital rubella. *J Pediatr* 1967; 71: 59.
8. Corcoran C, Hardie DR. Serologic diagnosis of congenital rubella: a cautionary tale. *Paediatr Infect Dis J* 2005; 24 (3): 286-7.

CASE REPORT

JIACM 2011; 13(1): 64-6

Late presentation of Bochdalek hernia with splenic herniation

G Eswar, K Ramalakshmi**, KV Seshaiah***, Harsha Vardhan Reddy K****, P Vasudev Chetty*****

Abstract

Congenital diaphragmatic hernias usually present in the neonatal period with respiratory distress. Rarely do they present during adult life. Because of confusing shadows in X-rays, there is always possibility of being wrongly diagnosed as pulmonary tuberculosis and other lung diseases as happened with our patient. We report a late presentation of Bochdalek hernia in a 21-year-old male with splenic herniation.

Key words: Congenital diaphragmatic hernia, absent breath sounds, CT imaging.

Introduction

Congenital diaphragmatic hernias primarily manifests in the neonatal period. Bochdalek hernia is the most common type of diaphragmatic hernia. Incidence is 1 in 2,200 to 12,500 live births and was first described by Vincent Alexander Bochdalek in 1848[1]. It is rare in adults and accounts for about 0.17% to 6% of all diaphragmatic hernias[2]. Up to 1992 , only 100 cases of symptomatic adult Bochdalek hernias have been reported in world literature[3]. As the usage of CT imaging is increasing, more and more number of congenital diaphragmatic hernias are being diagnosed in symptomatic as well as asymptomatic patients.

Case report

A 21-year-old unmarried male, non-smoker was admitted in our medical ward with complaints of breathlessness and left-sided chest discomfort of about 2 months duration. There was no history of previous admissions or out-patient visits indicating that symptoms were of recent onset. His dyspnoea progressed from grade 1 to grade 2 over 2 months duration. Chest discomfort was vague and continuous on the left side of chest, and it was more severe after taking his meal. He had no respiratory symptoms like cough, expectoration, etc. There was no history of palpitations. He was non-alcoholic, non-diabetic, and non-hypertensive. He had no bowel symptoms and micturition was normal.

At the onset of symptoms, he was treated elsewhere by a practitioner with antituberculous drugs. There was also history of attempt for pleural aspiration (outside this hospital), which was a dry tap.

On examination he was afebrile with pulse rate 100/min; blood pressure 110/70 mmHg; respiratory rate 22/min; had normal jugular venous pressure; and no pedal oedema.

Examination of respiratory system revealed diminished respiratory movements on left side, and apical impulse could not be felt. Percussion note was resonant in left supra- and infra-clavicular and left supra-scapular regions, with dull note in the remaining areas on left side. Auscultation could not reveal breath sounds, but some interrupted sounds mimicking bowel sounds were heard on left side with apnoeic auscultation.

His CBC and blood biochemistry profile were normal. X-ray chest PA view showed confusing shadows with non-homogeneous opacities with some translucencies in the left upper zone, with homogeneous opacity in left mid- and lower zones. Ultrasound scan revealed presence of bowel loops in the left hemi-thorax. Computed tomography confirmed presence of large and small bowel loops as well as spleen which occupied posteriolaterally in left hemi-thorax, with little hypoplastic lung tissue anteromedially. Contrast CT with oral and IV contrast confirmed the above findings. CT with oral contrast also revealed presence of stomach at lower position near pelvis. ECG showed poor R wave progression. 2-D echocardiogram was unremarkable.

Based on clinical examination and imaging studies, a

**** Professor and Head, ** Associate Professor, *** Assistant Professor, **** Post-Graduate Student, Department of Medicine, Siddhartha Medical College, Vijayawada - 520 002, Andhra Pradesh.***

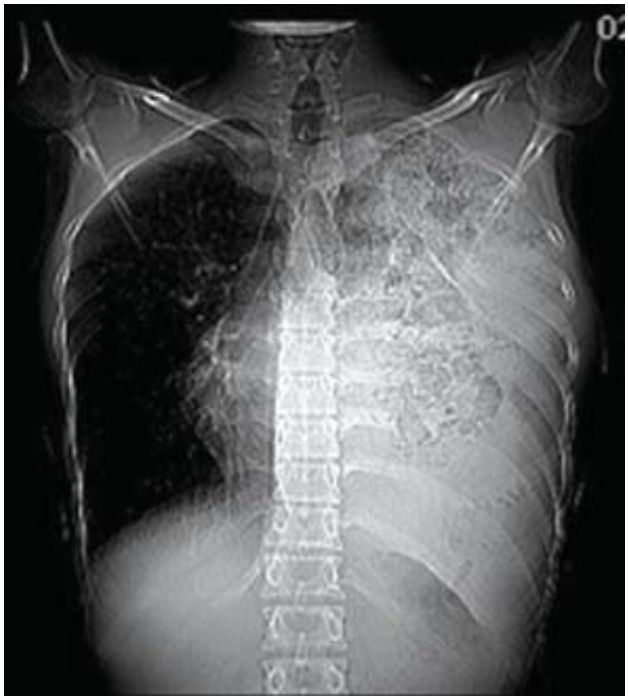


Fig. 1: *X-ray chest PA view showing mixed opacities in the left hemi-thorax with absent diaphragmatic outline.*

diagnosis of late presentation of left sided bochadalek hernia with splenic herniation was made. Elective surgery was planned for this patient, but he refused to undergo surgical treatment.

Discussion

Congenital diaphragmatic hernia may be an isolated defect or part of syndromes, as in Cornelia de Lange syndrome and Fryns syndrome. In the isolated group, 2%

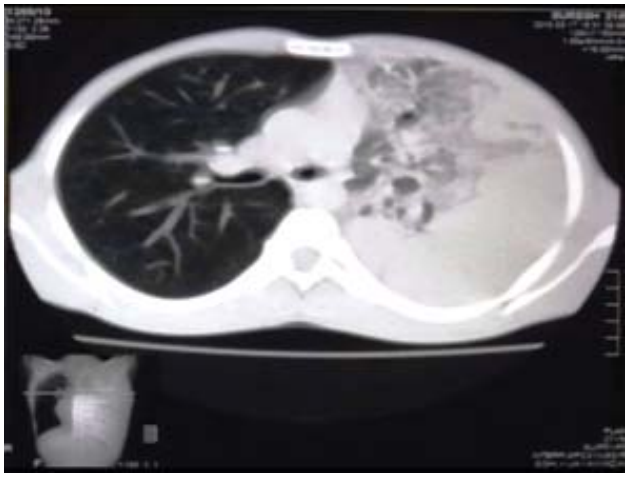


Fig. 2: *CT-chest (plain) showing spleen and interstines in the left hemi-thorax.*

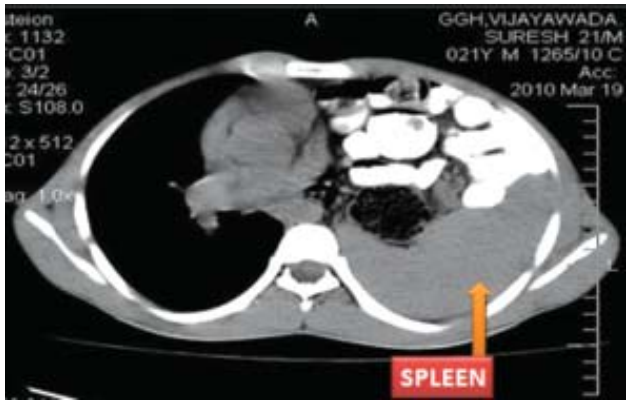


Fig. 3: *CT-chest with oral contrast showing contrast-filled interstinal loops and spleen on the left side.*

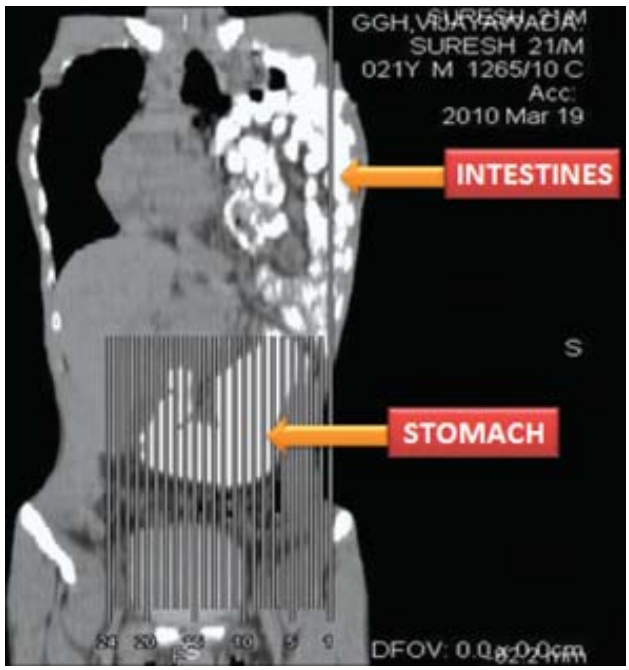


Fig. 4: *Reconstructed image of CT oral contrast showing interstines in the left hemi-thorax and stomach in the lower abdomen.*

are familial. Types of congenital diaphragmatic hernias:-

1. Posterolateral: Bochdalek hernia – Most common type. More common on left side, because left pleuroperitoneal canal closes late[4].
2. Anterior: Morgagni hernia.
3. Posterior: Rare. Aorta and oesophagus are involved.
4. Central: Rare.

Explanations given for late presentation of congenital diaphragmatic hernias are:-

a). Occlusion of diaphragmatic defect by an intra-abdominal viscus[5].

b). Rupture of previously confining pleuroperitoneal sac coincided with onset of symptoms in adults[6].

c. Trauma or increasing abdominal pressure from pregnancy or obesity may be precipitating factors.

Unlike infants who present with respiratory distress, the most frequent presentation in adults is abdominal pain in 50%, followed by vomiting, dyspnoea, and chest pain. Many patients are asymptomatic[7,8].

X-ray chest PA view shows confusing shadows. Differential diagnoses are cystic lung disease, necrotising pneumonia, pleural effusion, etc. Ultrasound scan may be useful in identifying presence of intestines and other masses in thorax. CT scan is most accurate and useful for diagnosis and assessment of diaphragmatic hernias[9].

Late presentation poses difficulty in diagnosis. Hence a careful examination, strong index of suspicion, and CT imaging are needed for a correct diagnosis. One should not be in a hurry to go for invasive procedures like ICD (inter-costal drainage) by wrongly diagnosing as pleural effusion or empyema. In one series, 18% of congenital diaphragmatic hernias were subjected to ICD leading to iatrogenic mortality[10].

Treatment of Bochdalek hernia is operative. Outcome in late presentation of congenital diaphragmatic hernias is good. Most of the morbidity and mortality relates to hypoplasia of the lung and pulmonary hypertension on the affected side[11]. Thus timely diagnosis and proper management is the key to survival.

Left sided Bochdalek hernias are usually associated with lung hypoplasia, extralobar sequestration, malrotation of mid-gut and cardiac defects, whereas right-sided hernias are generally associated with hypoplasia of the right lobe of liver[12].

