# C O N T E N T S

**Journal, Indian Academy of Clinical Medicine • Vol. 12, Number 3, July – September, 2011**

*Contains 84 pages from 165 to 248 inclusive of all advertisements*

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# Journal, Indian Academy of Clinical Medicine

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VIEWPOINT

JIACM 2011; 12(3): 176-8

# Viva Citas
# (Inhuman – "Non-human" – Human Beings)

*BM Hegde**

***"A reasoning, self-sufficing thing, An intellectual all-in-all!"***

– William Wordsworth.

Human beings have around 20 – 25 thousand genes in all, in the much talked about human genome, a little over the total number of genes in a small round worm! Fortunately, or unfortunately, we have more number of germs in very close proximity to us that their genes control our life much more than our own genes do. Although most of them have made their homes in our gut (mouth to the anus), lungs, vagina/penis, and skin, there are a lot more of them that have got into our cytoplasm during our evolution over millions of years from a unicellular organism. While we have roughly $10^{14}$ body cells in all, there are ten-times those numbers of germs in us. Together, we have a very large and complicated genome, hereinafter called the meta-genome, which includes bacteriomes, virinomes, and many of their metabolic end-products' genes, called metabolomes.

Even to raise a little finger, man needs the permission of a few germs whose genes control his actions! Man, proud man, please learn a biological lesson that pride hurts. Man is subservient to even those little bugs inside us. Indian ethos, which declares that education is, but acquiring humility, has been scientifically validated, if that is what the rationalists need. Now you do realise the importance of the title that mankind is inhuman, if not non-human! Let us then talk all about our lives-vivacitas in the new setting.

## Future research

This opens a new vista for future research in the area of genetic engineering and stem cell harvesting. Most of what we have been doing so far will, of course, come to naught. Reductionist medical research does not fit the bill for the future. Since we do not know man well, future research should, per force, be holistic. Better still would be outcomes research. *In-vivo*, *in-vitro*, and *in-silica* research of today will have to give place to observational outcomes research for the future. We have been doing that for the last ten years at the World Academy of Authentic Healing Sciences. Our journal is The Journal of the Science of Healing Outcomes (www.thejsho.com), available online.

## Chronic illnesses

In this setting chronic infections will have to be revisited and looked at more carefully. Many of the idiopathic diseases that we treat symptomatically will have to be reconsidered as some of the germs that we never knew existed could be their cause. Maybe the era of germs and diseases has not yet been conquered. Our present ability to culture germs in the laboratory Petridishes might be just identifying the tip of the iceberg of this huge germ world that lurks there under the water surface. When man discovers a new germ like the *Helicobacter pylori*, he gets the Nobel Prize. In that case we might have to have millions of Nobels to be given in the years to come. Infections as the cause of even degenerative diseases and vascular diseases will have to be explored. Heart attacks, strokes, hypertension, and many others could all come under that category. While there were occasional murmurs that viral infections could be the cause of atherosclerosis and cancer, the area was not seriously explored, especially with bacteria in view. Now that we know that there are billions of germs in this universe that the present science does not know, we will have to be alert. In this setting the whole vaccine industry will have to be on its toes.

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

## Auto-immune diseases

In our present knowledge these diseases are misfits where we have been contemplating that our own body cells are being attacked by antibodies produced in our own immune system. This goes against the very grain of biological rules. Paul Ehrlich himself had horrifying dreams of such a thing ever happening when he wrote about "horror autotoxicus." The dangerous part of our present therapeutic armamentarium for auto-immune diseases is the use of deadly steroids in large doses. These, at best, could only douse the fire to relieve symptoms while damaging our own system further. With the new knowledge of billions of germs making our body their safe haven, one of them might be tickled to infect and destroy our body cells like in many such diseases – rheumatoid arthritis, thyroiditis, gastritis, irritable bowel syndrome, scleroderma, polyarteritis nodosa and others. This could even be extended to cancer, at least of some varieties. This makes better sense instead of blaming our own cells for damaging their owner!

## Hurdles en-route

How is it that the wise men of our establishment missed out on such an enormous problem? Science should understand the working of this universe rather than trying to teach nature a lesson or two. Our bane has been the present division of this enterprise into narrow specialities. One of the laws of thermodynamics rightly notes that anything that divides disintegrates! That has happened to our present science where a biologist does not understand and talk to a physicist, and a chemist does not understand physics. Medical scientists sit in their own ivory towers. The whole gamut of above-mentioned new knowledge started with space scientists looking at their laboratories more carefully to see if their sterile areas for the manufacture of space crafts are truly sterile.

A few of them stumbled on the fact that their "so called" very, very sterile work areas, when looked through more carefully, were full of germs living in "bio-films" which prevent their being cultured by the known methods of microbiology today. This opened a new front for research as the space scientists were worried that they must have by now infected the moon, mars and other planets with dangerous germs from the earth! This should remind us as to how Europeans destroyed, unwittingly, thousands of the aboriginals of the 'New World' by the germs of plague, cholera, and small pox that they took with them when they reached the 'New World' in search of greener pastures. Local Ameri-Indians lived in a comparatively sterile environment when the Europeans landed there.

The "bio-film" protection has to be beaten to get at the newer microbes to understand man better in future. Of course, we did know about L forms in bacteria for some time now, but that was a small drop in the ocean. May be, we will be able to completely overhaul our therapeutics in the future relieving mankind from the ravages of Adverse Drug Reactions of today which kill millions. Me thinks this will take a very long time to accomplish but, start we must right away.

## NIH human micro-biome project

The National Institute of Health (NIH) has finally woken up from its deep slumber. Using the supercomputer, the Hospital for Sick Children in Ontario has been working on in-silica research on the bacterial genome with some success since 1981. The NIH to date has been able to decipher about 1087 bacterial genomes. NIH now thinks that 10% of our cells are human while 90% of our cells are bacterial in origin! This micro-biome study is very significant because the gene interactions between Homo sapiens and germs might open a new vista for the study of disease causation as also newer therapeutic stratagems. To give one example, the ACE (angiotensin converting enzyme) gene could be connected to renal, cardiac, and metabolic diseases but combined with a germ genome it could also be connected to sarcoidosis. The future possibilities are mind boggling. Many, many years from now our future generation might thank us for belatedly thinking of our close links with germs in this universe. We must get out of the mind-set that "germ evil – man good" thinking for good.

## Conclusions

With the newer knowledge from physics showing that "matter is not made out of matter", and matter and energy are the two faces of the same coin, we realise that the human body and human mind are but the same. This is a quantum leap for the medical world. This has opened the

huge possibility of the 'Placebo Effect' being the vital part of medical interventions and not the poisonous drugs that we administer. (Pharmacon = poison) Doctors should primarily be very good human beings to be effective placebos. Thanks to Hans Peter Duerr, a good friend of mine and the Emeritus President of Max Planck Institute in Munich, mankind has come to realise the truth of the Indian wisdom "*manaeveam manushyaanaam*". (Mind is but man himself). Similarly, another great physicist, Fritz-Albert Popp, has shown that every body cell DNA emits a photon light which can now be photographed (bio-photons). These lights show that the body cells are in sync in health, and when that co-operation gets disturbed illnesses set in. Future medicine, which I had labelled as 'Meta-Medicine', will be based on a better scientific foundation. We can now forget the faulty foundation of modern medicine of the 'Randomised Controlled Trials' (RCTs) and many other statistical measures for good. The Sun seems to be rising on the distant eastern horizon of meta-medicine. I wish that will help mankind to lead a happier and healthier life on earth as long as they live – live life more meaningfully – vivacitas.

***"Every man, as to character, is the creature of the age in which he lives. Very few are able to raise themselves above the ideas of their times".***

–Voltaire.

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ORIGINAL ARTICLE

JIACM 2011; 12(3) : 179-81

# Profile of Dengue Patients in A North Indian Referral Hospital

*Ruhi khan*, MS Zaheer**, Tamkin Khan***, Saif Quaiser****, MU Rabbani******

## Abstract

*The presence of thrombocytopenia was determined in 500 patients presenting with fever admitted to the Medicine wards of the Jawaharlal Nehru Medical College Hospital (JNMCH), AMU, Aligarh. A dengue serological test was performed on all 500 patients with a positive result in 300 (60%). NS1 antigen detection test was positive in 110 patients (36.6%), IgM antibodies against dengue virus were positive in 140 patients (46.6%), and IgG antibodies in 50 patients (16.6%). Since an accurate diagnosis was found only in a proportion of the cases, all the clinically suspected cases of dengue were analysed. Thrombocyte count of less than 100,000/ml was present in 445 (89%) cases on admission and during hospitalisation. In the serologically-confirmed cases, the prevalence of thrombocytopenia (count less than 100,000/ml) was 74.3% (223 cases), and 77 (25.6%) patients had a platelet count of > 100,000/ml. Severe bleeding was recorded in 40 (13.3%) of all dengue-confirmed cases and occurred more often in patients with severe thrombocytopenia. All 40 (13.3%) cases with bleeding received platelet transfusion; among them only 32 (10.6%) patients had a platelet count below 50,000/ml. In patients having a platelet count between 10,000 - 50,000/ml, only 9 patients with bleeding manifestations received platelet transfusion. In the remaining 54 patients, platelet transfusion was not given. No difference in the outcome of patients was observed comparing patients who received or those who did not receive a platelet transfusion (even in those with a platelet count 10,000 - 50,000/ml). In conclusion, a large number of patients with dengue fever at JNMC Hospital did not receive platelet transfusions, even if the thrombocyte count was between 10,000 - 50,000/ml. The study suggests that in most dengue cases, platelet transfusions do not influence the final outcome of patients who do not have bleeding manifestations. Treatment costs for such cases could be reduced if these unnecessary platelet transfusions are avoided. Further studies undertaken only in accurately confirmed cases are needed to clarify this finding.*

*Keywords: Dengue, thrombocytopenia, platelet transfusion, NS1Antigen.*

## Introduction

The clinical diagnosis of dengue haemorrhagic fever (DHF), especially in the early phase of illness, is not easy. Laboratory findings such as thrombocytopenia and a rising haematocrit in DHF cases are usually observed by day 3 or 4 of the illness[1]. Several studies have revealed a variable prevalence of thrombocytopenia. Sumarmo[2] found a prevalence of thrombocytopenia in 81% of the cases in the Department of Child Health, Cipto Mangunkusumo National Hospital, Jakarta, Indonesia. Ten years later, a prevalence of 59% was observed in the same department[3]. In the confirmed DHF cases, Samsi *et al*[4], in Jakarta, observed thrombocytopenia in 9% of the cases on admission and in 38% during hospitalisation. Published data from various institutions[5, 6, 7] have put varying figures as the trigger for platelet transfusion in hospitalised dengue patients. The DHS guidelines stipulate that platelet transfusion should be given to patients with platelet count < 20,000/cumm.

The use of platelet transfusions in DHF/DSS patients, therefore, remains controversial. One of the aims of this study was to evaluate the effect of platelet transfusions to prevent bleeding in DHF/DSS patients.

## Materials and methods

This study was a hospital-based surveillance study which was carried-out in patients admitted with fever and thrombocytopenia in JNMCH, Aligarh between September 2010 and October 2010. The study included all patients with a clinical diagnosis of dengue on admission and discharge, according to the opinion of the attending physician.

Laboratory tests to confirm dengue infection included the NS1 (non-structural) antigen detection test, and detection of the IgM and IgG antibodies against dengue virus.

The age of the patient, duration of fever before admission, result of the dengue confirmatory tests, platelet count on admission and during hospitalisation, presence of severe bleeding manifestations, administration of platelet transfusions, and dates of transfusions were recorded.

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Severe bleeding manifestations included haemoptysis, epistaxis, gum bleed, haematuria, haematemesis, melena, and disseminated intravascular coagulation (DIC).

## Study design

This was a hospital-based surveillance study conducted in patients admitted to the Medicine ward of JNMC hospital, Aligarh between september 2010 and october 2010.

## Results

Of the total 500 cases presenting with fever, 460 (92%) were males and 40 (8%) females; most patients were between 20 – 40 years of age.

Out of 500, 420 patients (84%) had 3 – 5 days of fever prior to admission. The remaining 80 patients had a history of fever for 8 – 10 days prior to admission. A dengue serological test was performed on the sera of all 500 patients which gave a positive result in 300 patients (60%), which included a positive NS1 antigen test in 110 patients (36.6%), a positive IgM antibodies test against dengue virus in 140 patients (46.6%), and a positive IgG antibodies test in 50 patients (16.6%) (Table I).

Of all the clinically diagnosed dengue patients, a thrombocytopenia less than 100,000/ml was present in 445 cases (89%). In the serologically confirmed cases, the prevalence of thrombocytopenia of less than 100,000/ml was 74.3% (223 patients) on admission and during hospitalisation. The remaining 77 (25.6%) of dengue confirmed cases had a platelet count of > 100,000/ml. Severe bleeding was recorded in 40 (13.3%) cases of all dengue patients (Table II).

Bleeding manifestations included epistaxis in 15 (5 %) cases, gum bleed in 11 (3.6%) cases, haemoptysis in 4 (1.3%) cases, haematemesis in 3 (1%), melena in 2 (0.6%), haematuria in 1 (0.3%), and DIC in 4 (1.3%) of the cases. Severe bleeding occurred more often in patients with severe thrombocytopenia (Table III).

**Table I: Distribution of confirmed dengue cases.**

| Serological test | No. of positive results | Percentage (%) |
|---|---|---|
| NS1 Antigen | 110 | 36.6 |
| IgM Antibody | 140 | 46.6 |
| IgG Antibody | 50 | 16.6 |
| Total | 300 | 100 |

**Table II: Occurrence of bleeding in patients with thrombocytopenia.**

| Platelet count | No. of patients (n) | Patients with bleeding | No bleeding |
|---|---|---|---|
| <10,000 | 146 | 23 | 123 |
| 10-50,000 | 63 | 9 | 54 |
| 50,000-100,000 | 14 | 6 | 8 |
| >100,000 | 77 | 2 | 75 |
| Total | 300 | 40 | 260 |

All patients with platelet count < 10,000/ml received platelet transfusion whether or not they had any bleeding manifestations. In patients with thrombocyte counts between 10,000 – 50,000/ml, 9 patients with bleeding episodes were given platelet transfusion. The remaining 54 patients with thrombocyte counts between 10,000 – 50,000/ml but no bleeding manifestation were observed and monitored and no platelet transfusion was given. No difference in the final outcome of patients was observed comparing the patients with platelet counts between 10,000 – 50,000/ml whether they received platelet transfusion or not.

**Table III: Bleeding manifestations in thrombocytopenic patients**

| Platelet count | Patients with bleeding | Haematuria | Haematemesis | Malena | Haemoptysis | Epistaxis | Gum bleed | DIC | No bleeding |
|---|---|---|---|---|---|---|---|---|---|
| <10,000 | 23 | 0 | 1 | 1 | 3 | 9 | 7 | 2 | 123 |
| 10-50,000 | 9 | 1 | 2 | 1 | 1 | 2 | 1 | 1 | 54 |
| 50,000-100,000 | 6 | 0 | 0 | 0 | 0 | 3 | 2 | 1 | 8 |
| >100,000 | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 75 |
| Total | 40 | 1 | 3 | 2 | 4 | 15 | 11 | 4 | 260 |

## Discussion

Dengue fever is a major public health problem in India. This study showed that the majority of dengue cases were young, with the largest proportion in the age group of 10 – 20 years. Early in the infection, it may be difficult to differentiate dengue fever from other febrile illnesses. Later, usually after three or four days, when thrombocytopenia and haemoconcentration are present, it is easier to diagnose. In this study, 500 fever cases were admitted. Thrombocytopenia was found in 445 (89%) of the confirmed cases on admission and during hospitalisation. This prevalence is in accordance with the findings of Sumarmo[2]. Similar to other studies, thrombocytopenia was found in the majority of cases between day 3 and day 7 after the onset of fever[1,8,9] (most often day 5). Bleeding manifestations are highly variable and do not always correlate with the laboratory abnormalities in the coagulation profile. Factors like mild degree of disseminated intravascular coagulation (DIC), hepatic derangement, and thrombocytopenia, act synergistically to cause bleeding in a dengue patient[10]. Severe bleeding is related to severe thrombocytopenia[11].

Severe bleeding occurred significantly more often in patients with more severe thrombocytopenia. In this study, a similar percentage of patients developed severe bleeding, whether or not they received a platelet transfusion.

## Conclusion

In conclusion, the study states that a large number of dengue-confirmed cases at JNMC hospital with thrombocyte counts between 10,000 – 50,000/ml, who do not have bleeding episodes do not require platelet transfusions. Also, platelet transfusions do not influence the final outcome of patients who do not have bleeding manifestations. Treatment costs for such cases could be reduced if these unnecessary platelet transfusions are avoided. A further study performed only in accurately confirmed cases is needed to clarify the findings of this study.

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ORIGINAL ARTICLE

JIACM 2011; 12(3) : 182-6

# Effect of Erythropoietin on Highly Sensitive C-reactive Protein Levels in Cases of Chronic Kidney Disease Undergoing Maintenance Haemodialysis

*N Nand*, M Chugh**, M Sharma****

## Abstract

***Introduction:*** *The role of chronic inflammation in the development of anaemia and erythropoiesis stimulating agents (ESA) hypo-responsiveness is now gaining increasing attention as a potential factor that might adversely affect patient outcome. In cases of chronic kidney disease (CKD) C-reactive protein (CRP) is probably the most notorious inflammatory marker. Recent research is destined to focus on future therapy of inflammation and its related complications. Anti-inflammatory properties of erythropoietin have been recently recognised. Hence, this study was undertaken to assess the effect of erythropoietin therapy on highly sensitive C-reactive protein (hs-CRP) levels in CKD patients.*

***Material and methods:*** *25 adult patients of end-stage renal disease (ESRD) who were undergoing twice weekly maintenance haemodialysis were administered subcutaneously 4,000 IU of recombinant human erythropoietin (rHuePo) twice weekly following dialysis. The effect of erythropoietin on hs-CRP and haemoglobin over six months was studied.*

***Results:*** *There was a significant response ($p < 0.05$) of erythropoietin on haemoglobin after 2 months of rHuePo therapy, but a plateau effect was observed thereafter. hs-CRP levels were within normal range in the study participants and rHuePo showed no significant effect ($p > 0.05$) in decreasing hs-CRP levels.*

***Conclusion:*** *Erythropoietin improves anemia of CKD, though target levels can only be achieved by increasing the dose of erythropoietin. hs-CRP levels did not decrease with anti-inflammatory (rHuePo) therapy as envisaged with twice weekly erythropoietin therapy.*

***Key words:*** *Highly sensitive C-reactive protein, erythropoietin, chronic kidney disease.*

## Introduction

CKD is emerging as a major public health problem globally. Anaemia is a well known and a major complication of CKD. Its presence is considered one of the hallmarks of chronicity of renal disease and the degree of anaemia correlates well with loss of renal function[1]. The role of chronic inflammation in the development of anaemia and erythropoiesis stimulating agents hypo-responsiveness is now gaining increasing attention as potential factors that might adversely affect patient outcomes[2-3]. Hyperparathyroidism, chronic inflammation, aluminium toxicity and iron deficiency are the major causes of erythropoietin resistance in CKD with anaemia.

