C O N T E N T S

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VIEWPOINT

JIACM 2007; 8(2): 130-4

Rounded Education for Social Development

BM Hegde*

"I don't give them hell. I just tell the truth and they think it is hell."

– Harry S. Truman.

What is the goal of education? All human endeavours should eventually lead to human development and human happiness. The British have been trying to educate us basically for their benefit and not for the total development of our personality. Has there been any radical change in that system after independence? Society is only a collection of individuals. Society reflects man's nature in a collective way. If one were to critically look at the social developments in the last couple of centuries, one observes a very important change in man's attitude to others. With the type of education that we have been fostering even after political independence from the British yoke in the last six decades, we see a steady fall in ethical standards in society. Corruption, greed, one-upmanship, deception, suppression, oppression, and denial resulting in total lack of social commitment in our dealings and reckless disregard for the inconveniences caused by our actions to others in society have all been on the rise with the steady rise in India's literacy, which is equated with education by our powers-that-be.

Everyone talks about the scientific temper without understanding the deeper meaning of those words. Today, scientific temper simply means understanding the modern western science and trying to ape the west in our research areas. If one were to look at our research output in every speciality in the last sixty years, one comes up with 99% repetitive research which hardly adds anything to the existing human knowledge. Refutative research, that which demolishes the existing myths, is hard to come by. There is nothing in our research activities that would set the river Ganges on fire after spending billions from the tax payers' money on research. There isn't much to write home about either. Creative thinking is never encouraged in our schools and colleges – what with their rota learning and parrot repeating for the present evaluation system!

History of science in the west clearly shows the dangers of encouraging repetitive research. For five centuries all western scholars thought it was right to believe that we live in a geocentric world as propounded by Ptolemy in Egypt in the second century. All research took that as the basis for five long centuries, only to be refuted by Copernicus in Greece in the seventh century with his heliocentric theory. Whereas we in India knew the correct world view for thousands of years, the west was groping in the dark for that long. Same applies to blood circulation that was thought to be from the liver, based on Galen's writing in 127 AD. For the next fifteen hundred years people acted on that, basing all their research on that presumption until William Harvey in 1628 refuted that to show that blood circulates from the heart.

Ayurveda knew the truth for thousands of years. Refutative research emanates from creativity in the young minds. Our present educational system seems to curb that basic human tendency of creativity in the bud itself. That has been the bane of western science and education for centuries as reflected by what Socrates said: "Let not my schooling come in the way of my education." Even *Guruji* Ravindranath Tagore could not tolerate the conventional schooling system as a child!

Is western science a religion?

Yes, says a great scientist who was nominated for the Nobel prize several times only to be shunned by the mainline science establishment. In his book *A New Paradigm*, John OM Bockris, a distinguished professor of chemistry in the A and M University in Texas, systematically demolishes the myth that western science is reliable in its present *avatar*. He claims, and rightly so in my opinion, that all the four pillars of modern science like the big bang theory, the Darwinian evolution, quantum physics, and relativity, are

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flawed. David Bergman expresses his concern thus: "We believe that modern science is a structure built on a foundation of sand and the entire structure seems about to topple." (Foundations of Science. 1 (1998) 1.) The foundation of all sciences – mathematics – itself has flaws as described by the great Albert Einstein himself: "Insofar as the propositions of mathematics give an account of reality, they are not certain; and insofar as they are certain they do not describe reality." (Denis Brian Einstein: A Life. J Wiley New York 1996, page 509). Be that as it may, let us look at what has this kind of science teaching based on technology done to mankind?

A mundane view could be that human life has become very comfortable with technology, thanks to western science. Technology has injected arrogance in our educated class. Rachel Carson in her book *Silent Spring* (September, 1962) goes into the question of the ultimate good to the world from reductionist scientific discoveries. One example would suffice. DDT was used against the mosquito carrying malaria. One of the most important unforeseen concomitant effects upon birds which ate the dead insects and through the food chain to man was good enough to kill. We have become unresponsive to the call of our inner conscience regarding our obligations to mankind. Making money has become our religion and money our God. Money has brought with it human misery. The gulf between the rich and the poor is widening by the day. The rich suffer from the fear of the poor as most terrorists, criminals, and muggers come from that class; and the poor pay for their poverty with their lives. Not knowing where your next meal comes from is the greatest risk for fatal illnesses!

There are, of course, socially sick individuals even among the rich who become terrorists, but that is an exception. Western science is looking for more converts in the present globalised economy! That is their rice bowl. In certain areas of science like cosmology, there are many amazing concepts which make good material for popular books that get millions of dollars for the writers. But the truth is that those concepts, though exciting to the reader, are impossible to falsify and do not give the true picture. These things make science a questionable mode of a transport to truth. Modern science of deterministic predictability has ruined the time honoured doctor-patient relationship in modern western medicine. Medical consultation, the summit of all else in medicine, is primarily based on trust that the patient has in his/her doctor. Today we have taken medicine to the market place with all the usual market forces working on it where the doctor has become a seller and the patient a buyer of "health care". The faulty science of linear mathematics in a non-linear human system has brought the medical establishment to the brink of being one of the major causes of human mortality and morbidity along with cancer and heart attacks. (Barbara Starfield. *JAMA* 2000; 284: 483).

Education as a social reformer

In the Indian context, in the distant past education fostered wisdom and not knowledge like today where knowledge seems to be synonymous with information – most of the latter is only noise and the occasional signal in there, if at all, gets lost in the midst of that noise and never gets into the heads of students. "Where is the wisdom we seem to have lost in knowledge, and where is that knowledge we seem to have lost in information?" wrote TS Eliot. Wisdom dwells in heads attentive to their own, but knowledge dwells in heads replete with thoughts of other men. While knowledge is very proud that it knows a lot, wisdom is very humble as it knows no more. Higher the educational level, the humbler should be the individual. Humility begets an inner vision. Present education has resulted in lots of external developments. Man has succeeded in going to the Moon and hopes to live on the planet Mars soon. True education, however, should be able to make man land in his neighbour's living room with a smile on his/her face to care and share. That has not happened with our education today. On the contrary, our present education has made man the greatest enemy of another man.

A friend of mine once remarked that "we live in apartments today keeping us apart and have stopped living in homes built with universal love". We live in the space age, thanks to science, which has resulted in increasing the space between man and man! Technological advances will make our sensex sky rocket, but our ethical standards plummet to rock bottom. Monetary economy and technological advances make man more anxious, resulting in exponential increase in all diseases ranging from common cold to cancer. Most

negative thoughts that are at the root of killer diseases emanate from hatred, greed and jealousy, the fallouts of the monetary economy. A detailed study of the aboriginal Innus off the coast of Saskatchewan in Canada had shown how they started with all their ills from the time Innu land was invaded by the Canadian monetary system in the mid eighteenth century. Innus had no illness in their recorded history in their sustenance economy prior to that. After money came into their lives, happiness became a thing of the past!

Social consciousness vs social conscience

Knowledge in the present system of education gives the recipient a fairly good knowledge of the society and how to survive in it. However, it never ever teaches him/her as to how to have an insight into others' problems – the social conscience. This world cannot go on like it is now for long. Mankind has come to the brink of self destruction, thanks to technology. Stock piling of atomic weapons and other weapons of mass destruction are adding to this race for supremacy. With the cold war ending and the breaking down of the monolith – the USSR – there are now smaller players vying with one another for the same cake. Size of the country or the military might in numbers is of little consequence in this era of nuclear arms and biological weapons. For this threat to diminish, education should inculcate social conscience in students right from the tender impressionable age.

Indian epics like *the Ramayana* and *the Mahabharata* would be ideal for a non-detailed study for the students. Comparing them with Homer's Iliad would teach the students the gross contrast between the eastern culture of India and the western culture of Greece. Whereas there are many things in common in these three epics – every one of them deals with a war – a war for the sake of a woman, the postwar ending gives the contrast in that Helen runs away with the enemy while Sita and Draupadi go back to their husbands. The contrast between Karna's devotion to his master and the ingratitude of Agmonon – Karna's counter-part for Achilles shows that the east was east and the west was west, the twain could never meet as prophesied by Rudyard Kipling. Writing on the *Mahabharata*, Chakravarti Rajagopalachari had this to say: "what is not in the Mahabharata is nowhere." He was referring to life's lessons for the reader in the epic. It is the depiction of all human qualities and emotions rolled into one – a beautiful story line. If Kipling were to see our country today with the IT boom and the BPOs, he would have changed his lines thus:

"East is east and the west is west,
When they meet it would be the best."

Awareness of the social conscience would bring man and man together. Although technology has shrunk the world into a small neighborhood, mankind's social conscience is yet to broaden to make it a brotherhood!

Teacher as a role model

Gurukulas of India used to be places where the teacher and the taught lived together to facilitate learning by observation. This had evolved into a great art. Teachers, in turn, used to be the role models for the students. How I wish that day would come again. Today teaching seems to be a job like any other, where the teacher gets his pay for teaching and that is the main reason why most teachers do what they do. Teacher should be like a midwife who stands by the side of a pregnant mother in pain-coaxing, cajoling, encouraging, empathising and helping the mother to deliver. Most of the present day teachers, however, only deliver lectures without trying to deliver (e = out; ducare = deliver) the best in the child to be polished and refined. "Education is the manifestation of the perfection already inside man," opined Swami Vivekananda long ago. Today's education is good for the present scenario in the monetary economy where the individual wants a job at the end of his schooling to earn a living. With the negative thoughts inculcated in the evaluation and grading based school systems, the next step in the evolution of that job seeker is to be better than his/her colleagues. That is fine in the good sense, but in the normal course being better is being richer. When everyone gets the same salary how could one be better than the rest, except by being corrupt? So corruption, which has become a norm than an exception today, could also be traced to the faulty educational system that we seem to have inherited from the west.

Future of higher education in India

We have about 300 universities in India as of now. With

the demographic predictions showing the likelihood of nearly 700 – 800 million young men and women looking for higher educational facilities in the next fifty odd years, we need thousands of good universities. Even now we lack the numbers. Britain, with a population of around 59 millions has 353 universities, while we in India, with a billion population, have just about 300. To be at par with them we need nearly 6,000 universities. Of course, the percentage seeking higher education might differ. No country, however high the GDP might be, will be able to give totally free higher education for its citizens from the tax payers' money. We will have to then look for private-public participation in this area. There is one danger that has to be rectified right from the start. Today many unscrupulous players in the arena think education is a very good money spinning business. They are hand-in-glove with the so-called watchdog bodies overseeing education in the license Raj that we run today, to make hay when the sun shines! Some of them are buying respectability for their black money through this source! In a buyers' market the product has to be good to be sold. The bad institutions would die a natural death without the need for routine inspection by the "corrupt" watchdog bodies in that set up. So let the institutions get students depending on their quality. If all the licensing is removed and the students given the true picture of the institutions' unbiased grading, the bad one's would not survive, as had happened after the Flexner report in the USA in the 50s.

To curb this tendency, the government should wash its hands off higher education leaving it to the buyers to choose the best model as people do in the filed of automobiles or other goods. Higher education should be fully self-financing, the rich paying for their education and the poor being assisted by interest free or very low interest educational loans through a new "Educational Development Bank", as suggested by the Late Ramakrishnan of the Bharatiya Vidya Bhavan. Just as the IDBI helped Indian industries to thrive, the EDB would help higher education to thrive in future. Additional advantage is that many of the students who get free higher education today, choose to go abroad, thus making the tax payer get nothing in return. Brain drain, as it is called, is good for the country as they are a good export commodity but their manufacture should be at their own cost and not that of the exchequer! Let our powers that be realise that man could achieve great things in life as long as he/she does not bother who gets the credit.

Education for all

Primary education, a true obligation of a welfare state, should be a fundamental right. The PROBE report 1999, (Public Report on Basic Education) in the five northern states makes a very sad reading. That must be corrected immediately. If India could give the best primary education to all its citizens, it will have made a quantum leap in its overall development. The need for a large number of higher educational facilities could be eased by having "Community Colleges' Model" of the USA, where these community colleges give vocational training for those who finish high school without much of an ambition for research, etc., to get one, two, three year diplomas to get well-paying jobs in various sectors of the economy. This could also be done through open universities with the technology available now online. The governmental effort could be canalised in this direction. This would ease the enormous load on conventional universities.

Another area where we could make a real thrust is in adult education in India by making every primary school an extended community school in the evening where some teachers and bright senior students could volunteer to teach elders who had missed the opportunity to study when they were young. This could cater to anybody and everybody who wants to study. Once allowed to go on track, this would mop up all the poor citizens to acquire enough knowledge for day-to-day existence. Poor illiterate persons could be easily deceived today by the crafty lot as the former do not even know how to sign their names. These extended community schools could also be used to spread health messages for healthy living and good agricultural practices in villages far removed from the five star culture of our mega cities, thus killing two birds with one stone.

After word

India had a hoary past in the field of education. Voltaire, the great French thinker, once wrote: "While we were hunter-gatherers, roaming the forests in Europe, India had some of the world's greatest universities which attracted students from all over the civilised world to acquire

wisdom. It does not behoove us today either to question their antiquity or their authenticity." Albert Einstein wrote that:" I owe a debt of gratitude to India that taught us how to count without which there would have been no scientific development." TZ Holwell, FRS, FRCP (London), in his report to the President and Fellows of the Royal College in 1747, wrote: "I had studied one of the most effective vaccination methods prospectively for 20 years in "The Bengall" and have come to the conclusion that 90% of those thus vaccinated survived without small pox and 90% of those unvaccinated died of small pox. This is the oldest method practised in India for "times out of mind" by the great physicians who came down from the great universities every winter to the villagers long before the summer epidemics start, to protect them. " This report was accepted by the King and Edward Jenner's single patient anecdotal experience of cow pox vaccination was then modified for universal vaccination. Medical science has been able to eradicate only one disease in all these years, i.e., small pox, by the original Indian vaccination methods. No other disease has ever been eradicated so far.

Unfortunately, vaccination still has the same old name (vacca = cow) even today. This is because Indian methods are not duly recognised in the west even today as we do not patronise them in our own country. While acupuncture could be respectfully and legally practised in New York, *Ayurveda* could not. Many of our people themselves have a holier than thou attitude towards *Ayurveda*. In addition, we do not try to authenticate our best practices. Let us not rest on our hoary past glory. Let us work hard to have our own systems in education and research and get western recognition that is our due. Let us wake up and sleep not till we reach our goal to hold our head high in this free country where all human qualities of head and heart could develop freely without shackles. May Indian education be the beacon light for all education in the world. Let me conclude by quoting McCauley himself: "a people who take no pride in the noble achievements of their remote ancestors will never achieve anything worthy to be remembered with pride by remote descendents."

"There are two kinds, of fools:
One says, 'This is old, therefore it is good';
the other says, 'This is new, therefore it is better'."

– Dean William R Inge.

ORIGINAL ARTICLE

JIACM 2007; 8(2) : 135-8

Serum Ceruloplasmin Level as an Extracellular Antioxidant in Acute Myocardial Infarction

HB Sirajwala, AS Dabhi**, NR Malukar***, RB Bhalgami**, TP Pandya***

Abstract:

Aim: *To determine the role of ceruloplasmin in patients of acute myocardial infarction (AMI) in view of its correlation with various diagnostic and prognostic tools, severity of AMI, and its role as an extracellular antioxidant.*

Study design: *A prospective study of 50 adult patients compared with disease-free healthy volunteers.*

Material and methods: *The study was conducted at the ICCU of Sir Sayajirao General (SSG) Hospital, Vadodara, Gujarat.*

Fifty consecutive patients admitted with the diagnosis of AMI formed the study group. They were compared with 50 healthy volunteers with identical demographic characteristics but without any disease. Serum ceruloplasmin level was measured in both the groups and compared.

Results: *Serum ceruloplasmin level in all patients of AMI was abnormally high, but there was no correlation between the site of AMI and rise of ceruloplasmin level. The high level of creatine kinase – MB fraction (CK-MB) – an established marker of AMI – correlates well with higher value of ceruloplasmin level.*

Conclusion: *Rise in serum ceruloplasmin level in patients of AMI is due to its property of acute phase reactant due to inflammation and/or necrosis in cardiac muscle.*

Key words: *Ceruloplasmin, Acute myocardial infarction, Acute phase reactant, Free radicals.*

Introduction

Acute myocardial infarction (AMI) is defined as a part of acute coronary syndrome characterised by a typical clinical syndrome consisting of chest pain, dyspnoea with rise and fall in troponin or creatine kinase – MB to values greater than 99% of a normal reference population[1].

Oxidative modification of low density lipoprotein (LDL) by lipid peroxidation leads to enhanced uptake of LDL by macrophages and cellular accumulation of cholesterol in the arterial walls , leading to atherosclerosis . Occlusion of coronary artery deprives the myocardium of oxygen, causing reduced fatty acid utilisation, increased lactate, and reduction in pH with free radical formation which damage the myocardium further.

Antioxidants play an important role in preventing free radical damage. Ceruloplasmin is an important extracellular antioxidant. Ceruloplasmin being an acute phase reactant protein, its level rises immediately after cellular damage in AMI. Ceruloplasmin acts as an antioxidant through ferroxidase activity, and it also scavenges superoxide anion radical ($\bullet O_2^-$)[2].

Ceruloplasmin is α 2 globulin – a glycoprotein carrying 6 copper atoms per molecule. It is one group of serum protein which rises after any form of tissue injury[3].

Ceruloplasmin synthesis and/or secretion is altered by inflammation, hormones, and copper. Physiological factors like cancer, exercise, chronic inflammation, pregnancy increase its level.

It also acts as a host defense mechanism by its radical scavenging and copper donor activity.

Function of ceruloplasmin as an antioxidant

Increased plasma ceruloplasmin levels are associated with the generation of oxidation products, i.e., $\bullet O_2^-$ and H_2O_2.

Oxidation of ferrous ion leads to superoxide ion and leads to peroxidative damage. Ceruloplasmin – due to its ferroxidase activity – can catalyze the oxidation of Fe^{2+} with concomitant production of H_2O from H_2O_2 and acts as an acute phase reactant[3].

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Antioxidant activity of ceruloplasmin has been studied from three different aspects[4].

1. Osaki *et al* suggested that ceruloplasmin might function as a ferroxidase enzyme by catalyzing the oxidation of (Fe^{2+} to Fe^{3+})[5].
2. Role of ceruloplasmin as an antioxidant may relate to its free radical scavenging properties.

Aims of study

The present study is undertaken:

1. To evaluate the serum level of ceruloplasmin in patients with AMI
2. To correlate ceruloplasmin levels with various diagnostic and prognostic tools of AMI
3. To correlate ceruloplasmin levels with severity of myocardial infarction.

Material and methods

In this prospective study, 50 consecutive patients presenting with clinical features of AMI admitted to the ICCU of SSG Hospital, Vadodara, Gujarat, were taken as the study group. Of the 50 patients, 39 were males and 11 were females.

Inclusion criteria

Patients with symptoms and signs suggestive of AMI supported by ECG and cardiac markers who presented within six hours were included in the study.

Exclusion criteria

Patients having hypertension, diabetes mellitus, and renal diseases and those with other major illness were excluded from the study.

Control group

In this groups, 50 healthy volunteers of identical age and sex without any disease were enrolled.

Sample collection and analysis

Blood samples from patients were collected for analysis at the time of admission to ICCU. Samples were analysed for estimations of ceruloplasmin, CK (total), and CK-MB levels.

Blood samples from the control subjects were also collected for similar testing. Blood sugar and urea levels were also done to rule out diabetes mellitus and renal pathology in both the groups. All patients were thrombolysed and given treatment according to standard protocol after blood samples were collected.

Ceruloplasmin estimation was done by O-dianisidine dihydrochloride oxidase method[6]. Its normal value is 62 – 140 U/l.

CK (total) and CK-MB estimation was done by 'Modified method of Szasz' (IFCC recommended). A kit from Autospan® was used[7].

Normal activity was taken at 37° C. For females, the normal range of CK (total) obtained was 96 – 140 IU/l, while for males it was 38 – 174 IU/l.

For CK-MB normal activity was taken at 37° C. In both sexes it was 0 – 24 IU/l.

Statistical analysis

All observations were tabulated and analysed.

As the number of subjects were less than 30 in each sub-group, 't'-test was applied to find out clinical significance. 'p' value < 0.05 was taken as significant.

Results

Fifty patients of AMI and 50 healthy volunteers were compared in this study.

Table I: Age distribution of patients with myocardial infarction.

Age	No. of patients			Percentage
(in years)	Male	Female	Total	(%)
35 – 40 years	11	4	15	30
41 – 50 years	13	2	15	30
51 – 60 years	8	2	10	20
60 – 70 years	6	2	08	16
> 70 years	1	1	02	04

Demographic profile

The age of patients ranged from 35 – 75 years. Majority of patients were 35 – 50 years (60%). Out of 50 patients in the

study group, 39 were males (78 %) and 11 (22%) were females. Thus, male: female ratio of the study group is 3.5:1.