References

1. Shin MS, Mulligan SA, Baxley WA, Ho KJ. Bochdalek hernia of diaphragm in the adult. Diagnosis by computed tomography. *Chest* 1987; 92: 1098-1101.
2. Mark E, Jeffrey SS, Saini SS, Peter RM. Prevalence of incidental Bochdalek's hernia in a large adult population. *AJR* 2001; 177: 363-6.
3. Marfan MJ, Coulson ML, Siu SK. Adult incarcerated right-sided Bochdalek hernia. *Aust NZ J Surg* 1999; 69: 239-41.
4. Nyhus L, Condon R. Hernia. 4th ed. Philadelphia, Pa: JB Lippincott Co; 1995; 555-66.
5. Nitecki S, Bar-Maor JA. Late presentation of Bochdalek hernia: our experience and review of literature. *Isr J Med Sci* 1992; 28: 711-4.
6. Osebold WR, Soper RT. Congenital posterolateral diaphragmatic hernia past infancy. *Am J Surg* 1976; 131 (6): 748-54.
7. Kirkland JA. Congenital posterolateral diaphragmatic hernia in the adult. *Br J Surg* 1959; 47: 16-22.
8. Ahrend TR, Thompson BW. Hernia of the foramen of Bochdalek in the adult. *Am J Surg* 1971; 122 (5): 612-5.
9. Wilbur AC, Gorodetsky A, Hibbeln JF. Imaging findings of adult Bochdalek hernias. *Clin Imaging* 1994; 18: 224-9.
10. Janokowski A, Klein S. Late diagnosis of congenital diaphragmatic hernia with spleenic infarction presenting as pleural effusion and respiratory distress. *Clin Pediatr* 1995; 34: 549-51.
11. Rees JR, Redo SF, Tanner DW. Bochdalek's hernia. A review of twenty-one cases. *Am J Surg Mar* 1975; 129 (3): 259-61. [Medline].
12. Marleta R. Diaphragmatic anomalies. In: Raffensperger JG, editor. Swanson's Textbook of Paediatric Surgery; 5th ed. NewYork: Appleton and Lange; 1990; 721-35.

CASE REPORT

JIACM 2011; 13(1): 67-69

A rare cause of ascites: Isolated complete pancreatic fracture

OP Jatav, Dharmendra Tiwari**, Muhammed Musthafa M****

Abstract

Abdominal trauma is frequently encountered in day-to-day practice. Many abdominal traumas are clinically obvious. But sometimes many have uncommon and atypical clinical presentations. One of them is pancreatic injury. Pancreatic fracture after blunt injury to abdomen is very rare. An early diagnosis is very difficult initially due to its subtle presentation. Here we present a case where a 35-year-old non-alcoholic man sustained isolated fracture of pancreas at neck region due to blunt abdominal trauma. He was managed in the district hospital and later referred to tertiary care hospital for evaluation and management of refractory ascites.

Key words: Pancreatic injury, blunt abdominal trauma, contrast-enhanced computed tomography (CECT).

Introduction

Isolated pancreatic injury due to blunt abdominal trauma is rare (< 1% of total abdominal injuries), occurring in 0.4 per 100,000 population or 1 per 250,000 hospital admissions[1]. Patients usually present late and may have only minimal symptoms and signs. An early diagnosis of pancreatic trauma can be challenging and difficult because of the lack of correlation between the initial presenting features, radiological and laboratory findings, and the severity of trauma[2]. A combined morbidity and mortality rate of around 50% has been reported in the literature[3]. A high index of clinical suspicion is needed to diagnose a pancreatic injury after a blunt injury to abdomen. Contrast-enhanced computed tomography (CECT) abdomen is the gold standard investigation[4]. Endoscopic retrograde pancreatography (ERCP) also has a role in diagnosing the rupture of the main pancreatic duct[4].

Case history

A 35-year-old male patient was referred to our department as a case of refractory ascites. He was referred after 5 days of treatment as an in-patient in a Government district hospital. His complaints were abdominal distension and abdominal pain. On examination he was afebrile, conscious, cooperative. His pulse rate was 110/min, BP -100/60 mmHg, RR - 16/min. On abdominal examination, marked tenderness was present in the epigastrium and the abdomen was distended due to ascites. The skin over the abdomen was normal. Other systemic examination was within normal limits. His detailed clinical interrogation revealed the previous history of blunt injury to his abdomen due to a forceful direct kick on his upper abdomen during an assault 20 days back; and the clinical symptoms started 2 days after that incidence as mild abdominal pain. He was initially treated conservatively as an out-patient for about 15 days in a peripheral hospital, and then he was admitted for 4 days there and underwent repeated ascitic drainage. When he presented to our department it was already 19 days late.

His initial medical reports showed haemoglobin of 9.2 gm%, TLC - 14,400/mm^3, renal function tests and liver function tests were normal. Chest X-ray and standing X-ray abdomen were also normal. Abdominal ultrasonography showed only ascites; pancreas and all other abdominal organs were within normal limits.

Investigations done again after 19 days showed, TLC - 25,800/mm^3, RBS - 139.8 mg%, serum amylase - 74.6 IU, serum lipase - 3,310.0 IU, lactate dehydrogenase (LDH) 127.2, and renal functions, liver function tests were normal. Ultrasonography of abdomen showed moderate ascites, pancreas showed decreased echogenicity and appeared bulky. There was presence of a pseudopancreatic cyst of 4.5 × 2.5 cm anterior to the

**** Professor and Head, ** Associate Professor, *** Post-Graduate Student, Department of General Medicine, G. R. Medical College, and J. A. Group of Hospitals, Gwalior - 474 001, Madhya Pradesh.***

pancreas. All other organs were within normal limits.

CECT (abdomen) showed post-traumatic complete fracture of pancreas at the neck region with distraction of pancreatic segment 2.9 cm apart with small amount of loculated cystic collections of 3.2 × 4.2 cm involving the fracture site, extending to superior recess of lesser sac (pseudopancreatic cyst), with soft tissue density mass in inferior recess of lesser sac (phlegmon), abutting the posterior wall of the transverse colon with associated diffuse soft-tissue oedema at right pararenal and retroperitoneal fascia – post-traumatic pancreatitis. Moderate ascites was also present.

Based on the clinicoradiologic and biochemical findings, a diagnosis of post-traumatic (blunt abdominal trauma) pancreatic laceration with ductal injury was made. The diagnosis was confirmed during surgery and distal pancreatectomy was performed. But due to post-operative complications, the patient succumbed to death after a few days.

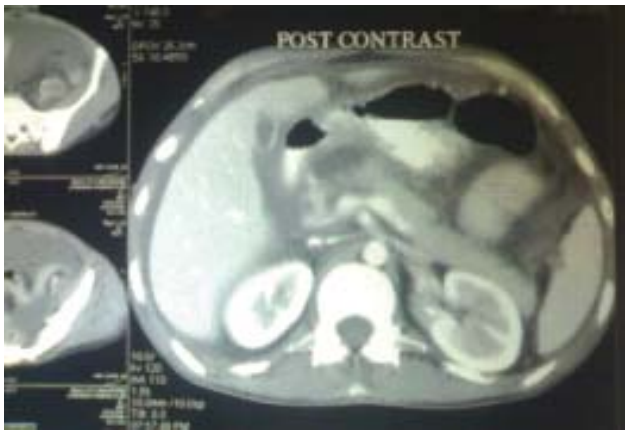


Fig. 1: *Contrast-enhanced computed tomography of abdomen showing complete pancreatic fracture in the neck region with formation of pesudocyst. All other abdominal organs are within normal limits.*

Discussion

Isolated pancreatic injuries are very rare (≈ 1% of all abdominal injuries)[1]. Penetrating injuries are three to four times more common than blunt injuries. In 50 - 98% of pancreatic trauma cases, there are associated injuries to other organs[1]. The deep, central, and retroperitoneal location of pancreas usually protects it from injury. But this also causes diagnostic challenges. Usual causes of pancreatic injury are steering wheel injury, seat belt injury and cycle handle injury[5]. In our case it was a direct kick over his upper abdomen during an assault.

Patients with isolated pancreatic injury after blunt trauma to abdomen usually present late, because of certain factors, viz.: (1) Could be symptom free (≈ 20% of cases; there may be no abdominal pain); (2) Initial laboratory findings may be non-specific, serum amylase may be normal in upto 25% of cases initially[1,3]; (3) Imaging modalities may report normal results in the early phase. A high index of clinical suspicion is needed to diagnose an isolated pancreatic injury after blunt abdominal trauma. Mortality ranges from 20 - 40% in cases of pancreatic injury[3]. Mostly death results from the haemorrhage from nearby vascular structures or as a delayed mortality from intrabdominal sepsis. Patient undergoing surgery after a long period of observation has a higher mortality[6]. Initial serum amylase levels have low sensitivity, but persistent high levels or rising levels may be a reliable indicator of pancreatic injury[1,3].

Ultrasound can also suggest pancreatic injury. The findings are pseudocysts/fluid collections associated with pancreatic injury (hypoechoic areas in relation to pancreas extending to the lesser sac). Post-traumatic pancreatitis may show an enlarged, bulky hypoechoic pancreas.

The gold standard investigation to diagnose pancreatic injury is CECT. Sensitivity is ≈ 85%[7]. But to detect ductal injuries, ERCP (sensitivity 100%) or MRCP is required[4]. The findings on CECT which may indicate pancreatic injury are:[4]

1. Intra- and extra-peritoneal fluid, fluid in the lesser sac
2. Pancreatic haematoma or laceration
3. Diffuse gland enlargement with pancreatitis or focal oedema at the site of injury.

CT findings can also suggest disruption of main pancreatic duct. The presence of a complete fracture is usually associated with a concomitant duct transection[4].

Minor injuries may be managed conservatively, but a major injury especially involving the main pancreatic duct should undergo surgery. Complications include bleeding, abscess formation, recurrent pancreatitis, fistula formation, pancreatic pseudocysts, sepsis, etc [8].

To conclude, isolated pancreatic injury is very rare after blunt abdominal injury. One requires a high index of clinical suspicion to diagnose a pancreatic injury. There may be a delay in presentation after blunt trauma and initial biochemical and radiological investigations may be normal. Contrast-enhanced computed tomography is the gold standard investigation. Pancreatic injury should be diagnosed as early as possible to avoid the serious complications and mortality that can result from delay.

References

1. Bradley EL, III, Young PR, Chang MC *et al*. Diagnostic and initial management of blunt pancreatic trauma. *Ann Surg* 1998; 227: 861-8.
2. Govaert MJ, Ponsen KP, Jonge Lde *et al*. Case report fracture of the pancreas in two patients after a go-kart accident. *J HPB (Oxford)* 2001; 3 (1): 3-6.
3. Jurkovich GJ, Carrico CJ. Pancreatic trauma. *Surg Clin North Am* 1990; 70: 575-93.
4. Mahale A, Gupta A, Paudel K. A rare case of pancreatic injury: A case report. *Ind J Radiol Imag* 2006; 16 (4): 437-9.
5. Buechester Kennan J. Blunt pancreatic trauma. *South Med J* 2000; 43: 383-5.
6. Ivatury R, Nallathambi M, Rao P. Penetratign pancreatic injuries. Analysis of 103 consecutive cases. *Am J Surg* 1990; 56: 90-3.
7. Khanna V, Gulati YS, Sreeram MN, Sharma R. A rare case of pancreatic injury. Case report with imaging perspective. *Asian Oceanian Journal of Radiology* 2004; 9: 64-7.
8. Mittal GS, Kumar S. Case report: isolated pancreatic injury in case of blunt trauma abdomen. *JK Science* 2007; 9 (3).