Inflammation in CKD could be due to bacterial or viral infections, surgical trauma including vascular access surgery, heart failure, and renal or systemic inflammatory diseases[4]. It leads to worsening anaemia, resistance to hormones such as erythropoietin and insulin, catabolism, and oxidative stress. The inflammatory and reactive oxygen species systems, besides enhancing each other, could lead to endothelial dysfunction, an important predictor of long-term prognosis[4]. Therefore, the focus of ongoing research is directed to look for various molecules which can reduce the inflammation in CKD patients, thereby decreasing excess morbidity arising out of anaemia and cardiovascular disease mortality. Potential treatment strategies which have been advocated include selective anticytokine therapy like anti-TNF-$\alpha$ antibodies, soluble TNF receptors and IL-1, IL-6 receptor antagonists[3]. Statins are also reported as having some role in reducing inflammation[5].

Recognising hs-CRP as a cause of poor response to erythropoietin in ESRD patients, there arises a need to

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decrease its levels with various treatment options available. Further, as erythropoietin has been shown to have anti-inflammatory effect, this study was planned to assess whether there is chronic inflammation in cases of CKD undergoing maintenance haemodialysis and whether erythropoietin has (if any) hs-CRP lowering effect or not.

## Material and methods

A total of 25 adult patients of CKD who were undergoing twice weekly maintenance haemodialysis were included. A pre-informed consent was obtained in every case. Every patient's baseline haemoglobin, total leucocytes count, differential leucocytes count, hs-CRP, and other baseline renal parameters including blood urea, serum creatinine, serum uric acid, serum calcium, serum phosphate, serum sodium, serum potassium, and creatinine clearance were estimated. Patients were administered twice weekly recombinant human erythropoietin 4,000 IU s/c after a 4-hour haemodialysis session alongwith injectable iron 100 mg in 100 ml of normal saline weekly. Patients were followed for 6 months and haematological and renal parameters were assessed every 2 months. hs-CRP levels were reassessed after 6 months of rHuepo therapy. Data was analysed for change in hs-CRP and haemoglobin concentration using paired student 't' test. Their correlation analysis was done using pearson correlation test.

## Results

The mean age of the patients was 43.28 ± 29.11 years. There were 20 men and 5 women. Hypertension was the most common cause of CKD with 8 patients followed by chronic glomerulonephritis[7], diabetic nephropathy[4], obstructive uropathy[3], autosomal dominant polycystic kidney disease[2] and 1 patient of renal amyloidosis.

All patients had severe anaemia and mean haemoglobin was 7.168 ± 0.9114 g/dl at the baseline with total leucocyte count of 10296 ± 4276.143/mm$^3$. The various renal parameters at baseline, two months, four months, and six months are shown in Table I. The level of haemoglobin increased significantly; however, it reached a plateau effect at two months as shown in Fig. 1. Haemoglobin rose from 7.168 ± 0.9114 g/dl at baseline to 7.984 ± 1.673, 7.912 ± 1.619, 8.028 ± 1.001 g/dl at two, four and six months respectively and rise was significant ($p < 0.05$) at two, four and six months.

Mean baseline hs-CRP values were within normal limits as defined in KDQOI guidelines. hs-CRP changed from 1.919 ± 0.7722 mg/l at baseline to 1.702 ± 0.4444 mg/l at six months as shown in Fig. 2. The difference was statistically non-significant ($p > 0.05$) indicating that twice weekly erythropoietin therapy did not influence the hs-CRP levels. Further, correlation analysis was done between change in hs-CRP levels over the study period and haemoglobin levels over the same period as shown in Fig. 3. It shows that correlation between the variables was statistically non-significant ('p' = 0.185, r = -0.274) at start and at six months of study.

**Table I: Basic parameters of study participants.**

| Parameter | Baseline | At two months | At four months | At six months |
|---|---|---|---|---|
| Haemoglobin (g/dl) | 7.168±0.9114 | 7.984±1.673* (<0.05) | 7.912±1.619* (<0.05) | 8.028±1.001* (<0.05) |
| PCV (%) | 27.016±1.781 | 29.20±2.843* (<0.001) | 29.120±2.743* (<0.001) | 29.52±2.124* (<0.001) |
| TLC (per cmm) | 10296±4276.143 | 8046±2181.739* (0.011) | 7288±1239.73* (0.003) | 7684±1644.34* (0.002) |
| B. urea (mg/dl) | 197.12±76.94 | 138±44.636* (<0.001) | 118.96±53.27* (<0.001) | 108.80±30.62* (<0.001) |
| S. creatinine (mg/dl) | 8.648±3.418 | 7.308±2.198* (0.005) | 6.6±1.693* (<0.001) | 6.560±1.271* (<0.001) |
| S. calcium (mg/dl) | 8.788±1.241 | 9.196±0.670* (0.02) | 8.8±0.924 (0.966) | 9.020±0.758 (0.423) |
| S. phosphate (mg/dl) | 6.628±2.044 | 6.056±1.639 (0.065) | 5.224±1.638* (<0.001) | 4.692±1.335* (<0.001) |
| S. uric acid (mg/dl) | 7.632±3.033 | 6.556±1.797* (0.032) | 6.484±1.415* (0.021) | 6.272±1.623* (0.010) |
| hs-CRP (mg/l) | 1.919±0.7722 | – | – | 1.702±0.4444 |

*n=25; data is represented as mean ± SD; *P<0.05 vs at the start of study; paired student 't' test.*

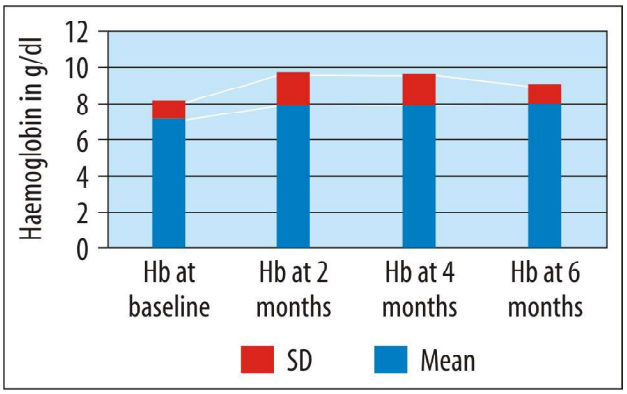


***Fig. 1:*** *Shows haemoglobin levels at baseline, two, four, and six months after erythropoietin therapy.*

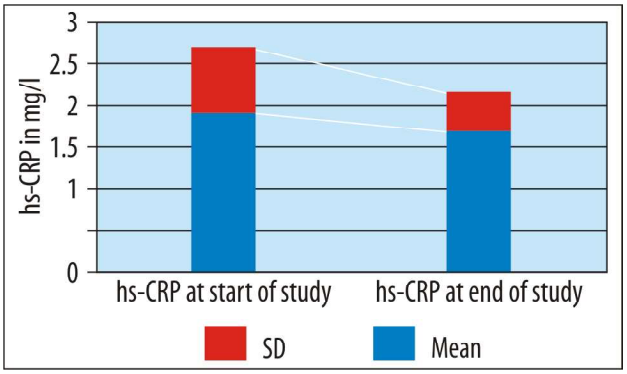


***Fig. 2:*** *Shows hs-CRP levels at baseline and six months.*

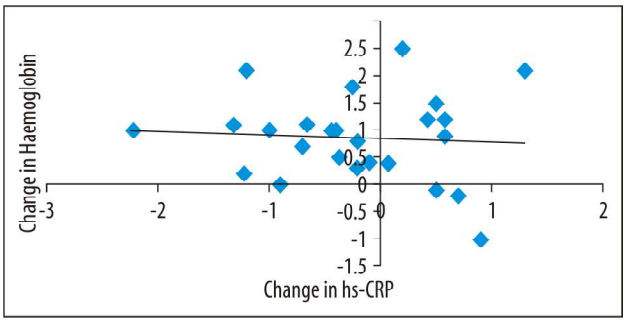


***Fig. 3:*** *Shows correlation between rise in haemoglobin and fall in hs-CRP levels after erythropoietin therapy.*

hs-CRP levels were further assessed in three different age groups (at baseline and at 6 months) of 20 – 40, 40 – 60 and 60 – 80 years to determine the effect of age. However, there was no statistically significant effect ('p' > 0.05). Data was further analysed in males and females separately. It was observed that though the mean values decreased from 1.890 ± 0.826 mg/l to1.663 ± 0.477 mg/l in the male participants and from 2.036 ± 0.564 mg/l to 1.696 ± 0.424 mg/l in the female participants, they were not statistically significant ('p' > 0.05).

When hs-CRP levels were subdivided into two groups with values less than 2 mg/l (group 1) and more than 2 mg/l (group 2), group 1 had 13 patients with mean hs-CRP levels of 1.30 ± 0.36 mg/l and group 2 had 12 patients with hs-CRP levels of 2.58 ± 0.48 mg/l. It was observed that haemoglobin levels in group 1 varied from 6.97 ± 0.94 g/dl at baseline, to 8.13 ± 2.22 at 2 months, to 8.05 ± 2.14 at 4 months to 7.87 ± 1.29 g/dl at six months. Similarly, haemoglobin levels in group 2 varied from 7.37 ± 0.85 at baseline, to 7.82 ± 0.80 at 2 months, to 7.75 ± 0.79 at 4 months to 8.19 ± 0.55 g/dl at 6 months. However, change in haemoglobin was non-significant ('p' > 0.05) between the two groups as shown in Fig. 4.

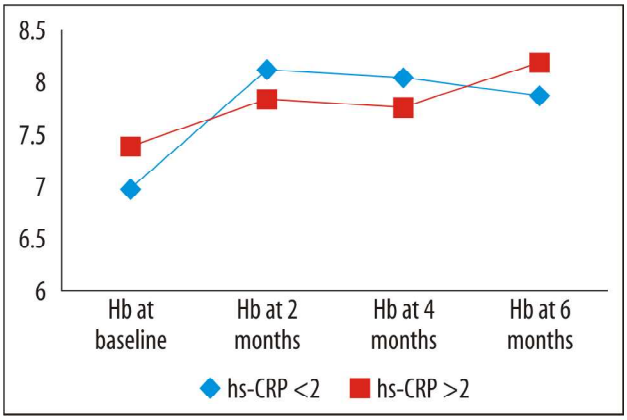


***Fig. 4:*** *Shows change in haemoglobin in the two subgroups of patients having hs-CRP > 2 and < 2 mg/l.*

Patients were evaluated for the development of complications of twice weekly erythropoietin therapy. It was observed that four had deterioration in their hypertension control. One patient had flu-like episodes. In two patients there was clot formation in the A-V fistula. None of the patients developed seizures with the erythropoietin therapy during the course of study period.

## Discussion

The main cause of mortality and morbidity in CKD patients is cardiovascular disease with an annual mortality rate of approximately 9% which is 10- to 20-fold higher than in the general population, even when adjusted for age, gender, race and the presence of diabetes mellitus[6]. A number of risk factors that provide rationale for the remarkable prevalence of vascular disease in ESRD have been recently identified and amongst these, inflammation has been the most important[7]. Also, inflammation in ESRD

has been found to be associated with markers of malnutrition, anaemia, and erythropoietin resistance[8]. Renal failure contributes to inflammation as a result of accumulation of pro-inflammatory compounds or products of metabolism. Inflammation and acute phase response interact with haematopoietic system at several levels resulting in reduced erythropoiesis, accelerated destruction of erythrocytes and blunting of the reactive increase in erythropoietin in response to reduced haemoglobin levels[9]. Cytokines also cause anaemia by inhibiting erythropoietin secretion[10].

Several inflammation biomarkers[11] namely CRP, IL-6, adiponectin, S. ferritin, TLC count, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM-1) and inflammatory molecules with negative acute-phase reaction, namely, S. albumin, S. transferrin, S. iron, S. ferritin have been defined for consideration as predictors of outcome in ESRD. Among these hs-CRP, which is a pentameric protein synthesised in liver, opsonises infection and activates complement has attracted the most interest[7]. CRP is secreted by liver and inflammation causes a rapid increase in its serum concentration. It plays a role in host defense by interacting with complement. Compared to measurement of other markers of inflammation and the acute phase reaction, serum CRP has several advantages. It is a simple, reliable, readily available, and an inexpensive test. It is also a long-term predictor of cardiovascular risk and mortality in the general population and in CKD patients[4]. Furthermore, high plasma concentrations of C-reactive protein (CRP) have shown to be associated with anaemia and ESA hypo-responsiveness in chronic haemodialysis patients[12].

Erythropoietin has revolutionised the treatment of anaemia associated with CKD. However, a proportion of patients treated with erythropoietin respond poorly, or not at all, and in a subset of these, no obvious cause such as iron deficiency could be found. The interactions between different inflammatory mediators and erythropoietin response appear to be complex. McDougall[13] has presented information regarding the non-erythroid effects of erythropoietin. EPO receptors have been detected in many tissues such as the brain and heart. EPO has been shown to possess antiapoptotic effects in many (non-erythroid) cell lines. In view of the increasing recognition of hs-CRP as a cause of poor response to erythropoietin in ESRD patients, there arises a need to decrease its levels with various treatment options available. Further, as erythropoietin has been shown to have anti-inflammatory effect, this study was planned to assess whether twice weekly erythropoietin in patients undergoing maintenance haemodialysis has any hs-CRP lowering effect or not.

The results of this study indicated that erythropoietin has no significant effect in lowering the inflammatory state. This finding may be related to the fact that hs-CRP levels observed at baseline were already within the normal range and did not decrease further. Haemoglobin levels rose significantly ($p < 0.05$); however, rise in haemoglobin achieved with erythropoietin reached a plateau effect at 2 months and could not rise further. A number of ways have been postulated to improve the response of epo therapy in cases of CKD[14]. These include treatment of chronic infection, congestive heart failure, cardiovascular disease, use of ultrapure dialysate, vitamin E supplementation and increasing the dose of epo. Inflammation is known to be associated with erythropoietin hypo-responsiveness in CKD patients and target haemoglobin levels can only be achieved by increasing the dose of erythropoietin[15]. Studies have also estimated that on an average, the required erythropoietin dose to maintain a certain haemoglobin level may be increased by 30 – 70% in dialysis patients with serum CRP > 2 mg/l as compared to those with a lower CRP concentration[12]. The observation of plateau effect after two months of therapy in patients would suggest that the dose of erythropoietin (4,000 IU s/c twice/week) was not enough in them. None of our patients had AVG's and we have been using biocompatible membranes (polysulphone). We did not give any vitamin E supplementation and fixed dose of EPO was used. As yet, there is no recognised treatment for ESRD patients with inflammation, but with estimation of hs-CRP we can identify patients with inflammation. Recent research has already opened-up new possibilities for future therapy of inflammation and its related complications.

The observations made in this study show that hs-CRP levels are within normal range in the study participants

and did not decrease further with anti-inflammatory therapy as envisaged with twice weekly erythropoietin therapy. Erythropoietin improves anaemia of CKD, though target levels can only be achieved by increasing the dose of erythropoietin. CRP should be included in the routine laboratory work-up for risk evaluation and stratification in the patients of ESRD. Thus future research should focus on elucidating the aetiology of the inflammation and studying the long-term effects of various anti-inflammatory strategies in patients of ESRD so that better outcome can be achieved in these patients.

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ORIGINAL ARTICLE

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# Impaired Fasting Glucose: A Study of its Prevalence Documented at a Tertiary Care Centre of Central India and its Association with Anthropometric Variables

*Shweta Sahai*, Deepak Vyas**, Sharad Sharma***

## Abstract

***Aims of Study:*** *To find out the prevalence of 'impaired fasting glucose' in a population reporting to a tertiary care centre of central India and correlate it with other variables like age, weight, body mass index, waist circumference, and waist-hip ratio.*

***Methods:*** *This was a cross-sectional study carried-out on consecutive subjects attending the OPD of Jayarogya Hospital, a tertiary care centre located in central India. A diagnosis of impaired fasting glucose (IFG) was made as per the American Diabetes Association (ADA) guidelines. Data was analysed using unpaired 't' test and Pearson's Chi-square test to assess whether the inter-group difference was significant or not. A p value of $< 0.05$ was considered significant.*

***Results:*** *The prevalence of impaired fasting glucose in the studied population was found to be 18%. There was no significant difference between the sexes. A higher prevalence was seen with advancing age. A significantly higher prevalence was found amongst lower body weight persons, contrary to expectations. No significant correlation was found with body mass index, but the prevalence of impaired fasting glucose increased with increasing waist circumference and showed a significant correlation with increasing waist-hip ratio.*

***Conclusions:*** *This study showed that the prevalence of impaired fasting glucose is very high in central India. The traditional risk factors like high total body weight and body mass index are not very good predictors for the development of diabetes mellitus in the rural/semi-urban populations. In fact, low total body weight might prove to be a stronger predictor of impaired fasting glucose alongwith high waist-hip ratio.*

***Key words:*** *Prediabetes, body mass index, waist-hip ratio, low body weight.*

## Introduction

Prediabetes[1] is a condition that has been projected as a precursor to diabetes. It refers to a state of impaired glucose tolerance, or, impaired fasting glucose either singly or in combination. Pre-diabetes can be diagnosed by blood sugar test such as fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT). The American Diabetes Association (ADA) criteria for diagnosis of pre-diabetes based on expert committee recommendations[2] are as follows:

- FPG =100 – 125 mg/dl (5.6 – 6.9 mmol/l) = impaired fasting glucose (IFG)
- 2-h post-load glucose = 140 – 199 mg/dl (7.8 – 11.1 mmol/l) = impaired glucose tolerance (IGT);
- HbA1c of 5.7 – 6.4% (this has been recently added)[2]

Patients with IFG and/or IGT are referred to as having 'pre-diabetes', recently reclassified as 'categories of increased risk for diabetes' by the ADA position statement 'standards of medical care in diabetes', released in 2010[2].

The purpose of this is obvious. It seeks to erase the impression of 'inevitable progression to diabetes' associated with the term 'pre-diabetes' and generate hope for reversibility to normoglycaemia. Hence, this group is an important target for vigorous intervention for primary prevention of diabetes.

### Epidemiology of pre-diabetes

Pre-diabetes is a common disorder in most populations. The reported prevalence of pre-diabetes appears to vary among populations with different ethnic background. 314 million people are currently affected with pre-diabetes all over the world, and by 2025, it is estimated that approximately 500 million people will have pre-diabetes[3]. The current estimates are that up to 70% of pre-diabetic subjects eventually get diabetes.

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**Clinical significance of pre-diabetes**

The progression of pre-diabetes to type 2 diabetes has been examined in a number of populations with varying results. In general, epidemiological studies indicate that ~ 25% of subjects with IFG or IGT progress to type 2 diabetes in 5 years, whereas about ~ 50% remain pre-diabetic and 25% revert to normal[4]. In an 11 year follow-up study among adults with IGT in Mauritius, 46% developed diabetes, 28% remained unchanged, and 26% reverted to normal. Those with the combination of IFG and IGT develop type 2 diabetes at approximately twice the rate[5] as do individuals who manifest a single abnormality. In comparison with adults who have normal glucose tolerance, people with impaired fasting glucose have a two- to three-fold increased prospective risk of cardiovascular events, which is most marked in younger subjects.

## Importance of pre-diabetes in India

As the prevalence of and progression to diabetes continues to increase in India, diabetes related morbidity and mortality have emerged as major public healthcare issues. Diabetes related damage in small blood vessels can lead to blindness, kidney failure, and amputation. Damage to larger blood vessels can result in heart disease, high blood pressure, and stroke[6]. In fact, impaired fasting glucose and impaired glucose tolerance are also independently associated with increased risk of cardiovascular events[7, 8]. The occurrence of diabetes in Indians is almost a decade earlier than in the western population[9-11]. Hence, most of the patients are from the economically productive age group. Moreover, the treatment cost of diabetes in an economically backward family may drain as much as 25% of the entire income for each person with diabetes[12, 13]. This information clearly dictates that clinicians must intervene at the pre-diabetic stage to prevent development of diabetes and a host of complications rather than ignoring pre-diabetes. Insufficient studies on pre-diabetes in central India and high projected prevalence and high conversion rate of pre-diabetes to diabetes (70%) generates the rationale behind the research.