The AMI patients were further divided into subgroups according to site of myocardial infarction (Table II).

Table II: AMI patients and site of infarction.

Site of myocardial infarction	No. of patients	Percentage (%)
Anterior and septal wall	26	52
Inferolateral wall	06	12
Inferior wall	07	14
Anterolateral wall	11	22

Maximum number of patients (52%) had anterior and septal wall MI and the remaining had infarcts related to other walls.

Ceruloplasmin level in myocardial infarction

From Table III it is evident that patients of AMI – irrespective of site of myocardial infarction – had very high level of ceruloplasmin as compared to healthy volunteers ($p < 0.001$).

Table III: Ceruloplasmin level in myocardial infarction.

Site of infarction	No. of cases	Mean U/l ± SD	'P' value
Anterior and septal wall	20	234.1 ± 54.33	< 0.001
Inferolateral wall	06	215.8 ± 33.73	< 0.001
Inferior wall	07	225.4 ± 36.16	< 0.001
Anterolateral wall	11	213.0 ± 33.05	< 0.001
Normal	50	92.01 ± 21.59	–

So in the present study, ceruloplasmin level was found to be highly significant in all groups of AMI patients.

Discussion

This study is an attempt to look for the diagnostic and prognostic importance of serum ceruloplasmin levels in patients of AMI.

The diagnosis of AMI was made from symptoms and signs of patients at presentation, alongwith supportive ECG findings and raised CK (total) and CK-MB enzyme levels in blood.

No correlation was observed between successful/failed thrombolysis and ceruloplasmin level.

No correlation was checked between timing of onset of AMI and ceruloplasmin level.

Ceruloplasmin level in AMI

Ceruloplasmin functions as ferroxidase by catalyzing the oxidation of (Fe^{2+} to Fe^{3+})[5], and correlates well with its level and antioxidant activity[2]. Ceruloplasmin is an important intravascular antioxidant and it protects tunica intima against free radical injury. Ceruloplasmin is an acute phase protein and is synthesised by the liver in response to tissue damage and inflammation.

This phenomenon is the basis for constantly observed sudden increase in serum copper and ceruloplasmin levels which decreases slowly and reaches to baseline within a month[8].

Ceruloplasmin exhibits a cardioprotective effect and prevents oxygen free radical induced release of noradrenaline, a powerful vasoconstrictor[9].

Ceruloplasmin promotes an increase in exercise tolerance, higher quality of life, and arrest of the disease progression. Treatment of coronary heart disease, incorporating ceruloplasmin, produced a positive effect on central haemodynamics and contractile pump capacity of the myocardium[10].

In the present study, ceruloplasmin level of all 50 patients with AMI showed a significant rise as compared with the normal subjects.

Mean ceruloplasmin level in patients with AMI was 226.1 Units/l against normal mean control of 92.01 Units/l and that was highly statistically significant (Fig. 1). Thus, ceruloplasmin level is a sensitive index of diagnosis of AMI.

In all subgroups of AMI patients, 'p' values were less than 0.001, which is highly significant statistically.

Different studies have been done to show the activity of serum ceruloplasmin as an antioxidant.

Reunanen *et al* in 1984 studied 104 patients of AMI. Their study showed high concentration of serum ceruloplasmin in patients with AMI and with other forms of coronary heart diseases and further showed that ceruloplasmin decreases

slowly and reaches the baseline within a month[11].

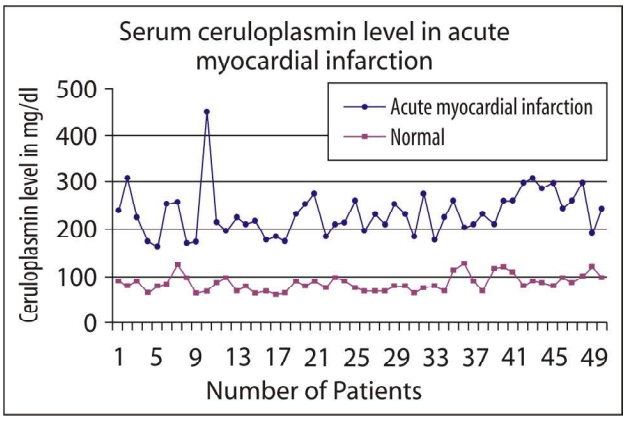

Fig. 1: *This graph compares the values of ceruloplasmin in serum of patients compared to controls. X-axis denotes the serial no. of the patient/control subject, while Y-axis plots the value of ceruloplasmin in each case in U/L.*

In the present study, ceruloplasmin level of all 50 patients with AMI showed a significant rise as compared with the normal controls as shown in Table III.

In patients with all groups of AMI, 'p' values were less than 0.001. But when compared between two subgroups of patients, the 'p' value was > 0.05. So there is no correlation between site of infarction and size of infarction with serum ceruloplasmin level.

Finally, from this study it can be said that rise in ceruloplasmin could be due to its property of an acute phase protein; hence, after necrosis or inflammation of the tissue, the level rises immediately.

However, further studies are necessary to assert the role of ceruloplasmin amongst persons of high risk groups such as hypertensives, hyperlipaemics, smokers, and family members of patients with acute coronary syndrome.

Summary and conclusion

From this study it is concluded that serum ceruloplasmin level in 50 patients of AMI were found to be abnormally high.

There was no correlation between site and size of infarction and degree of rise of ceruloplasmin level.

Follow-up study has to be done for further correlation.

Further, it is concluded that rise of serum ceruloplasmin level is due to its property of acute phase protein. However, further study on serum ceruloplasmin level and serial estimation of this level in AMI can throw some light on this aspect.

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ORIGINAL ARTICLE

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Bacteriological Profile and Antimicrobial Resistance of Blood Culture Isolates from a University Hospital

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Abstract

Context: *Blood stream infections are an important cause of mortality and morbidity and are among the most common health-care associated infections. Illness associated with blood stream infection ranges from self-limiting infections to life-threatening sepsis that require rapid and aggressive antimicrobial treatment.*

Aims: *The objective of the study was to describe the pattern of bacterial isolates from the blood cultures in a university hospital and determine their antibiotic resistance, so that the study can provide guidelines for choosing an effective antibiotic therapy in cases of septicaemia.*

Settings and design: *This is a retrospective study of 2,400 blood samples collected from clinically suspected cases of bacteraemia reviewed over a period of 2 years.*

Methods and material: *The isolates were identified by standard biochemical tests and antimicrobial susceptibility testing determined by National Committee for Clinical Laboratory Standards (NCCLS) guidelines.*

Results: *Positive cultures were obtained in 493 (20.5%) cases. Among culture positive isolates, Gram-negative bacteria accounted for 67.5% cases; most common being Pseudomonas spp. (16%) followed by Salmonella typhi and S. paratyphi A (14.2%). Of the pathogenic Gram-positive isolates, Staphylococcus aureus (8.3%) was the predominant isolate followed by Enterococcus faecalis (3.7%). Maximum Gram-negative isolates were sensitive to cefoperazone-sulbactam combination (81%). Vancomycin sensitivity was reported in 100% Staph. aureus and 83.3% Enterococcus faecalis.*

Conclusions: *This study provides information on antibiotic resistance of blood isolates. It may be a useful guide for physicians initiating empiric therapy and will help in formulation of antibiotic therapy strategy in this part of the country.*

Key words: *Septicaemia, Bacteraemia, Antibiotic resistance, Blood culture.*

Introduction

Blood stream infections are an important cause of mortality and morbidity and are among the most common health-care associated infections[1]. Illness associated with blood stream infection ranges from self-limiting infections to life-threatening sepsis that require rapid and aggressive antimicrobial treatment[2]. A wide spectrum of organisms have been described and this spectrum is subject to geographical alteration. Patients who are granulocytopenic or inappropriately treated may have a mortality rate that approaches 100%. Moreover, fatalities among patients infected with Gram-negative bacilli are higher than those among patients who have Gram-positive cocci as causative agents of their bacteraemia[3-6]. Increasing antimicrobial resistance is a worldwide concern. The prevalence of resistance in both out-patients and hospitalised patients with septicaemia is increasing, and it varies in accordance with geographical and regional location. In almost all cases, antimicrobial therapy is initiated empirically before the results of blood culture are available. Keeping in mind the high mortality and morbidity associated with septicaemia, a right choice of empiric therapy is of utmost importance. Therefore, the present study was undertaken to describe the antibiotic resistance of blood culture isolates as it may be a useful guide for clinicians initiating the empiric antibiotic therapy.

Material and methods

In this retrospective study, a total of 2,400 blood samples from the clinically suspected cases of bacteraemia were reviewed for a period of two years from October 2002 to September 2004. All the samples were collected at Sir Sunderlal Hospital – a 926 bedded, tertiary care, teaching hospital providing a full range of medical, surgical and super-speciality facilities. Processing of samples was done at the department of Microbiology, Institute of Medical Sciences,

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5 ml of blood was collected from each adult patient by nursing personnel, male orderlies, or physicians, using strict aseptic precautions, and inoculated immediately into 50 ml of 'Brain Heart Infusion' (BHI) broth with 0.025% of sodium polyanethol sulphonate as anticoagulant (HI media, a commercial firm). In paediatric cases 1 – 2 ml of blood was inoculated in 5 – 10 ml of BHI broth. The broths were subcultured on 5% sheep blood agar and MacConkey agar after overnight incubation. A negative result was followed-up by examining the broth daily and doing a final subculture at the end of seventh day. Positive growth was identified by Gram staining, colony characteristics, and standard biochemical tests[7]. Antimicrobial susceptibility testing was performed by Kirby-Bauer disk diffusion method as per NCCLS guidelines[8]. The antibiotic discs used were Ampicillin (10 mg), amoxycillin/clavulanic acid (20/10 mg), Penicillin (10 units), Vancomycin (30 mg), Erythromycin (5 mg), cephalexin (30 mg), ceftazidime (30 mg), ceftriaxone (30 mg), gentamicin (10 mg), tobramycin (10 mg), amikacin (30 mg), netilmicin (30 mg), ciprofloxacin (5 mg), chloramphenicol (30 mg), tetracycline (30 mg), trimethoprim/sulfomethoxazole (1.25/23.75 mg) and cefoperazone/sulbactam (75/30 mg). These were procured from Hi-media, Mumbai; the reference strains used as control for disc diffusion testing were *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 25923 and *E. faecalis* ATCC 29212.

All collected data was later on statistically analysed and presented.

Results

During the two-year study period 2,400 blood cultures were analysed. 493 microorganisms were isolated from 466 patients. Of all the isolates, 74.8% were isolated from hospitalised patients while the remaining 25.2% were from those who attended out-patients departments. This corresponds to a rate of 5.8 cases/1,000 hospital admissions. Most infections were due to a single organism, while 22 (4.5%) were of polymicrobial aetiology. In seventeen of these episodes, two different microbes were detected while in five patients three microbes were present. All the polymicrobial infections were from hospitalised patients.

Gram-negative bacteria were encountered more often – 332 (67.5%) – than Gram-positive organisms. The common Gram-negative organisms were *Pseudomonas spp.* (16%) followed by *Salmonella typhi and S. paratyphi A* (14.2%), *Acinetobacter spp.* (12.6%), *Escherichia coli* (11%), *Klebsiella pneumoniae* (7.3%), and *Citrobacter spp* (5%). Among the Gram-positive bacteria, coagulase-negative *Staphylococcus* was the predominant isolate (20.7%) followed by *Staphylococcus aureus* (8.3%) and *Enterococcus faecalis* (3.7%). The distribution of bacterial species of the 493 isolates collected are reported in Table I.

The *S. aureus* strains showed no resistance to vancomycin and resistance to amikacin was also relatively uncommon (19.5%). In *Enterococcus faecalis*, resistance to vancomycin by disc diffusion was seen in 16.6% isolates (Table II).

The most common bacterial isolate from OPD was *Salmonella spp.* Ceftriaxone and ciprofloxacin were very effective with low resistance of 8% and 30.3% respectively, among other enterobacteriaceae members high resistance was noted with tetracycline (89.5%) and ceftriaxone (65.2%). Among aminoglycosides least resistance was noted with amikacin (29.5%). Overall, the most sensitive drug was cefoperazone-sulbactum combination with a low resistance of 19 % (Table III).

Discussion

The results of our retrospective study demonstrate the distribution of microbial isolates causing septicaemia and their susceptibility pattern to most commonly used oral and parenteral antimicrobial agents. The incidence of septicaemia in Europe and USA has varied from 3.4 – 28/ 1,000 hospital admissions[9-11]. A report from Kuwait indicated an incidence of septicaemia to be 10.9/1,000 hospital admissions[12]. An incidence of 5.8/1,000 hospital admissions in our study is comparable with those reported elsewhere.

In most cases of septicaemia, a single microorganism was isolated from blood, while in 4.5% of cases two or more microorganisms were isolated. Septicaemia of polymicrobial aetiology was found only in hospitalised patients. The polymicrobial blood stream infections have been reported by various workers with an incidence ranging from 4.7 – 18.7%, most of which were hospital acquired[5,12].

Table I: Incidence and distribution of microorganisms isolated from blood cultures.

	OPD	Med	Paeds	ICU	Surg	Gynae	Total (n = 493)
CONS	20	32	34	5	6	5	102 (20.7%)
Pseudomonas spp	23	16	32	3	3	2	79 (16%)
Salmonella typhi and S. paratyphi A	32	8	25	3	1	1	70 (14.2%)
Acinetobacter spp.	13	16	21	7	3	2	62 (12.6%)
E. coli	12	9	18	9	3	3	54 (11%)
S. aureus	5	12	13	1	9	1	41 (8.3%)
Klebsiella pneumoniae	6	16	8	6	0	0	36 (7.3%)
Citrobacter spp.	7	4	11	2	0	1	25 (5%)
Enterococcus faecalis	6	5	5	1	0	1	18 (3.7%)
Others	1	1	2	1	1	0	6 (1.2%)

OPD: Out patient department, Med: Medicine ward, Paeds: Paediatric ward, ICU: Intensive care unit, Surg: Surgery ward, Gynae: Obstetrics and gynaecology ward, CONS: Coagulase-negative Staphylococcus, Others: include Proteus spp and Enterobacter spp.

Table II: Resistance pattern of Gram-positive isolates.

	Pn	Ox	Ap	Gm	Hgm	Am	Nt	Cf	Em	Vm	Mx
S. aureus	33 80.5%	31 75.6%	NT	23 56%	NT	8 19.5%	11 26.5%	20 48.8%	21 51.2%	0	16 39%
Enterococcus faecalis	NT	NT	84 4.5%	3 NT	16.7%	NT	NT	3 NT	NT	16.6%	NT

Pn = Penicillin, Ox = Oxacillin, Ap = ampicillin, Gm = gentamicin, Hgm = High-strength gentamicin, Am = Amikacin, Nt = Netilmicin, Cf = ciprofloxacin, Em = Erythromycin, Vm = Vancomycin, Mx = Cefoperazone-sulbactam combination, NT = Not Tested.

Table III: Resistance pattern of Gram-negative isolates.

	Enterobacteriaceae except *S. typhi* (n = 125)	*Salmonella typhi* (n = 66)	Non fermenters (n = 141)
Ampicillin	98 (78.4%)	36 (54.5%)	NT
Amoxycillin-clavulanic acid	93 (74.4%)	30 (45.5%)	NT
Cephalexin	91 (72.8%)	30 (45.5%)	NT
Ceftriaxone	38 (30.4%)	5 (7.6%)	112 (79.4%)
Ceftazidime	NT	NT	64 (45.4%)
Gentamicin	56 (44.8%)	22 (33.4%)	56 (39.7%)
Tobramycin	NT	NT	68 (48.2%)
Amikacin	37 (29.6%)	NT	45 (31.9%)
Netilmicin	60 (48.0%)	NT	62 (43.9%)
Ciprofloxacin	53 (42.5%)	20 (30.3%)	63 (44.7%)
Chloramphenicol	NT	46 (69.7%)	NT
Cotrimoxazole	NT	48 (72.7%)	NT
Tetracycline	103 (82.4%)	NT	NT
Cefoperazone-sulbactam	23 (18.4%)	NT	28 (19.8%)

NT = Not tested.

Early clinical suspicion, rigorous diagnostic measures, aggressive initiation of appropriate antimicrobial therapy, comprehensive support care and measures aimed at reversing predisposing causes (e.g., amelioration of an underlying disease, removal of foreign bodies, drainage of abscess) are the cornerstones of successful management of patients with sepsis syndrome[13]. Early initiation of appropriate antimicrobial treatment is critical in decreasing mortality and morbidity among patients with blood stream infections due to Gram-negative organisms[14]. The initiation of such therapy is almost always empirical requiring knowledge of likely pathogen and their usual antimicrobial susceptibility patterns[15,16].

The results of our study demonstrate that blood culture positivity rate in clinically suspected septicaemia cases was 20.5%. Overall, 67.5% of septicaemia was caused by Gram-negative bacilli and remaining 32.5% by Gram-positive bacteria; this was in accordance with other studies[5,17,18].

Like many other studies[19,20] Coagulase-negative Staphylococcus were the most common blood culture isolates; however, given that CONS isolated from blood are often contaminants (> 85% are clinically insignificant)[13], their antibiotic susceptibility was not determined. The most frequent pathogenic microorganisms included *Pseudomonas spp.* (16%) followed by *Salmonella spp.* (14.2%), which is similar to another study from north India[18].

S. aureus was frequently found to be penicillin resistant (80.5%). Antimicrobial resistance to erythromycin, gentamicin, ciprofloxacin were above 45%, but none of the strains showed resistance to vancomycin and it could be used in multidrug resistant strains. Similar results have been reported by other workers[17,18].

In the current study, among the antibiotics used for susceptibility testing for Gram-negative isolates, ceftriaxone was very effective against *Enterobacteriaceae*, whereas for non-fermenters like *Pseudomonas spp.* and *Acinetobacter spp.* amikacin was more active. However, the combination of cefoperazone-sulbactam put up for all Gram-negative isolates showed the highest activity among all antibiotics used for these isolates.

The present observation that ceftriaxone was most effective *in vitro* against *Enterobacteriaceae* family has been well documented by other authors as well[20-23]. Aminoglycosides, such as amikacin used singly has also exhibited increased susceptibility pattern[16,24].

None of the antibiotics used singly showed high susceptibility to all the Gram-negative bacilli, so a combination of two or more drugs is recommended to cover the broad range of possible pathogens which may be difficult to distinguish clinically. This may prevent the emergence of resistance as they may have additive or synergistic antimicrobial activity[19].

In conclusion, these data provided much needed information on the prevalence of antimicrobial resistance amongst pathogens causing blood stream infections. The rise in antibiotic resistance in blood isolates emphasises the importance of sound hospital infection control, rational prescribing policies, and the need for new antimicrobial drugs and vaccines. Our results seem helpful in providing useful guidelines for choosing an effective antibiotic in cases of septicaemia and for choosing salvage therapy against hospital resistant strains.

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Capecitabine-induced Hand-foot Syndrome

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A 56-year-old female developed multiple skeletal metastases four years after completing treatment for breast cancer. She was started on monotherapy with oral capecitabine 2,500 mg per day after she refused treatment with second line combination chemotherapy. Ten days later, she returned with pain, dysaesthesia, and erythema of both hands and feet. The skin over her palms and soles had become dry, with itching, rash, and desquamation (Fig. 1). The skin over the rest of her body was unaffected. She was diagnosed to have palmar-plantar erythrodysaesthesia (PPE) or the hand-foot syndrome (HFS), a known complication of capecitabine therapy.

Capecitabine was discontinued, and she was prescribed pyridoxine, intravenous fluids, non-steroidal anti-inflammatory drugs, and emollients. Gradual improvement was noted, and the symptoms resolved completely within ten days. She was re-started on oral capecitabine 500 mg twice daily. She tolerated the dose well, and this was stepped-up over a month to a total dose of 2,000 mg per day. She is on regular follow-up, and her skin symptoms have not recurred.

Discussion

The hand-foot syndrome, also known as palmar-plantar erythrodysaesthesia is a relatively common adverse effect of some chemotherapeutic drugs. 5-Fluorouracil (and its oral prodrug capecitabine), doxorubicin, docetaxel, idarubicin, and cytarabine are the most frequently involved agents.

This syndrome is clinically characterised by the gradual onset of bilaterally symmetric erythema, tenderness, tingling,

Fig. 1: *Dry rash, erythema, blistering, and desquamation of the palm following capecitabine therapy.*

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numbness, dry rash, and desquamation over the palms and soles. Histologically, HFS shows non-specific features like degeneration of the basal layer, necrotic keratinocytes, mild interstitial oedema, spongiosis and perivascular lymphocytic infiltrates.