CASE REPORT

JIACM 2011; 13(1): 70-1

Hyper-acute Guillain-Barré syndrome presenting as respiratory failure

Baiakmenlang Synmon, SK Saxena***, Alok Verma**, Praveen Paliwal**

Abstract

An adult female was admitted with sudden onset altered sensorium, respiratory paralysis, and acute lower motor neuron type of quadriparesis. Clinical examination, cerebrospinal fluid examination, MRI of brain and spinal cord, and nerve conduction studies confirmed this respiratory failure, hyper-acute GBS as a rare presentation of Guillain-Barré syndrome (GBS).

Key word: GBS and Respiratory failure.

Introduction

Guillain-Barré syndrome (GBS) is an acute, frequently severe, and fulminant polyradiculopathy. It is autoimmune in nature, usually preceded by an infection in 70% of cases, or immunisation in some by 1 - 3 weeks. It is characterised by ascending areflexic motor paralysis (LMN type) with or without sensory changes, without bowel and bladder involvement – if involved, is usually transient. The lower cranial nerves may be involved frequently leading to difficulty in handling secretions and maintaining the patency of the airway. Fever and constitutional symptoms are usually absent. Autonomic dysfunction is also common. It is usually progressive in nature and may lead to respiratory failure which can be fulminant.

Case report

A 40-year-old female presented to the emergency room with pain abdomen in the morning, and sudden onset altered sensorium two hours prior to admission. There was no history of headache, recent vaccination, altered bowel habit, fever, seizure, chest pain, cough.

On physical examination, the patient had altered sensorium and was cyanosed with no respiratory effort. Her vitals: blood pressure measured 130/70 mm of Hg, pulse rate was 88/min regular, respiratory rate was 6/min and shallow in nature. There was no pallor, no palpable lymph node, no icterus, no pedal oedema. The patient was intubated and plenty of secretions were aspirated. Therefore, the patient was put on ventilator. The ventilator support was weaned slowly when the patient's respiratory effort was regained.

On examination of the nervous system, patient was in altered sensorium (E1 V1 M1); higher mental function and cranial nerves could not be tested. There was a lower motor neuron type of quadriparesis showing areflexia, power was 0/5 of muscle acting at all joints. There was no fasciculation or wasting. Sensory system could not be tested during admission, but was found to be intact later on when the patient regained consciousness. Plantar response was non-elicitable.

Examination of all other systems was normal.

On laboratory examination, TLC was 10,000 (P - 72, N - 25, E - 02, M - 01), S. creatinine = 0.9, SGOT/SGPT = 21/49, S amylase = 98 IU/l, S. Na/K/Ca = 136/4/4.36. ABG showed CO_2 retention, sugessitive of hypoventilation. CSF examination done after 7 days of hospital stay showed 6 no. of cells (all lymphocyte), sugar = 84 mg% (blood sugar = 102), protein = 227 mg%. MRI of brain was normal and spinal cord showed degenerative changes in cervical region with no signs of myelomalacia. Her NCV was done on the 15th day and was normal.

The patient regained consciousness on the 5th day of admission and improved gradually with conservative management. She was extubated on the 8th day of admission, power of muscle become 3/5 on the 12th day of admission. The patient was then managed conservatively and subsequently discharged from the hospital.

Discussion

Guillain-Barré syndrome (GBS) is an acute, monophasic, symmetrically progressive, peripheral neuropathy. The outcome is generally favourable in most patients. Since the disease may be complicated by respiratory paralysis and/or severe autonomic instability, it is recognised as a

**** Resident, ** Consultant, *** Professor, Department of Medicine, GSVM Medical College, Kanpur - 208 023, Uttar Pradesh.***

potential neurologic emergency that may require intensive care and management. Respiratory failure is the most life-threatening complication of GBS, and 10 - 30% patients may require mechanical ventilation[3]. GBS may cause respiratory failure due to pheripheral neuropathy. This respiratory arrest – if emergency intubation is delayed – may lead to anoxic encephalopathy.

Deaths resulting from GBS are now-a-days uncommon because of advances in all the aspects of intensive care. Mortality rates vary widely, ranging from 1% to 18% in most reports from the West. Patients requiring mechanical ventilation may have higher mortality rates. A much higher mortality rate has been reported from some Indian centres, possibly related to less than ideal intensive care facilities due to financial constraints. In the modern era, death in GBS usually results from pneumonia, sepsis, adult respiratory distress syndrome, and less frequently, from autonomic instability or pulmonary embolism; most of these patients are on ventilatory support. Old age and associated comorbidities increase the risk of death. Ventilatory failure in severe GBS often requires prolonged respiratory support and respiratory intensive care unit (RICU) care. Mechanical ventilation itself is not difficult in these patients with normal lung mechanics and gas exchange. Most patients have a favourable outcome. Mortality is usually related to systemic problems or complications of hospitalisation, rather than the basic disease.

Conclusion

GBS, an acute polyradiculopathy can present rarely as acute respiratory failure for which emergency intubation should be done. This often require mechanical ventilation, and has a favourable outcome unless complicated by secondary causes.

References

1. Eelco FM, Wijdicks MD, Robert D *et al*. Emergency Intubation for Respiratory Failure in Guillain-Barré Syndrome. *Arch Neurol* 2003; 60: 947-8.
2. Stephen L, Arthur K, Asbury. Guillian-Barré syndrome and other immune-mediated neuropathies. Harrison's Principles of Internal Medicine 17th edition 380: 2667-70.
3. Aggarwal AN, Gupta D, Lal V *et al*. Ventilatory management of respiratory failure in patients with severe Guillain-Barré syndrome. *Neurol India* 2003; 51: 203. http://www.neurologyindia.com/text.asp?2003/51/2/203/1083.
4. Gnanamuthu C, Ray D. Outcome of patients with fulminant Guillain-Barré syndrome on mechanical ventilatory support. *Indian J Chest Dis Allied Sci* 1995; 37: 63-9.
5. Lawn ND, Wijdicks EFM. Fatal Guillain-Barré syndrome. *Neurology* 1999; 52: 635-8.
6. Ropper AH. The Guillain-Barré syndrome. *N Engl J Med* 1992; 326: 1130-6.
7. Wijdicks EF, Henderson RD, McClelland RL. Emergency intubation for respiratory failure in Guillain-Barré syndrome. *Arch Neurol* 2003; 60 (7): 947-8. [Medline].

CASE REPORT

JIACM 2011; 13(1): 72-3

Addison's disease presenting as hypoglycaemia

*RC Negi**, J Mahajan*, K Singh*, S Raina***, R Kashyap***, D Gupta*****

Abstract

Addison's disease is a rare endocrine disease. We present the case of a 56-year-old male presenting with non-specific symptoms and developed recurrent symptomatic hypoglycaemia during hospital stay. Clue for the diagnosis of Addison's disease was hypoglycaemia. The patient was managed with hydrocortisone and improved.

Introduction

Addison's disease refers to primary hypo-adrenalism caused by a total or near-total destruction or dysfunction of both adrenal cortices[1,2] Addison's disease usually presents with non-specific clinical features and sometimes only abnormal routine laboratory investigations like hypoglycaemia, hyponatraemia or hyperkalaemia are the clues for diagnosis. The non-specific symptoms are most often ignored or misinterpreted with other common diseases, and this disease is thus under-diagnosed. High index of suspicion is required for diagnosis so that morbidity and mortality can be reduced by early diagnosis and prompt treatment. About 70 per cent of reported cases of Addison's disease are caused by autoimmune disorders and adrenal insufficiency occurs when at least 90 per cent of the adrenal cortex has been destroyed.

Case

A 56-year-old male, not a known diabetic presented with complaints of nausea, vomiting, fatigue, anorexia, pain abdomen and loss of weight for 2 months. Patient had history of loose stools off and on, and feeling of tiredness and loss of 7 kg weight in 2 months. With these complaints, the patient was hospitalised in different health institutions before coming to our hospital. No significant past history was present. General physical examination revealed pallor, mood was depressed, pulse 80/min, BP 100/70 mmHg, RR 20/min, and systemic examination was normal. Possibility of dyspepsia with alarming signs to rule-out GI malignancy was kept and worked-up. Lab Investigations: Hb - 10 gm%, TLC - 7,400/cunm, DLC - P - 64, L - 29, M - 2, E - nil, RBS - 80 mg/dl, B. urea - 29 mg/dl, S. Cr - 0.8 mg/dl, total protein - 4.8 gm/dl and alb. - 3.5 gm/dl, S. bil. total - 0.3 mg/dl, Na - 138 meq/l, K - 3.6 meq/l, Cl - 104 meq/l, S. Alk. Phospatre - 129 units, SGOT - 48 IU, SGPT - 49 IU, PBF normocytic - normochromic anaemia, and thyroid function test was normal. The X-ray chest, ultrasonography abdomen, UGI endoscoy and CT abdomen were normal. ELISA for HIV was non-reactive. Patient developed recurrent episodes of symptomatic hypoglycaemia during hospital stay and RBS recorded was 34 to 60 mg and patient was managed with intravenous dextrose and evaluated for cause of hypoglycaemia. His fasting insulin level was 0. 74 mU/L (N = 1.7 - 31 mU/L), C-peptide level was 0. 19 ng/ml (N = 0.48 - 5.05), serum cortisol level was 0.42 mcg. Cortisol level less than 3 mcg is indicative of primary adrenal insuffiency and so ACTH stimulation test was not done. While giving intravenous dextrose, the patient developed hyponatraemia and fever. Patient was managed with hydrocortisone and he improved symptomatically; and hypoglycaemia, hyponatraemia also improved and the patient became afebrile. Considering the possibility of Addison's disease, a CT scan of head and MRI of abdomen was done to find out the aetiology, but both were normal and therefore the possibility of autoimmune adrenal insufficiency was kept.

Discussion

Thomas Addison (1855)[1] first described the clinical features of primary adrenal insufficiency, which may result from a variety of pathological processes. The characteristic form resulting from primary adreno-cortical insufficiency distinguishes Addison's disease from other forms of adrenal insufficiency which may result from pituitary or hypothalamic diseases. Addison's disease occurs in about 1 in 1, 00,000 people. It occurs

** Junior Resident, ** Senior Resident, *** Assistant Professor, **** Professor, Department of Medicine, Indira Gandhi Medical College, Shimla - 171 001, Himachal Pradesh.*

in all age groups and afflicts men and women equally[2]. The two most common causes of Addison's disease are autoimmune adrenalitis and tuberculosis. Other causes include invasion of glands by neoplastic cells, CMV virus, HIV, haemochromatosis, amyloidosis, haemorrhage (Waterhouse-Friderichsen syndrome) and surgical removal of glands[3]. Addison's disease usually presents with non-specific symptoms like worsening fatigue, muscle weakness, loss of appetite, weight loss, abdominal pain, unusual and excessive sweating on face and/or palms, possible skin rash, flank pain, irritability and depression, a craving for salty foods due to salt loss, hypoglycaemia. In the South-African experience, thirty-nine patients (78%) were hyponatraemic, 26 (53%) were hyperkalaemic, while only 9 (18%) patients had hypoglycaemia[4].