## Material and methods

The study was cross-sectional in design, spread over a period of 2 months – May and June, 2009. We included subjects attending the Medicine Out-patient department of Jayarogya hospital. This is a tertiary care centre, catering to a pre-dominantly rural and semi-urban population. 130 eligible subjects of both genders were enrolled consecutively and prospectively for the study. Fasting plasma glucose measurement was used as the screening test for the diagnosis of pre-diabetes, as recommended by the ADA 2004 guidelines. The FPG was preferred because it was easier and faster to perform, convenient, acceptable to patients and less expensive. The oral glucose tolerance test although considered the 'gold standard,' was more costly and time consuming than the FPG test and was less reproducible. The prevalence of impaired fasting glucose was determined using the American Diabetes Association guidelines. Weight, body mass index (BMI), waist circumference (WC), and waist-hip ratio (WHR) of all the participants were recorded.

**Exclusion criteria**

The subjects with a history of diabetes mellitus, tuberculosis, chronic asthma, Addison's disease, acquired adrenal insufficiency, acquired hypopituitarism, patients on long-term corticosteroid therapy, diuretics were excluded from the study.

The total body weight was taken by a weighing machine with the participants wearing indoor clothes without shoes. The body mass index was calculated according to the formula: weight in kg/height in metre$^2$. The waist circumference was measured at the level of the last rib after expiration. Hip circumference was taken at the level of maximum diameter of the hips as viewed from the side. The waist-hip ratio was calculated as waist circumference/ hip circumference. After this, the subjects were motivated to come the next day to the central pathology laboratory of the hospital after overnight fasting for blood sample collection.

**Laboratory analysis**

Laboratory measurement of fasting plasma glucose was performed on venous samples using glucose oxidase peroxidase test with fully automated analyser. The registered patients were informed of their fasting sugar values and those found pre-diabetic were taken care of

by appropriate consultation and treatment.

## Data processing and statistical analysis

Data was entered, compiled in the computer and analysed using Pearson's Chi-square test and students unpaired 't' test to assess if the inter-group difference was significant or not. A p value of $< 0.05$ was considered significant.

## Results

Out of 130 eligible subjects, 100 subjects were actually studied (response rate: 76.92%).This included 49% males and 51% females. The prevalence of impaired fasting glucose in population reporting to tertiary care centre was found to be 18%. 18.36% pre-diabetics were found among males and 17.64% among females. Among males, the highest percentage of pre-diabetics was found in the above 65 age group and lowest among 36 – 45 age group, whereas in females the highest percentage was found in the 56 – 65 age group and lowest among the 46 – 55 and above 65 age group (Table I and Fig. 1). Similarly, the highest percentage of pre-diabetics among males and females was found in the weight group 31 – 40 kg and 61 – 70 kg respectively. The lowest percentage among both males and females was in the weight group above 71 kg (Table II, Fig. 2). Significant difference was found in the prevalence of impaired fasting glucose among subjects of weight group below 51 kg compared to subjects of weight group 51 kg and above (p value $<$ 0.05) (Table III). No significant difference was found in the prevalence of pre-diabetics among men and women (p value $>$ 0.05). Similarly, difference in prevalence of impaired fasting glucose (IFG) in the age group below 46 yrs compared to 46 yrs and above age group was non-significant. (p value $>$ 0.05) (Table III). The mean BMI and mean WC were not found to be significantly different between the IFG and the normal populations. The mean WHR was found to be significantly higher in the pre-diabetic population (1.30) compared to the non pre-diabetic population (0.9) (Table IV).

**Table I: Prevalence of IFG according to age and sex.**

| Age group | Males | Number of pre-diabetics | Per cent of pre-diabetics | Females | Number of pre-diabetics | Per cent of pre-diabetics |
|---|---|---|---|---|---|---|
| 16 – 25 | 9 | 1 | 11.11 | 6 | 1 | 16.66 |
| 26 – 35 | 7 | 1 | 14.28 | 15 | 2 | 13.33 |
| 36 – 45 | 10 | 1 | 10 | 12 | 2 | 16.66 |
| 46 – 55 | 5 | 1 | 20 | 9 | 0 | 0 |
| 56 – 65 | 9 | 1 | 11.11 | 8 | 4 | 50 |
| Above 65 | 9 | 4 | 44.44 | 1 | 0 | 0 |
| Total | 49 | 9 | 18.36 | 51 | 9 | 17.64 |

**Table II: Prevalence of IFG according to TBW (total body weight).**

| Weight in kg | Males | Number of pre-diabetics | Per cent of pre-diabetics | Females | Number of pre-diabetics | Per cent of pre-diabetics |
|---|---|---|---|---|---|---|
| 31 – 40 | 3 | 2 | 66.66 | 11 | 1 | 9.09 |
| 41 – 50 | 11 | 4 | 36.36 | 18 | 5 | 27.77 |
| 51 – 60 | 13 | 1 | 7.69 | 12 | 1 | 8.33 |
| 61 – 70 | 13 | 2 | 15.38 | 6 | 2 | 33.33 |
| Above 71 | 9 | 0 | 0 | 4 | 0 | 0 |
| Total | 49 | 9 | 18.36 | 51 | 9 | 17.64 |

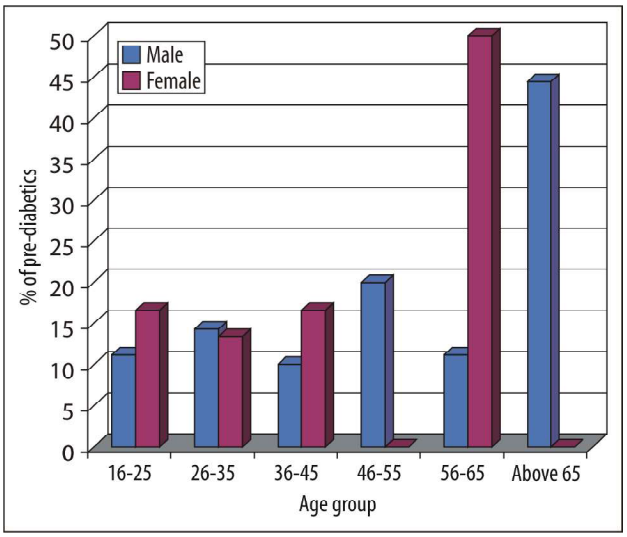


*Fig. 1: Showing percentage distribution of pre-diabetics according to age group and sex.*

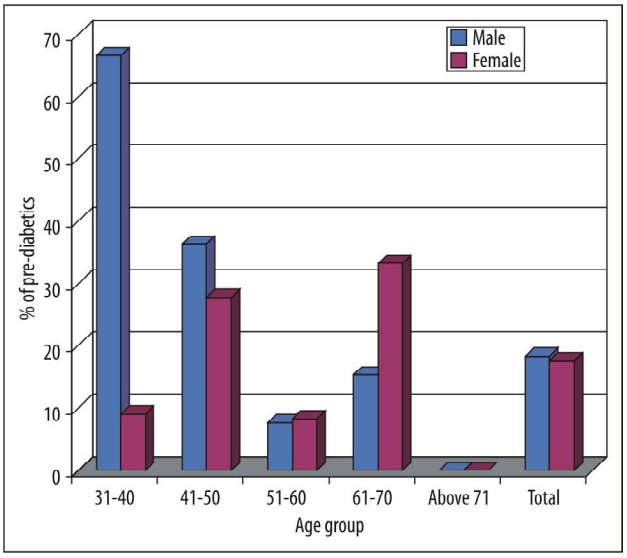


*Fig. 2: Showing percentage distributions of IFG according to weight and sex.*

**Table III: Prevalence of IFG according to various variables.**

| | | Pre-diabetic | Non pre-diabetic | p value |
|---|---|---|---|---|
| 1 | **Weight group** | | | |
| | Less than 51 kg | 12 | 31 | <0.05* |
| | 51 Kg and above | 6 | 51 | |
| 2 | **Sex** | | | >0.05 |
| | Male | 9 | 40 | |
| | Female | 9 | 42 | |
| 3 | **Age group** | | | >0.05 |
| | Less than 46 yrs | 8 | 51 | |
| | 46 yrs and above | 10 | 31 | |

**Statistically significant*

**Table 4: Prevalence of IFG according to anthropometric variables.**

| Anthropometric Parameter | Pre-diabetic | Non pre-diabetic | p value |
|---|---|---|---|
| Mean BMI | 19.2+2.8 | 20.1+2.6 | 0.1926 |
| Mean WC (in cm) | 82+1.6 | 81+1.2 | 0.1482 |
| Mean WHR | 1.30+0.08 | 0.9+0.08 | 0.0234* |

**Statistically significant*

*BMI = Body mass index; WC = Waist circumference; WHR = Waist-hip ratio*

## Discussion

The prevalence of impaired fasting glucose varies from study to study throughout the world. A study from the USA indicated that the prevalence of impaired fasting glucose in an adult population was nearly 26%[14]. This was much higher than the prevalence found in our study (18%). The Australian Diabetes Obesity and Lifestyle Study[15] reported the prevalence of impaired fasting glucose to be 16.4%, which is similar to the prevalence found in our study. As compared to our study, a lower prevalence of 11.2% was found in the Amrita Diabetes and Endocrine Population Survey (ADEPS)[16], which was a community-based cross-sectional survey done in urban areas of Ernakulam district in Kerala. A study in a developing rural area of Andhra Pradesh reported the prevalence of impaired fasting glucose (IFG) to be 15.5% which was lower as compared to our results[17]. The USA study also showed that the prevalence of impaired fasting glucose was significantly higher in males, whereas in our study we have found no significant difference in prevalence of impaired fasting glucose among males and females which is in agreement with the study of Shaw *et al*[5], who also reported that prevalence of impaired fasting glucose (IFG) was similar among males and females. In a study carried-out in a rural population of Tamil Nadu by Balagopal *et al*, the crude prevalence of IFG was 12.1%[18], which was slightly lower than the prevalence found in our study. This is probably because of the purely rural setting against semi-urban in our study. They also found a significantly higher prevalence amongst men as compared to women. The anthropometric findings in this study were quite similar to ours. The overall body mass index was within the normal range, though there was significant rise in the prevalence of impaired fasting glucose with increasing body mass index. The waist

circumference in most of the subjects was in the normal range, but waist-hip ratio was strongly correlated with rising prevalence of impaired fasting glucose, just like in our study. The findings of our study were at variance from 'The Kolkata Policeman Study'[19]. The authors had found a prevalence of impaired fasting glucose to be only 6.2%. There was a strong correlation with waist circumference and waist-hip ratio but no significant correlation with body mass index, just like in our study. The overall body mass index in the Kolkata Policeman study was much higher (mean body mass index 23.87 ± 2.83 in IFG group) than in our study (19.2 ± 2.8). This could be because the income of policemen is significantly higher than the predominantly agrarian population studied by us. The variation in the results of different studies on impaired fasting glucose is probably due to difference in cultural factors, genetic factors, lifestyle habits, ethnic variations, rural urban variations, selection of different age groups.

The notable finding in our study was the significantly higher prevalence of IFG among the low body weight population, raising the possibility of a higher prevalence of insulin deficient state than previously suspected.

The relationship between obesity and poverty is a complex one. In developing countries like India, the paradoxical finding is of underweight children and overweight adults. It has been postulated that intrauterine growth retardation leads to the acquisition of a 'thrifty gene' which causes the small babies to have rapid weight gain in early adulthood. The fat distribution has been consistently found to be concentrated around the abdomen, even though the bony frame remains smaller.

Various studies have demonstrated that diabetes in the Indian population has several unique features[20]. These include a younger age of onset (almost a decade earlier than other populations), a relatively low body mass index, higher intra-abdominal fat, high rates of insulin resistance and a high prevalence of insulin deficiency as evidenced by more patients requiring insulin therapy and at a younger age. The diabetes 'explosion' in India has been explained by the 'Thrifty Gene Hypothesis' and the 'Yajnik Paradox'[21].

The major limitation of the present study is that it was a hospital-based study and therefore may not represent the true status of the prevalence of impaired fasting glucose (IFG) in the general population. The postulated correlation of low body weight with insulin deficient state could not be confirmed in our study due to financial constraints. It would be helpful to find out the level of serum insulin in low body weight subjects showing impaired fasting glucose to predict the future development of diabetes.

To conclude, this study revealed that the prevalence of impaired fasting glucose in central India is high (18%) and is an under-diagnosed condition. 18 out of 100 individuals attending the out-patient department at Jayarogya hospital are pre-diabetics, indicating a need for greater emphasis on the early detection and timely intervention in order to effectively contain the diabetes epidemic. The traditional risk factors like total body weight and body mass index are not very good predictors for development of diabetes mellitus in the rural/semi-urban populations. In fact, low total body weight might prove to be a strong predictor of impaired fasting glucose alongwith high waist-hip ratio.

## Acknowledgement

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## I . A . C . M . NEWS

With the untiring efforts of President Dr. Madhuchanda Kar, a Monograph on Rheumatology edited by Dr. Alkendu Ghosh of Kolkata shall be released at the time of IACMCON-2011 at Patna. Also, the following four new IACM Chapters have been formed and six C.M.E. programmes have been held till date during the tenure of Dr. Kar:

1. Uttarakhand IACM Chapter was formed on 20th October, 2010, and a CME held under the Chairpersonship of Dr. Anita Sharma with Secretary Dr. S.K. Verma.
2. Tamil Nadu IACM Chapter has been formed under the Chairmanship of Dr. S.Chandrasekharan with Dr. M.A. Kabeer as Secretary on 20th March, 2011, and a CME was held.
3. Jharkhand IACM Chapter has been formed under the Chairmanship of Dr. J. Tripathy with Secretary Dr. Anil K. Virmani on 9th April, 2011, and a CME was held.
4. Tripura IACM Chapter has been formed under the Chairmanship of Dr. Krishna Basu Ray on 22nd May, 2011, and a CME was organised by Organising Secretary Dr. Pradeep Bhaumik.
5. A CME was held at Hotel Chankaya, Patna on 17th July, 2011.
6. A CME-National Update on Lymphoma was organised on 14th August, 2011 at Kolkata.

**Dr. Ashok Shiromany**
Secretary, IACM

ORIGINAL ARTICLE

JIACM 2011; 12(3) : 193-5

# Primary CNS Lymphoma in Immuno-competent Patients

*Charitesh Gupta*, Nadia Shirazi**, Sohaib Ahmad***, Sandeep K Burathoki****, SK Verma******

## Abstract

***Background and objectives:*** *Primary CNS lymphoma (PCNSL) is an extra-nodal non-Hodgkin's lymphoma originating from and confined to the central nervous system. Although the incidence is quite common in the immuno-compromised, e.g., AIDS, PCNSL in immuno-competent patients is rare and is associated with unique diagnostic, prognostic, and therapeutic issues. This retrospective study was conducted to investigate the clinical and radiological manifestations of this rare clinical entity in immuno-competent patients.*

***Material and methods:*** *Of the 92 patients diagnosed with brain tumours during the last 30 months, the demographic profile, clinical data, and radiological findings of 5 cases with pathologically confirmed PCNSL were studied. All patients tested negative for HIV and there was no history of immunosuppressive drugs or any other chronic illness.*

***Observations:*** *The median age of the cases with PCSNL was 50 years and females outnumbered the males. All five patients presented initially with features of intracranial mass lesion; bleeding occurred in the frontal lobe lesion in one patient. No ocular or systemic involvement was found. Pre-operative clinico-radiological diagnosis of gliomas or metastasis was suspected. However, after surgical resection, non-Hodgkin's lymphoma was confirmed by histopathology and subsequent immuno-histochemistry.*

***Conclusion:*** *The increasing incidence of PCNSL in immuno-competent patients with atypical clinico-radiological presentation leads to delayed diagnosis and treatment contrary to the peculiar presentation amongst the immuno-deficient. Early recognition and stereotactic biopsy in PCSNL may avoid surgery and prolong the survival of quite a few patients.*

***Keywords:*** *Primary CNS lymphoma, PCNSL, immuno-competent.*

## Introduction

Primary CNS lymphoma (PCNSL) was first described by Bailey in 1929 as "perithelial sarcoma" of the CNS until its lymphoid lineage was clarified. In the absence of systemic involvement, it is a rare malignant neoplasm of lymphocytic origin involving the brain, lepto-meninges, eyes, or spinal cord without evidence of systemic disease. According to the World Health Organization classification, most PCNSLs are diffuse large B-cell lymphomas (DLBCLs)[1], whereas T-cell, low-grade, anaplastic, and Hodgkin's lymphomas are rarely encountered[2].

Its incidence has increased during the last three decades in immune-compromised patients, especially those with acquired immunodeficiency syndrome, who get affected at a younger age as compared to their immuno-competent counterparts. The reported incidence of PCNSL ranges from 1 to 2.7% of all malignant diseases of the CNS. The greatest incidence is in the fourth through sixth decades with a mean age of 55 years[2, 3]. There is a male preponderance with a sex ratio of 2:1[4]. The lesions are usually solitary; however, a high incidence of multifocal (about 50%) or diffuse involvement has been emphasised in some series[1,2].

The differential diagnosis of PCNSL includes gliomas, metastatic tumours, demyelinating disorders, subacute infarcts, and space-occupying lesions due to an infectious aetiology. Brain biopsy with or without immuno-histochemistry, is confirmatory. The natural history of this disorder differs between immuno-competent and immuno-deficient patients with the overall survival being much better for patients without AIDS (18.9 vs 2.6 months)[5,6].

Here, we share our experience of PCNSL over the last 30 months at our medical college hospital in the north Indian state of Uttarakhand.

## Method

Ninety-two cases of brain tumours diagnosed during 30 months (January 2007 to June 2009) were retrospectively

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studied from the hospital records of which five (5.4%) were diagnosed as PCNSL. All the patients tested negative for HIV and there was no history of immunosuppressive drugs or any other chronic illness in any of the patients. Clinical data, CT/MRI imaging scans, intra-operative frozen preparation reports and surgical biopsy specimens were reviewed with special emphasis on immuno-histochemical B-cell markers namely LCA and CD20. Occult systemic disease had been excluded by staging with bone marrow biopsy and CT scans of the chest, abdomen, and pelvis.

## Results

Four of our patients were females; median age at presentation was 51 years (range 35 – 61) and the duration of symptoms was 2 to 5 months. These patients presented with symptoms and signs suggestive of intracranial mass lesion; history of generalised seizures was elicited in one patient. A patient with frontal lobe lesion presented as an emergency case of bleeding within the tumour (Figure 1). Periventricular white matter was the predominant site of PCSNL (n = 3) (Figures 2 and 3) and cerebellum was involved in one case. All lesions were solitary, well defined and enhanced homogeneously on imaging with contrast.

All patients underwent gross surgical decompression; intraoperative frozen sections were interpreted as high-grade glioma or round cell malignancy. The surgical specimens sent for histo-pathology and immuno-histochemistry were confirmed as low-to-high-grade Non-Hodgkin's lymphoma (microphotographs 1 and 2). Methotrexate-based chemotherapy was given to all of them alongwith radiotherapy. The mean follow-up as per the hospital records was 8 months (range 3-12).

## Discussion

Incidence of PCNSL in immuno-competent patients is approximately 51 per 10,000,000 per year[1]. The annual incidence from our hospital is 2% which is consistent with the available literature. The peculiarity with our experience is the occurrence of this entity in persons with intact immunity, though it is typically associated with the immuno-compromised. It might be because of relatively few patients diagnosed with HIV infection attending our hospital, as it was not a recognised anti-retroviral therapy dispensing centre till then.