The orally administered prodrug capecitabine is converted to 5-fluorouracil by the body. It is FDA approved for adjuvant treatment of colon cancer, metastatic colorectal cancer, and metastatic breast cancer. The hand-foot syndrome is a well-defined adverse effect of capecitabine; others being diarrhoea, nausea, and suppression of the bone marrow. The recommended dose of capecitabine is 2,500 mg per meter square in two divided doses; this often requires reduction due to toxicity.

The management of hand-foot syndrome entails immediate discontinuation of the offending drug and symptomatic care. Resolution of the lesions is usual. Anecdotal reports have noted response with steroids and pyridoxine. The offending drug may be cautiously re-introduced in a lower dose, which may gradually be stepped-up.

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UPDATE ARTICLE

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Cardiogenic Shock – Current Status

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Cardiogenic Shock (CS) is a dreaded clinical condition with a high mortality rate of 50 – 80% in patients of CS due to acute myocardial infarction[1]. Despite advancements in the treatment of acute myocardial infarction, which is one of the most important causes of cardiogenic shock, there has not been much pharmacotherapy available till now to the clinicians for the treatment of CS. Improved understanding of the pathophysiology of CS has led to renewed emphasis on the notion that stunned or hibernating myocardium may recover function with haemodynamic support and restoration of flow[1].

It is now well recognised that coronary revascularisation in patients of Ac MI is beneficial by reversing the vicious cycle in which ischaemia causes myocardial dysfunction, which in turn worsens ischaemia. It is an established fact that in patients with CS, complicating acute MI, one year survival is better in those receiving early revascularisation versus initial medical stabilisation; however, data demonstrating long-term survival was lacking[2]. SHOCK trial[3] report after 6 years of observation has revalidated this fact that emergency coronary revascularisation provides better long-term survival in patients of CS with acute MI as compared to medical management.

Hence, prompt triage of all patients in cardiogenic shock for early angiography, use of intra-aortic balloon pump counterpulsation, and early revascularisation with PCI or bypass surgery is now the preferred management strategy[4], in addition to supportive medical measures like dobutamine, dopamine, norepinephrine, or vasopressin.

Poor prognostic factors in cardiogenic shock[5]

i. Serum glucose > 200 mg%

ii. Serum creatinine > 1.5 mg%

iii. Serum uric acid > 6.5 mg%

iv. Serum lactate > 6.5 mmol/l

v. Age > 75 yrs.

vi. History of hypertension

vii. TIMI flow post-PCI </= 2.

Newer pharmacological agents in the treatment of cardiogenic shock[6]

1.	Calcium sensitisers	:	Levosimendan (Simdax)
2.	Recombinant B-type natriuretic peptide	:	Nesiritide (Netrecor)
3.	Endothelin antagonist	:	Tezosentan
4.	Nitric oxide synthase inhibitor	:	L-NAME (Nomega-nitro-L-arginine monomethyl ester)
5.	C_5 inhibitors		

Levosimendan[7] (available as Simdax in the international market).

In cardiogenic shock due to acute MI, myocardial stunning is the precipitating event producing shock. Myocardial stunning is mainly due to calcium overload in the cytosol of myocardial cells, the loss of myofilaments and their reduced sensitivity to calcium. Enhanced immune activation with inflammatory phenomena also plays an important role in the pathophysiology of cardiac dysfunction. Increasing evidence has shown that the myocardial ATP – dependent potassium channel (K-ATP) plays an important role in many myocardial cell functions and that it is involved in ischaemia-reperfusion injury and myocardial stunning. K-ATP is thus considered a therapeutic target in this setting. Currently used inotropic drugs like dobutamine improve contractility by increasing intracellular concentration of free calcium, but they increase myocardial consumption of energy and even produce arrhythmia; therefore, they do not seem to be pathophysiologically correct drugs. Levosimendan, a new calcium-sensitising agent, increases contractility by enhancing the sensitivity of myofilaments to calcium by

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binding to the C-cardiac troponin in cardiac muscle in a calcium dependent way. Levosimendan also exerts a coronary and systemic vasodilatory effect through its K-ATP channel-opening properties, and may exert other cardioprotective actions through this mechanism. Levosimendan produces positive haemodynamic effects without increasing myocardial oxygen demand or causing arrhythmias. Intravenous levosimendan is generally well tolerated and has been approved by several European countries and recently recommended in the European Society of Cardiology guidelines as inotropic therapy for the short-term treatment of acute severe decompensated heart failure in adults. Levosimendan has an active metabolite OR-1896. Just like levosimendan, the metabolite too exerts its positive inotropic and vasodilatory effects on the myocardium and vasculature[8]. The elimination half-life of levosimendan is about 1 hour. Thus, with IV administration, the parent drug rapidly disappears from the circulation after the infusion is stopped. The active metabolite, however, has a half-life of 80 hours, and can be detected in circulation upto 2 weeks after stopping a 24 hour infusion of levosimendan. There is no sign of development of tolerance even with a prolonged infusion upto 48 hours. Due to the formation of an active metabolite, the haemodynamic effects are maintained upto several days after discontinuing levosimendan infusion. Unlike dobutamine, the haemodynamic effects are not attenuated with concomitant beta-blocker use. Levosimendan has been shown to have favourable effects on symptoms of heart failure superior to placebo and atleast comparable to dobutamine. Mortality and morbidity is significantly lower as compared to dobutamine or placebo treated patients. Most common adverse events associated with levosimendan treatment are headache and hypotension, as a likely consequence of the vasodilating properties of the compound[9].

In conclusion, various trials like LIDO, RUSSIAN, CASINO, SURVIVE, and REVIVE have proven the benefit of levosimendan over dobutamine or placebo in the patients of acute decompensated heart failure[10].

B-type natriuretic peptide: Nesiritide (available as Natrecor)

Nesiritide is a recombinant form of B-type natriuretic peptide approved for the treatment of acutely decompensated heart failure[11]. Nesiritide has beneficial actions for treatment of heart failure, including arterial and venous dilatation, enhanced sodium and urinary excretion, and suppression of the renin-angiotensin-aldosterone and sympathetic nervous systems. It has been shown to improve haemodynamic parameters, primarily pulmonary capillary wedge pressure, as well as clinical symptoms in patients with acutely decompensated heart failure. Nesiritide produced more rapid haemodynamic improvement and caused significantly fewer adverse effects than IV nitroglycerine in VMAC trial[12]. The incidence of hypotension – the most common adverse effect – was comparable between nesitritide and NTG[12]. Additionally, nesiritide is associated with a lower incidence of arrhythmias than dobutamine and has a neutral effect on mortality[11].

Nesiritide offers an alternative for management of CS. It is considered an option for patients who do not respond to other vasodilators, inotropes, or diuretics, and for those at high risk of arrhythmias. The effect of nesiritide is not dependent on beta-adrenergic receptor signal transduction pathway, hence it is also effective in those patients who are on chronic beta-blockage[13].

However, of late, there have been concerns since nesiritide does not improve renal function in patients with chronic heart failure with deranged kidney functions[14]. The lack of effect may be related to renal insufficiency, haemodynamic alterations, sodium balance, severity of heart failure or drug dose[15]. As discussed earlier, renal function is an important prognostic factor for patients of CS. Whether worsening renal function reflects haemodynamic effect or renal injury is unknown, and needs further evaluation.

A pooled data analysis of randomised control trials[16] has raised the scare that compared with non-inotrope based control therapy, nesiritide may be associated with an increased risk of death after treatment of CS.

Endothelin antagonist (Tezosentan)

Endothelin – 1 is the most potent known endogenous, vasoconstrictor. It is released during ischaemia and elevated levels have been demonstrated in hypertension, acute MI, and heart failure[17].

Tezosentan is a dual endothelin receptor antagonist and inhibits endothelin-1 receptors A and B. By inhibiting these receptors, tezosentan may counteract the activities of endothelin-1, which include vasoconstriction, proarrhythmic activities, potentiation of other neurohormones and mediation of increased vascular permeability[18]. In studies on pigs[19], tezosentan improved cardiac performance. However, the effect was not sustained with higher doses of tezosentan, possibly due to reduced coronary perfusion pressure. In human trials – VERITAS[20] and RITZ-5[21], tezosentan did not affect the outcome of pulmonary oedema, possibly because of the high dose used. In RITZ-5 trial, the outcome of patients who received only 50 mg/hr tezosentan was better than patients in the placebo group, whereas patients receiving 100 mg/hr had the worst outcomes. Another study[22] has also concluded that doses of 1 – 25 mg/hr are efficacious in improving haemodynamics. But doses beyond 1 mg/hr increased plasma endothelin levels and reduced urine output, thus limiting their clinical efficacy.

Phase II and III trials of tezosentan[23] show that adverse event profile is significant for the incidence of headache, nausea, and hypotension compared with placebo.

Vasopressin V-2 receptor antagonist[18] (Tolvaptan)

It acts as an aquaretic, i.e., it increases urine volume and serum sodium with very little or no sodium loss.

Conclusion

Recent advances in the treatment of cardiogenic shock offer a mixed bag of therapies, some very promising while others have not fulfilled their initial expectations. But one thing is clear that an attempt is being made to accurately understand the mechanism of CS, and a multi-pronged strategy is being applied to find out remedies which act through different and unconventional ways. This offers us hope that the future of cardiogenic shock will not be as dreaded as it is now.

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UPDATE ARTICLE

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Chronic Kidney Disease: A Perspective

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Prevalence of chronic kidney disease (CKD) is rising worldwide. The global 'End Stage Renal Disease' (ESRD) patient population continues to grow at an alarming rate due to a number of factors. End stage renal disease occurs when kidney function is insufficient to sustain life and haemodialysis, peritoneal dialysis, or kidney transplantation is substituted for native kidney function. The cost of all these modalities is very high and this puts an enormous financial burden on the healthcare budget of any country. The progressive nature of CKD and the ensuing ESRD is putting a substantial burden on global health resources since all modalities of treatment are expensive[1]. There are multiple causes of kidney injury that lead to the final common pathway of ESRD, and this syndrome is characterised by hypertension, anaemia, renal bone disease, nutritional impairment, neuropathy, impaired quality of life, and reduced life expectancy. Increasing evidence acquired in the past decades indicates that the adverse outcomes of CKD such as renal failure, cardiovascular disease, and premature death can be prevented or delayed by early detection of CKD. Earlier stages of CKD can be detected through laboratory testing only. Treatment of earlier stages of chronic kidney disease, as well as initiation of treatment of cardiovascular risk factors at early stages of CKD should be effective in reducing the rate of progression of CKD to ESRD. This article discusses the epidemiology of CKD, the risk factors associated with it, and the measures needed to reduce the burden of CKD.

Epidemiology

Community based prevalence rates are not available in India. However, it is estimated that approximately 100,000 new cases of ESRD develop annually in India[2]. Patients with ESRD appear to be the tip of the iceberg, and those in the earlier stages of CKD – who are more in number – need attention, to retard progression[3]. The key factor is early detection of CKD. Despite limitations, serum creatinine remains the routine laboratory investigation for diagnosis and monitoring of CKD. Serum creatinine cannot accurately predict the onset of chronic kidney disease. The glomerular filtration rate (GFR) is the preferred measure, but it involves considerable effort, cost, and time. GFR provides an excellent measure of the filtering capacity of the kidneys[4]. A low or decreasing GFR is a good index of chronic kidney disease. Since the total kidney GFR is equal to the sum of the filtration rates of individual nephrons, total GFR can be used as an index of the functioning renal mass. A decrease in GFR precedes kidney failure in all forms of progressive kidney disease. Monitoring GFR can delineate progression of CKD. The level of GFR is a strong predictor of the time to onset of kidney failure as well as the risk of complications of CKD. Additionally, estimation of GFR in clinical practice allows proper dosing of drugs excreted by glomerular filtration to avoid potential drug toxicity[4]. In practice, it may not be possible to measure it routinely, more so, in the community set-up. The gold standard for assessment of GFR is inulin clearance or radio-nucleotide studies, which are institution-based investigations. In view of these difficulties, a number of mathematical formulae have been derived to determine GFR based on serum creatinine and incorporating demographic and clinical variables. There is a need to inculcate the habit of using these formulae routinely in clinical practice. Of these equations, MDRD equation is the most widely accepted[5, 6].

MDRD equation is as follows:

$$GFR\ (ml/min/1.73m^2) = 170 \times (Scr)^{-0.999} \times (Age)^{-0.176} \times (SUN)^{-0.170} \times (Alb)^{+0.318} \times (0.762\ \text{if female}) \times (1.180\ \text{if black})$$

And the abbreviated MDRD equation is

$$GFR\ (ml/min/1.73m^2) = 186 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.210\ \text{if black})$$

The abbreviated equation has performed similarly as compared to the 1st equation as far as accuracy is concerned.

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Thus the abbreviated MDRD equation provides a rigorously developed equation for estimating GFR. However, there are a few problems with the MDRD equation. Firstly, it is a complicated equation and its use requires Internet, which may not be available always in our country. Secondly, the equation has not been validated in different ethnic populations[5]. The other well-known equation is the Cockcroft-Gault equation. The C-G formula estimates creatinine clearance and is the most well-known equation used in clinical practice[7]:

$$Cr\,Cl = \frac{(140-age) \times wt\ (kg)}{72 \times Scr} \quad (\times 0.85 \text{ if female})$$

This equation can be corrected for GFR:

GFR = 0.84 x CrCl (by C-G formula)

Besides serum creatinine, cystatin C is another endogenous filtration marker being considered as a marker of GFR. Several studies have compared creatinine with cystatin C with conflicting results. It seems that cystatin C may have an advantage in detecting mildly decreased GFR, whereas serum creatinine may be better at the lower levels of GFR[8]. Moreover, cystatin C is not a cost-effective marker of GFR.

The worldwide rise in the number of patients with CKD is reflected in the increasing number of patients with end stage renal disease treated by renal replacement therapy-dialysis or transplantation. Two factors are important: first is the ageing of population; the menace of ESRD is higher in elderly people than in the general population. The second factor is the global epidemic of type 2 diabetes mellitus (DM); the number of people with DM is predicted to double within the next 20 years[9]. This increase will be most notable in the developing countries where the number of diabetic patients could increase from 99 million to 286 million by 2025 with an expected parallel epidemic of diabetic nephropathy[9]. During the last two decades, the USRDS has documented an epidemic of ESRD in the United States of America, and similar increases in the incidence of ESRD have been reported in other industrialised and developing countries. The incidence of ESRD in USA has increased from 219 per million in 1991 to 334 per million in 2000, an increase of 51% during one decade[10].

About 90% of treated ESRD patients come from developed countries that can still afford the cost of renal replacement therapy[11]. There is a clear and direct relationship between the gross national product and the availability of renal replacement therapy, with less developed countries unable to meet the increasing demand of renal replacement therapy. The huge disparity in the prevalence of ESRD between more and less developed countries probably stems from inadequacy of health care resource allocation to programmes of renal replacement therapy. But the disparity in incidence could also be due to racial and ethnic factors, for example in USA and Australia, the incidence of ESRD is much less in the white population than in the African-American or aboriginal people[12, 13].

The number of patients with ESRD probably underestimates the entire burden of CKD. This is because the number of patients with earlier stages, of CKD is likely to exceed the number of those reaching ESRD[3] by as much as 50 times. For instance, in the USA, data derived from the Third National Health and Nutrition Examination Survey have implied that upto 11% of the general population (19 million) could have some degree of CKD including more than 8 million individuals with GFR of < 60 ml/min. This analysis also estimated that 5.9 million people could have stage I CKD with normal or increased GFR (3.3%)[3]. Other screening surveys conducted in Australia, Japan, and Europe also identified between 6% and 11% of general population as having some degree of CKD[14-16]. The prevalence rate in Canada is 6% and the global prevalence rate is estimated to be 8%. The prevalence of CKD increases to 50 – 60% when individuals at risk are screened[17].

In India, currently some attempts are being made to find the prevalence of CKD in the general population. In a multistaged cluster sampling method, Agarwal *et al*, estimated that the prevalence of CRF in Delhi was 0.785. In this study serum creatinine was used as a diagnostic indicator for CRF. A serum creatinine > 1.8 mg% defined renal failure[18]. A repeat test for serum creatinine was done after 8 – 12 weeks to confirm chronicity of renal failure. If it was > 1.8 mg% after 3 months in the absence of reversible factors, CRF was diagnosed. A total of 4,972 persons were contacted for the study. Their mean age was 42 +/- 13 years; 56% were males. Out of the 4,972 who were initially approached, 4,712 agreed to give their blood sample, and

thus were included for the evaluation of CRF. CRF was found in 37 of them. The Third National Health and Nutrition Examination Survey estimates that 6.2 million Americans have serum creatinine greater than 1.5 mg/dl[19]. The K/DOQI work group more recently reassessed the NHANES III data and released estimates of the prevalence of each of the five stages of CKD. Their repeat analysis suggests that 8.3 million individuals in the United States have CKD based on decreased GFR (i.e. < 60 ml/min/1.73 m^2) with an additional 11.2 million individuals who have persistent proteinuria with normal or mildly decreased GFR (i.e. > 60 ml/min/1.73 m^2). Their figures suggest that 3.3% of the population 20 years of age or older has stage I CKD; 3% have stage II CKD; 4.3% have stage III CKD; 0.2% have stage IV CKD; and 0.2% have stage V CKD (with stage V including those on dialysis[20,21]. This shows the importance of estimating the prevalence based on GFR, rather than serum creatinine. In India only one group from Chennai (Mani MK *et al*) has done the renal function assessment in the community using the MDRD equation and estimated GFR. This ongoing study mainly attempted to identify patients with impaired renal function. The prevalence of impaired renal function (GFR < 60 ml/min/1.73 m^2) is estimated to be 13.9 per thousand or 1.39%[22]. Although this appears to be lower than the prevalence of CKD in the United States, the absolute number of people with CKD will be much more than that in United States and so will be the economic burden of the disease. The variation among communities in the incidence of ESRD mirrors that in the prevalence of diabetes, obesity, and hypertension[23]. This observation has worrisome implications for the future incidence of ESRD in the developing world, where the prevalence of diabetes is expected to double by 2030[24]. It is estimated that by that year, more than 70 per cent of patients with ESRD will be residents of developing countries, whose collective economies will account for less than 15 per cent of the total world economy[23].

Definition of CKD and classification of stages of CKD

The National Kidney Foundation Kidney Diseases Outcome Quality Initative (NKF – K/DOQI) clinical practice guidelines for chronic kidney disease recommend that CKD be adopted to define the presence of kidney injury and impaired kidney function. According to these guidelines, the defination of CKD is summarsed in Table I[4].

Table I: Definition of CKD.

1. Kidney damage for > 3 months, as defined by structural or functional abnormalities of the kidney with or without decreased GFR, manifest by either:
   a. Pathological abnormalities, or
   b. Markers of kidney damage, including abnormalities in the composition of blood or urine, or abnormalities in imaging tests.
2. GFR < 60 ml/min/1.73 m^2 for 3 months or more, with or without kidney damage.

This is irrespective of the primary cause of renal injury. Kidney damage is ascertained by either kidney biopsy or markers of kidney damage such as proteinuria, abnormal urinary sediment, or abnormalities on imaging studies. GFR< 60 ml/min/1.73 m^2 BSA is selected as cut-off value for definition of CKD because it represents a reduction by more than half of the normal value of GFR, i.e., 12 5 ml/min/1.73 m^{-2} in young men and women, and this level of GFR is associated with onset of laboratory abnormalities characteristic of kidney failure. Equations that convert the serum creatinine into an estimated GFR or creatinine clearance are available and should be used to avoid misinterpretation of serum creatinine results. An estimated GFR above 60 ml/min/1.73 m^2, in the absence of other anatomic, radiographic, or urinary abnormalities, is not classified as CKD.

Classification of chronic kidney disease: Table II shows the classification of chronic kidney disease including the population at increasing risk of developing chronic kidney disease[4]. This staging of chronic kidney disease by NKF – K/DOQI uses GFR. This classification however, is subject to debate[25]. Some authors have argued that stages 1 and 2 would be better classified by associated abnormalities (e.g., microalbuminuria, haematuria) [25].

Table II: Stages of chronic kidney disease.

Stage I:	Kidney damage (pathological abnormalities or markers of damage including abnormalities in blood or urine tests or in imaging studies with normal or raised GFR > 90 ml/min/1.73 m^2
Stage II:	GFR = 60 – 89 ml/min/1.73 m^2
Stage III:	GFR = 30 – 59 ml/min/1.73 m^2
Stage IV:	GFR = 15 – 29 ml/min
Stage V:	End stage renal disease with GFR < 15 ml/min.

Risk factors for CKD

Much epidemiological and clinical evidence has shown a link between several factors and the initiation and progression of CKD. These can be classified into two distinct categories: those proven to be causal (risk factors) and those that are associated with CKD in the absence of established causal relation (risk markers).

Susceptibility factors

1. Genetic or familial predisposition:

   CKD commonly clusters within families that implies genetic or familial predisposition. Genetic studies have suggested links between CKD and various alterations or polymorphisms of candidate genes encoding putative mediators; including the renin-angiotensin system[26].