Hyponatraemia and hypokalaemia are the usual findings in many cases of primary adrenal insufficiency. Severe hypoglycaemia is occasionally seen in patients with Addison's disease, more commonly described in children than in adults[4, 5]. The present case also had severe episodes of recurrent hypoglycaemia in absence of hyperkalaemia, hyponatraemia, and hyperpigmentation of skin. Hyperpigmentation may be absent in primary adrenal insufficiency[6] and a normal CT abdomen finding is also possible in a biochemically proven case of Addison's disease[4] as seen in our case. In the early phase of Addison's disease, there may be no demonstrable routine laboratory abnormalities but adrenal reserve is decreased. Basal steroid level may be normal, but sub-normal increase occurs after stress[6]. While giving dextrose infusion, our patient developed fever recorded up to103° F. It is known that if glucose infusion is given without glucocorticoid in patients with Addison's disease, they may develop high fever (glucose fever) followed by collapse and death[7]. Hypoglycaemia was the clue for work-up of Addison's disease in our case and then the patient developing fever while being administered IV glucose without glucocorticoid was also suggestive of Addison's disease retrospectively. The most specific test for diagnosis is the ACTH stimulation (Synacthen) test. Cortisol levels less than 3 mcg are indicative of primary adrenal insufficiency and obviate the need for other tests, while concentration more than 19 mcg excludes the disorder[8]. Imaging of adrenals usually supplements the diagnosis of adrenal insufficiency and points towards the underlying aetiology. Manifestations of Addison's disease are caused by the lack of cortisol and aldosterone. Cortisol is usually replaced orally by hydrocortisone, and aldosterone is replaced by fludrocortisone tablets. To simulate the normal diurnal adrenal rhythm, two-third of the dose should be taken in the morning and the remaining one-third is to be taken late in the afternoon. The doses of each of these medications are adjusted according to the individual's response and any co-existing medical condition. The response may be seen clinically by observing blood pressure, reduction in the hyper-pigmentation, and bio-chemically by improvement in the imbalance of the serum electrolytes, blood sugar and serum renin. Patients with Addison's disease should be taught to treat minor illness with extra salt and fluids. They should always carry the medical identification card stating his or her condition and advised to double the dose of hydrocortisone during intercurrent illness especially in the setting of fever. As long as the proper dose of replacement medication is taken every day, an Addisonian can lead a normal crisis-free life.

Conclusion

Addison's disease usually presents with non-specific symptoms and signs. Sometimes only biochemical abnormality likes hypoglycaemia may be the clue for the diagnosis of Addison's disease. Detailed history, clinical examination and biochemical investigations are a must for suspecting adrenal insufficiency for prompt diagnosis.

References

1. Hiatt JR, Hiatt N. The conquest of Addison's disease. *Am J Surg* 1997; 174: 280-3.
2. Fitzgerald, Chrouisos GP. Information of endocrine and metabolic disease. NIH publications, (www.endocrine.niddk. NIH), 2004; pp 04-30546.
3. A Mayo's Clinical staff. Addison's disease overview (www. Mayoclinic.co), Reg. no. DS00361, 6: 2006.
4. Soule S. Addison's disease in Africa- a teaching hospital experience. *Clin Endocrinol* 1999; 50: 115-20.
5. Unusual presentation of Addison's. *Pak J Med* 2007; 23 (3): 475-8.
6. Harrison's Textbook of Internal Medicine. 16th edition, Vol. 2, p 2242.
7. Ganong WF. Physiological effects of glucocorticoid on water metabolism. *Review of Medical Physiology* 2005; 22: 369-70.
8. Adrenal insufficiency. *Postgraduate Medicine* 2009; XXIII: 52-5.

CASE REPORT

JIACM 2011; 13(1): 74-5

Tuberculous abscess of liver

Deepak Sundriyal, Raj Kumar**, Gopal Chandra Ghosh***, Ajay Chauhan****, MPS Chawla******

Introduction

Liver abscess is a major health problem in India. The disease is usually caused by the intestinal parasite *Entamoeba histolytica*, which invades the intestinal mucosa and then spreads to the liver. Liver abscess can also be bacterial and very infrequently tuberculous. Tuberculosis of the liver usually manifests itself in association with pulmonary involvement or a gastrointestinal tract lesion but rarely as an isolated abscess. We report a case of isolated involvement of liver by tuberculous abscess in an immunocompetent individual.

Case report

A 38-year-old male labourer presented to us with history of pain abdomen localised mainly to right hypochondrium for the last 3 months and low grade fever for the last 1 month. There was no history of chest pain, cough, breathlessness, or jaundice. The patient was non-alcoholic and a non smoker. Past and family history was unremarkable. On examination, the patient was febrile, had blood pressure of 108/68 mmHg, pulse rate of 104/min, mild pallor with no icterus, clubbing, or palpable lymphadenopathy. Chest examination was normal. On abdominal examination, liver was found to be enlarged with a total span of 18 cms; thump sign was positive. No free fluid was appreciable. Rest of the systemic examination was normal. Investigations revealed haemoglobin of 9.5 gm/dl, total leucocyte count of 6,600/cumm, differential counts normal. Erythrocyte sedimentation rate (by WG method) was 35 mm at the end of 1st hour. Liver function and kidney function tests were within normal limits. ELISA for HIV 1 and 2 was non-reactive. Chest skiagram was normal except for slightly elevated right hemi-diaphragm.

Ultrasonography of the abdomen revealed an ill-defined heterogeneous hypoechoic lesion of size 6.6 cm X 4.8 cm in the right lobe of liver – suggestive of liver abscess. Patient was started on intravenous metronidazole therapy keeping in mind the possibility of amoebic liver abscess as the most common aetiology. However, after 5 days of therapy, there was no improvement in the symptoms and the patients continued to be febrile. Needle drainage of the abscess was done and 120 ml of thick yellowish pus was aspirated and was sent for microbiological examination. Pus was found to be positive for acid fast bacilli by Z-N staining. Subsequently, another sample of the pus was sent for polymerase chain reaction assay for *M. tuberculosis* and it was also found to be positive. There was no evidence of any bacteria in pus by Gram's staining or culture. Trophozoites of *Entamoeba histolytica* were not seen. The patient was prescribed antitubercular therapy (H, R, Z, E) and there was considerable improvement after 4 weeks. A repeat ultrasonography of the abdomen was suggestive of regression of the lesion. Patient was discharged, and was advised to complete the therapy.

Discussion

Tuberculosis of the liver can occur in 3 clinical forms: miliary involvement of the liver together with pulmonary tuberculosis, granulomatous hepatitis, and the least common in the form of tuberculoma or abscess[1]. Tuberculous liver abscess is seen in 0.34% of patients with hepatic tuberculosis[2]. It is usually associated with a focus of infection in the lung or gastrointestinal tract[3]. Involvement of the liver without any pulmonary or gastrointestinal involvement is an exceedingly rare condition even in India where tuberculosis is widely prevalent[4-6]. The presenting features of tuberculous liver abscess are non-specific including fever, pain abdomen, anorexia, nausea and rarely jaundice. The clinical diagnosis is difficult owing to the rarity of the disease, non-specific clinical findings, and a subsequent low clinical index of suspicion. Tuberculous liver abscess can be well confused with pyogenic abscess, hepatoma, and amoebic abscess;

** Senior Resident, ** Ex-Senior Resident, *** Post-Graduate Student, **** Assistant Professor, ***** Senior Physician, Department of Medicine, PGIMER-Dr. Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.*

and radiology cannot distinguish between these conditions. The ultimate diagnosis is therefore based on demonstration of the bacteria by AFB staining, PCR assay or culture. Treatment is like any other form of extrapulmonary tuberculosis as per recommendations. It should be kept in mind that an increased number of cases of tuberculous abscess can be seen, in the presence of immunocompromised states, such as acquired immunodeficiency syndrome, diabetes mellitus and chronic renal failure and a high index of suspicion is required for diagnosis of tubercular liver abscess in these patients or those who fail to respond to antiamoebic or antibacterial treatment. Our patient was however immunocompetent and still developed tuberculous abscess.

References

1. Spivach A, Turoldo A, Pistan V *et al*. Inflammatory pseudotumor of the liver: case report and review of the literature. *Chir Ital* 2005; 57: 229-37.
2. Essop AR, Segel I, Posen J *et al*. Tuberculous abscess of the liver: a case report. *S Afr Med J* 1983; 63: 825-6.
3. Leader SA. Tuberculosis of the liver and gallbladder with abscess formation: a review and case report. *Ann Intern Med* 1952; 37: 594-606.
4. Baveja CP, Gumma V, Chaudhary M *et al*. Primary tubercular liver abscess in an immunocompetent adult. *Journal of Medical Case Reports* 2009; 3: 78.
5. Bangroo AK, Malhotra AS. Isolated Hepatic tuberculosis. *J Indian Assoc Pediatr Surg* 2005; 10 (2): 105-7.
6. Gracey L. Tuberculous abscess of the liver. *Br J Surg* 1965; 52: 442-3.

CASE REPORT

JIACM 2011; 13(1): 76-8

Medulary sponge kidney in a child with distal renal tubular acidosis and nephrocalcinosis with failure to thrive

Shashi Kumar, Venkatramana*, Sham Sundar**, HS Mahapatra****

Introduction

Medullary sponge kidney (MSK) is a rare developmental abnormality characterised by cystic dilatation of the collecting tubules in one or more renal pyramids in one or both kidneys. This characterisation contrasts with autosomal recessive polycystic kidney disease and with autosomal dominant polycystic kidney disease, in which cysts predominantly develop along the cortical collecting tubule or the entire nephron, respectively. Medullary cysts give the kidney the gross anatomic appearance of a sponge. In the absence of haematuria, renal calculi, or infection, the disease is an asymptomatic non-progressive condition.

Its precise prevalence is not known but has been estimated to be around 1 in 10,000 to 20,000. Most authors agree that it is a congenital anomaly with delayed expression[1]. It is thought to be secondary to abnormal renal embryogenesis which is supported by the finding of embryonic tissue in the affected papillae. Familial forms have also been described and the dominant mode of transmission has been proposed.

Medullary sponge kidney is usually diagnosed in people aged 10 to 30 years on the basis of laboratory and radiological findings[2]. Discovery of a responsible gene(s) would be a great step forward in understanding the disease.

Case presentation

A 14-year-old male child was admitted to our unit with complaints of pain in both flanks since two years. It occurred off-and-on and was moderate-to-severe colicky in nature. It had no aggravating factors and relieved on its own or sometimes after taking some medication. Now he presented with dysuria and passing of gravel in urine. He is the only child of his parents and there is no history of similar complaints in the parents or other family members.

He was strongly considered to have distal renal tubular acidosis (dRTA) based on the presence of the following reasons:

Failure to thrive, growth retardation, hyperchloraemic metabolic acidosis with respiratory compensation and persistent alkaline urine (pH > 7). Urine and blood tests were performed to confirm the diagnosis and distinguish between proximal and distal renal tubular acidosis.

Investigations performed

Hb	11.3 gm%
TLC	8,700 (N-72, L-24)
Platelet count	2,80,000/cu mm
Random blood sugar	115 mg/dl
Blood urea	20 mg/dl
Serum creatinine	0.5 mg/dl
Na+	133 meq/l
K+	2.2 meq/l
Uric acid	3.2 mg/dl
Ca++	9.6 mg/dl
PO4	3.2 mg/dl
Serum protein	7.7, alb 4.2
Creatinine clearance	116 ml/min
24-hr urinary calcium	306 mg/dl
24-hr urinary protein	Trace
24-hr urinary creatinine	510 mg/dl
Arterial blood gas analysis	pH-7.24, HCO_3-12, CO_2-27
Urine R & M	pH-8, sp. gr.-1007.
Serum anion gap	8

Ultrasonography of KUB region

Rt. kidney - 9.2 x 3.6 cm, with dense calcification in the

** Senior Resident, ** Professor and Head, *** Assistant Professor, Department of Nephrology, PGIMER, Dr. Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.*

calyces with distal acoustic shadow.