The most typical presentation of PCNSL in an immuno-competent patient is progressive focal symptoms indicative of a mass lesion, seizures, or nonspecific mental status changes. We encountered almost similar presentations which were subsequently followed by radiological imaging. Primary lymphomas of brain are commonly located in the basal ganglia, thalamus, corpus callosum, and periventricular white matter. The supratentorial structures in contact with ependyma, meninges or both, are involved in 75 – 85% of patients while the cerebellum is a less favourable site[7]. The lesions may be solitary; however, a high incidence of multifocal (up to 50%) or diffuse involvement has been reported by Lukin *et al*[1,2]. Except for one patient with a cerebellar lesion, the other four patients in our series had a periventricular mass; but notably, all lesions were solitary.

Following administration of either iodinated contrast for CT or gadolinium for MRI, almost all PCNSLs enhance homogeneously because of hyper-cellularity and lesser degree of perilesional oedema[8]. PCNSLs are assumed to be diffusely infiltrative at the time of presentation. Peripheral rim enhancement with central necrosis, typically seen in immuno-compromised patients, is seen in three of our patients[8]. Moreover, haemorrhage in tumour, (as yet unreported, to the best of our knowledge), was seen in one patient. These imaging findings are unusual and could be mistaken as high grade glioma, especially in an immuno-competent patient.

Although intense enhancement and minimal perilesional oedema raised the suspicion of lymphoma in two cases, empirical pre-operative corticosteroid therapy did not result in reduction of the lesion size on repeat radiological scans. Hochberg and co-workers found corticosteroids having a cytotoxic effect responsible for transient remission in 80% of patients[7, 9]. Thus, all lesions were not morphologically suspected before surgical resection as none of radiological findings nor therapeutic response with steroids was suggestive of a possible lymphomatous pathology. De Angelis recommended withholding corticosteroids prior to biopsy in a suspected case of PCNSL as it may eliminate the possibility of establishing diagnosis with certainty[10]. It may be difficult to distinguish high grade glioma from lymphoma on frozen sections having artifacts – as happened in all our cases[11]. Biopsy and histo-pathological analysis is indispensible for establishing the diagnosis. The diagnosis of PCNSL was

deferred in our cases till the surgical specimens were analysed.

The optimal treatment for primary CNS lymphoma continues to be debated and is the subject of ongoing clinical trials. Resection provides no therapeutic benefit because of the depth and diffuse nature of the tumour and should be reserved for the rare patient with neurological deterioration due to brain herniation[12]. Emergency therapeutic surgery was performed in the case with tumour bleed; however, lack of clinico-radiological suspicion in the rest of our cases led us to exercise the surgical option for establishing a morphological diagnosis.

Whole-brain radiation therapy alone is insufficient for durable tumour control and is associated with a high-risk of neurotoxicity in patients over 60 years of age. The initial response to radiation therapy in immuno-competent patients is excellent, often resulting in complete resolution of radiographic abnormalities. Nevertheless, the duration of response is short, and median survival duration with radiation therapy alone averages only 18 months. Relapse in patients with parenchymal disease is usually within the brain, though leptomeningeal, vitreous and, rarely, systemic recurrences are reported[10]. High-dose methotrexate regimen together with radiotherapy has shown promising results and better survival in our patients although the patients need to be followed-up for a longer period to validate the outcomes from our centre.

## Conclusion

One should consider PCNSL in the differential diagnosis of a solitary circumscribed intracranial lesion irrespective of the patient's age, sex, site, immune status and clinical presentation. Such clinico-radiological presentations in the immuno-competent cases should prompt the neurosurgeon to consider a stereotactic biopsy for confirmation and early chemo-radiation for remission.

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ORIGINAL ARTICLE

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# Correlation of Tumour Necrosis Factor-α and Interleukin-6 with Anthropometric Indices of Obesity and Parameters of Insulin Resistance in Healthy North Indian Population

*Niti Agarwal*, Anubhuti Chitrika**, J Bhattacharjee**, SK Jain**

## Introduction

White adipose tissue (WAT) is now seen as a highly dynamic organ, being involved in a wide range of physiological and metabolic processes far beyond the paradigm of fuel storage. This changed perspective has occurred through the recognition that WAT is an endocrine organ, which secretes several major hormones including leptin and adiponectin together with a diverse range of other protein signals and factors collectively termed as adipokines. The group includes cytokines like tumour necrosis factor-alpha (TNF-α), Interleukins like IL-6, IL-8, IL-10, acute phase proteins, e.g., PAI-1, haptoglobin, CRP, serum amyloid A and inflammation related proteins like adiponectin, nerve growth factor (NGF) and monocyte chemoattractant protein-1 (MCP-1)[1].

Previous reports suggest a positive association between components of the insulin resistance syndrome and the acute phase reactants including C-reactive protein, von Willibrandt's factor, fibrinogen, etc[2,3]. CRP is the most extensively studied inflammatory marker in prospective setting. The production of CRP by the liver is under the control of cytokines, which are elevated in acute infection states. Cytokines mainly IL-1, IL-6 and TNF-α exert major stimulatory effects on hepatic synthesis of acute phase proteins. IL-6 and TNF-α are soluble polypeptides acting as important hormonal regulators in immunoregulation, haematopoiesis and the inflammatory cascade[4,5,6].

Since pathological conditions association with insulin resistance syndrome were associated with high TNF-α, it was suggested that it might play an important role in the development of insulin resistance. It has since been demonstrated by many researchers that serum levels of TNF-α are elevated in obesity[7-9] and that the levels fell after weight loss[9]. In contrast to this finding, there are reports that have not been able to demonstrate any relation between circulating TNF-α and obesity, insulin resistance, or impaired glucose tolerance[10-13]. Since the cytokines are difficult to measure, people have tried to establish association between insulin resistance/obesity and TNF-receptors and TNF-α mRNA. These studies have produced equally conflicting results with some showing increased expression[14] while others were not able to provide any such evidence[15].

Role of IL-6 in cardiovascular diseases is also well studied. There is a positive correlation between IL-6 and risk of future myocardial infarction[16], unstable angina[17] and death[18]. A report from the Rural Health Study has shown that elevated concentration of IL-6 predicts total cardiovascular mortality over a 5-year follow-up, the association being independent of vascular disease, smoking, and traditional risk factors[18].

It has been demonstrated in various studies that circulating IL-6 levels are elevated in insulin resistant states such as obesity[19], impaired glucose tolerance and type 2 diabetes[20,21]. Weight reduction by diet and exercise reduce plasma IL-6 levels[22]. Elevated IL 6 levels have been demonstrated to be associated with dyslipidaemia by some researchers[23]. In contrast to some of the existing evidence, few studies have found that IL-6 did not alter the effects of insulin on glucose homoeostasis[24] and that no significant difference is seen in plasma TNF-α or IL-6 levels between obese and non-obese subjects[25].

In the present study, we have studied the correlation of TNF-α and IL-6, with anthropometric indices of obesity, insulin resistance, and dyslipidaemia in healthy North Indian population.

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## Material and methods

The study was conducted at a tertiary care government hospital at Delhi, India. 101 healthy individuals (50 males and 51 females) (age group 19 – 60 years) were enrolled after obtaining their written consent. All volunteers went through a detailed medical history and examination to ensure that they did not suffer from any medical illness – acute or chronic – at the time of study. Pregnant females, current smokers, chronic alcoholics, subjects with past or present malignancy, gout, endocrine disease, rheumatoid arthritis, osteoarthritis, personal or family history (in first degree relatives) of diabetes mellitus or hypertension, history of chronic hepatitis, chronic renal failure, coronary artery disease, polycystic ovarian disease, any history of febrile illness or any major illness during previous 30 days, history of using oral contraceptives or other drugs affecting the metabolic profile (beta-blockers/ antihypertensives/ adrenergic drugs/steroids/other hormones), or any chronic inflammatory diseases and any evidence of infection were excluded from the study.

Anthropometric assessment included measurement of height, weight, waist circumference, hip circumference and skin fold thickness (subscapular, suprailiac, biceps, and triceps). All indices readings were taken in triplicate and the mean of three readings was used for analysis. Height was measured to the nearest 1 mm. Weight was measured to the nearest 1 kg using Beurer weighing machine (MS 01). The body mass index (BMI) was calculated as kg/ height$^2$ (in metres). Waist circumference was measured midway between the iliac crest and lower-most margins of the ribs, and the hip girth was measured at the maximum circumference of buttocks with the subject wearing minimum clothes with feet placed together. Waist hip ratio was calculated using the formula: circumference at waist/circumference at hip.

Triceps, biceps, suprailiac, and subscapular skinfold thickness were measured using skinfold calipers. All skinfolds were measured to the nearest 0.1 mm. All readings were taken on the right-side of the body with the subject standing in a relaxed condition. A mean of the three readings was recorded. Percentage body fat (%BF) was calculated using the standard equation of Durnen and Womersely.

All subjects underwent liver function tests, kidney function tests including uric acid, haemogram, detailed serum lipid profile (fasting) and 75 gm OGTT which included measurement of fasting glucose/2-hour post-prandial glucose and fasting insulin/2-hour post-prandial insulin. Glucose and lipids were measured by autoanalyser. Principle of glucose measurement was the glucose oxidase method. Total cholesterol, HDL-C and triglycerides were measured directly and LDL-C and VLDL-C calculated indirectly using Friedewald formulae[82]. Cases found to be diabetic were excluded from the subsequent study. All subjects underwent measurement of IL-6 and TNF-$\alpha$.

Two ml of venous blood sample was collected in a plain vial under sterile conditions. The samples in plain vials were allowed to clot at room temperature. The clotted blood sample was then centrifuged for 5 minutes. The serum was then stored at –20° C till serum insulin was batch analysed.

The serum insulin was estimated by Sandwich ELISA method. Read on the Vmax ELISA Reader and the absorbance of each well recorded at 450 nm (versus 650 nm) and 490 nm (versus 650 nm) using polychromatic model. The values of more than 25 IU/L was taken as hyperinsulinaemia.

TNF-$\alpha$ was measured using diaclone (Sandwich ELISA) commercial kit for research use only. The absorbance was read on a spectrophotometer using 450 nm as the primary wavelength with 620 nm reference wavelength. IL-6 was measured using DIACLONE (Sandwich ELISA) kit for research use only. The absorbance was measured on a spectrophotometer using 450 nm as primary wavelength with 620 nm as reference wavelength.

21 subjects selected randomly from the study population underwent insulin suppression test by Modified Horano Method to study the metabolic clearance rate (MCR) of glucose and insulin clearance rate (ICR).

Statistical analysis was performed using Microsoft excel and SPSS softwares.

## Results

BMI did not correlate significantly with either of the inflammatory markers studied in the total study group or

in either sexes individually. The inflammatory markers did not show any trend with BMI quartiles and the median values of TNF and IL-6 in the total study population. BMI quartiles in females showed a rising trend with TNF but no such trend was observed with IL-6. No such trend was seen in the males for TNF or IL-6 (Fig. 1).

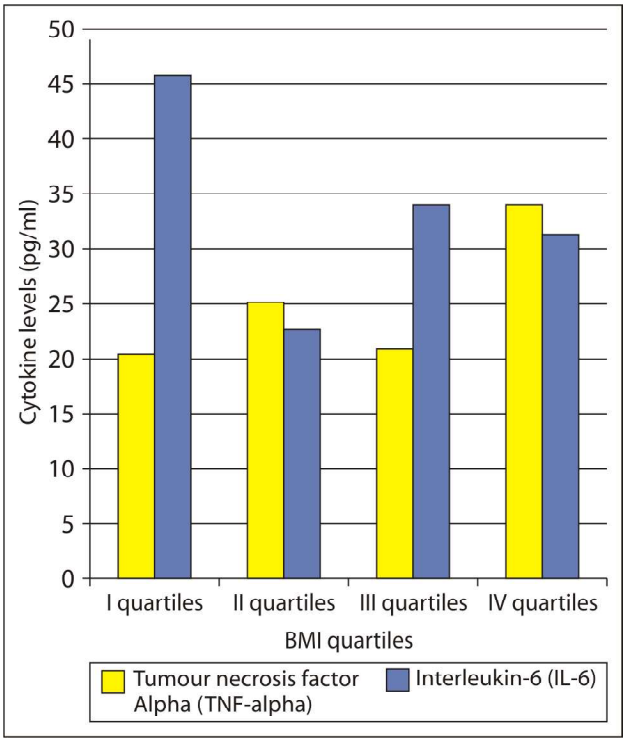


***Fig. 1:*** *BMI quartiles and mean cytokine levels in females.*

The study population was divided into two groups of obese and non-obese based on the modified WHO criteria of the Asia Pacific region[26], obesity being defined as BMI ≥ 25 kg/m$^2$, and the median levels of TNF and IL-6 compared. The TNF level in the obese was higher than those in non obese (11.25 pg/ml vs. 9.375 pg/ml) (Fig. 2). However, the levels of IL-6 were higher in the non-obese group.

No significant correlation of WHR with any of the inflammatory markers was found in the females, males, or the total study population. The WHR quartiles however showed a rising trend of TNF and a declining trend with IL-6 in females. No such trend was observed with mean levels of cytokines in males (Fig. 3).

WC was not found to be significantly correlated with either TNF or IL-6 in either groups. Median values of TNF were studied with obesity using waist circumference as criteria (males > 94 cm and females > 80 cm) and a rising trend

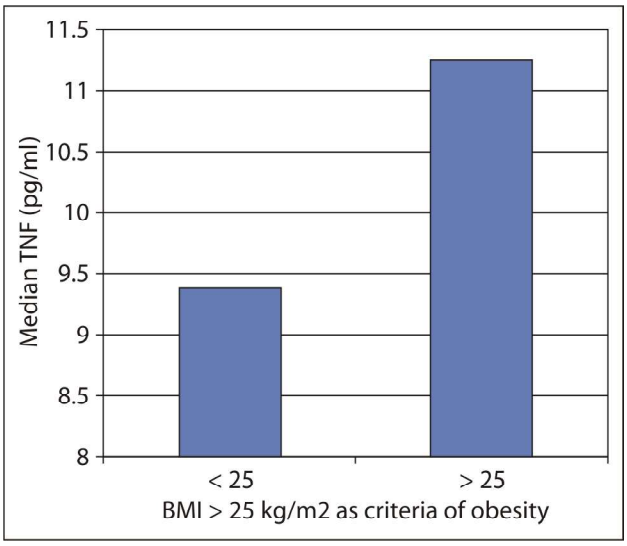


***Fig. 2:*** *Median TNF with obesity (BMI).*

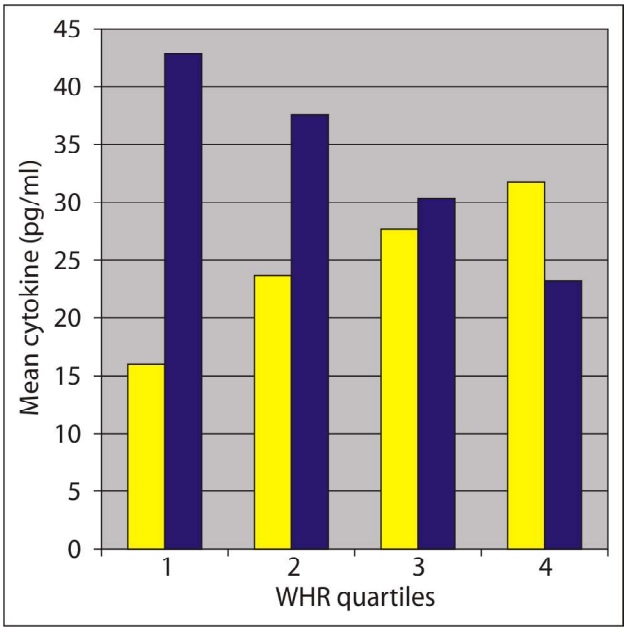


***Fig. 3:*** *WHR quartiles and mean cytokines in females.*

was observed with obesity defined by this criterion (Fig. 4 and 5). However, median values of IL-6 showed a declining trend with obesity defined by waist circumference. Median values of IL-6 in non-obese males was 37.5 while in obese males was 11.5 pg/ml. In females, IL-6 in non-obese was 57.75 and in obese was 20.75 pg/ml.

None of the parameters were significantly correlated with HC. TNF and IL-6 were not found to be significantly associated with PBF in either of the groups. TLC

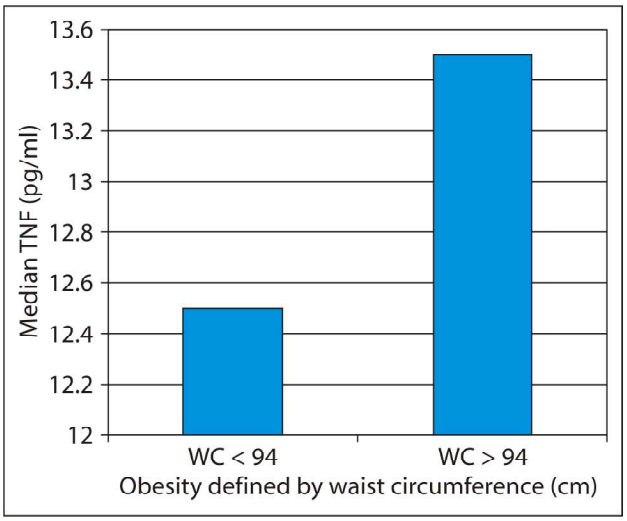


***Fig. 4:*** *Median TNF with obesity defined by WC (males).*

| | | |
|---|---|---|
| Ratio (HDL/LDL) | .482 | .200 |
| .969 | .454 | .448 |
| .015 | | |

TNF-α correlated significantly with fasting insulin, fasting GIR (negatively) and HOMA-IR in the total study population with p-value of < .05 in each. None of the other parameters correlated significantly with TNF-α. In males, it correlated significantly negatively with diastolic blood pressure only. In females, only fasting blood sugar was found to be significantly correlated with TNF-α with a p-value of < .05. TNF levels increase with increasing insulin quartiles and showed a rising trend with increasing fasting blood sugar (Fig. 6).

Arbitrarily taking HOMA-IR of 4.0 as cut-off, the median

significantly correlated with PBF only in the males.