2. Racial factors:

   Racial factors also have a role in the susceptibility to CKD as shown by high prevalence of CKD related to hypertension, diabetes, or both, among Africans and native Americans in USA as well as Afro-Caribbean and Asian individuals in UK[27].

3. Low birth weight and infant malnutrition in some ethnic communities may be associated with a reduction in number of nephrons, predisposing to hypertension and renal disease in later life[28].

4. Male and elderly people may be more susceptible to CKD, which would explain the high proportion of these population groups in renal replacement therapy programmes[12].

Initiation factors

Several initiation factors have been identified on various cohort studies in USA and Japan.

Those include the following as risk factors or markers in the general population for development of CKD:

1. **Hypertension** is the second most common cause of ESRD in the United States, accounting for 23% of incident ESRD patients between 1996 and 2000 (USRDS Annual data report: National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2002)[10]. Elevated blood pressure is also an important modifiable risk factor for progressive CKD regardless of the initial cause of renal injury. Observational studies have established that patients with non-malignant, non-accelerated hypertension are at high risk of progressive renal insufficiency[29]. Evidence from clinical trials show that blood pressure reduction reduces the rate of loss of renal function and progression to renal failure, and this information has been incorporated into widely disseminated clinical practice guidelines. The crucial role of blood pressure control and blockade of the renin angiotensin system has been incorporated in the JNC VII guidelines published in 2003[30]. The blockade of renin angiotensin system is not only beneficial in diabetic patients but also in non-diabetic hypertensive patients. JNC VII guidelines recommend that the presence of CKD, defined by either an estimated GFR below 60 ml/min/1.73 m^2 or an albumin to creatinine ratio of 200 mg albumin/g creatinine or greater be considered a compelling indication to adopt the therapeutic goals to slow deterioration of renal function[30]. The guidelines recommend that these CKD patients have a more aggressive blood pressure management goal of less than 130/80 mm Hg and agents that block the renin angiotensin system should be the first line drugs for management of hypertension[30].

2. **Diabetes** is the most common cause of ESRD as reported by the USRDS. It accounts for nearly 45% of all new cases of ESRD starting renal replacement therapy between 1996 and 2000 (USRDS Annual data report: National Institute of Health. National Institute of Diabetes and Digestive and Kidney Diseases; 2002)[10]. The incidence of renal failure caused by diabetes is increasing at a 10% per year rate and if sustained the number of new patients being treated for diabetic renal failure will double in the next 8 years[10]. Diabetic nephropathy is one of the leading causes of ESRD (exceeding 30 – 40%) in countries such as Malaysia, Turkey, Qatar, and the Philippines[10]. Strict control of hyperglycaemia reduces the rate of loss of renal function and progression to renal failure among patients with both type 1 and type 2 diabetes mellitus. Further, blood pressure control and use of renin angiotensin system blockers are also essential steps in the management of diabetes mellitus that can delay or prevent the occurrence of ESRD.

3. **Cardiovascular disease as risk factor for progressive CKD**

Patients undergoing coronary angiography, patients treated with percutaneous coronary interventions and coronary artery bypass surgery, and participants in clinical trials of atherosclerotic disease are at increased risk of CKD[31-33]. A prevalence estimate of CKD among people with cardiovascular disease varies from 10% to over 60% with an average of 29.9%[33-36]. This variability in the presence of CKD is caused, in part, by the differences in study source populations and inclusion and exclusion criteria. They provide substantial evidence, however, that persons with cardiovascular disease are at high risk of having CKD.

Patients with cardiovascular disease and CKD are at an increased risk of developing ESRD. For example a study of 12,000 hypertensive male veterans found that the risk of developing ESRD was increased two-fold among individuals who experienced a new myocardial infarction and five-fold among those who developed heart failure during follow-up[29]. Autopsy studies too have found a correlation between the extent of atherosclerosis and degree of glomerular scarring[37]. Based on these observations, clinicians should carefully screen individuals with cardiovascular disease for the presence of kidney disease and include interventions to preserve kidney function in their management plans.

Not only is cardiovascular disease a risk factor for initiation of CKD, but the converse is also considered to be true, i.e., CKD is also a risk factor for cardiovascular disease. Many CKD patients do not reach ESRD because either the CKD is not progressive or they die first, the major contributor of mortality being CVD[38]. CKD imparts cardiac risk through co-existing diseases, such as hypertension, atherosclerosis, diabetes, or hyperlipidaemia; through factors associated with CKD including anaemia, inflammation, divalent ion abnormalities, and hyperhomocysteinaemia, and other putative risk factors, including oxidative stress. The risk factors associated with CKD that increase the risk of cardiovascular disease in patients of CKD are enlisted in Table III[39].

Table III: Risk factors associated with cardiac disease.

Traditional
Age
Gender
Race
Smoking
Diabetes
Body mass index
Hypertension
Dyslipidaemia
Left ventricular hypertrophy
CKD-related risk factors
Uraemia related
Anaemia
Calcium phosphate
Electrolyte imbalance
Malnutrition
Hypoalbuminaemia
Inflammation
C-reactive protein
Increased oxidative stress
Endothelial activation
Prothrombotic factors
Hyperhomocysteinaemia
Cytokines
Advanced glycation end-products
Therapy-related
Dialysis
Transplant
– Acute rejection
– Immunosuppressives

4. **Hyperlipidaemia**[40]

5. **Obesity**[40]

6. **Smoking**[40]

In developing countries, evidence is lacking regarding the aetiology of CKD because of poor data collection and absence of renal registries. Infectious diseases and infection related chronic glomerulonephritis form a major cause of CKD and end stage renal disease. The infections include HIV (40 million infected worldwide), hepatitis C virus (170 million), malaria (300 million), schistosomiasis (200 million), and tuberculosis (200 million) (WHO, World Health Report 2003. Geneva, WHO, 2003)[41]. Inspite of this, it is believed that diabetes and hypertension are the leading causes of CKD in India.

Progression factors

The progression of CKD is variable and depends on various factors or markers. These can be modifiable or non-modifiable risk factors.

Non-modifiable risk factors:-

1. **Sex:** rate of progression is faster among males[42]
3. **Age:** rate of progression is faster among elderly[43]
3. **Race:** rate of progression is faster among African Americans[44]
4. **Genetic factors**

Modifiable risk factors

1. **Systemic hypertension:** Systemic hypertension is not only an initiation risk factor for CKD but uncontrolled hypertension is also responsible for a rapid progression of CKD. A study in Japan had shown that there is an independent strong and graded relationship between higher levels of current systolic blood pressure and the risk of CKD progression during antihypertensive therapy with or without ACE inhibitors in patients with non-diabetic kidney diseases[45]. They found that after adjustment for systolic blood pressure, diastolic blood pressure was not a risk factor for CKD. The risk for kidney disease progression seemed to be lowest at levels of current systolic blood pressure of 110 to 129 mm Hg.

2. **Proteinuria (albuminuria):** Proteinuria is a reliable marker of severity of CKD and independent predictor of its progression[46]. Patients with persistently high rates of urinary protein excretion (> 3 – 5 g/24 hrs) in general have much faster rate of progression than those with mild or moderate proteinuria (< 1 – 3 g/24 hrs)[47].

3. **Hyperglycaemia:** Poor blood sugar control accelerates the progression of diabetic nephropathy in both type 1 and type 2 diabetes as established by the Diabetes Control and Complications Trial (DCCT), and the UKPDS study[48, 49].

4. **Hyperlipidaemia:** Experimental evidence has also shown a link between hyperlipidaemia and progression of nephropathy[50]. This was first suggested by Moorhead *et al*, and evidence in support of a role of lipids in progression of CKD has steadily accumulated[51]. At present, hyperlipidemia must be considered a risk factor for both cardiovascular disease and progressive renal insufficiency, and lipid lowering therapy may be both reno-protective and cardio-protective.

5. **Hyperuricaemia:** A link between hyperuricaemia and the development of systemic hypertension, cardiovascular disease, and renal disease has also been postulated[52].

6. **Obesity:** The worldwide pandemic of obesity could also affect the progression of CKD. Obesity has been associated with initiation and progression of glomerulonephritis[53]. The incidence of focal and segmental glomerulosclerosis is higher in obese than in lean individuals, and the progression of IgA nephropathy is thought to be faster in obese patients[54,55]. Among NHANES III participants, the risk of either incident ESRD or kidney disease related death was independently associated with physical inactivity, smoking, and a body mass index greater than or equal to 35 kg/m^2 with a relative risk of 2.3 among the morbidly obese individuals[56]. Obesity has also been associated with changes in renal function. Obese participants in the Framingham study who were initially free of kidney disease at baseline were more likely to have a decrease in estimated GFR[57]. There is strong evidence that weight loss preserves renal function[58].

7. **Cigarette smoking:** Has been implicated in initiation as well as progression of CKD. The incidence of ESRD was increased by 5.9 times among heavy smokers (> 15 pack years)[59]. In another study, heavy smokers (> 20 pack years) had a risk of developing albuminuria three times that of non-smokers[60].

8. **Alcohol:** Regular and heavy (> two drinks daily) consumption of alcohol might also increase the risk of ESRD according to a survey undertaken in the USA[61].

9. **Analgesic abuse:** Some studies have linked the consumption of analgesics, especially paracetamol and NSAIDs with a higher risk of developing CKD[62]. One of the largest case control studies showed an odds ratio of 2.4 for patients with lifetime cumulative consumption of 5,000 or more paracetamol tablets compared with individuals taking 1,000 or fewer tablets[63].

10. **Dietary protein consumption:** It is not well established that restricting the amount of protein consumed in the diet delays the progression of CKD to ESRD. Fouque *et al* conducted a meta-analysis of six early-randomised trials of dietary protein restriction among patients with mild-to-moderate CKD[64]. A difference in 0.2 g/kg/day of protein consumption between intervention and comparison group was associated with a 44% reduction in end-point of either death or dialysis. On the other hand, MDRD study had some conflicting results. The study found that patients on a low protein diet had a more rapid decline in GFR for the first 4 months and had a slower decline thereafter. Among patients with more severe renal insufficiency, a very-low-protein diet, as compared with a low-protein diet, did not significantly slow the progression of renal disease[65].

Strategies to reduce the progression of chronic kidney disease

CKD and ESRD are a huge financial burden on the health resources. In the USA, the annual cost of managing patients with ESRD is predicted to be more than $ 35 billion by 2010[66]. Despite this, these patients continue to experience significant morbidity and mortality. It is estimated that slowing the progression (by decreasing the rate of decline in GFR by 10%, 20%, and 30% in patients with GFR of less than 60 ml/min from the year 2000 through 2010 and preventing patients from reaching the ESRD level can potentially lead to cumulative direct healthcare savings of $18 - $60 billion[67]. Interventions that may prevent or slow the progression of CKD towards ESRD are extremely important.

1. Renin-Angiotensin System (RAS) inhibitors as renoprotective agents

The angiotensin-converting enzyme inhibitors are considered to be reno-protective. In diabetic nephropathy they are often used to retard the progression of renal disease. In type 1 diabetes, ACE inhibitors retard the progression of microalbuminuria. They are also useful in preventing the progression of CKD in diabetic nephropathy as demonstrated by the Captopril Collaborative Study Group[68]. In type 2 diabetes, the ACE inhibitors have not shown consistent reno-protective effects. While some studies have shown a reduction of proteinuria alongwith stabilisation of renal function[69, 70] some other studies have not found any association between a reduction in proteinuria and stabilisation of renal function[71, 72]. The UKPDS and the Appropriate Blood pressure Control in Diabetes (ABCD) trials failed to demonstrate any beneficial effect on either reduction of proteinuria or stabilisation of renal function[49, 73]. Several studies, however, have shown the beneficial effects of ACEIs on reducing microalbuminuria or the risk of its progression to macroalbuminuria[72, 74, 75]. To summarise, it is justifiable to recommend the use of ACEIs in all type 1 diabetic patients with microalbuminuria or macroalbuminuria, data regarding use in normoalbuminuric patients is not conclusive. In type 2 diabetics, ACEIs are definitely indicated in patients with microalbuminuria; their beneficial effect in patients with overt nephropathy is not conclusive. Considering the association between type 2 diabetes and cardiovascular diseases, however, it is justifiable to consider ACEI therapy in such patients to reduce cardiovascular risk.

In non-diabetic nephropathy also, several studies have demonstrated the beneficial effects of ACEI therapy. The Ramipril Efficacy in Nephropathy (REIN) study showed that ramipril delayed the progression of CKD to ESRD in non-diabetic nephropathy and decreased the rate of decline in GFR[76]. The AASK trial (African American Study of Kidney diseases) also observed that ramipril was more reno-protective than amlodipine. They also observed that effectiveness of the beta-blocker metoprolol was not significantly different from ramipril[77].

Angiotensin receptor blockers (ARBs) exert their effects by inhibiting the type 1 angiotensin II receptor. In general, they have a more favourable side-effect profile compared with ACEIs. Two large, prospective, randomised control trials recently demonstrated that interruption of the renin-angiotensin system with ARBs delays the progression of CKD in type 2 diabetic patients with overt nephropathy[78, 79]. Although data from large clinical studies evaluating the role of ARBs in retarding the progression of CKD in patients with type 1 diabetes and non-diabetic patients are still awaited, preliminary data suggest that they are as effective as ACEIs.

The progression of CKD can be further reduced by the combination of ACEIs and ARBs. In general, this combination is well tolerated in patients with moderate CKD. Recently, the results of the COOPORATE trial have demonstrated the more robust reno-protective effect of the combination as compared to either drug alone[80]. Presently the combination of ACEI and ARB is recommended only in patients who are not able to achieve the goal of proteinuria < 0.5 g/d and GFR decline < 2 ml/min/year with maximum monotherapy dose of either drug.

It is important to note that despite the documented evidence of utility of these agents in retarding the progression of CKD, both these agents are under-utilised in clinical practice. This is mainly due to the physician's fear of potential adverse effects such as hyperkalaemia and a rise in serum creatinine, particularly in patients with CKD. At the same time it should be emphasised that patients with CKD are the ones who will benefit most with the use of ACE inhibitors and ARBs.

2 Treatment of hypertension

It is now widely accepted that high blood pressure is one of the most important factors in the progression of CKD and that lowering of blood pressure can slow or even prevent progression of CKD in both diabetic and non-diabetic patients. The MDRD study clearly demonstrated the beneficial effect of lowering blood pressure on the progression of CKD[65]. As a result, the MDRD study group recommended a blood pressure goal of 130/80 mm Hg for patients with less than 1 g/d of proteinuria, and a goal of125/75 mm Hg for patients with proteinuria greater than 1 g/day. It should be remembered, however, that these goals should be achieved with caution in patients with labile blood pressure, severe arteriosclerosis, and autonomic neuropathy, who were not included in the MDRD study. With respect to calcium channel blockers and dihydropyridine subclass in particular, data from the REIN study as well as the AASK trial showed an association between their use and faster decline of GFR[77]. Their use should be restricted to CKD patients in whom they are necessary to control blood pressure and only in combination with an ACEI or ARB.

3 Proteinuria

The association between continued proteinuria and irreversible impairment of renal function has been known for some time, but not until the past two decades has proteinuria been recognised as a possible contributor to the progression of renal disease – rather only as an ominous biomarker of the degree of glomerular and tubulointerstitial damage[81]. Glomerular hypertension and damage to the glomerular barrier causes non-selective proteinuria; this excess of protein is taken up by proximal tubular cells by way of endocytosis. This in turn activates a host of inflammatory and cytokine responses, which ultimately results in the fibrosis and scarring of the kidney and the progression of CKD[82]. In studies of diabetic and non-diabetic kidney diseases, early reduction in proteinuria is associated with slower progression of CKD[83, 84]. The MDRD study has also clearly documented that a reduction in the urine protein excretion was independently associated with lower risk of progression of CKD[85]. It is justified to state that as for hypertension, reducing the rate of proteinuria to a target of < 0.5 g/day should be vigorously pursued as an independent therapeutic goal[83].

Dietary protein restriction

Dietary protein restriction has always been regarded as one of the most important clinical interventions for retarding the progression of CKD[86]. The results from recent clinical trials including the MDRD study have been controversial and inconclusive. The primary results of the study failed to show a significant beneficial effect of low protein diet and were not conclusive. The secondary analysis of the MDRD study suggested a beneficial effect of low protein diet on CKD progression[87]. In fact, there was an initial drop in the GFR in the group receiving low protein diet during the first four months. This was probably caused by functional factors other than nephron loss. This decrease was followed by a slower rate of deterioration in renal function in the low protein group, which might have achieved significance if the follow-up period had been longer. Two relatively recent meta-analyses of randomised studies showed an overall beneficial effect of dietary protein restriction on the progression of CKD in both diabetic and non-diabetic patients[88, 89].

The available data indicate that recommending dietary protein restriction (0.6 - 0.8 g/kg/day) is justifiable in patients with CKD as part of an integrated approach to retard the progression of CKD. So protein restriction is beneficial in CKD, but at the same time care should be taken to prevent malnutrition in patients on low protein diet.

4 Treatment of dyslipidaemia

Dyslipidaemia commonly accompanies CKD in the form of high VLDL, high LDL, and low HDL[90]. Whereas the role of dyslipidaemias in atherosclerotic cardiovascular disease is well known, their role in the initiation and progression of CKD is less clear. An association between hypercholesterolaemia and a faster rate of CKD progression has been shown in diabetic patients[91]. The MDRD study as well as the Helsinki Health Study found low HDL and an elevated LDL to HDL ratio as an independent risk factor for the deterioration of kidney function[92, 93]. The mechanism by which dyslipidaemias may affect renal function is not completely understood. A recent meta-analysis showed a significant decrease in the GFR decline and a trend towards reduction in albuminuria and proteinuria with the use of lipid lowering agents (statins or triglyceride lowering agents)[94]. It is noteworthy that statins, apart from their lipid lowering effect, exert other functions (e.g., down-regulation of transforming growth factor, anti-oxidant effect), which may be beneficial in retarding the progression of CKD[95].

5 Smoking cessation

Available data are suggestive of adverse effects of smoking on the kidney; and that smoking increases the risk of proteinuria and the rate of progression of CKD. In the Heart Outcome Prevention Evaluation (HOPE) Trial, microalbuminuria was associated with several risk factors for cardiovascular disease, including current smoking[96]. In patients with essential hypertension, smoking almost doubles the risk of microalbuminuria and macroalbuminuria[97]. In addition, smoking may accelerate the rate of progression of CKD in hypertensive patients[98]. This justifies the statement that smoking cessation may retard the progression of CKD and that all patients with CKD should be counselled in this regard.

6 Anaemia

It has been proposed that hypoxia of the renal tubular cells exerts a role in the progression of CKD by stimulating extra-cellular matrix production, and inducing production and release of profibrotic cytokines. Decreasing the hypoxia by correcting anaemia may be helpful in retarding the progression of CKD. In a study by Kuriyama *et al*, 73 CKD patients (mean serum creatinine of 2.9) with anaemia (haematocrit < 30%) were randomly assigned either to receive (42 patients) or not receive (31 patients) erythropoietin. This study also included a third group as less anaemic control patients (Hct > 30%, and serum creatinine of < 2.6 mg/dl). After 36 weeks, serum creatinine doubled in 84% of untreated patients, whereas doubling of serum creatinine in erythropoietin treated group and the less anaemic group averaged 52% and 60% respectively[99]. Although the role of erythropoietin in retarding the progression of CKD awaits larger randomised controlled trials, the role of effective treatment of anaemia in improving survival and quality of life, and in decreasing morbidity and mortality in patients with CKD, justifies its use in the pre-ESRD management of patients with CKD. The United States NKF-K/DOQI Guidelines, initially published in 1997 and revised in 2001, recommended a target haematocrit between 33% and 36% or a haemoglobin concentration of 11 - 12 g/dl[100]. The European Best Practice Guidelines recommend a target haemoglobin of greater than 11 g/dl or haematocrit greater than 33%, without a guideline for the upper limit[101]. The United States Normal Haematocrit study evaluated 1,233 haemodialysis patients with clinical evidence of congestive heart failure or ischaemic heart disease. The risk ratio (for death and non-fatal myocardial infarction) was 1.3 for the normal haematocrit group as compared to the low haematocrit group[102].

7 Obesity

Animal studies have shown an association between obesity and glomerular hyperfilteration. In a study of a group of patients with obesity-related proteinuria, dieting led to a mean weight loss of 12% and a reduction in proteinuria of greater than 80%[103].