Lt. kidney - 9.7 x 4.0 cm, with dense calcification in the calyces with distal acoustic shadow.

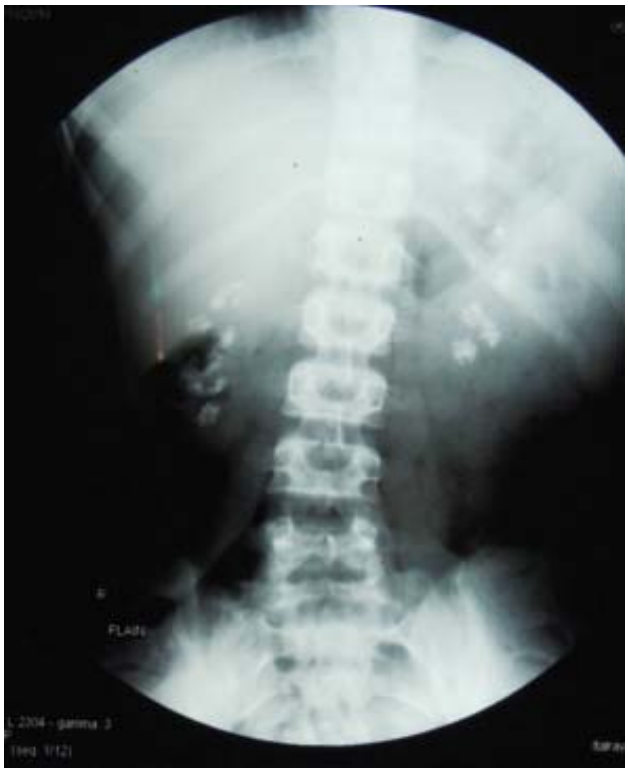


Fig. 1: *Plain film showing calcification in renal areas.*

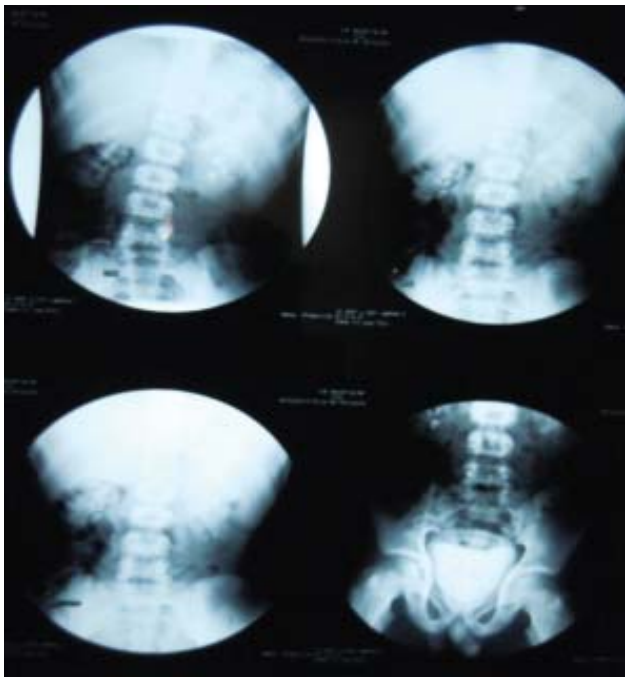


Fig. 2: *Intravenous urography.*

Intravenous urography: s/o dilated calyces with calcification giving paint brush radiating outwards from calyces which is strongly suggestive of MSK (Fig. 1 and 2).

Pathophysiology

The kidney is the primary organ affected in MSK. Ectasia and cystic malformation are present along the intrapyramidal or intrapapillary portion of the medullary collecting duct. Cysts may be heterogeneous in size within one kidney or in both kidneys, ranging in size from 1 - 3 mm. Cysts may communicate and often contain spherical concretions composed of apatite.

The association of medullary sponge kidney with different malformation conditions suggests that it belongs to the developmental disorders that result from disruption of the ureteric bud-metanephric blastema interface. This is based on the occasional presence of remnant embryonal tissue in the affected papillae. Pathological studies suggest that medullary sponge kidney is due to an obstruction of the foetal-collecting duct or to a structural defect caused by hypercalciuria. Although the cause of medullary sponge kidney is unknown, family occurrence suggests a genetic component.

Medullary sponge kidney has been linked to defects in tubular function, including acidification and concentration.

Medullary sponge kidney may be a part of other syndromes and conditions such as Beckwith-Wiedemann syndrome (BWS), hemi-hypertrophy, Caroli disease, Marfan syndrome, Ehlers-Danlos syndrome, and pyloric stenosis. Medullary sponge kidney may occur in as many as 12.5% of cases of BWS, if congenital hemi-hypertrophy is part of the clinical picture. Finally, medullary sponge kidney was recently described in a 10-year-old boy with Rabson-Mendenhall syndrome (i.e., severe insulin resistance, hyperinsulinaemia, post-prandial hyperglycaemia, growth retardation, and dysmorphic features).

Discussion

Our patient clearly developed a significant hyperchloraemic metabolic acidosis with respiratory compensation and normal anion gap associated with

recurrent infection, failure to thrive, and renal nephron calcinosis. The presence of hyperechoic medulla in both kidneys raised the diagnosis of medullary sponge kidney as an underlying cause.

Hyperechoic medulla with or without shadowing has been documented in gout, Sjögren syndrome, systemic lupus erythematosus, hyperparathyroidism[3], glycogen storage diseases, Wilson disease, primary aldosteronism, and pseudo-Bartter syndrome[4]. These aetiologies were excluded in our patient both clinically and from the results of laboratory tests. Intravenous pyelography (IVP) is another radiological measure of high value in diagnosing MSK which is quite suggestive in this case.

There are very few previously published works about MSK associated with d-RTA as a cause of persistent metabolic acidosis and nephron-calcinosis. Renal stones in these patients are usually composed of calcium phosphate and calcium oxalates and risk factors are hyper-oxaluria, hyperuricosuria, hypocitraturia, and decreased absorption of calcium from damaged tubules. Medullary sponge kidney is usually diagnosed in the second or third decade of life due to delayed expression of the gene(s) responsible for this anomaly, although Belde *et al*[5] reported a 5-year-old girl with MSK and growth retardation. This may indicate the possibility of early gene(s) expression in MSK.

The expected renal outcome in MSK is excellent as long as urinary tract infections and nephrolithiasis can be prevented[6]. Although significant renal impairment is uncommon for this disorder, Pesce *et al*[7] reported a child with bilateral medullary sponge kidney and chronic renal insufficiency.

Fewer than 5% of cases are familial and a clear genetic basis for medullary sponge kidney has not been established. The only genetic pattern observed in select pedigrees is an autosomal dominant type of transmission[2,8,9].

Conclusion

Medullary sponge kidney associated with dRTA should be considered in any patient with recurrent renal calculi, recurrent UTI, and failure to thrive presentation.

Simple oral alkali therapy is sufficient to treat some metabolic disorders associated with distal renal tubular acidosis and nephrocalcinosis.

References

1. Davidson AA, Cameron JS, Grunfield JP *et al*. *Oxford Textbook of Clinical Nephrology*. 2nd edition. Edited by: Cameron JS. Oxford University Press; 1998; 2565-9.
2. Hildebrandit F, Jungers P, Grunfield JP. *Diseases of the Kidney*. Volume 1, 6th edition. Edited by: Schrier RW Gottschalk CW. Little Brown; 1997; 499-522.
3. Toyoda K, Miyamoto Y, Ida M *et al*. Hyperechoic medulla of the kidneys. *Radiology* 1989; 173: 431-4.
4. Ginalski JM, Portmann L, Jaeger P. Does medullary sponge kidney cause nephrolithiasis. *AJR Am J Roentgenol* 1990; 155: 299-302.
5. Belde K, Alper S, Oðuz Ô *et al*. Sponge kidney associated with distal renal tubular acidosis in a 5-year-old girl. *Eur J Pediatr* 2006; 165: 648-51.
6. Denis R, Yves P. Medullary sponge kidney-part of congenital syndrome. *Nephrol Dial Transplant* 2001; 16: 634-6.
7. Pesce C, Colombo B, Nicolini E *et al*. Medullary sponge kidney with severe renal function impairment: a case report. *Pediatr Med Chir* 1995; 17: 65-7.
8. Abeshouse BS, Abeshouse GA. Sponge kidney: a review of the literature and a report of five cases. *J Urol* 1960; 84: 252-67.
9. Patriquin HB, O'Regan S. Medullary sponge kidney in childhood. *AJR Am J Roentgenol* 1985; 145: 315-9.

CASE REPORT

JIACM 2011; 13(1): 79-80

A case of Poncet's disease

Gopal Chandra Ghosh, Deepak Sundriyal**, MPS Chawla***, BB Gupta*****

Introduction

This case is reported because of its rarity and in a tuberculosis endemic country like India, one should keep this possibility in mind in patients with polyarthritis as early recognition of this complication is of major importance to avoid delayed initiation of appropriate treatment.

Case description

A 17-year-old female presented to us with complaints of low grade fever and joint pains for 6 weeks. There was no history of photosensitivity, malar rash, oral ulceration, back pain, rash over the body, diarrhoea, or burning micturition. On examination, pallor was present and there was involvement of 2nd, 3rd proximal and distal interphalangeal joints of right hand, right 1st carpometacarpal joint, both shoulder joints, both hips, knees, and ankle joints, and bilateral proximal interphalangeal joints of great toe. There was no lymphadenopathy or erythema nodosum. Investigations revealed an ESR of 32 mmHg per 1st hour, haemoglobin of 8 gm% and microcytic hypochromic picture on peripheral smear. Mantoux test was strongly positive (16 x 12 mm). Rheumatoid factor, anti-nuclear antibody, anti-CCP antibodies, c-ANCA and p-ANCA were negative. Urine routine examination was normal. Chest X-ray (Fig. 1) revealed nodular opacities bilaterally in mid-zones. Sputum Ziehl-Neelsen (Z-N) staining was positive for AFB (+++). CECT chest revealed multiple nodular opacities in both lung fields. X-rays of the involved joints (Fig. 2) showed periarticular soft tissue swelling, and there were no changes of active tuberculosis. Joint fluid aspiration revealed leucocyte count of 5 x 10^9/L; there were no crystals and the cultures were sterile.

We gave the patient anti-tubercular therapy. On follow-up she became afebrile, and joint pains and joint swelling reduced after 2 weeks of treatment. After 6 weeks of treatment the patient completely became free of joint pain.