**Results**

| | **TNF** | | | **IL-6** | | |
|---|---|---|---|---|---|---|
| **p-value** | **Total** | **Males** | **Females** | **Total** | **Males** | **Females** |
| BMI | .761 | .056 | .266 | .189 | .418 | .340 |
| WHR | .389 | .066 | .822 | .073 | .116 | .177 |
| PBF | .508 | .691 | .252 | .114 | .387 | .110 |
| WC | .884 | .122 | .168 | .074 | .217 | .222 |
| HC | .363 | .296 | .088 | .234 | .385 | .573 |
| Fasting insulin | .031 | .113 | .141 | .993 | .959 | .954 |
| Post-prandial insulin | .078 | .822 | .046 | .253 | .182 | .961 |
| FBS | .975 | .598 | .647 | .152 | .367 | .249 |
| PPBS | .648 | .963 | .662 | .069 | .189 | .269 |
| Fasting GIR | .025 | .118 | .111 | .986 | .558 | .501 |
| Post-prandial GIR | .058 | .400 | .101 | .036 | .015 | .721 |
| MCR | .933 | .067 | .778 | .721 | .863 | .465 |
| ICR | .941 | .140 | .665 | .839 | .682 | .271 |
| Homa-IR | .033 | .176 | .105 | .784 | .801 | .909 |
| SBP | .998 | .329 | .439 | 1.000 | .432 | .174 |
| DBP | .719 | .019 | .093 | .403 | .354 | .902 |
| Total cholesterol | .627 | .268 | .214 | .571 | .555 | .779 |
| HDL cholesterol | .078 | .779 | .056 | .327 | .929 | .065 |
| LDL cholesterol | .771 | .184 | .260 | .813 | .242 | .332 |
| Triglycerides | .884 | .700 | .671 | .583 | .389 | .032 |

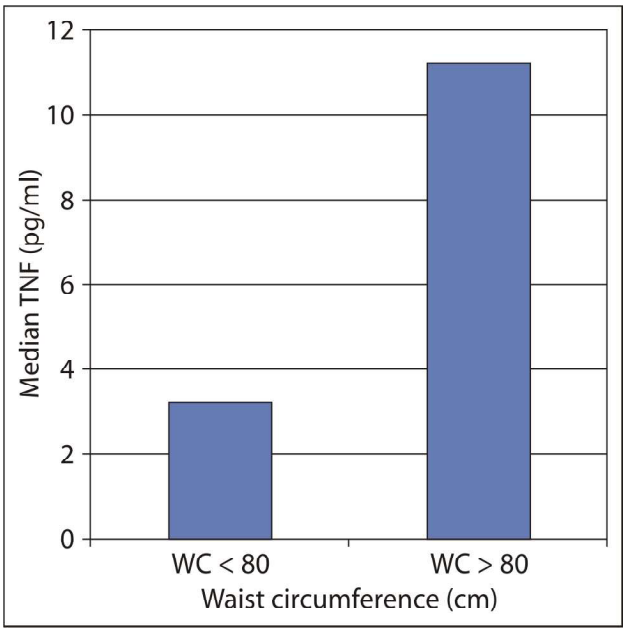


***Fig. 5:*** *Median TNF with obesity (WC) in females.*

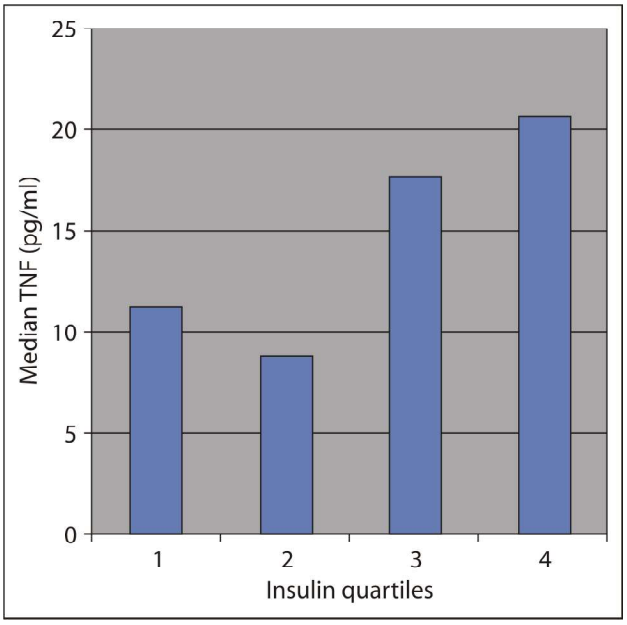


***Fig. 6:*** *Median TNF in fasting insulin quartiles.*

values of TNF and IL-6 showed that TNF-α levels are higher in subset with greater insulin resistance in the total population and females. IL-6 levels were also found to be higher in subset with higher insulin resistance. TNF-α levels are higher in patients with impaired glucose tolerance (Fig. 7, 8, 9). Similarly median TNF levels showed rising trend with IGT in all the subgroups considered (Fig. 10, 11, 12).

TNF-α did not correlate significantly with any of the lipid

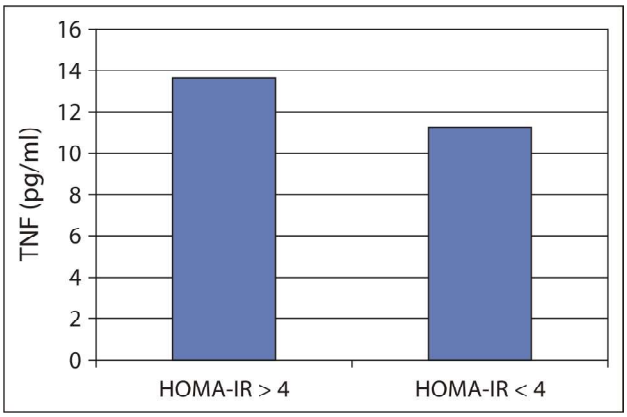


***Fig. 7:*** *Median TNF HOMA-IR in total population.*

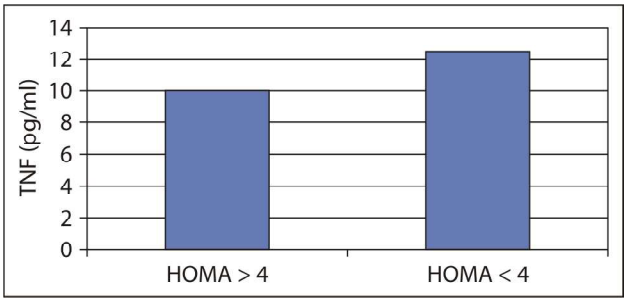


***Fig. 8:*** *Median TNF with HOMA in males.*

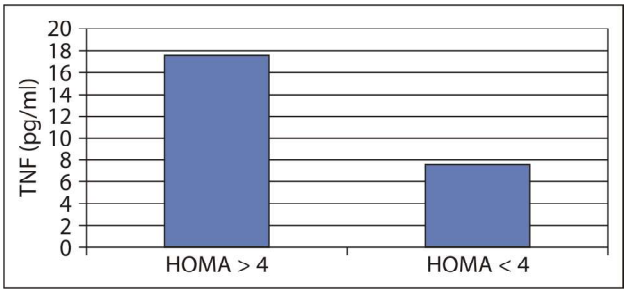


***Fig. 9:*** *Median TNF with HOMA in females.*

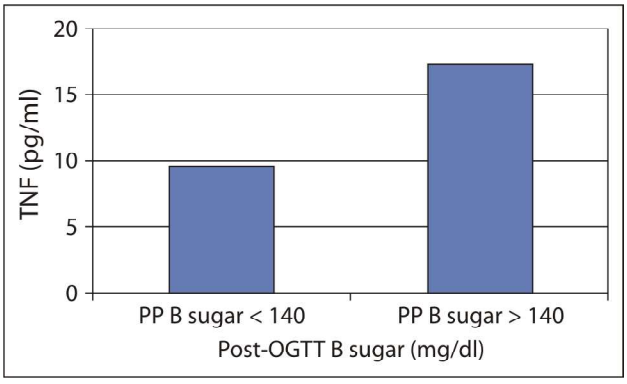


***Fig. 10:*** *Median TNF with B sugar in total study population.*

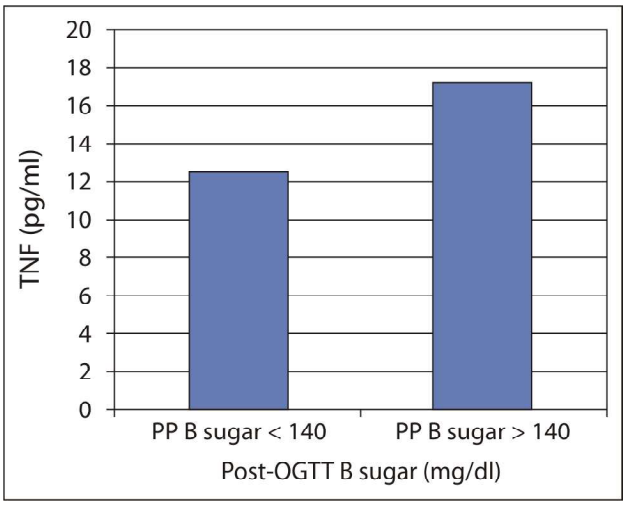


***Fig. 11:*** *Median TNF with B sugar in males.*

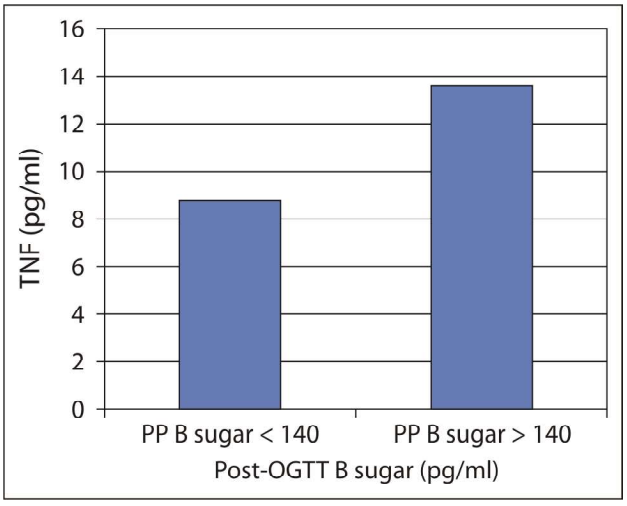


***Fig. 12:*** *Median TNF with B sugar in females.*

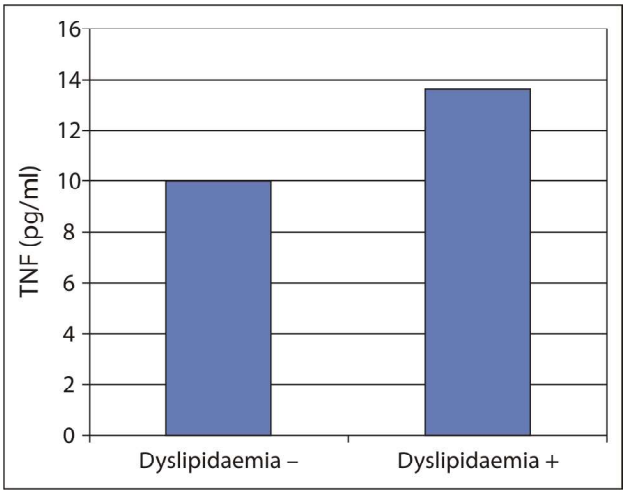


***Fig. 13:*** *Median TNF with dyslipidaemia.*

parameters in either of the groups. TNF levels show a rising trend when dyslipidaemia is defined as triglycerides as cut-off. However, no such expected trend is observed when HDL-C cut-off values are used (Fig. 13).

IL-6 correlated significantly with PPGIR in the total study population and males only. None of the other parameters correlated significantly with IL-6 in any of the study groups. One important thing which is noted is that although not significantly correlated, the correlations with fasting and postprandial insulin and sugar and HOMA-IR are negative.

IL-6 correlated significantly with triglycerides and HDL/LDL ratio in females. In males and the total study population none of the lipid parameters were found to be significantly correlated with IL-6. With dyslipidaemia, IL-6 surprisingly showed a declining trend.

## Discussion

### Obesity

In our study conducted in healthy north Indian population, we found no significant correlation between serum levels of TNF-α or IL-6 with any of the anthropometric measures of obesity. However, when we studied the mean TNF-α levels with increasing quartiles of BMI and WHR, we found a rising trend. No trend could be demonstrated for IL-6. Similar to our findings, Carvalho *et al* found no differences related to the peripheral expression of the cytokines were found among the eutrophic, euthrophic with high percentage body fat and overweight groups[27].

Our findings are consistent with the findings of Pincelli *et al* and Kern *et al*, who also found no correlation between serum TNF-α values and obesity[10,11]. Our findings are in accordance with the study conducted by Tseigos *et al* who also found no significant difference in plasma IL-6 levels between obese and non-obese subjects[25]. Choi *et al* found a negative correlation (though insignificant) between IL-6 and obesity[12].

In contrast to our findings, there are studies, which have demonstrated a significant positive correlation between IL-6 and obesity[19,22,29]. In the Whitehall II study, which followed-up subjects for 11 years, the mean increases in CRP and IL-6 were 0.08 (95% CI, 0.07 – 0.09) mg/litre and 0.04 (95% CI, 0.03 – 0.05) pg/ml per 1 kg increase in body

weight during follow-up[30]. In Asian Indians, Yudkin *et al* found a ten-fold higher levels of IL-6 in slum dwellers despite their lower waist hip ratio, when compared with villagers. However, they also found a three times higher level of IL-6 in middle class subjects (who had a higher waist hip ratio), as compared with villagers[31]. Elevated plasma leptin, hsCRP, IL-6, and FFA concentrations are associated with obesity and not necessarily with the type 2 diabetic state[32].

But studies by Zahorska Markiewicz *et al*, Laimer *et al*, Yudkin *et al* and Berberoglu, observed elevated serum TNF-α in obesity[7,8]. Dandona *et al* found that obesity is associated with increased plasma TNF-α concentrations in women and the levels fall with weight loss[9]. Esmaillzadeh *et al* found those with the high TG and waist circumference phenotype had higher circulating levels of CRP, TNF-α, IL-6 and E-selectin compared with those with normal WC and normal serum TG levels and these correlations persisted despite adjustment for body mass index attenuated the associations, but all were still statistically significant[33].

Though ELISA method for measurement was considered superior, some other authors have also reported inconsistent resuts with IL-6 and CRP being significantly correlated with BMI ($r = 0.42$ and $r = 0.55$), but MCP-1 and TNF-α were not ($r = -0.07$ and $r = 0.06$)[34].

**Insulin resistance**

Our study did not demonstrate any significant correlation between circulating TNF-α or IL6 and the markers of insulin resistance studied (FBG, PPBG, GIR, HOMA-IR). Median TNF levels showed a rising trend when studied in increasing quartiles of fasting serum insulin. Bluher *et al* and Muller *et al* found that plasma levels of TNF-α are not elevated in insulin resistant obese individuals with impaired glucose tolerance[13,35]. Hube *et al* also did not find significant difference in the levels of TNF-α between obese individuals with and without impaired glucose tolerance/ NIDDM[36]. In study conducted by Choi *et al* in elderly, non-smoking and non-diabetic Korean women, serum proinflammatory cytokine TNF-α and IL-6 concentrations were neither increased in subjects with IGT nor closely correlated with the components of the metabolic syndrome[21].

Our findings are in contrast with studies which have demonstrated a significant positive correlation between IL-6 and insulin resistant states[20,37].

In our study when the median values of subjects with post-OGTT blood sugar > 140 and those with normal GTT were compared, it was observed that subjects with IGT had a higher median TNF. The findings are in accordance with those of Tsigos *et al* who showed that, although no significant difference in plasma TNF-α levels exists between obese and non-obese subjects overall. TNF-α levels were significantly elevated in obese subjects with 2 h glucose level of more than 140 mg/dl compared with other obese and non-obese controls[25].

**Lipids**

We did not find any significant correlation between lipid parameters and TNF or IL-6, apart from significant correlation between IL-6 and triglycerides in females. Using the cut-off values proposed by NCEP to define dyslipidaemia in metabolic syndrome, we could not demonstrate any positive trend. In fact, surprisingly we observed a negative trend between dyslipidaemia and IL-6 similar to the findings of Choi *et al*[12]. In their study among adolescents, Carvalho *et al* found significant correlation between IL6 and triglycerides[27].

TNF-α has limited half-life and is difficult to measure in large scale epidemiological studies. Since the action of TNF-α and IL-6 may be autocrine or paracrine, it is possible that circulating levels of measured TNF-α may not reflect the true biological activity of the cytokines. Also, the bioavailability and/or action of circulating TNF in obese might depend upon the circulating TNF receptors[38,39].

Although, IL-6 has been described as a pro-inflammatory cytokine, there is evidence that suggests a role of IL-6 in counteracting the manifestations of the inflammatory response. IL-6 has been shown to increase insulin resistance and enhance lipogenesis, while at the same time there are studies which demonstrate its role in promoting lipolysis[40-42].

Also, the dispersion of the TNF and IL-6 levels in our study was very wide. The TNF levels varied from undetectable levels to 111.25 pg/ml (excluding one value of 225 pg/ml) and IL-6 ranging from 1.75 pg/ml to 148 pg/ml. The

levels were not significantly different in the two sexes. The levels of TNF and IL-6 in various studies have not been consistent. They have been found to be high (55.3 ± 14.28 pg/ml in controls and 42.2 ± 12.81 pg/ml in females)[11] to low (2.10 ± .19 pg/ml and 1.65 ± .18 pg/ml in obese and controls)[43], (.25 pg/ml in men and .02 pg/ml in women)[15] and even undetectable levels. From our study, we could not establish any significant role of TNF-α or IL-6 in relation to obesity or insulin resistance.

From the observations and results of our study, we conclude that there is no significant role of IL-6 in obesity and insulin resistance. And these parameters have no clinical utililty in north Indian population.

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REVIEW ARTICLE

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# Natural Phytoestrogens in Health and Diseases

*Nalini Mishra*, VN Mishra**, Devanshi****

## Abstract

*'Lifestyle modification' and 'healthy diet' are buzz words of modern medicine. Natural phytoestrogens are photochemical substances that are found in foods of plant origin and possess a wide range of biochemical benefits which have been found to contribute favourably in different health-related problems. Consumption of phytoestrogen rich diet as seen in traditional Asiatic societies is protective against many diseases such as cancerous illnesses of breast, prostate, and colon, cardiovascular diseases, dyslipidaemia, post-menopausal symptoms and osteoporosis. These compounds appear to be biomarkers of the so-called 'healthy diet'.*

*Key words: Phytoestrogen, soy proteins, healthy diet.*

## What are phytoestrogens?

Plants and animal kingdom share a common evolutionary ancestry; hence, many of the mechanisms at the molecular level remain similar in plants and human beings. Natural phytoestrogens are photochemical substances that are found in foods of plant origin and possess a wide range of biochemical benefits which have been found to contribute favourably in different health-related problems. Phytoestrogens exert an oestrogenic and antioestrogenic effect due to their similarity in structure to oestrogen, and are non-steroidal in nature. There are three main classes of phytoestrogens, namely: isoflavones, lignans and coumestans. The most important of these is Isoflavones which are natural non-steroidal molecules with structural similarity to 17-beta oestradiol and selective oestrogen receptor modulators (SERM). Isoflavones have a phenolic ring which is essential for binding to oestrogen receptor. In addition to this, they have lower affinity for serum protein and hence better bioavailability at receptor site.

Isoflavones have emerged as the most interesting class of phytoestrogens as they have an extensive range of beneficial effects on the human body[1,2]. Epidemiological studies have revealed that average intake of isoflavones in Japanese population is about 50 mg/day[3]; rest of Asia has an average consumption of 25 to 45 mg/day; while the western consumption is less than 5 mg/day[4]. Consumption of phytogen rich diet as seen in traditional Asiatic societies is protective against many diseases such as cancerous illnesses of breast, prostate, and colon, cardiovascular diseases, dyslipidaemia, post-menopausal symptoms, menstrual irregularities, and osteoporosis. These compounds appear to be biomarkers of the so-called 'healthy diet'.

## Dietary sources of phytoestrogens

Phytoestrogens consist of more then 20 compounds and could be found in over 300 plants[5, 6]. Important sources of various classes of phytoestrogens are as follows:

(A) **Isoflavones:** Soya bean and soy products are richest source of isoflavones. Soybean contains highest concentration of isoflavones, i.e., up to 300 mg per 100 gm. Common isoflavone fractions present in soya are genistein (4', 5, 7-trihydroxy-isoflavon) which constitutes 50% of soya isoflavone, diadzein (4', 7-dihydroxy isoflavone) 40% along with their beta-glycosides – genistein, diadzein; and glycetein (7, 4'-dihydro-6-methoxyisoflavone) remaining 5 to10%. Wheat, Bengal gram, moong beans, chick peas, cherries, parsley, apples, alfalfa and red clover are other sources of isoflavones in Indian diet.