Multiple risk factor intervention in CKD

To achieve a more effective reno-protection, a comprehensive strategy using multiple therapies and directed at different aspects of pathophysiology underlying the progression of CKD is required. Table IV shows a comprehensive strategy to achieve maximal reno-protection in patients with CKD. The focus of CKD care therefore must be broadened to include multiple risk factor intervention[104] including CVD reduction in addition to, or concomitant with, reducing the progression of kidney function decline. With the increasing understanding of kidney disease pathophysiology and CVD within the CKD population, it has become clearer that treatment and care options are increasingly complex. Given the multiplicity of goals of care and complexity of treatment options, the increasing comorbidity of the patient population, and the accumulating data describing best practices, an individual nephrologist is unlikely to be able to manage CKD care alone, therefore a team approach with well-defined roles, responsibilities, and objectives seems to be logical and practical. To execute a change in the management of patients with CKD, medical students, healthcare professionals, and established physicians, need to be educated about the prevalence and consequences of CKD. The concept that CKD is a risk factor for cardiovascular disease, and needs to be managed (as does diabetes and dyslipidaemia), should be emphasised[105]. Collaborative management of CKD in patients between different physicians and multidisciplinary teams, in conjunction with the ongoing investigation of treatments and treatment strategies by both clinicians and researchers, may well lead to improved outcome for patients with CKD.

The concept of multidrug therapy was put forward after a meta-analysis of more than 750 trials involving around 400,000 participants suggested that upto 80% reduction in cardiovascular disease events could be obtained by a combination treatment with ACE inhibitors, statins, and other cardio-protective agents such as aspirin and antioxidants. Whether a similar therapeutic approach, based on a combination of generic drugs, would be appropriate in the future for some patients of CKD remains to be determined[106]. The use of a single daily pill ("polypill") – containing generic angiotensin-converting enzyme inhibitors, statins, aspirin, and folic acid in order to simultaneously control blood pressure, dyslipidaemia, and thrombogenic tendency – should be on the agenda of many developing countries[107].

There is thus a need for studies to measure prevalence/incidence rates of the spectrum of CKD in our country. There is a strong need to develop a database on CKD at different levels which may be helpful in understanding the epidemiological spectrum of CKD[108].

To summarise, CKD deserves attention, examination, and the possibility of integration with other major NCDs. These issues need to be brought to the notice of research managers, planners, academicians, public health managers, scientists, and conscientious clinicians in the field of health.

Table IV: Interventions and strategies to retard the progression of CKD.

Intervention	Goal
ACE inhibitor or ARB, may consider combination therapy if goal is not achieved with full dose monotherapy	Proteinuria <0.5 g/day GFR decline <2 ml/min/year
Treatment of hypertension Initially with ACE inhibitors Add salt restriction/diuretic for maximal effect Add ARB or nondihydropridine CCB or beta-blocker if goal not achieved	BP <130/80 if proteinuria <1 g/day BP <125/75 if proteinuria >1 g/day
Dietary protein restriction	0.60–0.80 g/kg/day
Tight glycaemic control in diabetes	HBA1c <6.5 g/dl
Cholesterol lowering therapy	LDL <100 mg/dl
Erythropoietin therapy	Hb >12 g/dl
Dietary salt restriction	3–5 g/day
Smoking cessation	Abstinence
Weight control	Ideal body weight
Antiplatelet therapy	

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REVIEW ARTICLE

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Chikungunya Fever

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Abstract

Chikungunya fever is a viral disease resembling dengue, transmitted to humans by the bite of an infected Aedes aegypti mosquito. It is endemic in East Africa and parts of Asia. Its recent epidemic has badly hit India – especially southern and central India – and like malaria and dengue, this infection has almost become endemic. Symptoms of sudden onset of fever, chills, headache, nausea, vomiting, joint pain with or without swelling, low back pain, and rash are very similar to those of dengue. But, unlike dengue, there is no haemorrhagic or shock syndrome. Chikungunya is a self-limiting illness that requires no specific treatment.

Introduction

Chikungunya is a relatively rare and benign form of viral fever caused by an alphavirus that is spread by mosquito bites from the infected *Aedes aegypti* mosquito. The name chikungunya, is given by Lumsden's initial 1955 report, which is derived from the Makonde word 'kungunyala', meaning to dry-up or become contorted. Subsequently, Marion Robinson[1] who first described the disease following an outbreak in 1952 on the Makonde plateau, between Tanganyika and Mozambique, glossed the Makonde term more specifically as "that which bends up".

This refers to the stooped posture adopted by the patient as a result of the arthritis symptoms that the patient develops.

In India it was first reported in 1963 at Calcutta[2]. Its recent epidemic which started in December 2005[3], involving southern and central India has grabbed much attention. Chikungunya is not considered to be fatal. However, in 2005 - 2006, 200 deaths have been associated with chikungunya of Reunion Island and widespread outbreak in southern India[4].

Clinically, it is characterised by abrupt onset of fever, chills, headache, joint pain, and swelling especially involving small joints. Various types of rashes develop usually after the subsidence of fever and in the convalescent phase.

Chikungunya is closely related to O'nyong-nyong virus[4], and clinical features are very similar to those of dengue fever. However, unlike dengue, there is no haemorrhagic or shock syndrome form.

Aetiology

Causative organism – Chikungunya virus

Alternate name – Buggy Creek virus

ICTV acronym – CHIKV

Virus classification

Group: Group IV [(+) SS RNA]

Family: Togaviridae

Genus: Alphavirus

Species: Chikungunya virus

Mode of transmission

- Chikungunya is spread by the bite of an infected Aedes mosquito, primarily *Aedes aegypti*.
- Recently, research by the Pasteur Institute in Paris has found a mutation that enables it to be transmitted by *Aedes albopitcus* (Tiger mosquito), which appears to be the cause of the recent epidemic in Asia.
- Few cases of mother to foetus infection have been reported from Asia, which occurs between 3 and 4 months of pregnancy.

Reservoir

- Humans are the major source of reservoir of chikungunya virus for mosquitoes.
- Some non human primates like monkeys are the reservoir in Africa, in which it is transmitted by *Aedes furcifer* and *africans*.

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Epidemiology and recent outbreaks

Chikungunya was first described in Africa (Tanzania) in 1952[1]. Then an outbreak was seen in Port Klang in Malaysia in 1999 affecting 27 people[4]. It is endemic in parts of Africa (Transvaal, Uganda, Congo, Nigeria, Ghana, Zimbabwe, Senegal, Burkina Faso, and Cameroon). Sout-east Asia (Philippines, Malaysia, Cambodia) and the Indian sub-continent (Pakistan and southern India).

In February 2005, an out break was recorded on the French island of Reunion in the Indian Ocean where 258,000 residents had been hit by the virus and 219 official deaths have been associated. In Mauritius, an outbreak has been recorded in 2005[4].

In 2006, there was a big outbreak in Andhra Pradesh in India where the initial cases were reported at Hyderabad and Anantpur districts in December 2005 and is continuing unabated[3]. There have been reports of large scale outbreaks of chikungunya in Gulbarga, Tumkur, Bidar, Raichur, Bellary, Kolar, and Bijapur districts in Karnataka state since December 2005[5].

A separate outbreak of chikungunya fever was reported in Maharastra and Orissa in March 2006[6]. In May 2006, in Bangalore, the state capital of Karnataka, there appeared to be an outbreak of chikungunya with arthralgia/arthritis and rashes. On 23/06/2006, fresh cases of this disease were reported from Chennai, Tamil Nadu. On 24th August 2006, *The Hindu* newspaper reported that the Indian states of Tamil Nadu, Karnataka, Andhra Pradesh, Maharashtra, Madhya Pradesh, Gujarat, and Kerala had reported 1.1 million cases.

Recently, in August – September 2006, many cases of fever, arthralgia/arthritis and rashes have been reported from Ajmer, Bhilwara district of central Rajasthan, where 3 cases were found to be positive for chikungunya in Hurda village, district Bhilwara.

Re-emergence of chikungunya virus

- Chikungunya virus is no stranger to the Indian sub-continent. Since its first isolation in Calcutta in 1963, there have been several reports of chikungunya virus infection in different parts of India. The last outbreak of chikungunya virus infection occurred in India in 1971[7]. A study conducted at the National Institute of virology (NIV), Pune, India, has confirmed CHIKV as the causative agent for large outbreaks of fever with arthralgia and arthritis in 3 Indian states. Thus, chikungunya fever has emerged in an outbreak form after 32 years[8].
- A recent report of large scale outbreaks of chikungunya virus in southern India has confirmed the re-emergence of this virus[9].
- The precise reasons for the re-emergence in the Indian sub-continent as well as in southern India, of this viral infection, are due to a variety of social, environmental, behavioural and biological changes.
- Genetic analysis of chikungunya viruses have revealed that two distinct lineages were delineated[10]. One containing all isolates from Africa, and the second comprising all African as well as Asian strains. Phylogenetic trees corroborated historical evidence that the virus originated in Africa and subsequently was introduced into Asia[11]. The Indian viruses isolated from 1963 through 1973 belonged to the Asian genotype, whereas the current isolates from the 3 Indian states and the Yawat isolate belonged to the central/east African genotype[8]. A simplistic view is that the lack of herd immunity within the country is probably responsible for the epidemic. A serosurvey conducted in Calcutta a decade ago revealed that only 4.3% of the sera tested were positive – these are of 51 to 55 years age group. No child or young adult was found to be positive[11].

Clinical features

- Full-blown disease is most common among adults in whom the clinical picture may be dramatic.
- The abrupt onset of clinical manifestations follows an incubation period of 2 to 3 days. Silent CHIKV infections do occur, but the number and incidence is not yet known. Fever is sudden onset, high grade (> 40° C, 104° F) with chills and rigors; fever is biphasic or saddle back (fever subsides in 2 to 3 days and than comes back after 1 day); the second phase of fever is usually associated with bradycardia. Fever is associated with constitutional symptoms such as headache,

photophobia, conjunctivitis, anorexia, nausea, and abdominal pain.

- Arthralgia/arthritis in chikungunya has been quite crippling in recent outbreaks in southern India.
- Migratory polyarthritis mainly affects the small joints of hands, wrists, ankles, and feet. Rash may appear at the outset or several days after the illness i.e., in the convalescence phase.
- Dermatological manifestations observed in a recent outbreak of chikungunya fever in southern India include the following[4]:
  1. Maculopapular rash.
  2. Blotchy, nasal erythema.
  3. Freckle-like pigmentation over centro-facial area.
  4. Flagellate pigmentation on face and extremities.
  5. Lichenoid eruption and hyperpigmentation in photo distributed areas.
  6. Multiple aphthous-like ulcers over the scrotum, crural areas, and axilla.
  7. Lymphoedema in acral distribution (bilateral/unilateral).
  8. Multiple ecchymotic spots (children).
  9. Vesiculobullous lesions (infants).
  10. Subungual haemorrhage.
  11. Photourticaria.
  12. Acralurticaria.

Fever typically last for two days and then abruptly comes down. However, joint pain, headache, insomnia, and various degrees of prostration last for a variable period, usually for about 5 to 7 days. Chikungunya is a self-limiting disease, and recovery is the rule, but little mortality has been reported in the recent outbreaks in southern India. In July 2006, a team analysed the virus RNA and determined the genetic changes that have occurred in various strains of the virus and identified the genetic sequence which led to the increased virulence of the recent strains[12].

The symptoms are most often clinically indistinguishable from those observed in dengue fever. Indeed, simultaneous isolation of both dengue and chikungunya from the sera of some patients has been reported earlier, indicating the presence of dual infections[13]. Therefore, it is very important to clinically distinguish dengue from chikungunya virus infection. Unlike dengue, haemorrhagic manifestations are relatively rare, and as a rule, shock is not observed in chikungunya virus infection. Other important clinical conditions for differential diagnosis are West Nile fever, O'nyong-nyong fever.

Diagnosis

The tests available are:-

- Detection of antigen and antibody in serum by ELISA test.
- IgM capture ELISA is necessary to distinguish the disease from dengue fever.

These tests are available at National Institute of Virology at Pune, Maharashtra.

Treatment

- There is no specific treatment for chikungunya. The illness is usually self-limiting and will resolve with time. Supportive care with rest is indicated during the acute joint symptoms. Ibuprofen, paracetamol relieve symptoms of fever and aching.
- Movement and mild exercise tend to improve stiffness and morning arthralgia, but heavy exercise may exacerbate rheumatic symptoms.
- In unresolved arthritis refractory to NSAIDs, chloroquine phosphate (250 mg/day for several weeks) has given good results[14].
- Vaccine for commercial purpose is not available and is under trial.

Complications

Chikungunya is a self-limiting illness. The major causes for morbidity are severe dehydration, electrolyte imbalance, and hypoglycaemia.

Recovery is the rule, but 10 - 15% patients had chronic joint pain and stiffness.

Major complications, though rare, are:-

1. Bleeding disorder (epistaxis, UGI bleed) as it causes thrombocytopenia, superadded by injudicious use of NSAIDs.
2. Neurological complications[15]:
   a. Meningoencephalitis.
   b. Paresis of limbs.
   c. Slurring of speech.
3. Cardiovascular decompensation[16].
4. Pneumonia and respiratory failure[16].
5. Deaths – Few deaths have been reported in the recent epidemic in Reunion Island and in southern India[4].

Prophylaxis and prevention of chikungunya

- As there is no vaccine available yet, the only way to prevent it is to eliminate mosquito breeding sites and to prevent mosquito bites.
- Aedes mosquito vector for this disease breeds in artificial accumulations of water in and around human dwellings, such as water found in disused wares, broken bowls, flower pots, earthen pots. Therefore, these sites should be eliminated by responsible human behaviour and social education.
- Aerosol spray of ultra low volume quantities of malathion or sumithion (230 ml/litre) has been found to be effective.
- Mosquito net and repellents which contain 20 – 50% DEET (N, N-diethyl-meta-tolnamido) should be used to prevent mosquito bites. As mosquito bites during daytime, mosquito repellants should be used during daytime also and, not only during the night.
- Use of full sleeve clothing is effective in preventing mosquito bites.

Chikungunya fever with pregnancy

There have been cases of mother-to-foetus infection which have occurred between 3 and 4 months into pregnancy[17]. Before and after that period in pregnancy, cases have not been recorded. IgG that is produced around day 15, passes through the placenta and confers immunity to the foetus. However, there is a 48 per cent risk of infection at birth if the virus is present in the mother's blood[18]. Such an infection in the foetus is rarely serious, and more than 90 per cent of the infected newborns recover quickly without sequelae.

Information to travellers

In 2006, CHIK fever cases also have been reported in travellers returning from known outbreak areas to Europe, Canada, the Caribbean (Martinique), and South America (French Guyana). During 2005 – 2006, 12 cases of CHIK fever were diagnosed serologically and virologically at CDC in travellers who arrived in the United States from areas known to be epidemic or endemic for CHIK fever[19]. Currently, there is no restriction on travel to islands in the Indian Ocean. Travellers should be careful to take necessary precautions to prevent mosquito bites[20].

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SHORT REVIEW ARTICLE

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Tumour Necrosis Factor-α and Receptor System

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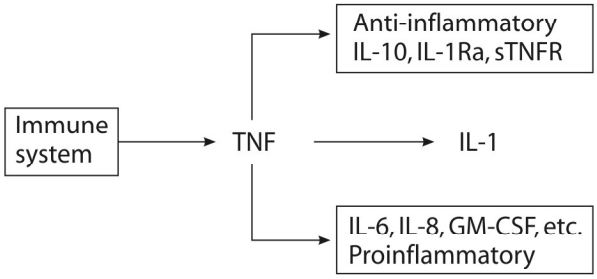
Abstract

TNF-α is an inflammatory mediator that is relevant to several autoimmune diseases. Macromolecular inhibitors (monoclonal antibodies and soluble TNF receptor) of TNF-α have proven therapeutically useful in some preliminary studies. Small molecule TNF-α antagonist have been developed, based on the crystal structure of TNF receptor complex. This small molecule TNF-α inhibitor is specific and mediates biological function similar to the inhibitory soluble TNF receptors.

The main function of the immune system is to eradicate foreign organisms such as viruses or bacteria. Defense against foreign organisms is mediated by innate immunity and by specific (or adaptive) immunity. The effector phases of both innate and specific immunity are largely mediated by protein hormones called cytokines. In innate immunity, the effector cytokines are mostly produced by mononuclear phagocytes and are therefore called monokines. Phagocytes accumulate at the site of infection and secrete monokines that include interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-12 (IL-12), and tumour necrosis factor-α (TNF-α) as shown in Fig. 1. Most of these molecules are pleiotropic (i.e., effect different biological functions), and have effects on immunological processes such as inflammation and cellular responses such as apoptosis. TNF-α is one of the 10 known members of a family of ligands that activate a corresponding family of structurally related receptors as shown in Table I.

In the last century, Coley observed the benefit of inflammatory effects in the terminally ill cancer patients. Much later, in 1985, Old identified a protein in the serum of endotoxin-treated rabbits that was responsible for the haemorrhagic necrosis of tumour. It was named tumour necrosis factor (TNF) for its ability to trigger necrosis and involution of transplantable tumours, and later named TNF-α after the discovery of lymphotoxin or TNF-β. TNF-α is highly toxic to both humans and animals. In unrelated experiments, cachectin isolated from waste body fluids of animals and humans with chronic disease were found to be identical to the necrosis factor. Finally, the study of lipopolysaccharide (LPS) -induced biological functions led to the conclusion that TNF-α is a mediator of the shock, disseminated coagulation, metabolic acidosis and end-organ damage brought about by LPS.



TNF has a pivotal role, regulating both pro- and anti-inflammatory mediators. TNF is in turn, regulated by the immune system. IL - Ra. IL-receptor antagonist; sTNFR, soluble TNF receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor[1].

Fig. 1: *TNF-α-dependent cytokine cascade.*

Several biochemical and biological properties of TNF-α have been elucidated since the mid-1980s when TNF-α was cloned, sequenced, and purified[20-21]. The major source of TNF-α is the activated monocytes/macrophages. TNF-α is synthesized as a 26 kDa soluble TNF-α molecule and observed as homotrimer under physiogical conditions[22].

Most of the cellular actions of TNF-α have been attributed to the activities of two distinct receptor molecules TNF receptor I (TNFRI, p55), and TNFRII (p75)[23] which are expressed ubiquitously. TNF RI knockout mice are resistant to endotoxin shock, but succumb to infection, indicating that TNFRI plays an important role in defense against microorganisms[21]. The extracllular portions of both TNF receptors can also be shed from the cell surface through proteolytic cleavage and exist in soluble form; and moreover, soluble receptors retain the ability to bind TNF-α and thus may act as physiological modulators of TNF activity *in vivo*[25, 2].

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Table I: Recently characterised members of the TNF-ligand and TNF-receptor families.

Ligand	Source of ligand	Receptor	Distribution of receptor	Ability to initiate apoptosis	Cytoplasmic mediators	Mutation or knockout phenotype	
						Ligand	Receptor
TNF and lymphotoxin-α	TNF: Macrophages, lymphocytes, keratinocytes, others	55-kd TNF receptor	Many cells	Yes (Strong)	TRADD[3], TRAP-1[3], 55.11[4]	Both TNF and lymphotoxin-α: absent lymphnodes, decreased lipopolysaccharide responses	Decreased lipopolysaccharide responses, failure to contain listeria or mycobacteria infection[5-6]
	T cells	75-kd TNF-receptor	Many cells	Yes	TRAF-1[7], TRAF-2	Lymphotoxin-α absent. lymph nodes[8]	Decreased lymphocyte proliferation; decreased TNF-induced lethality[9]
Lymphotoxin-β heterotrimer	T cells, other	Lymphotoxin-β receptor (TNF-receptor-related protein)	T cells, B cells, other	Yes	LAP-1 (CRAF-1)[10]	ND	ND
Fas ligand	T cells	Fas receptor	Many cells	Yes (Strong)	Tyrosin[11] phosphatase (FAP-1), FADD (MORT-1)[12]	Lymphoproliferation	Lymphoproliferation
Nerve growth factor	NA	Nerve growth factor receptor	Neurons, others	No	ND	NA	Neuropathy[13]
CD40 ligand	T cells	Nerve growth factor receptor	B cells, T cells	No	CRAF-1, CAP-1[14-16]	X-linked immunodeficiency with increased IgM and decreased or absent IgG, IgA, IgD[17-19]	X-linked immunodeficiency with increased IgM and decreased or absent IgG, IgA, IgD[20]
CD27 ligand	T cells	CD27	T cells	ND	ND	ND	ND
CD30 ligand	T cells	CD30	T cells	ND	ND	ND	ND
OX-40 ligand	T cells	OX40	T cells	ND	ND	ND	ND
4-1BB ligand	T cells	4-1BB	T cells	ND	ND	ND	ND

TRADD denotes TNF-receptor-associated death domain; TRAP-receptor associated protein 1; TRAF-TNF receptor-associated factor; LAP-1 latent membrane protein type 1-associated protein; CRAF-1 CD40 receptor associated factor 1; ND not determined; FAP-1 Fas-associated protein 1; FADD (or MORT-1)-Fas-associated death domain; NA – not applicable; and CAP – 1 Cd40 – associated protein

Binding of TNF-α to its membrane-bound receptors induces diverse effects in different organs and tissues. Recently several TNF receptor-associated proteins have been cloned. The cytoplasmic domains of TNF receptors do not have any intrinsic enzymatic activity, and hence they signal by inducing aggregation of intracellular adaptor molecules. The cytoplasmic domains of TNFRI bear a motif termed as 'death domain' (DD). The DD is a protein-protein interaction motif that allows two proteins with DD to bind to each other. Binding of TNF to TNFRI induces recruitment of the DD-containing protein TRADD to the DD of TNFRI. Overexpression of TRADD also induces TNF-regulated apoptosis and activation of the transcription factors $NF-_{k}B$ and Jun Kinase. The group of TNF receptor-associated factors (TRAF) also interact with members of the TNFR family. Most of TRAF proteins interact with receptor molecules either directly, or indirectly through binding to other TRAF, or through binding to TRADD. TNFRII contains cytoplasmic TRAF binding motifs and is able to bind directly to TRAF proteins. Because TRAF2 can bind to TRADD, which in turn can associate with TNFRI, TRAF2 can indirectly participate in signalling from this receptor as well. Studies of TRAF2 and TRAF3 knockout mice have revealed that TRAF proteins are required for activation of Jun/AP-1 signalling by TNF receptors. However, the details of signal transduction via TNF receptors are still unknown. Further studies are expected.