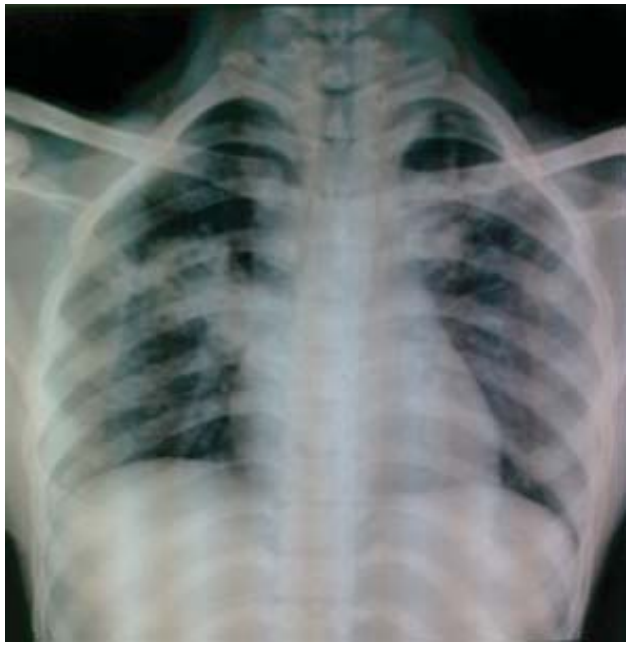


Fig. 1: *Chest X-ray showing nodular opacities in both mid-zones.*

Discussion

Active tuberculosis may be complicated by reactive arthritis known as Poncet's disease. It is widely known that tubercular septic monoarthritis, in which *M. tuberculosis* may be isolated from the joint, may complicate tuberculous infection; that active TB may be complicated by a sterile reactive arthritis is less known and therefore often missed.

Poncet's disease is used to indicate an aseptic polyarthritis, presumably a reactive arthritis, developing in the presence of active TB elsewhere[1]. Although Poncet's disease is considered a reactive arthritis, the clinical presentation of Poncet's disease differs from the classical pattern of reactive arthritis[2,3]. In contrast to reactive arthritis, the onset of symptoms in Poncet's disease before the start of arthritis is much longer than

**** Post-Graduate Student, ** Senior Resident, *** Senior Physician, **** Professor and Consultant,***
Dept. of Medicine, PGIMER-Dr. Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.

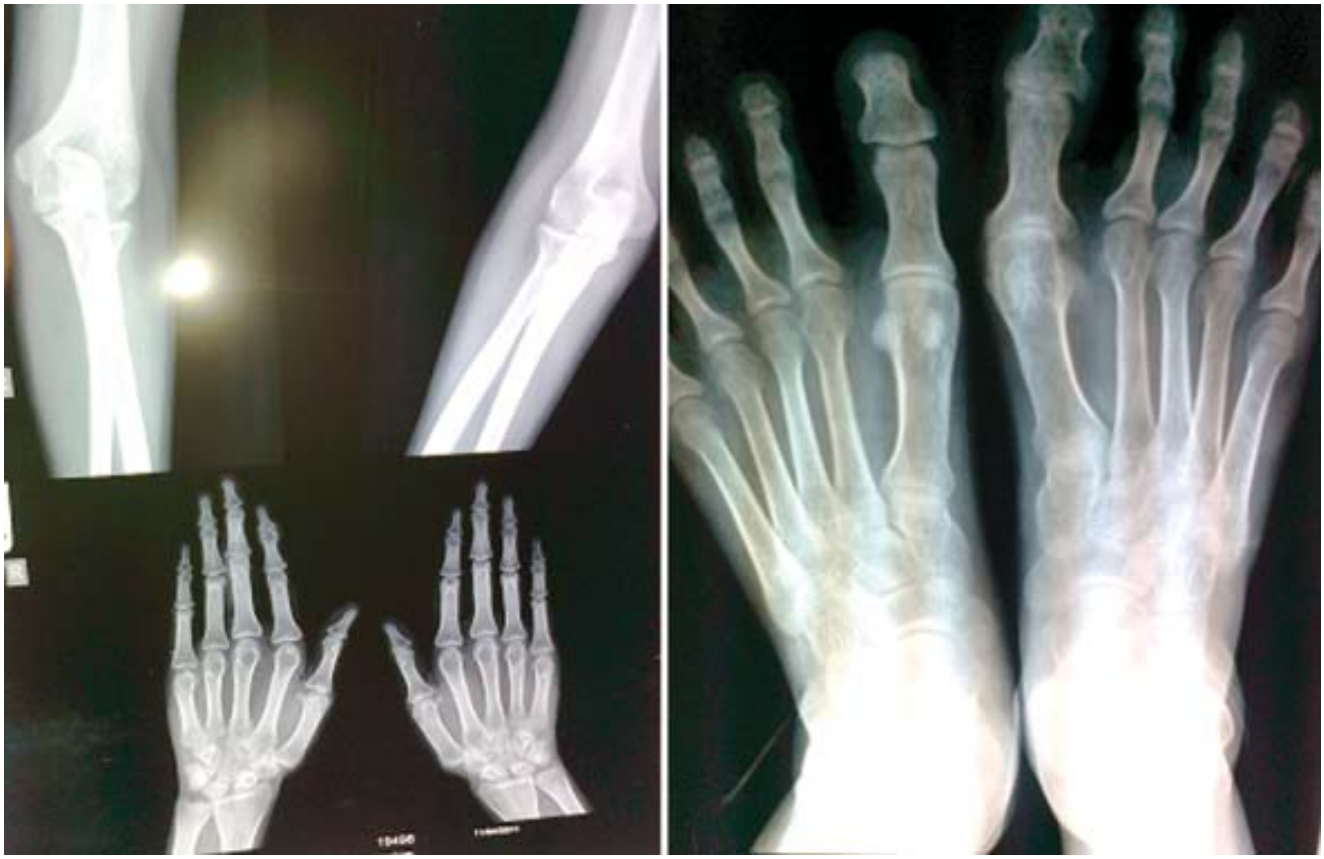


Fig. 2: *X-rays of the involved joints showing periarticular sof-tissue swelling without any changes of tuberculosis.*

just a few weeks, whereas resolution of arthritis upon starting of adequate anti-tuberculous therapy is mostly within a few weeks. Chronic arthritis has never been reported in Poncet's disease. Furthermore, Poncet's disease is generally – except in two reports[4,5] – not associated with sacroiliitis. It has been hypothesised that after infection, as a result of systemic immunisation, sensitised CD4 cells together with bacterial antigens migrate to the joints and cause arthritis. In conclusion, the differential diagnosis of patients at risk for TB presenting with arthritis should definitely include Poncet's disease.

References

1. Bocanegra TS. Infection: Mycobacterial, Brucella, fungal and parasitic arthritis. In: John H Klippel, Paul A Dieppe, eds. Rheumatology, second. London: Mosby, 1982; Chapter 46.4.4.
2. Toivanen A, Toivanen P. Reactive arthritis. *Best Pract Res Clin Rheumatol* 2004; 18: 689-703.
3. Flores D, Marquez J, Garza M, Espinoza LR. Reactive arthritis: newer developments. *Rheum Dis Clin North Am* 2003; 29: 37-59.
4. Wilkinson AG, Roy S. Two cases of Poncet's disease. *Tubercle* 1984; 65: 301-3.
5. Kumar PD, Sasidharan PK, Paul BJ *et al*. Poncet's disease. *J Assoc Physicians India* 1993; 41: 400.

POST-GRADUATE CLINIC

JIACM 2011; 13(1): 81-5

Subtle ECG changes in acute myocardial infarction

*SR Mittal**

Abstract

Classical ECG changes of anterior myocardial infarction are easily picked-up. However, more than 50% of patients with acute anterior myocardial infarction may have only subtle ECG changes during each hour of the infarction. Knowledge of these changes is necessary so that the diagnosis is not missed during early hours following infarction and patient gets proper treatment.

Key words: Electrocardiography, myocardial infarction, infarction.

Anterior and lateral myocardial infarction

Classical ST segment elevation of anterior MI (Fig. 1) is easily diagnosed.

(A) Classical ECG changes anterior MI

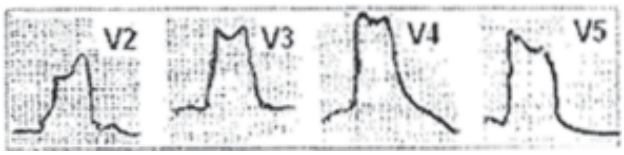


Fig. 1

However there are several subtle changes which are frequently missed.

(a) Early uptake of ST segment (Fig. 2, 3)

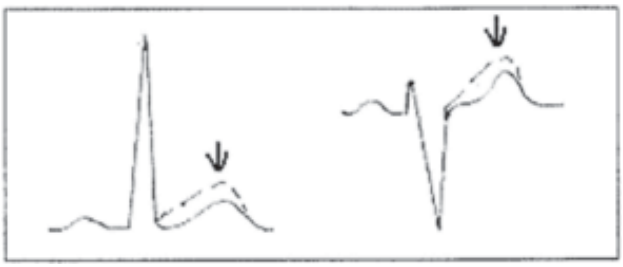


Fig. 2

Early uptake of ST segment

First ECG: Early uptake of ST segment V2 to V4 (arrow).

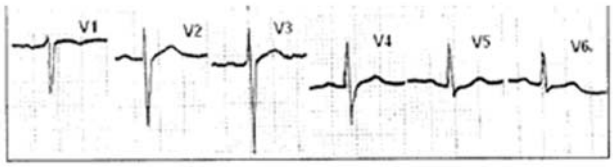
Second ECG : Deep symmetrical T inversion in lead V2-V5

(b) Tall T in V2 and V3 (Fig. 4)

First ECG: Showing T taller than R in V1 to V3

Second ECG: Showing loss of R and classical ST segment elevation in V2 to V4 with terminal T inversion in V4

At admission



After 24 hours

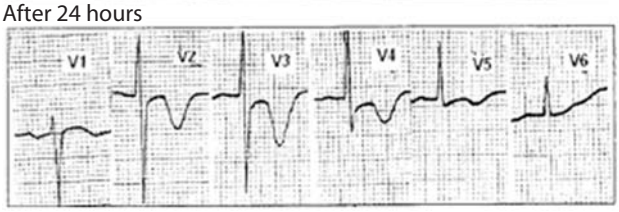


Fig. 3

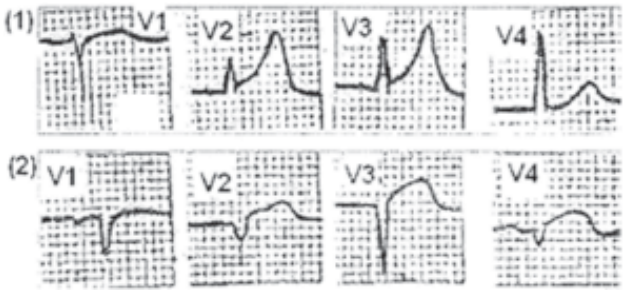


Fig. 4

(c) ST depression (Fig. 5)

First ECG: Shows only ST segment depression in leads V3 to V6.

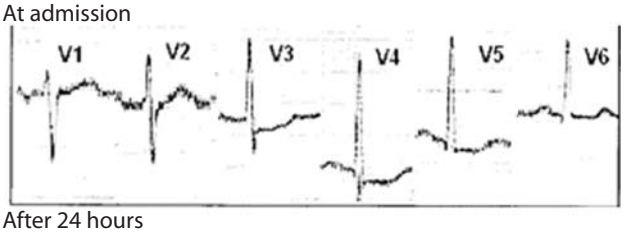
Second ECG: Shows classical deep symmetrical T inversion in V2 to V6.

(d) ST segment elevation in leads aVR and V1 (Fig. 6)

First ECG: Shows ST elevation in leads aVR and V1 (arrow) with reciprocal ST depression in lead I, II, III, aVF and V3 to V6.