(B) **Lignans:** are found in oil seeds such as flax seeds (linseed), rye, millet, sesame and sunflower seeds besides legumes, pulses, and whole grains.

(C) **Coumestans:** Sunflower seeds, alfalfa and clover are rich sources besides bean sprouts. Soya sprout is a potent source of coumestans.

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## Metabolism

Isoflavones are found in nature as glycones or beta-glycoside (unconjugated form). Malonyl and acetyl glycosides are also found in nature but they are heat labile and are easily converted into more stable beta-glycosides. Naturally found glycosides do not have active oestrogenic potential but are readily hydrolysed to oestrogenically active glycones during cooking or as a result of action of intestinal microflora. Biological activity of individual glycosides is not known but diadzein metabolite equol is known to exert significant biological effect and greater antioxidant activity than other phytoestrogens and is found in highest concentration in blood and urine of humans.

Linseed is a rich source of lignans. On fermentation of ligan by intestinal microflora there is production of two types of diphenols – namely, enterodiol and enterolactone – which are structurally similar to oestradiol[7]. After absorption, these products are excreted in urine. Courestrol has been studied least for its biological activity and metabolism. Phytoestrogen level could be measured in urine, plasma, faeces, saliva, semen, bile and breast milk but for various reasons the concentration of metabolites differ widely even after administration of controlled quantities of food supplement.

## Mechanism of action

Because of molecular resemblance of isoflavones to natural oestrogen, these are known to possess both oestrogenic and antioestrogenic properties. *In vivo* assays have shown glycetein to have maximum oestrogenic activity followed by genistein and diadzein. There are two types of oestrogen receptors in human body – ER-alpha (predominantly found in breast and uterine tissue) and ER-beta (distributed in bone, brain, vascular endothelium, and bladder). The binding affinity of isoflavones to beta receptor is better than alpha receptor. Because of this agonistic action they provide cardio-protective, bone strengthening effect and help in relieving symptoms of menopause. Besides their natural 'selective oestrogen receptor modulator' effect they are known to possess other mechanisms to influence body functions which are as follows:

**Cancer enzyme inhibitor:** Genistein has been found to possess anticarcinogenic potential for carcinoma breast, prostatic carcinoma[8, 9] and endometrial carcinoma. Possible anticarcinogenic mechanisms include: Inhibition of angiogenesis, inhibition of enzymes DNA topoisomerase I and II and tyrosine kinase[10], and possible upgradation of apoptosis. Its weak oestrogenic activity might be helpful in its activity against prostatic cancer, beside inhibition of NF (Nuclear Factor) – kappa-beta in prostate cancer cells, and by increasing concentration of TGF-beta (Transforming Growth Factor)[11].

**Antioxidant property:** Genistein may increase production of super oxide dismutase (SOD) – a powerful antioxidant that quenches superoxide radicals[12].

**Immune enhancer:** Animal studies have shown that diadzein increases the activity of T-lymphocytes and macrophages.

## Role of isoflavones in various diseases

### In cardiovascular diseases

Epidemiological studies suggest that mortality due to cardiovascular disorders is similar in men and women. Serum lipid levels are low in women up to the age of 50 years as compared with men; however, after menopause, serum cholesterol level in women exceeds that of men[13]. Elevated cholesterol level accompanied by loss of endogenous oestrogen secretion increases the risk of developing coronary artery disease in post-menopausal women[14]. Many epidemiological studies in humans reveal lower rates of cardiovascular diseases in East-Asian countries compared with Western countries, and a diet rich in phytoestrogen is thought to be responsible for this protection[15]. Soy foods which contain maximum concentration of natural isoflavone may reduce the risk of coronary heart disease. It seems clear that whole-soy protein is associated with a favourable effect on lipid profile, arterial compliance, atherosclerotic plaque, and blood pressure. Separation of protein component from dietary soy protein loses the effect. This effect depends on inhibition of cholesterol absorption by the non-isoflavone protein. The mechanism involves up-regulation of the LDL cholesterol receptor and catabolism of LDL cholesterol, leading to increase in bile excretion. The soy

peptide binds bile acid and prevents resorption. This is proved by the fact that alcohol extraction removes the isoflavone from the soy protein and hence causes loss of beneficial effect on atherosclerosis in monkeys[16, 17].

The US Food and Drug Administration (FDA) in October 1999 authorised the use in food labelling of health claims related to the association between soy protein and reduced risk of coronary heart disease. In the year 2000, the American Heart Association (AHA) updated their guidelines for soy protein and cardiovascular diseases, according to which daily consumption of more then 25 grammes of natural soy protein can improve lipid profile in hypercholesterolaemic individuals[18], it should be remembered that both protein and isoflavones are needed for a cardiovascular effect. Isoflavones by themselves have no effect on lipids[19]. In a meta-analysis of 38 controlled clinical trials with an average soy intake of 47 gm/day it was found that there was 23.2 mg/dl reduction in total cholesterol, 21.7 mg/dl decrease in LDL-C, and 13.3 mg/dl decrease in triglyceride levels; beside this, a nonsignificant increase in HDL- C levels was also noted.

Other mechanisms by which phytoestrogens exert beneficial cardiovascular effects include inhibition of coagulation process by inhibition of tyrokinase and platelet aggregation. Results of studies on the role of genistein on platelet function suggest a protective action against platelet aggregation; this could be explained on the basis of the fact that genistein is a known protein tyrosine kinase inhibitor. Platelet activation causes a rapid increase in protein tyrokinase that act as a transducer of the signal initially received by the platelet plasma membrane[20]. Oxidation is important in protecting the arterial wall from atheroma, and isoflavones seem to protect LDL-C from oxidation. The antioxidant effect of isoflavones is observed with relatively low levels of isoflavones[21]. Long-term studies of ovariectomised monkeys have shown that soy protein with isoflavone is associated with a significant reduction in atherosclerotic plaque progression when compared to soy protein isolate without isoflavones[22].

In experimental studies it has been found that soy lowers high blood pressure in salt-loaded hypertensive rats. A significant decrease in diastolic blood pressure was found when a soy protein supplement was given twice daily to non-hypertensive perimenopausal women in a placebo controlled trial. The same trial also demonstrated significantly improved lipid and lipoprotein levels in the study group.

**In managing symptoms of menopause**

At present the menopausal population of India is estimated to be about 103 million. Vasomotor symptoms are the most common cause of menopausal women seeking medical advice. HRT has been used for the treatment of menopausal symptoms for the last many years. However, the recent shift toward a more conservative use of hormone therapy may partly be attributed to concerns regarding the safety of HRT especially regarding cardiovascular events, thromboembolism, and breast cancer after the publication of the results of the Women's Health Initiative (WHI) Trial in 2002[23]. This milestone mega-study was a randomised placebo-controlled double blind primary prevention trial on 16,608 healthy post-menopausal women. On the other hand, piling evidence of the usefulness of isoflavones in clinical management of menopausal symptoms such as hot flushes and vaginal dryness has shifted the balance in favour of use of soy and its products.

**Hot flushes:** About 70 – 80% post-menopausal women in western countries complain of hot flushes as compared to 10 to 20% Asian post-menopausal women. This has been attributed to dietary differences, especially soy and vegetable contents that are high in phytoestrogens[24]. In his study, Murky found a statistically significant decline in hot flushes in post-menopausal women with dietary soy flour supplementation[25]. Similar observations have been made by other workers who found statistically significant reduction in hot flushes every week from week 3 to 12 of the study. However, an Italian study by Albertazzi *et al* found only 45% reduction in flushes with 60 gms of isolated soy protein daily (76 mg isoflavones), compared with 30% reduction in the placebo group[26]. Two other studies with 50 mg/day of isoflavones found a similar 5% reduction in the number of hot flushes compared with placebo[27]. Many other clinical trials have shown improvement in hot flushes although not found to be statistically significant. In three more twelve-week studies

in which soy isoflavones were found to be more effective than control, the incidence of hot flushes was reduced by 40%, 54%, and 45% in the study group vs. 25%, 35%, and 30% respectively in the control groups[28].

**Vaginal dryness:** Effect of high phytoestrogen on vaginal cytology was evaluated in a double blind randomised cross-over study in post-menopausal women and it was found that phytoestrogen rich diet alters the vaginal cytology maturation index to a more oestrogenic epithelial pattern. Another randomised study after four weeks of soy supplemented diet found oestrogenic effect on vaginal cytology. These studies confirm that phytoestrogens have a favourable role to play in vaginal dryness in post-menopausal women[29].

**Role in bone health and prevention of osteoporosis**

In post-menopausal women, oestrogen deficiency is the major risk factor for osteoporosis, and incidence of hip fracture is increased[30]. Isoflavones help in preservation of the bones and fight osteoporosis. Inspite of their weak oestrogenic action, they have a powerful bone building effect. This is the reason why in China and Japan, osteoporosis is rare after menopause despite a low consumption of dairy products in comparison to Europe and North America. In a study on Chinese pre- and post-menopausal women, Mei demonstrated that high isoflavone diet is associated with high BMD in both spine and hip region in post-, but not in pre-menopausal women[31]. The same has been concluded in a recent meta-analysis[32].

Experts often ascribe soy's mechanism of action on bone to the isoflavone's oestrogenic effect which is more pronounced on trabecular rather than cortical bone, which is consistent with the action of oestrogen. However, other mechanisms also seem to be involved, e.g., genistein directly inhibits osteoclast activity, thereby causing a decrease in osteoclast-induced bone loss during menopause instead of causing enhancement of bone mass. Phytoestrogen also have a conservatory effect on calcium excretion[33]. Isoflavones have been proposed to inhibit-activities of osteoclast like cells by interfering with tyrosine kinase activity of epidermal growth factor receptor protein[34]. Antioxidant properties of isoflavones may also be playing some role as *in vivo* and *in vitro* studies indicate that osteoclast formation and bone resorption are enhanced due to generation of free radicals.

**Phytoestrogens and cancerous illnesses**

In recent years, phytoestrogens have attracted considerable attention for their potential anticancer activity. In those parts of the world where soy intake is high there is lower incidence of breast, endometrial, ovarian, colonic, and prostate cancer. A case control study found 54% reduced risk of endometrial cancer[35]. Another case control study indicated reduction in risk of breast cancer in women with high consumption of soy and other legumes[36]. High soy and tofu consumption, and high urinary excretion of isoflavones have been reported to be associated with a lower risk of breast cancer in Singapore, China, and Australia. Apart from dietary evidences, animal studies indicated that soy supplementation resulted in inhibition of chemical and radiation-induced breast tumours in rodents[37].

Phytoestrogen can mimic as well as antagonise the effect of endogenous oestrogen, based upon their conformational binding to ER-alpha and ER-beta (more strongly), and both agonistic and antagonistic effects. Therefore, the phytoestrogen have been argued to be considered as selective oestrogen receptor modulators (SERM). Apart from hormonal actions, they also modulate a diverse array of intracellular signal transduction cascades. Genistein inhibits tyrosine protein kinase, which is coded by proto-oncogenes and plays a key role in tumourigenesis. It also inhibits DNA topoisomerase I and II and may prevent cell mutation by stabilising cell DNA. Diadzein and genistein both have got established antioxidant properties. Genistein has been shown to inhibit angiogenesis[38], it induces apoptosis and may reduce malignant cell metastasis, and all of these activities make them potential anticancer agents.

Epidemiological studies suggest the role of phytoestrogens in reducing the risk of prostate cancer as mentioned above. In a recently published study from Japan (2007), increased intake of soy isoflavone has been found to cut the risk of prostate cancer by 58%. Intake of genistein has been shown to inhibit the activity of 5- alpha reductase enzyme which converts testosterone into

dihydrotestosterone which stimulates the growth of prostate tissue. Another indicator of androgen blockade is seen in the form of inhibition of production of androgen regulated proteins including prostate specific antigen (PSA)[39]. The clinical data regarding the effect of isoflavone or soy on other cancers are sparse and inconclusive, although epidemiological data suggests that soy may reduce the risk of lung cancer; and recently, genistein was shown to inhibit murine blood cancer. Studies have suggested their protective role in thyroid[40], stomach, colon[41], and skin cancers. However, further research is warranted at this time.

#### Role in cognitive functions and Alzheimer's disease

HRT is thought to improve cognitive function and perhaps reduce onset of dementia in post-menopausal women[42]. Phytoestrogen too may play a positive role in these conditions. File *et al* evaluated the role of phytoestrogen on memory, attention, and frontal lobe function in healthy volunteers and found improved cognitive performance in these persons[43]. Improvement in brain functions have also been reported in animal studies following soy therapy[44].

Although clinical data is sparse regarding definitive influence of isoflavones in Alzheimer's disease (AD), epidemiological studies have shown that post-menopausal women who undergo oestrogen replacement therapy have significantly lower risk for onset of AD than women who do not[45], hence the focus has shifted to isoflavone as a possible candidate for a novel drug for AD. In a study on ovariectomised cynomolgus monkeys, soy treatment for three years was shown to sharply decrease phosphorylation of the brain protein tau which is an important biochemical parameter associated with development of AD. The use of soy-based foods for protection against post-menopausal neurodegeneration is gaining ground as more studies are on to evaluate its efficacy.

### Other effects

The isoflavones have been found to be potent inhibitors of human aldehyde and alcohol dehydrogenase isoenzyme and it is proposed that they might be useful in the treatment of alcohol abuse[46]. There is increasing evidence that phytoestrogens may be beneficial in chronic renal disease[47].

### Lignans

Flax seed also known as linseed was used by ancient Egyptians. It is a rich source of lignans as well as dietary fibre that can lower cholesterol levels besides being useful in atherosclerotic heart diseases, hypertension, and prevention of cancerous illnesses. Other rich sources of lignans are – rye, millet, Bengal gram, sesame and sun flower seed, besides legumes and beans[48]. Linseed oil contains both omega-3 fatty acid and omega -6 fatty acid and liberal quantity of phytoestrogen. The content of omega-3 fatty acid is more than double in quantity in fish oil. Alpha linoleic acid which is an omega-3 fatty acid, improves arterial function by increased strength, flexibility, and permeability of cell membrane; this in turn is thought to be responsible for reducing the risk of atherosclerosis[49]. It also blocks platelet aggregation, reduces blood pressure and fibrinogen level. Traditionally, whole and crushed flax seeds have been used for their laxative, anti-inflammatory, demulcent, emollient, and expectorant properties in chronic constipation, irritable colon, diverticulitis, gastritis, and enteritis. Lately, it has been found that they have a preventive role in colorectal cancer[50], mammary tumours[51] and even skin malignancies such as melanoma[52].

### Coumestans

These represent the last natural group of phytoestrogens. A single plant often contains more than one class of phytoestrogens, for example, the soy bean is rich in isoflavones, but the soy sprout is a potent source of coumestans. Coumestrol is the biologically active substance in human being. Alfa-Alfa and clover are good sources of coumestans. They have been used for ages in traditional system of medicine of China, India, and same parts of Europe. Among various phytoestrogens, isoflavones – especially, genistein and diadzein – have been most extensively studied. There are only a few studies on lignans and hardly any on coumestans, but this in no way reduces their clinical importance.

### Conclusion

The overwhelming wealth of information available today

from a large number of clinical trials and epidemiological data clearly proves the role of natural phytogens in the management of menopausal symptoms and in preventing or delaying the debilitating complications such as osteoporosis, cardiovascular diseases, cancerous illnesses, dementia, and Alzheimer's disease.

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REVIEW ARTICLE

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# Midlife Blues – The Metabolic Syndrome

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## Abstract

***Transition from normally menstruating to post-menopausal state marks a change in a woman's health status. There is increased incidence of weight gain, hypertension, dyslipidaemia, and cardiovascular events. Here we present a commonly encountered case with a brief review of literature. It is important that the treating physicians recognise the metabolic changes associated with the physiological condition and aggressively manage the various components to prevent the associated cardiovascular events. Similar increase in cardiovascular events is seen in men with testosterone levels declining during midlife.***

### Case

A 55-year-old lady presented to the emergency with acute retrosternal chest pain. She was non-diabetic, had recently developed hypertension (on atenolol 50 mg once daily) and dyslipidaemia (decreased HDL and increased LDL with normal triglycerides). She was post-menopausal for about 5 years. She had been active throughout her life and indulged in regular physical activity. Despite the regular exercise she had been experiencing weight gain for the past 4 years. On examination, she had evidence of acanthosis. She was 163 cm and 85 kg with BMI 32 and waist circumference of 94 cm. Her BP was 144/90 mmHg and her systemic evaluation was normal. On evaluation she was found to have acute anterior wall myocardial infarction.

## Review of literature

The metabolic syndrome (MetS) is the coexistence of signs and symptoms which are important cardiovascular disease (CVD) risk factors. It has been variously defined by different bodies but common factors include obesity, dyslipidaemia, hypertension, and hyperglycaemia[1,2,3]. The syndrome is evident in 20% to 30% of middle-aged women. It has long been believed that the oestrogen (E) deficiency during the menopausal transition was responsible for the increased risk of CVD seen in post-menopausal women. However, prospective randomised clinical trials have not demonstrated cardiovascular disease protection from oestrogen therapy[4,5,6], calling this long-standing hypothesis into question. Adrenal androgens decline by almost 80% between the ages of 20 and 70 years, and this is unaffected by the process of menopause[7,8]. Circulating testosterone (T) decreases by about 50% over the middle adult years. However, only minimal decline occurs through the menopause transition. As sex hormone binding globulin (SHBG), the primary protein carrier for T, also declines during the menopause transition, the free androgen index (FAI) may actually increase during the menopause transition[9].

In the multiethnic cohort of 1,862 pre- and peri-menopausal women without diabetes enrolled in the Study of Women's Health Across the Nation (SWAN), new cases (n = 257) of the metabolic syndrome were identified in the cohort during 6,296 woman-years of follow-up. The age-adjusted total T/E ratio increased 10.1% per year during the 5 years of follow-up. Neither baseline nor change in oestradiol was associated with incident metabolic syndrome. Low sex hormone biding globulin, free androgen index and high total testosterone at baseline all increased the risk of metabolic syndrome but their change over time did not. Both baseline total T/E ratio (1.41; 95% CI = 1.17 – 1.1.69; P 0.001) and its rate of change (1.24; 95% CI = 1.01 – 1.52; P 0.04) were associated with increased incident metabolic syndrome independent of ethnicity. The authors concluded that the interaction between testosterone and oestradiol during the menopausal transition, rather than the individual change of each over time, is a factor in determination of risk for developing the metabolic syndrome during the menopausal transition. This relationship was independent of ethnicity and other factors associated with prevalent metabolic syndrome prior to the onset of the menopausal transition[10].

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Over their lifespan, women are more likely to experience cardiovascular disease and disability than men. In Europe, 55% of women will die of cardiovascular disease as opposed to 43% of men. Epidemiology, symptoms, and progression of cardiovascular disease are different in women than in men. Typically, women develop cardiovascular disease about 10 years later than men. Although cardiovascular events are a rare occurrence in pre-menopausal women, their incidence increases most markedly after the age of 45 – 54 years (i.e., at the time of the menopause). The 1-year mortality after myocardial infarction is higher in women, whereas in congestive heart failure the prognosis is better in women than in men. New cases of angina pectoris as an initial presentation are more common in women. The incidence of uncomplicated angina in post-menopausal women is equal to or may even exceed that in men. Men are more likely to present with an acute event, either myocardial infarction or sudden death, as the initial presentation of coronary disease in all age groups. After the menopause, the incidence of myocardial infarction in women also increases, although absolute rates remain lower than in men until the eighth decade. The presence of hypertension mirrors the prevalence of cardiovascular disease, with increases in prevalence in women after the menopause[11].