High concentrations of plasma TNF-α have been found in a variety of infections and inflammatory disease. TNF-α plays a critical role in the development of autoimmune processes such as rheumatoid arthritis (RA) and Crohn's disease, as well as other disease conditions associated with bone resorption; sepsis syndrome and AIDS is also exacerbated in the abnormal production of TNF.

The therapeutic application of TNF-α has been investigated in several malignant diseases, but has remained limited due to severe side-effects. On the other hand, multiple roles mediated by TNF-α in the development of autoimmune disease prompted efforts to refocus on TNF-α as a viable therapeutic agent for diseases. Inhibition of TNF-α has proven to be useful in some preliminary general studies. Experimental studies have shown that TNF-α blocked by monoclonal antibodies or by soluble TNF receptors reduces the extent and severity of arthritis, both in collagen-induced arthritis in mice and transgenic mice overexpressing TNF-α which develop a rheumatoid-like destructive arthritis. Also, anti- TNF-α agents may be valuable in the treatment of bone resorption, obesity due to insulin resistance, and eye injury.

In contrast to macromolecular TNF-α inhibitors, a novel anti-TNF peptidomimetic has been developed based on a detailed structural knowledge of the TNF receptor (55 kd) and its complex with TNF-β. Peptidomimetic (WP9QY) is one of the first peptides to demonstrate anti-TNF-α activity *in vivo* and can be further improved as a substitute for anti-TNF-α antibody or soluble receptor. Three dimensional structures of TNF-β and TNF receptor and its complex with TNF-β enabled us to design first anti-TNF small molecules that are specific and selective. Further, the structural study of TNF receptor not only enhanced our understanding of their function, but also led to the realisation that the TNF receptor's topology is not unique, but is being shared by many other receptors. TNF receptor and its ligand complex has become the template for understanding other receptors such as Fas, CD40, RANK, etc., and their functions. Crystal structure of TNF receptor complex led to the molecular modelling of other receptors allowing the development of therapeutic agonists and antagonists for other receptors.

After a decade, drugs discovered based on three dimensional structures are proving to be clinically useful and cost effective. Enzyme inhibitors have been successfully developed into useful drugs; HIV protease inhibitors and anticoagulants are some illustrative examples. Still, the challenge to translate other bioactive molecules into clinically useful drugs largely remains unsolved. But studies reported recently suggest that it may be possible to use peptides as drugs.

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CASE REPORT

JIACM 2007; 8(2) : 173-5

Recanalisation of Cerebral Venous Thrombosis in a Patient Presenting with Subarachnoid Haemorrhage

Rakesh Shukla, Priyanka Vinod*, Rakesh K Gupta** Parthiv Desai**

Cerebral venous thrombosis (CVT) is being recognised as a frequent cause of stroke in India affecting young to middle aged patients[1]. Subarachnoid haemorrhage as a sole presentation of CVT is rare. New imaging tools help us to promptly diagnose and treat it. Here, we are reporting clinico-radiological outcome of a case of cerebral venous thrombosis.

A middle-aged, non-hypertensive man presented with sudden onset bursting holocranial headache associated with vomiting, photophobia, and phonophobia. Two days later he developed right focal seizures with secondary generalisation followed by right hemiparesis. His vital functions were stable. Neurological examination showed Glasgow coma scale E4M4V2, normal bilateral fundi, neck stiffness, right UMN VII cranial nerve palsy and right hemiparesis (grade 2/5 power). Investigations revealed normal haemogram and biochemical parameters. Non-contrast CT scan of head showed blood in the left sylvian fissure. CSF was turbid and red in colour; TLC-100/cumm, 80% lymphocytes and 20% polymorphs, RBC count was 185,000/cumm, and smear showed 40% crenated RBCs; consistent with subarachnoid hemorrhage (SAH). Digital subtraction angiography (DSA) done by percutaneous transfemoral route showed normal arterial and capillary branching pattern, but venous phase revealed non-opacification of superior sagittal sinus, transverse sinuses and inferior sagittal sinus, and multiple collaterals. MRI brain (T1 and T2) images were normal. MR venography (3D TOF technique) confirmed thrombosis in various sinuses described above (Figure 1 and 2). A comprehensive hypercoaguability work-up was unrevealing. Patient was managed with decongestives and anticonvulsants. The right hemiparesis recovered fully in the next 24 hours. He was simultaneously started on oral warfarin preceded with initial 7 days overlap of low molecular weight heparin (LMWH). Warfarin was continued for 1 year and International Normalised Ratio (INR) was maintained between 3 - 3.5. In the next 5

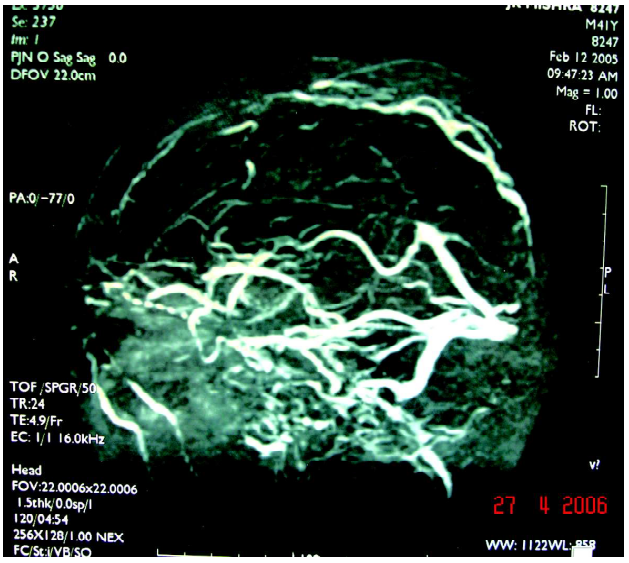

Fig. 1: *MRV (3D TOF) lateral view showing non-opacification of SSS, ISS, and transverse sinus.*

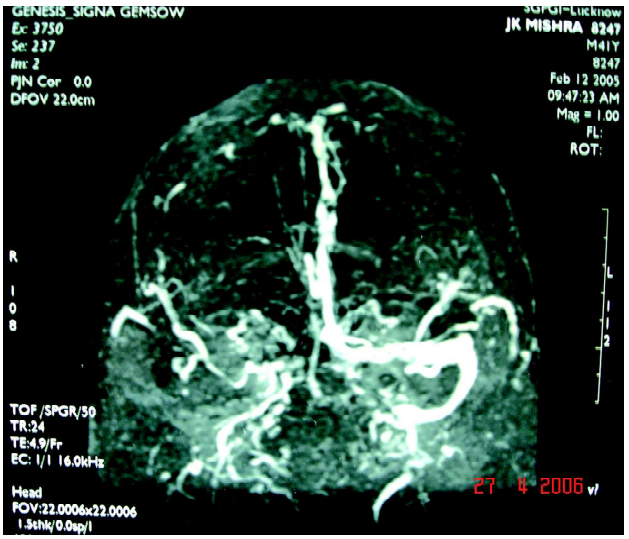

Fig. 2: *MRV (3D TOF) anteroposterior view showing non opacification of SSS, ISS, and transverse sinus (right > left).*

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months, headache resolved completely. A repeat MR venogram (MRV) done after 1 year showed near complete recanalisation of all the previously thrombosed venous channels (Figs. 3 and 4) and warfarin was subsequently stopped. At present he is seizure free on antiepileptic drugs.

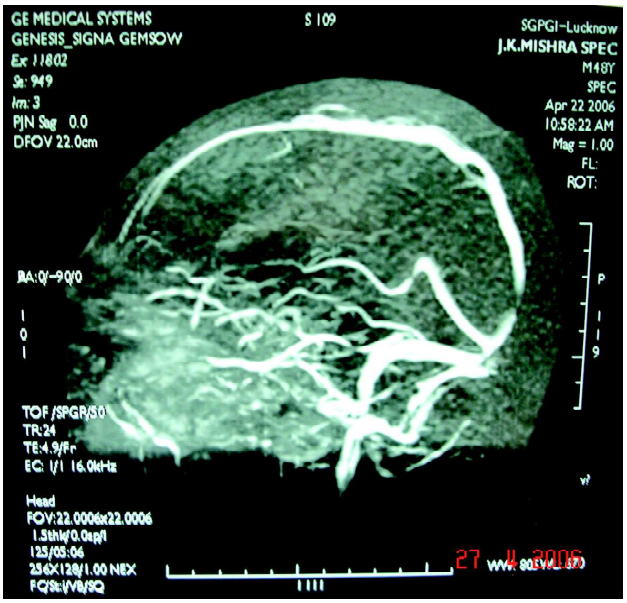

Fig. 3: *Repeat MRV (3D TOF) lateral view showing recanalisation of previously obstructed venous channels.*

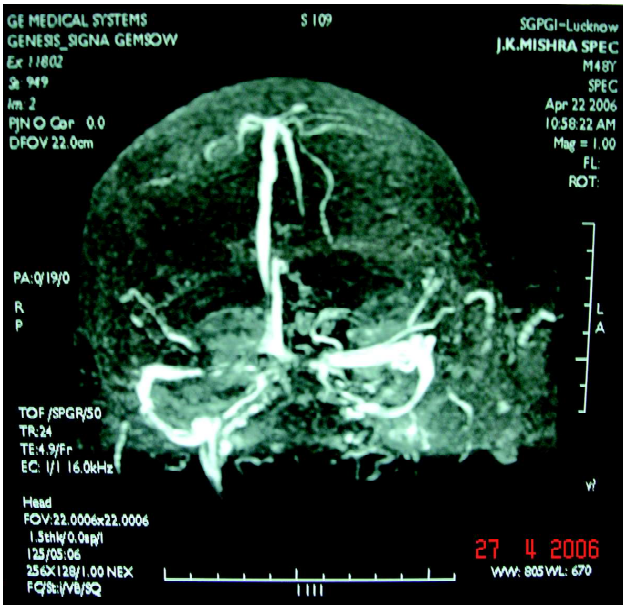

Fig. 4: *Repeat MRV (3D TOF) anteroposterior view showing recanalisation of SSS, ISS, and transverse sinus.*

Discussion

Our case reveals cerebral venous thrombosis manifesting solely as localised SAH without underlying parenchymal involvement. The exact incidence of SAH as a manifestation of CVT is not known as there are no prospective clinical studies. There are few case reports only[2, 3]. One case report mentioned SAH as an only manifestation of CVT in 3 patients, and the precipitating factors were intake of oral contraceptives, sepsis, and idiopathic[2]. The exact cause of SAH in CVT is not known. Most plausible is the extension of the venous haemorrhagic infarct into the subarachnoid spaces. But in absence of parenchymal signs, the mechanism of SAH could be rupture of dilated, fragile, thin-walled cortical veins. The venous hypertension secondary to back pressure changes as a result of blocked cerebral venous system also contributes to this[4]. In the present case, multiple collaterals were present as evident on MRV, and one of the collaterals might have ruptured and resulted in SAH. Other possible causes of unilateral, focal, non-traumatic SAH are dural arteriovenous fistula (AVF), arteriovenous malformations (usually has parenchymal involvement). These possibilities were ruled-out by DSA in our case. One important point is that SAH at convexity without basal involvement should prompt the physician to look for other non-aneurysmal causes like CVT. Thrombosis of cerebral veins is a potentially fatal condition accounting for 1 – 2 % of strokes in young adults and death rates ranging between 5% – 30%[5]. Because of varied clinical spectrum, diagnosis is challenging and is typically made on imaging basis. In the past, conventional angiography was the gold standard diagnostic tool. In the present era, Magnetic Resonance Imaging (MRI) is the preferred diagnostic modality as it is non-invasive, less cumbersome, and more reliable. MRI gives added advantage of detecting parenchymal changes associated with venous thrombosis. An early diagnosis lessens the morbidity and mortality associated with it. In its natural course, outcome of CVT is variable, ranging from complete recovery to severe focal deficits or deaths. The optimal treatment of CVT is unclear as no prospective trial has yet examined the issue. Anticoagulant treatment has raised much controversy because of the tendency of venous infarcts to become haemorrhagic. Early administration of heparin has shown favourable results[6]. A more recent trial comparing low molecular weight heparin (LMWH) and

placebo for 3 weeks failed to demonstrate any benefit with heparin, but confirmed that there was no significant increased risk of haemorrhage with heparin. Hence there remains some uncertainty as to the relative efficacy of heparin and LMWH in dural sinus thrombosis. A meta-analysis of the two trials shows a relative risk reduction with heparin of 70% in death, and 56% for death or dependency. Nagaraja *et al* in a case control trial on 57 patients with non-haemorrhagic puerperal CVT observed beneficial effects of heparin without any haemorrhagic complications[7]. Anticoagulants are safe even in presence of haemorrhagic infarction and there appears to be a trend in favour of using anticoagulants (Level of evidence B)[8, 9]. But no adequate studies are available to address the optimal duration of anticoagulation in CVT and their follow-up. One study on 33 patients of CVT showed that recanalisation occurred within 4 months of treatment and it did not differ if the warfarin was extended for 1 year period. The recanalisation was complete for deep cerebral veins and cavernous sinus followed by superior sagittal sinus (SSS) - 94%, and minimum for sigmoid sinus (41%)[10]. There is lack of large studies on natural course of the disease as it involves ethical issues in studying a placebo arm so the exact figures of spontaneous recanalisation is lacking. Clinical recovery precedes recanalisation and there is no correlation between clinical recovery and recanalisation. It has been observed that maximum recanalisation occurs during initial months, and rate of recanalisation does not differ thereafter even if the anticoagulants are continued. MRV seems to be a reasonable follow-up screening tool which may help us to decide regarding stopping anticoagulants. Our patient had symptomatic resolution by 5 months and near complete recanalisation after one year of anticoagulant therapy in adequate doses. A follow-up MRV may prove to be a reasonable, non-invasive tool and thus a future guide in deciding the optimal duration of anticoagulation in patients with CVT.

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CASE REPORT

JIACM 2007; 8(2): 176-8

Osmotic Demyelination Syndrome

Anup Kumar Bhattacharya, Amarendra Bikas Bera**, Suman Kr Roy***,*

Abstract

A case of acute onset of ataxia and dysarthria due to central pontine and extrapontine myelinolysis is described. Management of this rare condition involves recognising the patient at risk, preventing rapid correction of hyponatraemia, making a prompt diagnosis, and managing associated complications.

Introduction

Central pontine myelinolysis (CPM) was first recognised as a clinical entity in the year 1959 by Victor and Adams in Boston[1]. CPM has been documented in a wide range of patients. Most cases have been associated with alcohol abuse and/or malnutrition. Another subgroup considered particularly vulnerable is liver transplantees. All patients receiving sodium correction do not suffer CPM. The most critical points are that the aetiology of hyponatraemia and the background predisposition of the patient for the development of this heterogeneous disorder. Diseases associated with CPM are chronic and excessive alcohol intake, adrenal insufficiency, brain tumours and cerebral oedema, lymphoma and leukaemia, chemotherapy, congestive cardiac failure, hyperglycaemic coma, malnutrition, liver failure and transplantation, renal disease, sepsis, HIV, and hyperemesis gravidarum.

When the pathologic process involves extrapontine sites such as internal capsule, basal ganglia, cerebellum, and cerebrum, the term osmotic demyelination syndrome (ODS) is used[3]. The clinical features vary according to site of involvement and are: quadriparesis or quadriplegia, ataxia, dysarthria, tremor, seizure, ocular involvement and pupillary abnormalities, "locked-in" syndrome, fatigue, incontinence, and changes in corticospinal reflexes.

The clinical and laboratory data implicate hyponatraemia as a potent risk factor predisposing to CPM and ODS[4-6]. (Norenberg and Papendick, 1984; Verbalis and Drutarosky, 1988; Verbalis and Martinez, 1991). The severity of ODS is mainly related to the rate of sodium correction in hyponatraemic patients and this is the predominant pathogenic stimuli to glial damage[7].

Case study

A 55-year-old female housewife was admitted with severe vomiting of two days duration. There was history of analgesic (NSAID) intake for low back pain. There was no history of fever, cough, breathlessness, or headache. Her pulse was feeble with a rate of 112/min, all peripheral pulses were palpable. Blood pressure was 90/60 mm of Hg. On the day of admission, her serum sodium was 108 mmol /l and her serum was hypoosmolar at 218 mmol/kg. She was given 3 units of intravenous 0.9% saline with 20 mmol potassium chloride during the first 12 hrs, followed by another 3 units in 24 hrs. Her serum sodium on the the second day was 128 mmol/l and reached a peak of 136 mmol /l the third day.

Five days after the initial presentation, she was found to be grossly ataxic. She had coarse tremor with slurred speech. She was extremely prostrated and was started on nasogastric feeding. Neurogical examination revealed gross incoordination, brisk reflexes throughout with extensor plantars. Computed tomogram of brain on the second day of onset of neurological symptoms was found to be normal.

Magnetic Resonance imaging of brain done after twelve days of onset showed prominent high signal in pons and basal ganglia in T_2 weighted and fluid-attenuated inversion recovery (FLAIR) images. T1 weighted images showed hypointensity in pons with minimal enlargement (Figure 1 and 2). The MRI findings suggested osmotic myelinolysis (pontine and extrapontine) which developed as a complication of rapid correction of hyponatraemia.

At two months follow-up, the patient had mild dysarthria and was walking with support. She was put on rehabilitating physiotherapy with which she improved gradually.