**** Ex-Senior Professor and Head, Department of Cardiology, Jawaharlal Nehru Medical College, Ajmer - 305 001, Rajasthan.***

At admission



After 24 hours

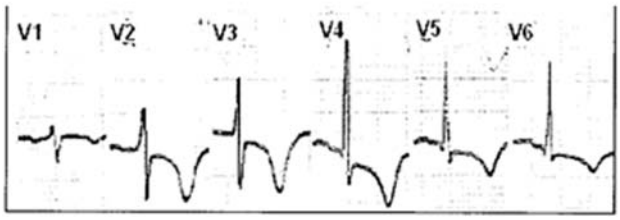
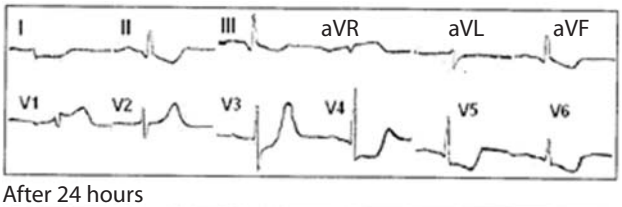


Fig. 5

At admission



After 24 hours

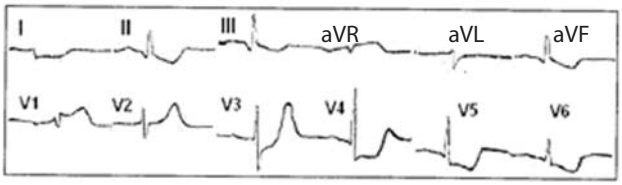
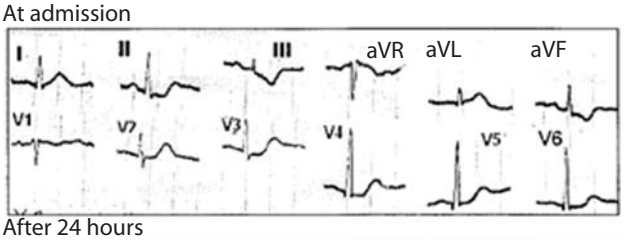


Fig. 6

Second ECG: QS pattern in V1 to V3 confirming anterior MI with reduction in reciprocal ST depression.

(e) Isolated ST segment elevation in lead I and aVL: high lateral MI (Fig. 7)

At admission



After 24 hours

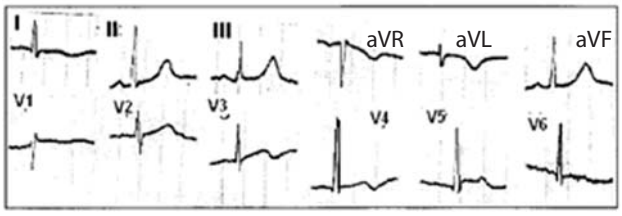


Fig. 7

First ECG showing slight uptake of ST in I and aVL (arrow).

Significant ST depression in II, III, aVF should alert to possibility of ST elevation in I and aVL.

Second ECG: T inversion in I, aVL, V3, V4 with normalisation in II, III and aVF.

(f) ECG changes seen only in higher intercostal space: high lateral MI (Fig. 8)

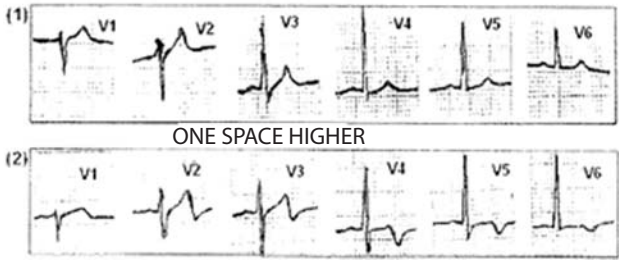


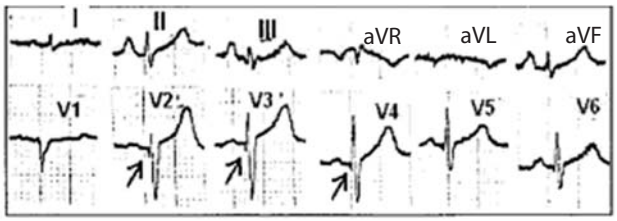
Fig. 8

First ECG: Conventional precordial leads showing normal ECG.

Second ECG: Precordial leads recorded in higher intercostal space showing T wave inversion in V1-V6.

(g) Small 'Q' wave in V2 and V3 (Fig. 9)

At admission



After 24 hours

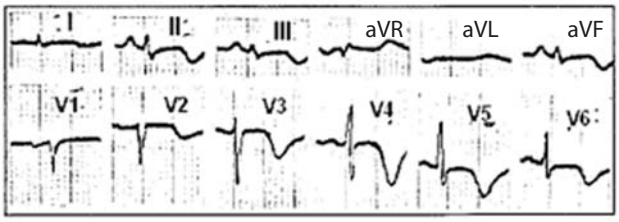


Fig. 9

First ECG: Admission ECG showing small 'Q' in V2 to V4 (arrow).

Second ECG: Sequential T inversion in inferior leads and leads V2-V6.

(h) Non-progression of 'R' wave

Normally height of 'R' wave increases from lead V1 to V5 (Fig. 10).

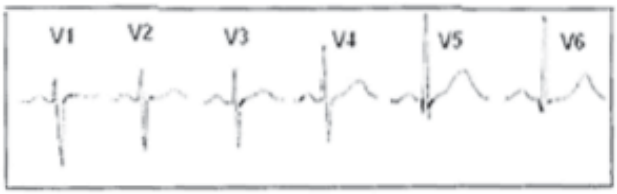


Fig. 10

Normal Progression of 'R' wave

Non-progression of 'R' wave is a marker of infarction (Fig. 11).

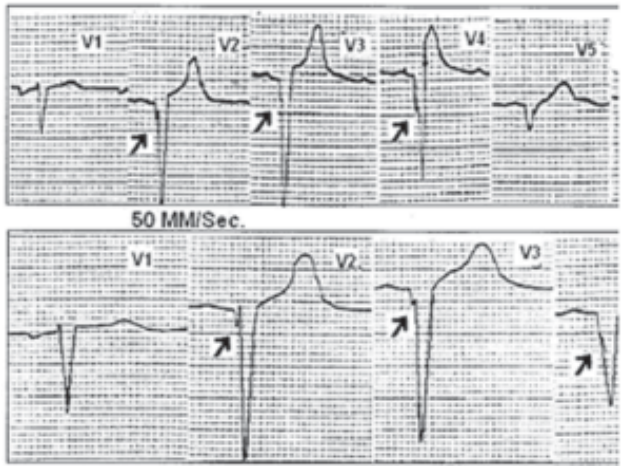


Fig. 11

First ECG: Non-progression of 'R' in V2-V4 suggesting anterior MI.

Second ECG: Recording at 50 mm/sec speed clearly shows the slurring on down-stroke of QRS in V2 to V4 (arrow).

(i) Reverse progression of r wave

Normally height of 'R' wave increases from lead V1 to V5 (Fig. 10). Paradoxically, if the height of 'R' wave decreases rather than increasing, it is a marker of anterior MI (Fig. 12).

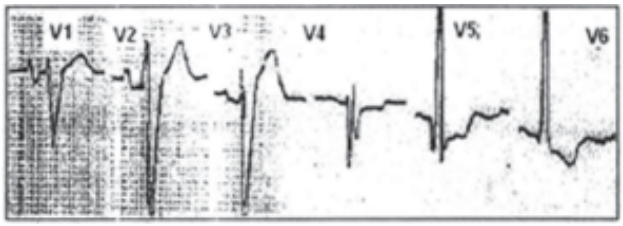


Fig. 12

Showing reverse progression of 'R' wave from lead V2-V4.

(j) Ventricular ectopics with RBBB configuration showing 'Q' wave (Fig.13)

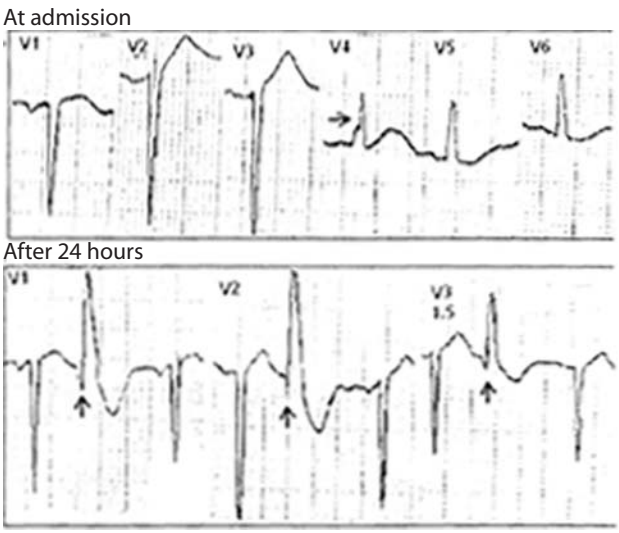


Fig. 13

First ECG: Shows non-progression of 'R' in leads V1 to V3 with notching in QRS (arrow) in V4.

Second ECG: Ectopic beats with RBBB configuration show a clear Q wave (arrow) confirming anterior MI.

(k) Mid-QRS change

Normally the up-strokes and down-strokes of QRS are equal and smooth (Fig.14).

Fig. 14

Any loss of QRS vollage with slurring suggests death of part of myocardium. It produces changes in mid-part of QRS (Fig. 15, 16).

Fig. 15

Mid-QRS changes due to loss of different parts of electric potential (arrow).

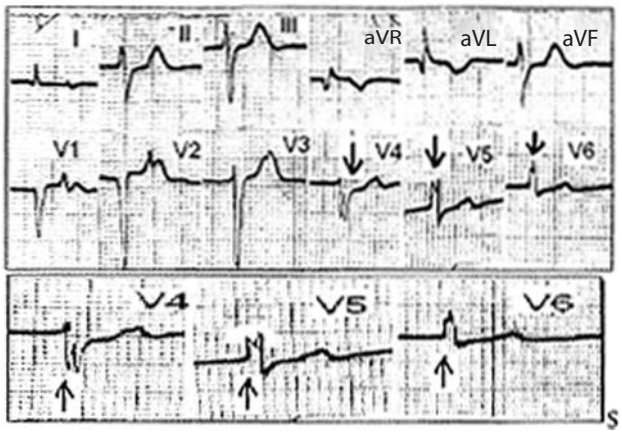


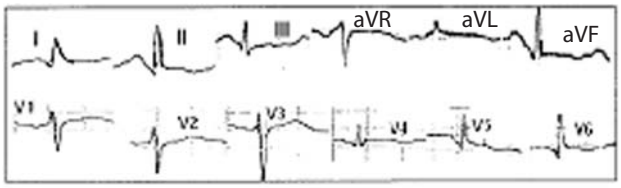
Fig. 16

Showing T inversion in aVL and V1 with q wave in aVL and slurring of QRS in V4 to V6 (arrow).

Lower strip shows magnified leads V4 to V6.