Menopause is associated with metabolic changes contributing to increased CV risk. Weight gain frequently occurs in peri-menopausal women not receiving hormone replacement therapy. This is mainly attributed to an increase in body fat, which is concentrated in the abdomen (android) rather than subcutaneously (gynoid). Increased body mass index tends to reduce insulin sensitivity and increase systolic blood pressure. The decline in serum high-density lipoprotein cholesterol levels and the increase in low-density lipoprotein cholesterol levels is an important contributor to increased CHD. Increases in systolic and diastolic blood pressure coincide with the menopause[12,13,14,15].

Data from observational studies have suggested that hormone replacement therapy may enhance survival in women after coronary artery bypass grafting[16] and myocardial infarction[17]. Other potentially favourable actions of oestrogens include significant increases in high density lipoprotein and decreases in low-density lipoprotein cholesterol levels in post-menopausal women with accompanying favourable effects on the coagulation profile[18]. With regard to added progestins for uterine protection in non-hysterectomised women, it appears that potential cardiovascular benefits of post-menopausal oestrogen treatment can be attenuated by medroxy-progesterone acetate, but possibly not by other progestins[19]. Medroxyprogesterone acetate has been shown to overcome the vasodilatory effect of oestrogens on coronary arteries, increase the progression of coronary artery atherosclerosis, accelerate the low-density lipoprotein uptake in plaque, increase the thrombogenic potential of atherosclerotic plaques, and promote insulin resistance and hyperglycaemia[19]. Observational studies have suggested a cardiovascular benefit of hormone therapy. However, randomised clinical trials such as the WHI study, which enrolled women without known CHD, demonstrated that oestrogen plus progestin did not result in cardiovascular protection and may increase the risk of CHD in older post-menopausal women[20]. Nurses' Health Study showed that the relative risk of myocardial infarction was not increased in women who started hormone therapy within 10 years of the menopause[21]. The WHI also demonstrated that there was an increased risk of venous thrombosis associated with oestrogen plus progestin therapy that again was greater with age[22] and an increase in the risk of ischaemic stroke[23]. A consensus statement issued by European Cardiologists and Gynecologists recommends that as cardiovascular risk associated with hormone therapy exceeds the benefit in elderly post-menopausal women; hormone therapy should not be used for the primary or secondary prevention of cardiovascular disease in older women. In treating the younger, peri-menopausal woman for menopausal symptoms, the benefits should be weighed against the potential risks of hormone replacement therapy[11].

In men, testosterone has traditionally been believed to be a risk factor for cardiovascular diseases. However, few, if any, recent observations support a causal relation between higher testosterone levels and heart disease[24,25].

On the contrary, several studies suggest that higher testosterone levels are associated with a more favourable risk effect on the risk of cardiovascular disease[26]. A recent

study showed that men with coronary artery disease had lower levels of testosterone than controls and that testosterone levels were inversely correlated to the degree of coronary atherosclerosis[27]. In the Rotterdam study, the association between total and bioavailable testosterone and aortic atherosclerosis was evaluated in 504 non-smoking men aged X55 years. They found that men in the highest tertile had a risk reduction of 60 – 80% of severe aortic atherosclerosis after controlling for age and CV risk factors[28].

The association between low testosterone D low SHBG levels and the metabolic syndrome is beyond any reasonable doubt now. The cause and effect relation remains, however, a subject of further study. Low testosterone levels and sex hormone-binding globulin (SHBG) were predictive of the metabolic syndrome and development of diabetes mellitus type 2, not only in obese men but also in men with a body mass index (BMI) < 25[29,30,31,32]. Interestingly, concentrations of free and bioavailable testosterone even in the low-normal range are associated with diabetes, after adjusting for adiposity[30]. Similarly, low total testosterone levels independently predict development of the metabolic syndrome in middle-aged men[32].

Role of testosterone therapy in cardiovascular disease is now being studied. Interventional trials have shown that testosterone administration results in an increased glucose uptake by the muscles, thereby improving insulin sensitivity. Research shows that physiological testosterone replacement is at least neutral (if not beneficial) to lipids. Evidence that testosterone therapy may be beneficial for men with cardiac disease is becoming stronger. Studies of testosterone therapy have not demonstrated an increased incidence of cardiovascular disease or events such as myocardial infarction, stroke or angina[33]. In humans, transdermal testosterone therapy improves exercise induced myocardial ischaemia (measured as time to ST depression) during an exercise stress test in men with stable angina[34], with men having the lowest baseline testosterone levels benefitting the most. A recent study using oral testosterone in hypogonadal men with coronary artery disease showed increased myocardial perfusion[35]. These vasodilatory effects of testosterone are reflected by the fact that men with prostate cancer undergoing androgen deprivation therapy experience arterial stiffness[36]. It is believed that testosterone causes both endothelium-dependent and endothelium-independent vasodilation. A prospective study of 794 men, aged 50 – 91 years, looked at the relationship of testosterone with all-cause mortality over two decades. Men with total testosterone levels in the lowest quartile were 40% more likely to die than men with higher androgen levels, independent of age, adiposity, lipids, adipokines and lifestyle. In cause-specific analyses, low testosterone predicted increased risk of mortality due to CV and respiratory disease[37].

In conclusion, midlife in both men and women is associated with increased risk of components of metabolic syndrome and cardiovascular events. However, a cause and effect relationship has not been established and further research is needed in this regard.

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POST-GRADUATE CLINIC

JIACM 2011; 12(3):216-20

# Approach to a Patient with a Continuous Cardiac Murmur

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A 21-year-old labourer, working in Delhi presented with a history of palpitations since 3 years on moderate-to-heavy exertion and relieved by rest. He also had progressively increasing breathlessness for the same duration; associated orthopnoea was present. There was no history of chest pain, syncope, repeated chest infections, cyanotic spells, sore throat, or migratory polyarthritis.

On examination, he had a pulse rate of 110/minute. The pulse volume was high, it was collapsing in character and synchronous in all four limbs. The blood pressure was 140/40 mmHg and 170/78 mmHg in the right upper and lower limbs, respectively. His arm span-to-height ratio was less than one, and there were no Marfanoid features or stigmata of syphilis. Cardiovascular examination revealed a visibly displaced apical impulse in the left fifth intercostal space. On palpation, the apical impulse was hyperdynamic in character and there was an associated left parasternal thrill with systolic and diastolic components. On auscultation, a continuous murmur (Grade 5/6) was widely heard over the entire precordium with maximum intensity in the left fourth intercostal space. Respiratory examination revealed bilateral fine basal crackles.

The haemogram, liver and kidney functions tests were normal. A chest radiograph showed LV enlargement, prominence of central pulmonary arteries and increased bronchovascular markings. ECG showed LVH by voltage criteria and evidence of LV diastolic overload (q waves, relatively tall symmetrical T-waves and j-point elevation in leads v5, v6) as shown in Figure 1.

## What is a continuous murmur and what are its common causes?

A continuous murmur is one which begins in systole and extends uninterrupted up to diastole, not necessarily occupying the whole length of systole and diastole. It results from blood flow from a high pressure chamber to a low pressure system associated with persistent pressure gradient between the two during systole and diastole. It may occur due to aortopulmonary connections, arteriovenous communications, and disturbances in flow patterns in the arteries or veins[1].

Important causes of a continuous murmur are[1, 2]:

1. **Patent ductus arteriosus (PDA):** A relatively common cause. The murmur is known as Gibson's murmur. It is best audible at the left infraclavicular area or upper left sternal border and is loudest towards the end of systole and early diastole. Differential cyanosis and clubbing may be present if there is reversal of shunt.

2. **Ruptured sinus of Valsalva aneurysm:** It produces a to-and-fro continuous murmur which tends to be louder in diastole and is heard lower down to the left of the sternum.

3. **Aortopulmonary window:** An extremely rare cause. Because of the large size of the communication, pulmonary vascular resistance and pulmonary diastolic pressure tend to be higher, resulting in a shorter diastolic component of the murmur.

4. **Arteriovenous fistulae:**

   a) **Coronary artery venous fistula:** The location, duration, and character of the continuous murmur depend upon the anatomical type of fistula. The right coronary and right atrial, or coronary sinus communication produces a murmur located along the parasternal area. The murmur of circumflex coronary artery and coronary sinus communication is located in the left axilla. The configuration of the murmur and its systolic and diastolic intensities are variable.

   b) **Systemic AV fistula:** It results in a loud murmur

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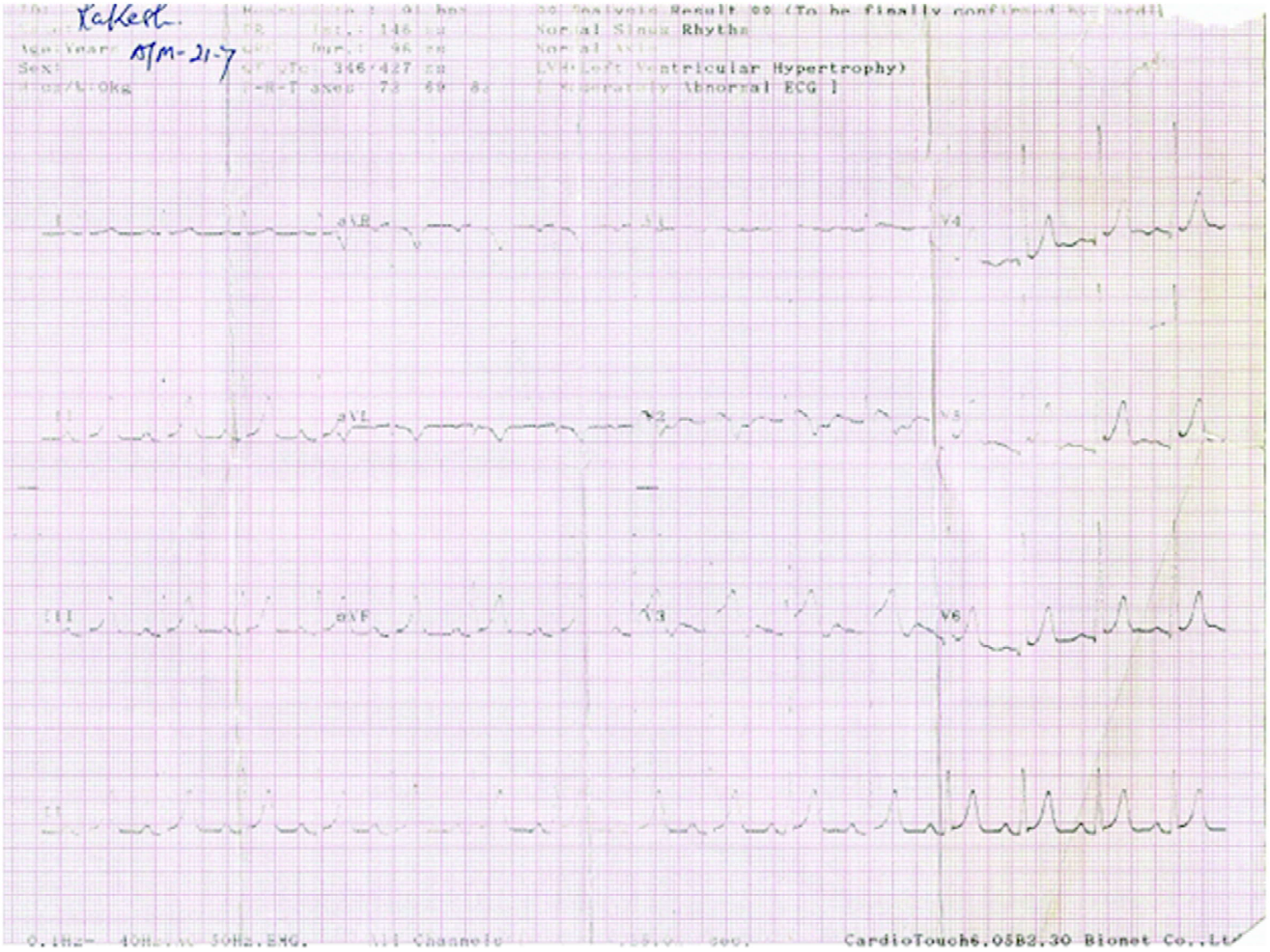


***Fig. 1:*** *ECG showing LVH by voltage criteria and evidence of LV diastolic overload (q waves, relatively tall symmetrical T-waves and j-point elevation in leads v5, v6).*

localised over the fistula (e.g., head/neck).

(c) **Pulmonary AV fistula:** The murmur is usually softer and may be primarily systolic. It is usually audible over the back with cyanosis and clubbing present in the absence of cardiomegaly.

5 **Constriction in systemic/pulmonary arteries:** The murmur in this case is a result of persistent pressure gradient across the narrowed segment of the vessel.

(a) **Coarctation of aorta:** The murmur is audible in the intercostal spaces, usually bilaterally, also over the back, overlying the area of constriction.

(b) **Bronchial arterial collaterals:** These occur in certain cyanotic congenital heart diseases (tricuspid atresia, pulmonary atresia with VSD), may result in loud continuous murmur heard along the parasternal area.

(c) **Peripheral pulmonary artery stenosis:** A continuous murmur is audible all over the thorax. This often accompanies William's syndrome or rubella syndrome.

6 **Innocent continuous murmurs:**

(a) **Venous hum:** It results from altered flow in veins causing an innocent murmur, best heard with the patient in the sitting position, usually in the supraclavicular fossa and it frequently disappears when the patient moves to the supine position. It can also be abolished by compression of the ipsilateral internal jugular vein.

(b) **Mammary soufflé:** Associated with pregnancy, it may be systolic or continuous. The innocent

murmur is usually of higher frequency and louder in systole.

## How will you confirm the diagnosis?

A 2D-Echo study is usually sufficient to establish the diagnosis. In our patient, it revealed rupture of the sinus of Valsalva aneurysm draining into the right ventricle with left ventricular volume overload, normal left ventricular systolic and diastolic function, and ejection fraction of 75% as shown in Figure 2 and 3.

## What is sinus of Valsalva?

The sinus of Valsalva is a specialised dilatation of the aortic valve lumen, being walled by the valve cusp medially and by the origin of aorta laterally. There are three aortic

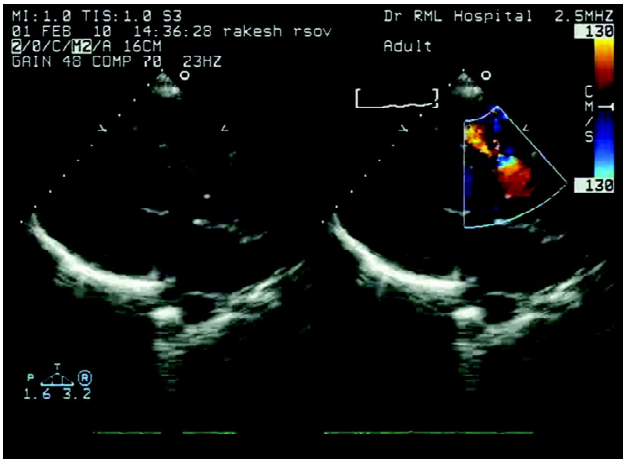


***Fig. 2:*** *Parasternal long axis view showing colour flow through the defect.*

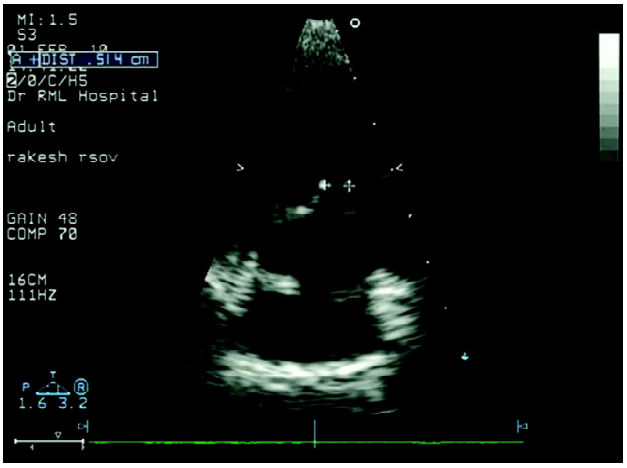


***Fig. 3:*** *Parasternal short axis view showing the defect (marked between two "+" signs).*

sinuses named in relation to their valve cusps. The left and right sinuses are the ones above which the left and right coronary arteries arise, respectively. The posterior sinus (the non-coronary sinus) is not directly related to a coronary arterial ostium[3].

A sinus of Valsalva aneurysm, first recognised by John Thurman (1840), is a rare condition resulting from separation between the aortic media and the annulus fibrosis. Inadequate fusion of the conus ridges, truncus ridges, or endocardial cushion tissue is also postulated as the cause for the developmental defect[3,4,5].

Apart from being congenital, which is the most common type and usually involves a single cusp, the condition may be inherited as in Marfan's syndrome. Acquired causes include endocarditis of the aortic valve, syphilis, atherosclerosis and dissecting aneurysms[6].

Approximately 65 – 85% of sinus of Valsalva aneurysms arise from the right coronary sinus, followed by non-coronary sinus (10 – 30%), and the left sinus accounts for less than 5% of cases. The defect is more common in Asians (0.46 – 3.6 %) compared to Western population (0.14 – 0.23%)[6,7].

## What is the clinical presentation of sinus of Valsalva aneurysms?

A sinus of Valsalva aneurysm usually presents in three ways. The unruptured aneurysm is usually asymptomatic and often detected incidentally on 2D-Echo. Sometimes the aneurysm may compress the interventricular septum and present clinically as complete heart block, or the coronary artery may be compressed resulting in angina. There may be an initial small rupture which is initially asymptomatic, but as it enlarges over the years it may present with symptoms related to volume overload. Lastly, an aneurysm that ruptures acutely may present with acute chest pain and the triad of pulsating neck veins, a collapsing pulse and a continuous murmur. A ruptured sinus of Valsalva usually presents during the period from puberty till age 30 years. Rupture, most often, involves the right coronary sinus draining into the right ventricle followed by the non- coronary sinus into the right atrium. Rupture of a left sinus aneurysm is rare and may occur into the pericardial space[8,9].

## What are the associated defects with sinus of Valsalva aneurysms?

Ventricular septal defect (VSD) is the most common associated defect and is usually found in 30 – 60% of patients, followed by aortic regurgitation (44 – 50%) and bicuspid aortic valve (15 – 20%). Less commonly, pulmonary stenosis, atrial septal defect, and coarctation of the aorta may be associated. About 10 % of patients with Marfan's syndrome will have a sinus of Valsalva aneurysm[6].

## How will you evaluate a patient with a sinus of Valsalva aneurysm?

A patient presenting with suggestive clinical features should undergo thorough clinical evaluation including detailed history and physical examination. Apart from routine haematological and biochemical investigations which include blood cultures to rule-out infective endocarditis, an ECG should be done which may show sinus tachycardia and evidence of left ventricular diastolic volume overload. A chest radiograph may show cardiomegaly with prominent pulmonary vasculature.

Although transthoracic 2D-Echo is usually sufficient to confirm the diagnosis, revealing typical "windsock" deformity, transoesophageal echocardiography (TEE) provides conclusive information and allows precise identification of structural anomalies and shunt locations for perioperative assessment. The definitive diagnosis can be confirmed by performing a retrograde thoracic aortography or cardiac catheterisation. MRI has also been evaluated as a diagnostic tool[6,8,9].

## What is the treatment of ruptured sinus of Valsalva aneurysm?

Surgical repair is the definitive treatment, and a patient diagnosed with a ruptured aneurysm should be immediately taken-up for surgery. Medical therapy involves stabilising the patient preoperatively. Transcatheter closure of ruptured sinus of Valsalva aneurysm (SVA) has been successfully performed using Amplatzer devices[6,8].