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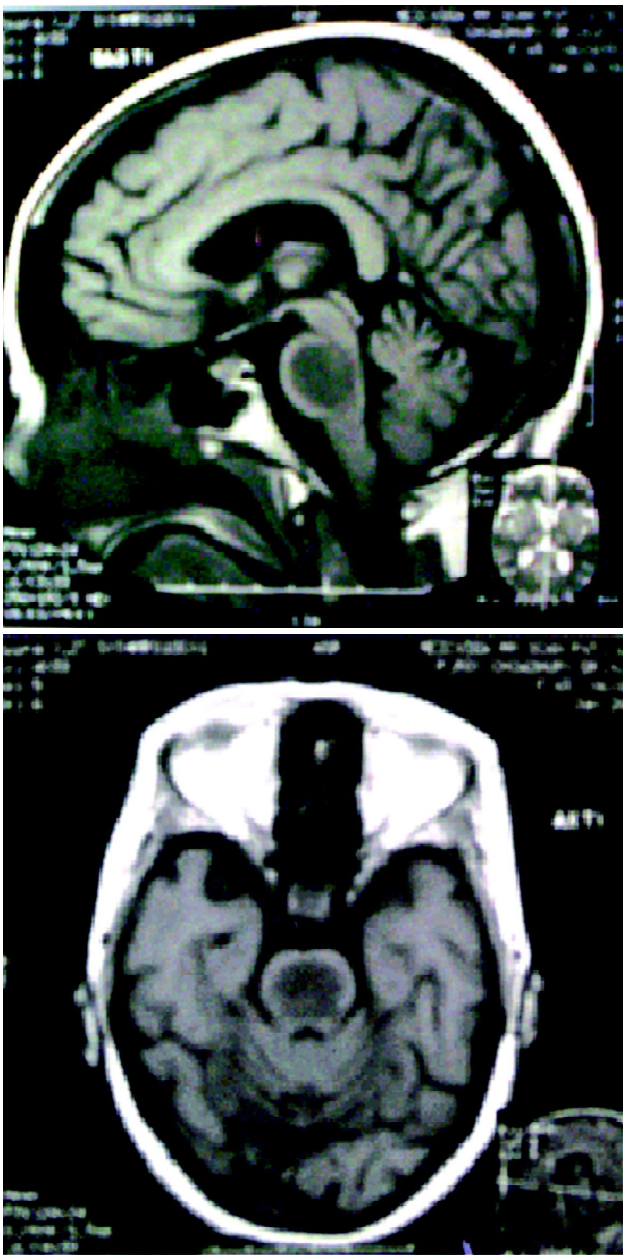

Fig. 1: *T1 weighted image showing pontine hypodensity.*

Discussion

ODS is a well-recognised clinical entity and is a dreadful complication that classically occurs several days after aggressive therapy for hyponatraemia. It has also been described in patients who are treated for hypernatraemia and in individuals with a prolonged period of hyperosmolality[8]. Adams *et al* while introducing the concept of central pontine myelinolysis described a symmetrical butterfly- shaped patch of demyelination within the dorsal basis pontis[1]. The histological picture

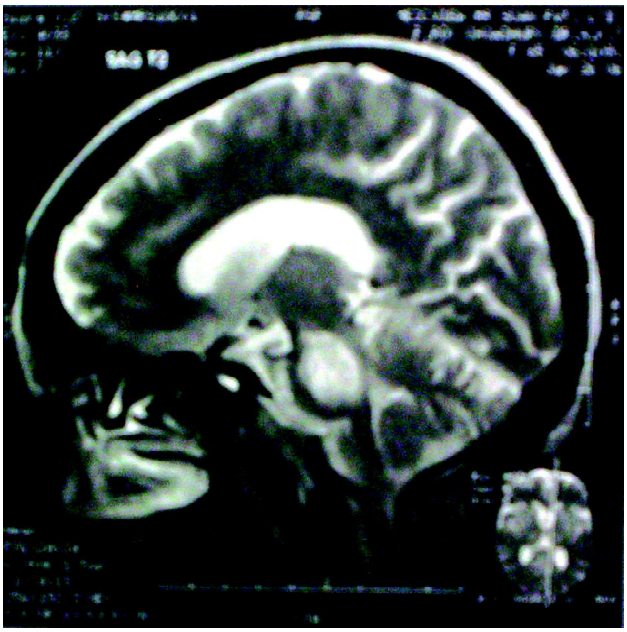

Fig. 2: *T2 weighted image showing pontine hyperintensity with minimal enlargement.*

shows symmetrical demyelination with gliacytic proliferation and decomposition of fat within basis pontis with intact neurons. As the name suggests, CPM is due to dissolution of myelin sheaths and sparing of the axons within the central aspect of basis pontis. Cell death is however, not confined to the pons, and extrapontine extension has also been identified. Improvement in clinical parameter may occur with recession of myelinolysis[9]. There is a notable absence of scavenger cells in this extensive myelinolysis which indicate an apoptic process (a form of cell death with minimal immune response)[10].

Classically, CPM is associated with dysarthria and dysphagia, due to corticobulbar fibre involvement, and quadriparesis due to corticospinal tract lesions. Extrapontine myelinolysis is characterised by tremor and ataxia[8]. In extreme cases, a 'locked-in syndrome' is present[11].

Before the advent of CT scan, antemortem diagnosis of CPM was very difficult. The CT shows hypodense shadows in the centre of the pons. Presently, the diagosis is confirmed by magnetic resonance imaging. The lesion (both pontine and extrapontine) appears as hypointense on T1 weighted images and hyperintense and symmetrical on T2 weighted images. The lesions are non-contrast enhancing. MRI findings tend to lag behind the

clinical features in some cases even by weeks[12]. In the early phase, CT and MRI findings are often missed as the demyelinating patches are not clear until 2 weeks, and therefore a repetition of neuroimaging after 10 – 14 days can help confirm the clinical suspicion. Similarly, MRI findings may persist for months after clinical remission[13]. CPM should be considered in patients suffering from chronic alcoholism, electrolyte disturbances, as well as liver transplant patients presenting with brainstem symptoms even in absence of CT or MRI findings. The MRI changes are also not relevant for prognostic purposes[14].

Rapid correction of osmolar deficiency together with deficit in organic osmolytes makes the brain cells – particularly oligodendrocytes – at risk of cell shrinkage, and hence demyelination. Alcoholics and malnourished patients have a greater deficiency of osmolytes and hence a greater risk of cell shrinkage[15].

The following formula is useful for working-out the rate of infusion of the chosen infusate[16] and to measure the serum sodium concentration every 3 hrs. The aim is to raise the serum sodium concentration between 1 mmol and 3 mmol (maximum) every 3 hrs. The rate of correction should not exceed 10 mmol /l/day.

$$\text{Change in serum } Na^{+} = \frac{(\text{Infusate } Na^{+} + \text{Infusate } K^{+}) - \text{Serum } Na^{+}}{\text{Total body water (L)} + 1.}$$

The management of patients with CPM and ODS is prolonged neurorehabilitation. In addition to the generally applied therapeutic measures, there are four additional treatment modalities. These are administration of TRH, plasmapheresis, corticosteriods alone or in combination with plasmapheresis, as well as intravenous immunoglobulin – however, there is no specific choice[17, 18].

The ODS is a complication of treatment of patients with life-threatening hyponatraemia. It occurs as a consequence of a rapid rise in serum sodium thereby contributing to raised serum tonicity. Sodium rise need not be in excess of 10 mmol/l/day to avoid this condition to develop.

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CASE REPORT

JIAOM 2007; 8(2) : 179-81

A Rare Complication of Pulmonary Tuberculosis

R Raghava Sharma, K Vishak Acharya**, Vinaya Poornima****

Abstract

We report a case of lower leg deep vein thrombosis (DVT) in a young patient without any risk factors. Patient also had concomitant severe pulmonary tuberculosis. The cause-effect relationship between pulmonary tuberculosis and DVT is discussed in this case with such a rare association with significant therapeutic implications.

Key words: Pulmonary tuberculosis, Deep vein thrombosis.

Introduction

Pulmonary tuberculosis is known to cause a wide variety of local complications, some of which may be life-threatening. However, systemic haematological complications are rarely demonstrated with pulmonary tuberculosis (PTB). Our case highlights the occurrence of deep vein thrombosis in a patient with severe pulmonary tuberculosis, a significant but rare association posing a diagnostic dilemma.

Case summary

A 21-year-old male patient presented to the medical outpatient department with 2 weeks history of productive cough and high grade fever. Patient was a non-addict without a relevant past history of any disease. Chest examination revealed crepitations in the left upper lobe areas. On investigation, the patient had leucopenia with elevated ESR and normal differential count. Peripheral smear showed adequate platelets with absence of malarial parasite. Frontal chest radiograph (Fig. 1) showed a non-homogeneous opacity in the left upper lobe, suggestive of consolidation.

Patient was started on empirical parenteral 3rd generation cephalosporin, while sputum reports were awaited. Meanwhile, sputum for acid-fast bacilli by Gabbot's methods was positive, and the patient was started on 4 drug anti-tuberculosis treatment (ATT) (ethambutol, isoniazid, rifampicin and pyrazinamide) daily regimen as per body weight.

Since the patient continued to be febrile intermittently while on ATT, a bronchoscopy was done which was a normal study, but bronchial lavage grew Methicillin resistant *Staphylococcus aureus* (MRSA), sensitive to clindamycin and rifampicin. An appropriate antibiotic switch was made as per the sensitivity report.

The patient complained of pain in his left calf five days after starting ATT. A doppler study of the lower limbs showed a thrombus in the venae comitans of the posterior tibial artery with extension into the popliteal veins (Fig. 2). Protein C antigenic assay levels were 65 per cent (normal value 58 - 148%) and protein S antigenic assay level was 72 per cent (normal value 58 - 148%), bleeding time was three minutes and clotting time was four minutes. However, fibrin degradation product (FDP) was elevated with decreased antithrombin III. Patient was treated for DVT with unfractionated heparin alongwith supportive measures on the next day. On the 8th day oral anticoagulant warfarin was added to heparin. Heparin was stopped after 10 days (after 2 days of overlap) and oral anticoagulant continued with monitoring alongwith ATT. A repeat doppler study after 10 days of treatment with heparin showed absence of thrombus with normal flow and phasic variation with respiration and augmentation with distal compression (Fig. 2). The patient showed good response to ATT with sputum conversion after 2 months and cure after 6 months of treatment without recurrence of DVT or any further complications.

Discussion

Pulmonary tuberculosis (PTB) is one of the most prevalent chronic infectious disease in India and worldwide. The mortality rate in pulmonary tuberculosis is high in those with advanced disease and in presence of complications.

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Local pulmonary complications like haemoptysis are frequently encountered by treating physicians during the management of pulmonary tuberculosis. However, systemic complications like vascular and haematological abnormalities are uncommon in pulmonary tuberculosis. Although haematological abnormalities often co-exist with miliary tuberculosis, they are uncommon with fibro-caseous pulmonary tuberculosis as in our case. Systemic haematological complications reported rarely with PTB are disseminated intravascular coagulation (DIC) and deep vein thrombosis as observed in our patient.

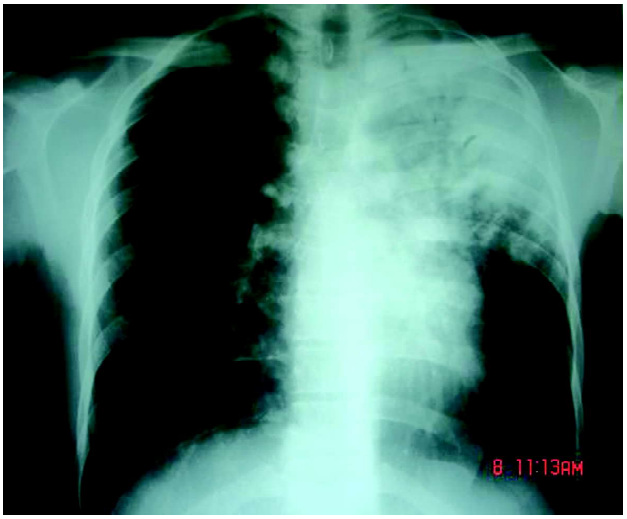
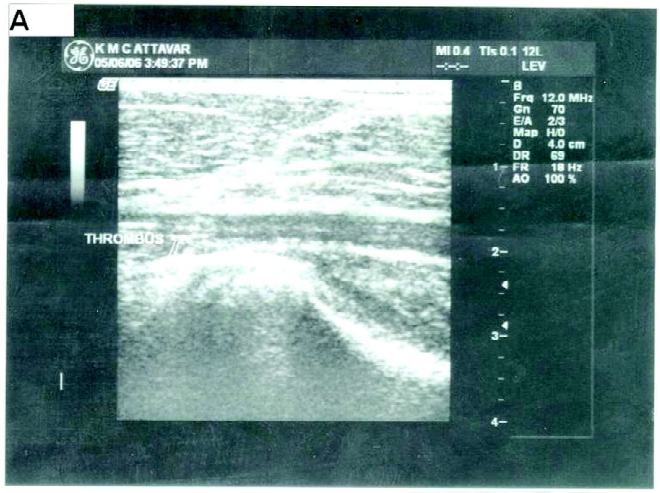


Fig. 1: *Frontal chest radiograph showing a non-homogeneous opacity in left upper lobe, suggestive of consolidation.*

There have been few reported associations between PTB and disseminated intravascular coagulation. Studies have shown subtle changes in blood rheologic properties and in the haemostatic system in patients with PTB[1]. A study by Kaminiskia *et al* showed erythrocyte oedema, their more rapid depletion, lower resistance, and higher aggregation which is accompanied by increased haematocrit and normal erythrocyte count. There was also an increase in activated partial thromboplastin time (APTT) and thrombin time, a reduction in the values of the prothrombin indices and antithrombin III activity. The fibrinogen levels are within normal limits or reduced despite an increase in other acute phase reactants, followed by the appearance of large amounts of blocked fibrinogen in the blood.

The analysis of the above findings enabled the authors to regard these changes as a sign of latent DIC syndrome. This is clinically supported by an incidence of 3.2% of DIC in culture proven tuberculosis[2], but mortality is high (63%) in these patients. There have also been isolated reports of DIC due to antituberculous drugs, probably rifampicin[3].

It is also postulated that association between inflammation and haemostatic changes arising in pulmonary tuberculosis can result in hypercoagulable state which may predispose to deep vein thrombosis. Sequential analysis in a central group with active PTB showed anaemia, reactive thrombocytosis, elevations in plasma fibrinogen degradation products (FDP), tissue plasminogen activator and inhibitors with depressed antithrombin III levels which



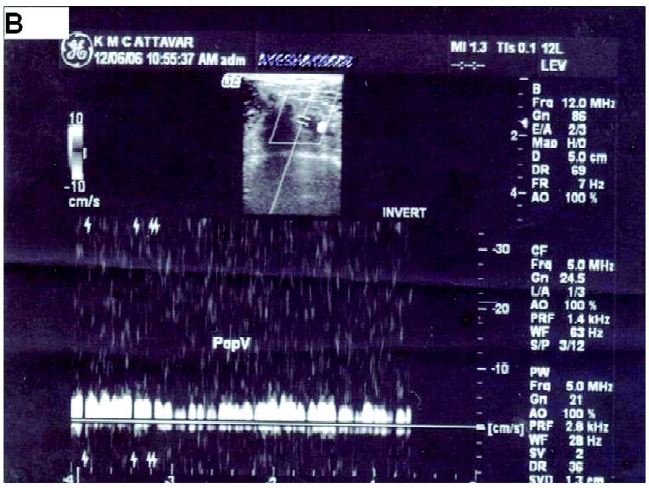


Fig. 2: Image A: *shows intraluminal thrombus in the venae commitans of posterior tibial artery in the distal part extending partially into popliteal vein.*

Image B: *shows normal flow in politeal vein and phasic variation with respiration.*

appear to favour the development of DVT in PTB[4].

Studies have also demonstrated that these haematological parameters worsen during the first 2 weeks of therapy in many cases, but they normalise after a month of anti-tuberculous therapy. The return of these haematological parameters to a normal level is a good indicator of disease control and they correlate with sputum conversion in sputum positive tuberculosis patients. As in our case, some authors correlate the risk of developing deep vein thrombosis increasing with the severity of pulmonary tuberculosis[5]. Cases of deep vein thrombosis have been reported in patients with intra-abdominal lymphadenopathy of tubercular aetiology[6]. High frequency of anti-phospholipid antibodies detected in patients with tuberculosis and deficiency of protein-S is also mentioned in the literature[7]. In critically ill patients with tuberculosis, the degree and rate of spontaneous and stimulated platelet aggregation are decreased which perhaps creates an additional pre-requisite for progression of microthrombogenesis.

Studies have also demonstrated a possible association between DVT and use of rifampicin with a relative risk of 4.74 in patients treated with rifampicin containing regimens[8]. This does not contraindicate the use of this drug in patients at risk, but such patients should be supervised.

It is recommended not to use routinely deep vein catheters in patients with severe tuberculosis, and potential value of heparin prophylactic therapy is also stressed to prevent venous thrombosis and its complications in patients with severe pulmonary tuberculosis. It is possible that one of the causes for sudden unexplained deaths in patients with tuberculosis may be undiagnosed pulmonary thromboembolism secondary to clinically asymptomatic DVT.

In our case, association between DVT and pulmonary tuberculosis is plausible as the patient was a young patient with no specific risk factors for DVT; other causes for DVT were ruled out systematically. Occurrence of DVT coincided with development of extensive pulmonary tuberculosis, and DVT resolved alongwith improvement in pulmonary tuberculosis with symptomatic treatment alongwith anti-tuberculous drugs without recurrence.

Our case highlights the risk of deep vein thrombosis developing in patients with severe pulmonary tuberculosis even in the absence of specific risk factors. We emphasise the potential seriousness of this underreported phenomenon, need for establishing an early diagnosis, and institution of prompt treatment for deep vein thrombosis while continuing the antituberculosis treatment.

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CASE REPORT

JIACM 2007; 8(2): 182-4

c-ANCA (Antineutrophil Cytoplasmic Antibody) Vasculitis with Tubercular Osteomyelitis

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Abstract

A 37-year-old male with tubercular osteomyelitis presented with rashes and palpable purpura which were considered to be drug-induced. The presence of RBCs in urine examination prompted a search for the underlying cause. The case was ultimately diagnosed as cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) positive vasculitis. This case illustrates that uncommon cases of c-ANCA vasculitis can masquerade as drug-induced vasculitis.

Keywords: Microscopic polyangiitis, c-ANCA, RBC casts.

Introduction

Microscopic polyangiitis (MPA) is a small vessel vasculitis affecting lungs and kidneys[1]. It is a necrotising systemic vasculitis with few or no immune complexes. Other systems that may be involved are nervous system, gastrointestinal system, and skin[1]. We report an uncommon association of c-ANCA positive microscopic polyangiitis with tubercular osteomyelitis.

Case report

A 37-year-old male presented to the out-patient department with a discharging sinus from the right tibia. Pus culture and polymerase chain reaction (PCR) from the sinus revealed *Mycobacterium tuberculosis*. The patient was started on 4 drug anti-tubercular therapy (rifampicin, ethambutol, pyrazinamide, and isoniazid) on diagnosis of tubercular osteomyelitis. He remained asymptomatic initially, but presented with fever, arthralgias, skin rashes, epistaxis, and haemoptysis three months later.

On examination, the patient was febrile, pale, with palpable purpura over the extremities. Other systemic examination was unremarkable. Provisional diagnosis of tubercular osteomyelitis with drug-induced purpura was considered. His rifampicin and ethambutol were stopped and he was treated with 3 drug ATT (pyrazinamide, isoniazid, and prothionamide) with steroids.

Investigations revealed anaemia (Hb 8.0 g%), leucocytosis (TLC 16,600 mm^3), raised ESR (98 mm in 1st hour by Wintrobe method) with normal kidney and liver function tests. His ELISA for HIV 1 and 2 were negative. Urine examination showed RBC casts and dysmorphic RBCs. Sputum for acid-fast bacilli, bronchoalveolar lavage, chest x-ray, CT thorax, pulmonary function tests were normal. Now, possibility of microscopic polyangiitis was considered, and subsequent investigations showed negative ANA, positive cANCA, necrotising glomerulonephritis on renal biopsy and leucocytoclastic vasculitis on skin biopsy.

A final diagnosis of microscopic polyangiitis with tubercular osteomyelitis was made. The patient was treated with steroids, cyclophosphamide alongwith antitubercular treatment. 3 and 6 months follow-up showed significant clinical improvement.

Discussion

Microscopic polyangiitis is the most common ANCA-associated small-vessel vasculitis and is characterised by the presence of ANCA and few or no immune deposits in the involved vessels[2-5]. The kidneys are the most commonly affected organs in 90 per cent of patients who have this type of vasculitis[3, 5]. Patients present with variable combinations of renal manifestations, palpable purpura, abdominal pain, cough, and haemoptysis[4].

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Other illnesses that manifest with similar symptoms are Wegener's granulomatosis, microscopic polyangiitis, Goodpasture's syndrome and systemic lupus erythematosus. ANA, anti-dsDNA, ANCA, anti-GBM antibodies form the important initial serological tests. SLE patients are accompanied by high ANA and anti-dsDNA titres and reduced complement levels. A positive serological test for circulating anti-GBM antibodies is seen in Goodpasture's syndrome. ANCA are the antibodies directed against specific antigens present in the cytoplasm of neutrophils. Perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) are the antibodies reactive with myeloperoxidase (MPO), elastase, or lactoferrin, and are termed as perinuclear. Antibodies to serine proteinase-3 give diffuse cytoplasmic staining to immunofluorescence and are called c-ANCA[6]. Diagnosis of microscopic polyangiitis is based on histological evidence of vasculitis with compatible clinical features of multisystem disease[5].

This was a diagnosed case of tubercular osteomyelitis on antitubercular treatment. His purpuric rashes, and arthalgia were attributed to the drugs ethambutol and rifampicin. It was the presence of dysmorphic RBCs and red cell casts which prompted us to investigate the patient for small vessel vasculitis. Therefore, urine examination in patients presenting with constitutional symptoms and pulmonary manifestations is mandatory. This case is also a reminder to consider diagnostic possibilities other than drug-induced purpura in patients on anti-tubercular treatment.

It may be difficult to clinically differentiate drug-induced purpura from microscopic polyangiitis, however, the distinction is vital for initiating appropriate therapy and preventing serious morbidity or mortality. Useful differentiating features include renal involvement, lung involvement and musculoskeletal system involvement with ANCA positivity as in this case. Drug-induced vasculitis usually develops within seven to 21 days after a drug is started and may be confined to the skin[3]. Skin lesions are identical to those seen in systemic small vessel vasculitis. Drugs cause approximately 10 per cent of vasculitic skin lesions. Drugs that have been implicated include penicillin, aminopenicillins, sulphonamides, allopurinol, thiazides, quinolones, hydantoins, and propylthiouracil[3]. Some drugs, such as propylthiouracil and hydralazine, appear to cause vasculitis by inducing ANCA[3]. In the reported case, the signs and symptoms suggestive of systemic involvement appeared one month after the start of drug therapy, that is, later than the projected time for development of drug-induced vasculitis. Secondly, ATT has not been implicated in induction of ANCA or small vessel vasculitis. It has however been associated with drug-induced lupus. In our case, ATT is unlikely to be the offender as our patient was ANA negative.