(l) QT prolongation (Fig. 17)

At admission



After 24 hours

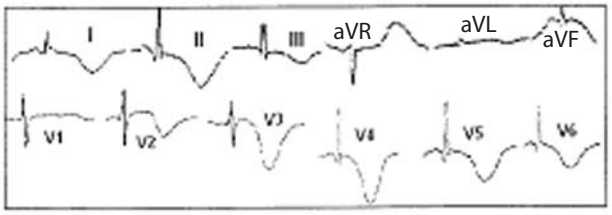


Fig. 17

Admission ECG: Slight prolongation of QT

After 48 hours: QT prolongation with deep T inversion I, II, III, aVF, V2-V6.

(m) U wave inversion (Fig. 18)

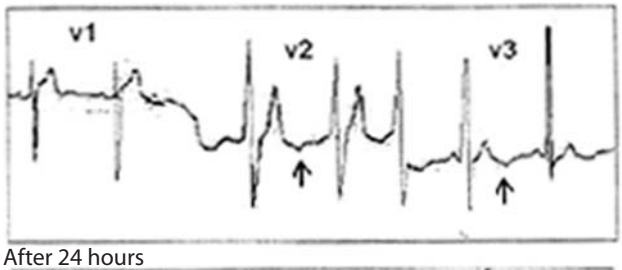
First ECG: Showing only U wave inversion (arrow).

Second ECG: Showing classical deep symmetrical T wave inversion in leads V2-V3.

(n) Pseudonormalisation during evolution of ECG changes (Fig. 19)

During acute stage of MI, ST segment is elevated. With evolution, ST segment settles (pseudonormalisation, before T wave finally becomes inverted).

At admission



After 24 hours

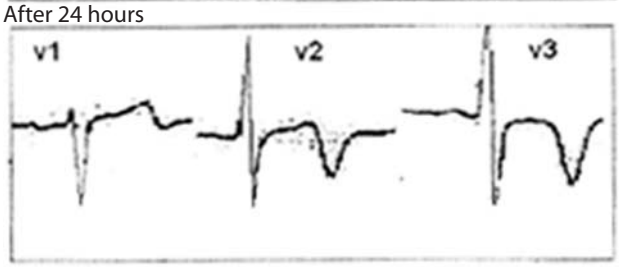
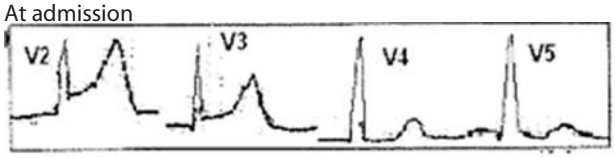
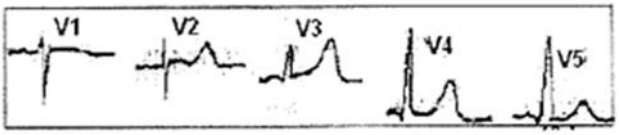


Fig. 18

At admission



After 24 hours



After 48 hours

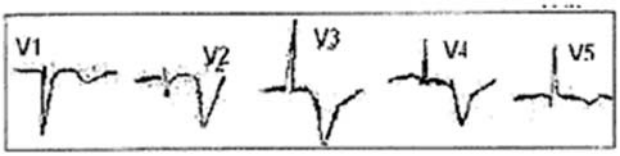


Fig. 19

First ECG: Shows classical ST segment elevation in leads V2 and V3.

Second ECG: Appears apparently normal 'pseudonormalisation'.

Third ECG: Shows sequential T inversion in leads V1 to V6 confirming anterior MI.

(o) Pseudonormalisation with recurrence of ischaemia in same area (Fig. 20)

First ECG: Shows symmetrical T wave inversion in leads V2-V4 (old anterior MI).

Second ECG: Change in 'T' polarity with 'pseudonormalisation' of ECG during recurrence of chest pain.

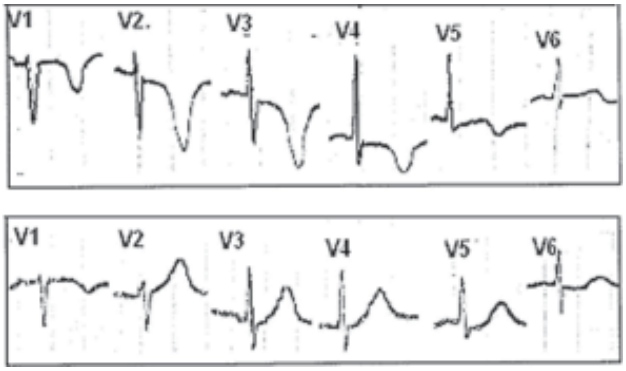


Fig. 20

(p) Late appearance of ECG change (Fig. 21)

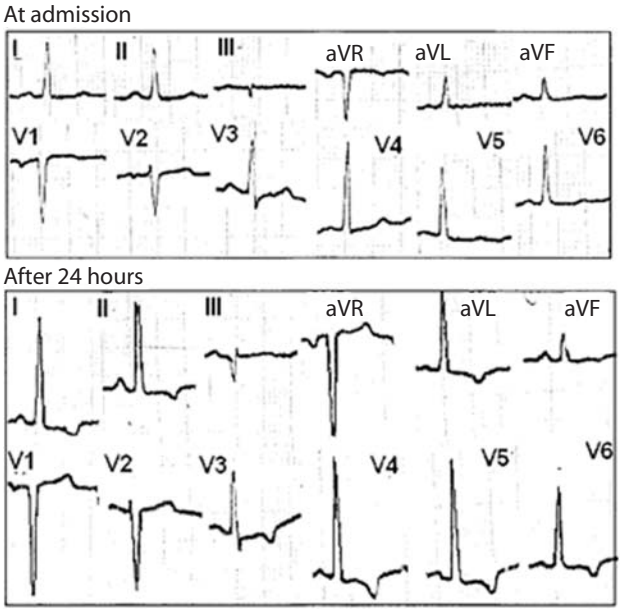


Fig. 21

First ECG: Show apparently normal ECG.

Second ECG: T wave inversion I, II, aVL, V3 to V6 (anterior subendocardial infarction).

(q) Presentation as atrial fibrillation (Fig. 22)

First ECG: Atrial fibrillation.

Second ECG: Loss of R in V2 with T inversion V2-V6.

(r) Masking of old anterior MI by fresh inferior MI (Fig. 23)

First ECG: Showing classical anterior MI.

Second ECG: Masking of ST evelation in leads V1 to V6 by fresh inferior MI.

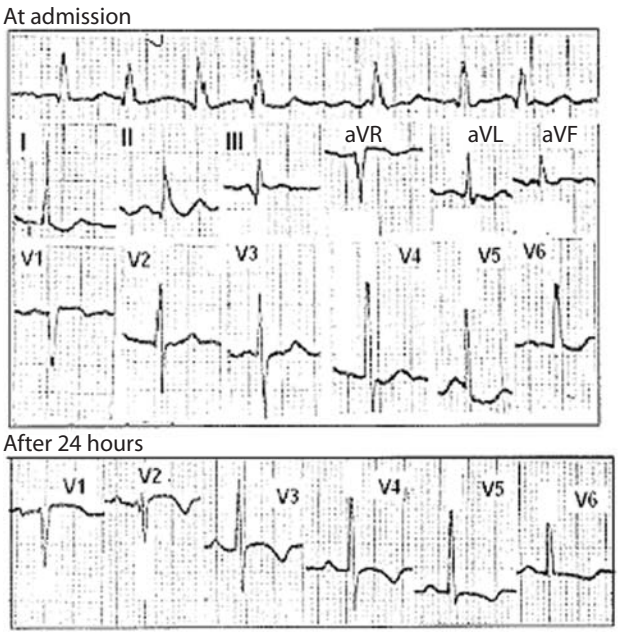


Fig. 22

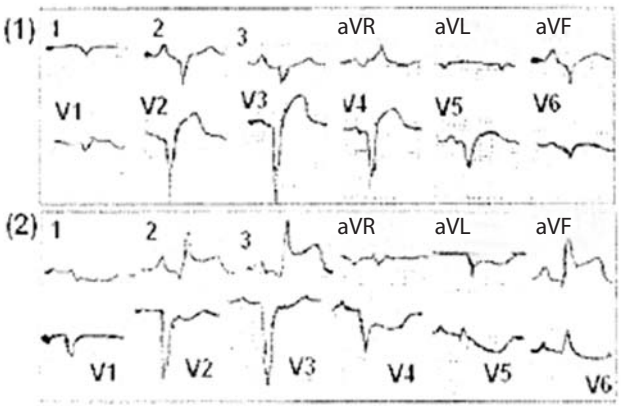


Fig. 23

(s) Atrial infarction (Fig. 24)

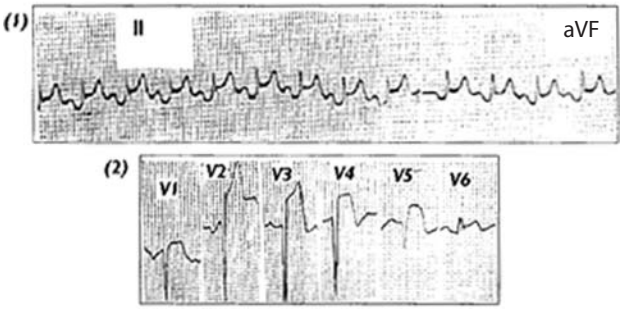


Fig. 24

First ECG: Lead II and aVF show depression of PR segment (arrow) suggestive of concomitant atrial infarction.

Second ECG: Shows classical anterior MI.

FORMAT FOR NOMINATION FOR ORATION

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

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

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

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

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

Signature ..... (Proposer)

Name:

Fellowship/Membership No.:

Signature ..... (Seconder)

Name:

Fellowship/Membership No.:

CONSENT OF NOMINEE

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

Signature

(Name of Nominee)

Fellowship/Membership No. .....

RULES FOR ORATIONS/ORATORS:

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

Please send your Nominations for Orations to:

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

Annual Subscription
Journal, Indian Academy of Clinical Medicine

Now, subscribe to the *Journal, Indian Academy of Clinical Medicine* without being a Member or Fellow of the Indian Association of Clinical Medicine. Keep abreast with the latest in the field of clinical medicine with your personal copy of the *JIACM*. The *Journal* covers the entire gamut of internal medicine with an in-depth, yet well-balanced mix of theoretical and practical aspects relevant to the teaching and practice of medicine in the Indian subcontinent.

Offer open to all Medical Colleges/Institutions/Libraries/Academic Bodies.

No subscription needed for Members/Fellows.

SUBSCRIPTION SLIP

Yes, I/we would like to subscribe to the *Journal, Indian Academy of Clinical Medicine (JIACM)*, published quarterly.

One-Year subscription (4 Issues) :	Inland	–	Rs. 1,000.00
	: Overseas (Air Mail)	–	US$ 100.00

Name : Dr. .....

Postal Address : .....

.....

.....

City ..... State ..... PIN .....

Please find enclosed Cheque/DD No. ..... dated ..... for

Rs./US$ ..... drawn on (Bank) .....

favouring "Journal, Indian Academy of Clinical Medicine" payable at New Delhi.

Date ..... *Signature .....*

Send your Cheque/Demand Draft to:
Dr. D.G. Jain, Editor, JIACM
Barnala House, 867, Guru Gobind Singh Marg,
Karol Bagh, New Delhi - 110 005.

Indian Association of Clinical Medicine

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

MEMBERSHIP / FELLOWSHIP FORM

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

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

Photograph

We hereby propose the admission of

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

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

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

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

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

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

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

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

Note by the Hony. General Secretary

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

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