Absence of granulomas distinguishes microscopic polyangiitis from Wegner's granulomatosis. Absence of eosinophilia and lung infiltration alongwith absence of asthma-like symptoms or upper respiratory system involvement rules out the possibility of Churg Strauss syndrome[7, 8].

The association of cANCA positive vasculitis with tuberculous osteomyelitis has not been reported in the literature to the best of our knowledge. In the Indian context, given the ubiquity of pulmonary tuberculosis, haemoptysis is frequently interpreted as pulmonary tuberculosis particularly when extrapulmonary tuberculosis is present. A rare disease thus masqueraded as a common clinical entity.

A rapid diagnosis of ANCA-associated small-vessel vasculitis is critically important, because life-threatening injury to organs often develops quickly. This can be mitigated dramatically by immunosuppressive therapy[2, 9]. This case report illustrates the importance of urine analysis in patients with systemic vasculitis like features. A high index of suspicion, early diagnosis, and prompt institution of therapy may decrease both morbidity and mortality of these life-threatening group of small vessel vasculitis syndromes.

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CASE REPORT

JIACM 2007; 8(2) : 185-7

Takayasu's Arteritis – An Unusual Presentation

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Abstract

Coronary artery involvement as initial presentation of Takayasu's arteritis is rare. Axillary artery stenosis and iliac artery involvement are also rare sites of the disease. We report a young male patient with Takayasu's arteritis with presenting feature of coronary artery disease, who also had involvement of left axillary artery.

Introduction

Takayasu's arteritis (TA) is a form of large vessel non-specific granulomatous panarteritis known as "pulseless disease", "Occlusive thromboaortopathy", "Martorell syndrome", or "Non-specific aortoarteritis". It is a chronic inflammatory disease of unknown cause which predominantly affects the aorta and main branches[1]. There is granulomatous vasculitis of medium and large arteries. Stenotic lesions are more common; however, mixed lesions and dilatation leading to aneurysm formation may also be seen[2]. Most of the patients present with decreased/absent pulses and blood pressure differences. We report a case where the initial presentation was due to involvement of coronary artery.

Case report

A 27-year-old male presented with 2 years history of retrosternal chest pain on exertion, which became more frequent over the past 2 months. He occasionally complained of numbness of the left upper limb. However, there was no history of pain, claudication, or loss of power of limb. This patient also had generalised weakness and malaise for the last 2 months. There was no history of fever, arthralgias, dyspnoea, syncope, blurring of vision. He was non-smoker, non-diabetic, and normotensive.

The physical examination revealed feeble left brachial and radial pulses. All other peripheral pulses were palpable and equal in volume. There was no radio-femoral delay.

The blood pressure in the right arm was 110/70 mm Hg and 84/40 mm Hg in the left arm. Bruit was present over the right carotid, left upper abdomen, and right femoral arteries. On cardiac auscultation, a pansystolic murmur (grade III/VI) was heard at the apex and radiating to back. Rest of the examination including fundi was normal.

Laboratory investigations revealed a normal haemogram and ESR of 60 mm/1st hour. Blood sugar, renal, and hepatic parameters were normal. Cardiac enzymes and lipid profile were normal. CRP was negative. Mantoux test was negative and VDRL was non-reactive. Anti-nuclear antibody was positive, anti-ds DNA and ANCA were negative. Rheumatoid factor was also negative. ECG showed T wave inversion and ST segment depression from $V_3 - V_6$. Echocardiography revealed moderate MR with akinesia of left ventricular wall and of posterior and inferior interventricular spectrum with dilated LA. The LV ejection fraction was 38%.

The patient was subjected to coronary angiography alongwith thoracic angiography. An 80% ostial stenosis of the left main coronary artery (LMCA) was found. There was also 80% blockage of the left axillary artery. No significant stenosis of the subclavian or other branches of the aortic arch were seen.

MR angiography of the thoracic and abdominal aorta depicted long segment irregular narrowing of the abdominal aorta in the distal part with tapering and a corrugated appearance upto the aortic bifurcation. The origins of bilateral common iliac arteries were also narrowed with greater narrowing on the right. A focal saccular aneurysm arising from the abdominal aorta on the left-side approximately 2.5 cms above the origin of left renal artery was also detected with no evidence of dissection, thrombus, or calcification in the aneurysm. The combination of clinical findings, laboratory results with slightly increased inflammatory parameters, and typical changes on thoracic angiography and MR angiography led to the diagnosis of TA with ostial stenosis of LMCA.

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The patient was treated with steroids in a dose of prednisolone 1 mg/kg/day. He was also given anti-platelets and coronary vasodilators. He was advised coronary artery bypass grafting (CABG) for the coronary lesion.

Discussion

TA a rare disease but more frequent in South-east Asia, India, and Mexico; is predominantly seen in females, with female: male ratio of 9:1. However, in India, a greater percentage of male patients have been observed with F:M ratio varying from 1:58:1 to 3:1 in various studies[3]. The mean age at presentation is 30 years, ranging from 4 – 63 years. Two stages of the disease process have been described. A systemic or "pre-pulseless" phase characterised by non-specific symptoms followed by a sclerotic or pulseless phase during which vascular insufficiency develops with diminished pulses, especially in the upper limbs and bruit over diseased arteries[4]. The mechanism of vessel involvement are secondary to thickening of large vessels secondary to fibrosis of all three vessel layers. This leads to narrowing of the lumen, which is often multi-segmental with normal areas in-between.

The aetiology of TA remains obscure. Tuberculosis, viral infection[4], and immunological dysfunction have been implicated, but the exact stimulus for activation remains uncertain[3].

The clinical features may be non-specific in the form of fever, malaise, night sweats, etc., and may be specific depending on the vessel involved. Decreased/absent pulses and blood pressure discrepancies appear. The patient may present with singular or combination of cerebrovascular disease, ocular disorders, pulseless disease, atypical coarctation, renovascular hypertension, aneurysm formation, and pulmonary involvement[5, 6]. Various diagnostic criteria have been proposed, the latest being modified diagnostic criteria by Sharma *et al* in 1995[7]. Angiography remains the gold standard for diagnosis of disease, but the ability to measure disease activity is limited[4].

The most common clinical manifestation of TA is the affection of aorta and its main branches, but the involvement of coronary arteries is also well known though rare, and can be fatal. The incidence of coronary artery involvement has been reported to be 9% to 12%[8], and is observed mainly in autopsy cases because coronary artery disease is usually not evident until the occurrence of angina pectoris, myocardial infarction, and congestive heart failure. However, there are only a few cases published where a TA initially presented with coronary symptoms as seen in our patient.

The first case of coronary involvement was reported by Froving and Loken[9]. Angina pectoris in TA is usually caused by involvement of proximal segments of coronary arteries. Coronary artery involvement consists mostly of stenosis or occlusion of coronary ostia (73%) followed by non-ostial proximal lesions (18.5%)[10]. Angina pectoris may be related to extrinsic compression of the coronary tree or a steal phenomenon[11]. Narrowing of the coronary arteries is mainly

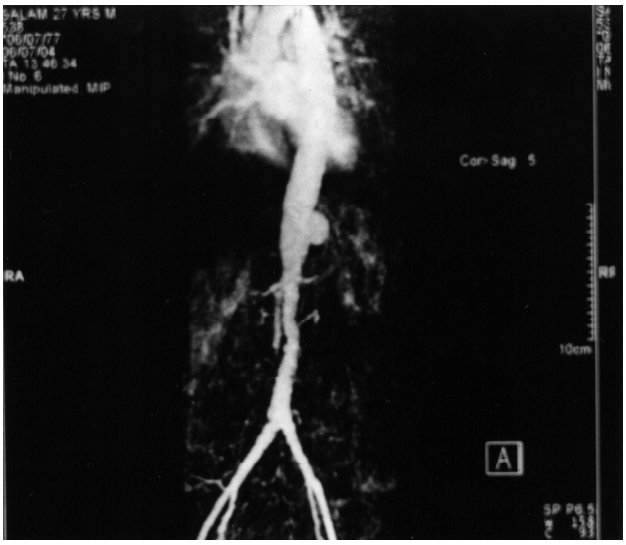

Fig. 1: *MR angiography of thoracic and abdominal aorta showing long segment irregular narrowing of abdominal aorta.*

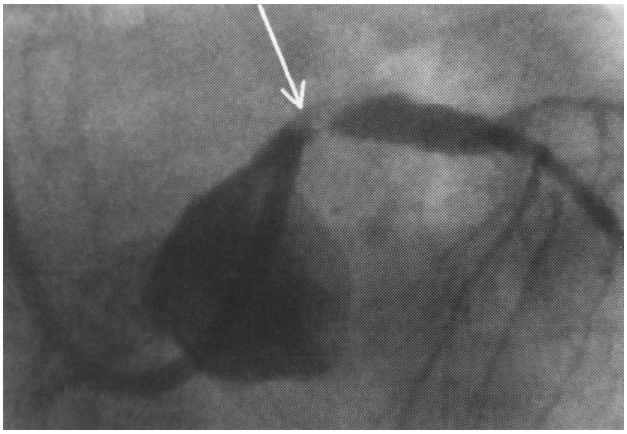

Fig. 2: *Showing 80% ostial stenosis of left main coronary artery (LMCA).*

due to extension of the inflammatory processes of proliferation of the intima and contraction of the fibrotic media and adventitia from the ascending aorta. Diffuse lesions of the coronary artery and coronary artery aneurysm seem to be very rare in TA[12].

This male patient presented to us with classical symptoms of coronary artery disease. However, in view of young age and absence of well known risk factors, i.e., hypertension, diabetes, and smoking, further investigations[3] were done and he was found to have TA with predominant involvement of axillary arteries, abdominal aorta, and bilateral iliac arteries. Coronary artery disease as an initial presentation of TA is rare (< 12% of cases). Also, axillary artery stenosis and iliac artery involvement are rare sites of disease in TA.

This case highlights the enigmatic nature of TA, and reiterates that a high index of suspicion is required in clinical practice to make an early diagnosis of the disease.

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CASE REPORT

JIACM 2007; 8(2) : 196-8

Metastatic Mandibular Adenocarcinoma

Md Shamim Akhtar, Rakesh Bhargava*****, Nazoora Khan****, Zuber Ahmad***, Nishat Afroz***

Abstract

Metastasis of lung cancers to jaw bones – especially in females – is an extremely rare phenomenon. Analysis of literature shows that the most frequent primary site for metastasis to jaw bones are breast in females, followed by thyroid and kidney; lung being extremely rare primary site for metastasis to oral region. We report a case of 60-year-old lady who presented with a painful jaw swelling with minimal chest symptoms and was later diagnosed cytologically to have a metastatic tumour in the mandible that originated from lung adenocarcinoma.

Key words: Metastasis, Adenocarcinoma, Lung, Mandible, Jaw.

Introduction

Metastatic tumours to the jaws and oral tissues are uncommon and represent less than 1% of all malignant tumours affecting the mouth[1]. Nevertheless, they do occur at times, and when a malignant tumour is encountered in the mouth, metastasis must be considered in the differential diagnosis. Worth and Lichtenstein[2] have stated that metastatic or secondary carcinoma is the most common malignant tumour of bone. Despite this, metastasis to mandible is extremely rare[3]. Bhaskar[1] stated that less than 1% of all malignant tumours of the body metastasise to the jaws.

Primary carcinoma metastasising most frequently to the jaws are from breast (33%), thyroid (18%), kidney (16%), prostate in males (6%) and colon (6%)[4].

The preferred sites for the metastasis of adenocarcinoma lung are adrenals, CNS, liver, and bones. The favoured sites for bone metastasis are ribs, vertebrae, and long bones of legs and arms. Very few cases of metastasis to jaw bones from primary in the lungs have been reported in the literature; none of them were females.

The purpose of this report is to present a cytopathologically proven case of adenocarcinoma of the lung with metastasis to the mandible; and to alert the clinician that any swelling in the jaw bones in an elderly patient could be metastatic.

Case report

A 60-year-old female was referred by a dentist with the complaints of non-productive cough and exertional dyspnoea of 2 months duration. She also complained of chest pain – dull aching type – on the left-side anteriorly, with no radiation, since one month. The patient had two months history of gradually progressive swelling and dull aching pain over the left mandible for which she consulted a dentist. There was no history of fever, dysphagia, hoarseness of voice, or haemoptysis. Clinical examination revealed a swelling over the anterior aspect of left mandible, near the angle. It was 5 x 3 cm in size, hard, fixed to the bone, with no movement in any direction, and was slightly tender. There was no redness or pus discharge. Chest examination showed decreased breath sounds on the right-side with dull percussion note in the right inter-scapular area and mid-axilla, whereas there was stony dull note in the right infra-scapular and lower axillary regions. There was also a palpable lymph node in the left cervical region which was 2 x 3 cm in size, hard, fixed to the underlying skin, and non-tender.

Plain radiograph of the jaw revealed a poorly defined osteolytic lesion at the angle of the mandible (Figure 1). Computerised tomographic scan (CT scan) of the jaw demonstrated expansile mixed lytic/sclerotic mass lesion in the angle of mandible with perforation of the lateral cortical plate of the mandible.

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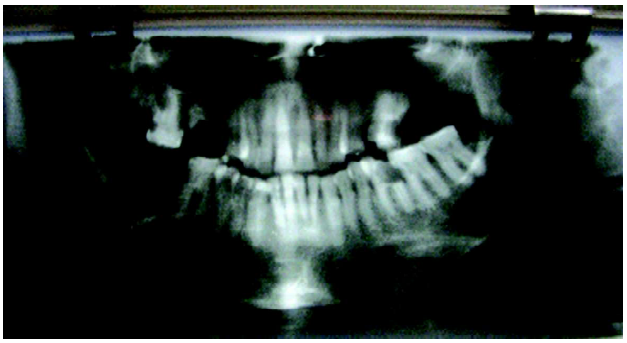

Fig. 1: *Plain X-ray jaw showing osteolytic lesion at the angle of left mandible.*

Chest radiograph showed a homogeneous opacity involving the entire mid-and lower zones of the right lung with blunting of the right costophrenic angle and non-homogeneous infiltrates in the left upper zones with erosion of the posterior aspect of the 5th rib.

CT scan of the chest showed a heterogeneous mildly enhancing mass in the superior segment of right lower lobe with right-sided pleural effusion with collapse/ consolidation of the right upper and middle lobes with parenchymal nodules in the left lung with sclerotic lesions in the bodies of multiple dorsal vertebrae and posterior aspect of left 5th rib (Figure 2).

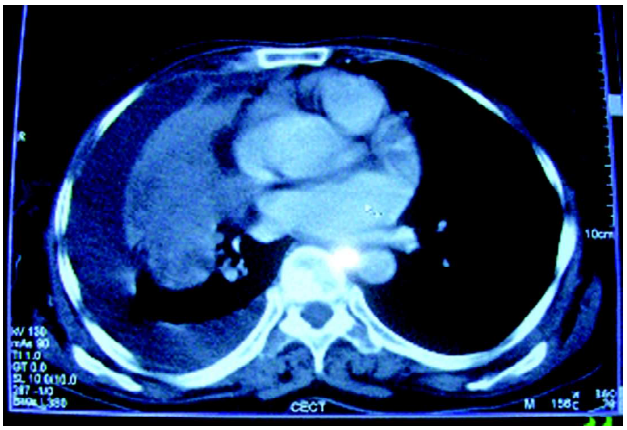

Fig. 2: *CT scan thorax showing a heterogeneous enhancing mass lesion in the right lower lobe with right-sided pleural effusion with sclerotic lesions in dorsal vertebrae and posterior aspect of the left 5th rib.*

Fine needle aspiration cytology (FNAC) from the left mandibular mass and cervical lymph node revealed well-defined acinar structures composed of round cells and abundant cytoplasm. Nuclei showed pleomorphism, hyperchromasia, and prominent nucleoli – features consistent with adenocarcinoma (Figure 3).

Bronchial aspirate cytology was done that showed cytological features similar to the mandibular lesion (Figure 4).

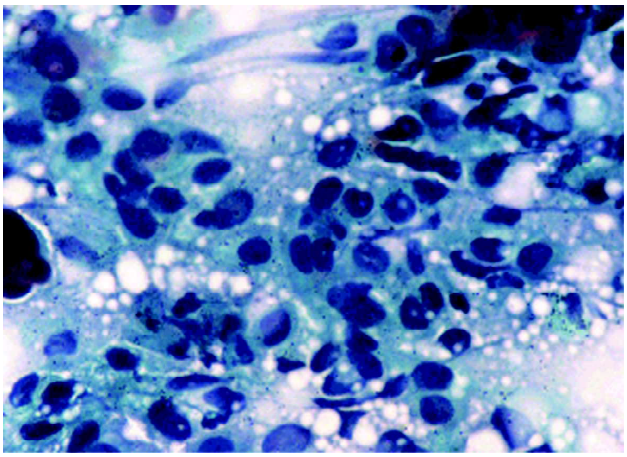

Fig. 3: *FNAC of mandibular lesion showing well-defined acinar structures having abundant cytoplasm and hyperchromatic to vesicular nuclei.*

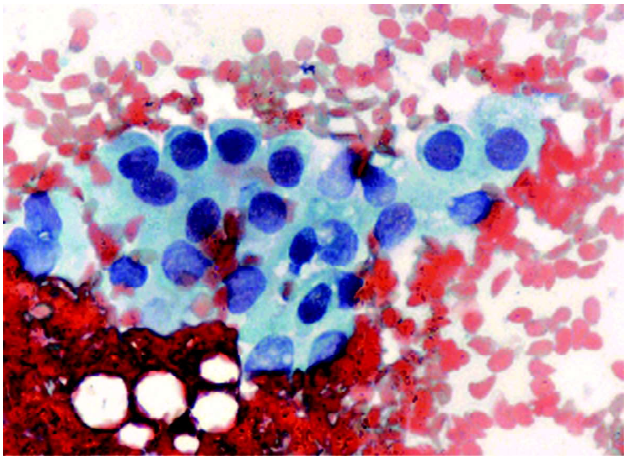

Fig. 4: *Bronchial aspirate cytology consistent with adenocarcinoma.*

The cytological finding of the lung tumour was completely compatible with that of the mandibular lesion which was finally diagnosed to be an adenocarcinoma of the lung metastatic to the mandible.

Discussion

Lung cancers are characterised by insidious onset, difficulty in detection, early metastatic spread, and poor prognosis[5]. Although bone metastasis from adenocarcinoma lung is quite common, nevertheless,

very few cases of metastasis to jaw bones have been reported. The most frequent origin of jaw metastasis in females is the breast, followed by thyroid and kidney. No such case of metastasis to mandible from adenocarcinoma lung has been reported in females[6].

Pathogenesis of metastasis to jaw bones is unclear but possible predilection for mandible is due to large amount of red bone marrow and increased flow of the circulating blood. Most of the red marrow in the jaws is found in the mandibular third molar region that is most often involved in metastatic spread[7]. Metastasis to the jaw bones may produce a variety of signs and symptoms including swelling, pain, loose teeth, and paraesthesia. In many instances, only swelling is the notable symptom. Clausen and Poulsen[5] found 12 cases of histologically verified metastatic carcinoma to the jaws which were more common in females but none were from the lungs. The most common symptoms were pain and swelling, but the most significant symptom was paraesthesia of the mandible.

Bone metastasis shows two main radiographic appearances:

1. Frank destruction of an area of bone with new bone formation within the lesion or adjacent bone.
2. Appearance mimicking osteomyelitis characterised by presence of many areas of destruction[8].

Most of the bony metastatic lesions are osteolytic and appear radiolucent on the radiograph; those of the prostate and breast may be osteoblastic and appear radio-opaque. Metastatic tumours in the jaw bones are difficult to recognise for a number of reasons, such as:

1. The lesions are centrally located in the bone.
2. There are very few subjective symptoms except at a very late stage.
3. Radiographs are usually non-specific

Consequently, metastatic invasion many-a-times has been erroneously diagnosed as various types of cysts, benign tumours, or infective lesions.

In this case, the patient had clinical features of cough, dyspnoea, chest pain, alongwith pain and swelling of the anterior aspect of the mandible. CT of the mandible demonstrated mixed lytic and sclerotic lesion of the mandible, and CT thorax showed a mass lesion in the lung, and both the lesions were later confirmed to be adenocarcinoma on cytological examination.

In conclusion, this case highlights a very rare occurrence of mandibular metastasis from lung adenocarcinoma in an elderly female, and thereby emphasises that metastatic tumours should be considered in the differential diagnosis of a destructive lesion of the mandible.

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