Our patient was treated with diuretics and ACE-inhibitors for features of cardiac failure. He was operated upon to repair the sinus of Valsalva aneurysm and a pericardial patch closure of an associated small perimembranous ventricular septal defect (4 mm).

## What are the complications of a sinus of Valsalva aneurysm?

A sinus of Valsalva aneurysm (ruptured or unruptured) may result in the following complications:-

- Myocardial infarction (from coronary arterial compression by adjacent unruptured SVA)
- Complete heart block (from compression of conduction tissues by adjacent unruptured SVA)
- Right ventricular outflow tract obstruction
- Sudden cardiac death
- Infective endocarditis
- Tamponade, due to rupture into the pericardium
- Rarely, cerebrovascular emboli

## What is the prognosis?

Prognosis is poor with progressive aneurysmal dilatation or rupture unless early surgical repair is performed.

- Actuarial survival rate for patients with congenital SVA is 95% at 20 years, since most SVAs do not rupture prior to age 20 years.
- Unruptured SVAs have been observed in serial monitoring up to several years after initial diagnosis, but most unruptured SVAs have been found to progress and rupture.
- Untreated SVAs may rupture, and patients with ruptured SVAs die of heart failure (with left-to-right shunting) or endocarditis within 1 year after onset of symptoms of ruptured SVA.
- In a series of 86 patients who underwent SVA repair, rupture occurred in 34%. Six (7%) died perioperatively; the actuarial 10-year survival rate was 63%. These patients often required concomitant surgical repair of associated ventricular septal defect, atrial septal defect, and the aortic valve[6].

## Acknowledgement

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# Idiopathic Intracranial Hypertension: Role of Imaging in Diagnosis and Follow-up

*Amritpal Singh**

Idiopathic intracranial hypertension also known as pseudotumour cerebri is a syndrome which is characterised by raised CSF pressure in the absence of hydrocephalous or any space occupying lesion (SOL) or sinus thrombosis with normal CSF biochemistry and cytology and with no or minimal neurological findings alongwith normal level of consciousness. The hallmark of idiopathic intracranial hypertension is papilloedema, which can be unilateral or bilateral, but it can be absent also[1,3]. The role of imaging has been mainly to exclude any SOL, sinus thrombosis, hydrocephalous, and meningitis. There are some findings on MRI, which can help us in reaching the diagnosis and also monitoring the success of treatment, whether medical or surgical. We report a case of idiopathic intracranial hypertension, with typical finding on MRI.

This is a case of a 20-year-old female who presented with headache and some visual loss. On physical examination, she was obese with a body mass index (BMI) of 27, with no evidence of any thyromegaly. Routine laboratory investigations were normal. Fundoscopic examination revealed papilloedema. She was not taking any medicine and was referred to our department for MRI of head to exclude any SOL as she was having repeated attacks of headache for one year. Cranial MRI was performed, which showed bilateral flattening of the posterior sclera and distension of the perioptic subarachnoid space. Thin saggital images of the pituitary were taken, which revealed partially empty sella with flattening of the pituitary gland and midline infundibulum. MRI venography and screening of spine was normal. Post-contrast imaging did not reveal any abnormal meningeal enhancement. Therefore, based on these findings, a diagnosis of idiopathic intracranial hypertension was made. A lumbar puncture was done in the left lateral decubitis position, which revealed an elevated CSF pressure of 121 cm of $H_2O$ with normal CSF composition, thus confirming the diagnosis of idiopathic intracranial hypertension. Treatment was started with acetazolamide, which resulted in improvement of the symptoms. A repeat MRI was done after 4 weeks, which showed normal contour of the posterior sclera with no abnormal distension of the perioptic subarachnoid space and return of the normal shape and size of the pituitary, thus indicating successful treatment.

## Discussion

Idiopathic intracranial hypertension can occur at any age but it is far more common in young obese females[2,4]. Several theories have been proposed to explain the pathophysiology of idiopathic intracranial hypertension including increased blood volume, CSF production and decreased rate of CSF absorption. This syndrome can be seen in cases of hypervitaminosis A, endocrinopathies, tetracycline therapy, birth control pills, Guillian-Barré syndrome and lithium therapy. Permanent visual loss due

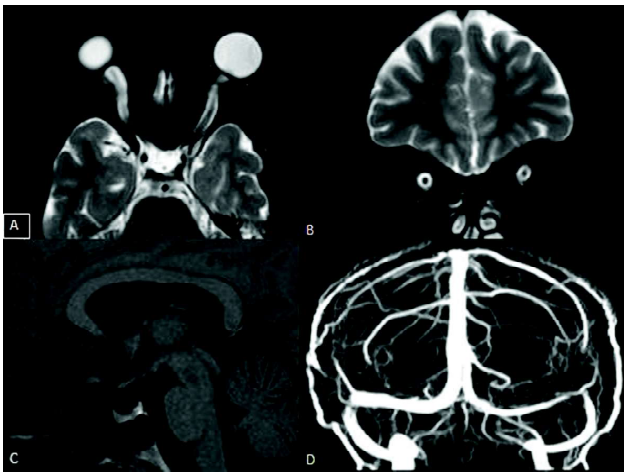


***Fig. 1:*** *(A and B) are transverse and coronal T2-weighted fat saturated images shows marked distension of the perioptic subarachnoid space with flattening of posterior sclera . (C) Sagittal T1-W images shows flattening of the pituitary gland (D) MR venography shows no evidence of sinus thrombosis.*

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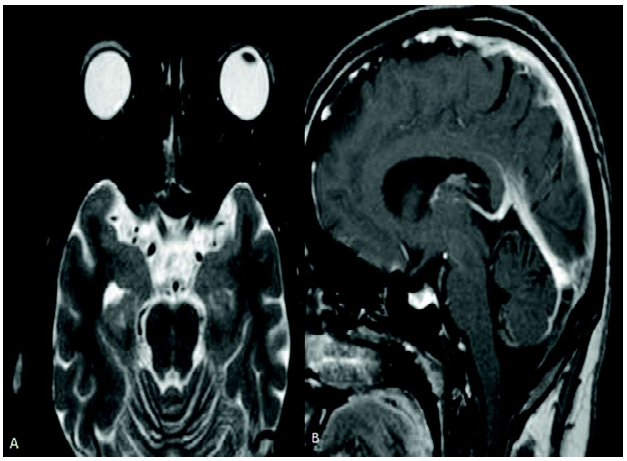

***Fig. 2:*** *Repeat MRI after treatment shows no abnormal distension of the perioptic subarachnoid space with normal contour of the posterior sclera (A) with return of the normal height and size of the pituitary gland (B).*

to chronic papilloedema is a great hazard. After the diagnosis by means of imaging and lumbar puncture, continued follow-up is necessary to decide whether to continue with medical treatment or to perform an invasive procedure like optic nerve fenestration or lumbo-peritoneal shunting[2].

Direct transmission of the elevated CSF pressure results in distension of the perioptic subarachnoid space and ballooning of optic papillae[1]. Empty sella develops due to intrasellar herniation of CSF and arachnoid membrane through an absent or open diaphragm sellae, causing flattening and distortion of the pituitary gland. Infundibulum is midline and extends to the floor of the sella turcica[5]. High resolution MRI improves visualisation of optic nerve and pituitary gland, thus helping in diagnosis of idiopathic intracranial hypertension[2]. In a study, MR imaging disclosed flattening of the posterior sclera (80%), an empty sella (70%), distension of perioptic subarachnoid space (45%), enhancement of the pre-laminar optic nerve (50%), vertical tortuosity of optic nerve (40%)[1]. In another study, 94% cases showed some degree of empty sella[2].

Therefore, attention to the optic nerve and pituitary gland is to be given so as not to miss a case of idiopathic intracranial hypertension. So when suspecting idiopathic intracranial hypertension, high-resolution sequences of optic nerves and pituitary gland are to be taken/ requested, alongwith routine brain sequences. Thus, dedicated MRI imaging can be used for monitoring patients with idiopathic intracranial hypertension especially those without papilloedema, instead of lumbar puncture which is distressing to the patient and with the theoretical risk of developing intraspinal epidermoid tumour and low backache[1].

To conclude, MR imaging of the optic nerves and pituitary gland provide important clues for the diagnosis of idiopathic intracranial hypertension, with return to normal appearances after normalisation of the CSF, thus indicating successful treatment.

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CASE REPORT

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# A Large Retropharyngeal Abscess Following Spinal Tuberculosis Presenting as Life-threatening Stridor in A Child

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## Abstract

***Chronic retropharyngeal abscess secondary to tuberculosis of the spine is a rare entity. Though rare, it can lead to life-threatening airway obstruction requiring prompt diagnosis and treatment to prevent fatal consequences. We report one such case of a large tuberculous retropharyngeal abscess presenting with life-threatening airway compromise and stridor in a 9-year-old female. Drainage of the abscess led to prompt relief from life-threatening stridor. Anti-tuberculous therapy started alongside was continued under DOTS regime with child doing well at 1 and 3 month follow-up.***

***Keywords: Tubercular, retropharyngeal abscess, stridor.***

Tuberculous retropharyngeal abscess (TRA) is rare when compared to pyogenic abscesses in the paediatric age group. These are usually secondary to tuberculosis of the spine which is the most common form of skeletal tuberculosis. In skeletal tuberculosis, the most common areas of involvement are the lower thoracic, lumbar, and cervical spine in that order of frequency. The source of infection are usually the pelvic organs from where infection spreads via the Batson's plexus to involve the more superior structures of the spine, thereby leading to less common involvement of the atlantoaxial spine[1,2].

The incidence of cervical spine involvement among the Pott's spine cases is around 7%, while atlanto-axial involvement is seen in only 1% of the cases[3]. Spinal tuberculosis can lead to paravertebral abscess in around 57% of cases, but the incidence of TRA in such cases is not known.

## Case report

A 9-year-old female child presented to us with history of fever, neck stiffness, dysphagia since the past 1 month, and progressively increasing stridor and breathing difficulty (more so in the lying-down position) since the past 6 days. No history of any penetrating trauma, ear discharge, seizure attack, or weakness in any of the limbs was present. The child undertook treatment from private practitioners in the form of oral antibiotics and antipyretics but to no avail. The child was thinly built (13.5 kg grade III malnutrition), febrile, had severe torticollis and stridor. On oral examination, a big bulge was seen on the posterior pharyngeal wall on the left which crossed the midline. The mucosa was normal and no membrane was visualised. No cervical lymphadenopathy was found. Lateral view X-ray of soft tissues of neck (STN) showed a large prevertebral soft tissue swelling compressing the airway with reduced intervertebral disc spaces between $C_1$, $C_2$ and $C_3$ with partial erosion of vertebrae. Contrast-enhanced CT scan of the neck showed a large abscess (44 mm × 32 mm × 55 mm) in the retropharyngeal region extending from the base of the skull on the left-side to the hypopharynx. The abscess compressed the air space which appeared chinked-up, thereby causing airway compromise and stridor (Fig. 1). The atlas vertebra appeared distorted and eroded. Fossa of Rosenmüller was compressed by the lesion on the left-side. Chest X-ray was normal. Mantoux test was positive (17 mm at 72 hours), and ESR was 83 mm/first hour. Keeping the clinical and investigative picture in view, anti-tuberculour therapy (ATT) by DOTS regimen was started and the abscess was drained by the ENT surgeon by a transoral approach under general anaesthesia (GA), thus providing prompt relief from stridor. About 40 ml of cheesy, necrotic aspirate was drained and sent for work-up. The aspirate showed an increased adenosine deaminase (ADA) level of 110 u/l, and acid-fast bacilli (AFB) grew on culture (by BACTEC method). Reformed abscess underwent repeated aspirations under ATT and antibiotic cover during hospital stay. On discharge

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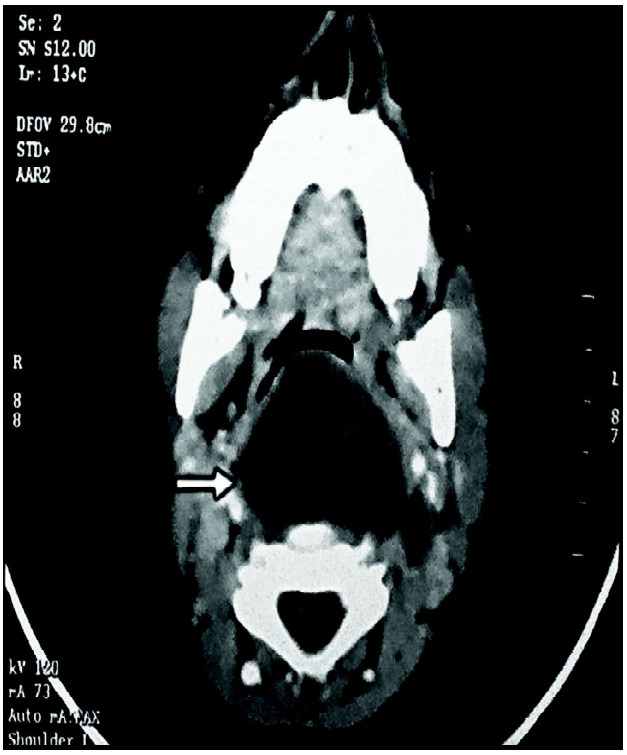


***Fig. 1:*** *CECT neck (axial section) showing large retropharyngeal abscess compressing the airspace which appears chinked-up.*

at 2 weeks, the child was stridor free, afebrile with an improved appetite and sent home on ATT. The child was doing fine at 2-month follow-up with a weight gain of 5 kilogramme.

## Discussion

TRA usually present with fever, drooling of saliva, dysphagia, neck stiffness; though stridor and/or life-threatening respiratory distress might sometimes be the only presentation in children[4]. Hsu and Leong studied the symptoms of tuberculous retropharyngeal abscess following cervical spine tuberculosis in 40 children and found that children < 10 years had large-sized retropharyngeal abscess with stridor and dysphagia as the presenting features, while older children had smaller abscesses and greater frequency of paraplegia as the presenting feature[5]. Radiographically, TRA is diagnosed by widened soft-tissue space at the level of axis vertebra (greater than 7 mm at lower border of axis or > 2/3 of the width of body of corresponding vertebra in lower cervical region) and destruction of associated cervical spine[1]. CT scan of the neck is a more sensitive investigation showing a central hypodensity with a surrounding thick rim of enhancement with a diameter more than twice of the contiguous vertebrae at $C_2$ level[6].

Treatment of TRA involves surgical drainage of the abscess under ATT cover. Securing the airway (either by intubation or tracheostomy) should take precedence in any case with features of airway compromise leading to impending failure. In the index case, however, neither of them were required and the abscess was drained surgically under GA by the ENT surgeon by transoral approach similar to one used by Kohli *et al*[7]. For retropharyngeal abscesses involving the lower cervical spine, the external cervical approach is generally recommended[8].

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**ACKNOWLEDGEMENT**

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-Editor

CASE REPORT

JIACM 2011; 12(3): 225-6

# Galactorrhoea: A Rare Side-effect of Domperidone

*P Agarwal*, AK Gupta**, V Goyal***, A Raj*, S Pandey****

## Abstract

***Galactorrhoea is a rare side-effect of domperidone. We report a case of a female patient who was prescribed domperidone for gasto-oesophageal reflux disease. While taking the drug she developed galactorrhoea, and after discontinuing domperidone therapy, her galactorrhoea subsided.***

***Key words: Galactorrhoea, domperidone, drug-induced galactorrhoea.***

## Introduction

Domperidone is generally safe drug with very few side-effects, of which galactorrhoea is very rarely seen. Domperidone is one of the cheapest and also effective anti-emetic drug which is very commonly used as an over-the-counter drug. Other side-effects of domperidone are dry mouth, loose stools, headache, rashes, cardiac arrhythmias.

Although domperidone is implicated as a cause of galactorrhoea, online search reported only a few case reports from India[4] and one report from Britain[2]. The first report was published in 1983[2] from Britain, and a report from India was published in 1991[4]. Here we are reporting a case of domperidone-induced galactorrhoea in which domperidone was used in a therapeutic dose (30 mg).

## Case report

A 28-year-old female, housewife by occupation, non-smoker, non-alcoholic, a known case of gasto-oesophageal reflux disease was admitted in our ward for treatment. She was discharged on rabeprazole 20 mg with domperidone 30 mg. But after 10 days of the treatment she visited our out-patient department with complaints of painful enlargement of both breasts with moderate grade fever with chills, and galactorrhoea for 3 days. The patient had her menses 9 days back and her menses were regular (every 30 days for 2 days). She gave no history of taking any other drugs like oral contraceptive pills, antidepressant, or anti-tuberculous drugs. On examination, the patient had tenderness of both breasts with oozing of milk from both nipples, and without any mass on palpation. Her secondary sexual characters and external genitalia were found to be normal and she had bilateral tender mobile breasts. Other systemic examination was normal. On investigation, the patient's haemoglobin was: 10 gm/dl; total leukocyte count: 12,400/cumm; differentials: N-80, L-19, M-1; urine routine and microscopy, LFT, and RFT were normal. Chest X-ray and ultrasound abdomen was normal. Her MRI brain was normal. Ultrasonography of bilateral breast and mammography was normal. The patient's, hormone levels (TSH, LH, FSH, prolactin, oestradiol, and testosterone) were normal. On further evaluation, she was diagnosed as a case of domperidone-induced galactorrhoea. For this, domperidone was stopped. After 6 days of stopping domperidone, the fever, pain and galactorrhoea subsided.

## Discussion

Galactorrhoea, the inappropriate discharge of milk containing fluid from the breast, is considered abnormal if presents for longer than 6 months after childbirth, or after discontinuation of breastfeeding[1].

It can be physiological as in pregnancy, lactation, chest wall stimulation, sleep, and stress, or pathological. Pathological causes are tumours (craniopharyngioma, prolactinoma), trauma, acromegaly, hypothyroidism, cirrhosis of liver, chronic renal failure. It can be drug-induced also. Drugs causing galactorrhoea are phenothiazines, chlorpromazine, perphenazine, haloperidol, metoclopramide, α-methyldopa, reserpine, opiates, ranitidine, amitriptylline, amoxapine, fluoxetine, verapamil, oestrogens[1]. Most of these drug-induced galactorrhoea cases were reported through various case

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reports. Here we are reporting a case of galactorrhoea induced by domperidone.

Domperidone is a D2 antagonist, and very poorly crosses the blood-brain barrier so it has a benefit of minimal CNS side-effects as compared to metoclopramide. Galactorrhoea is a rare side-effect of domperidone and very few cases have been reported. Other side-effects are gynaecomastia, impotence, menstrual disorders. These side-effects occur because of elevated prolactin level[3]. Some other side-effects are diarrhoea, dry mouth, rashes.

Treatment of galactorrhoea depends upon its cause. Drug-induced galactorrhoea generally responds to discontinuation of the offending drug. As mentioned in our case report, the patient responded well to the discontinuation of the drug. Sometimes, the addition of dopamine agonist (bromocriptine or cabergoline) may be required fo the management of galactorrhoea[1].

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CASE REPORT

JIACM 2011; 12(3) : 227-9

# Jugular Foramen Schwannoma Presenting as Collet-Sicard Syndrome – A Rare Entity

*Vandana Verma*, MP Singh**, AK Gupta***, TP Singh****, Aneesh MM*****, Nitin Jaiswal ******

## Abstract

***The most frequent site of origin of a schwannoma is the cerebellopontine angle, more precisely from the 8th nerve. Other cranial nerves involved, in order of frequency, are 5th nerve, 7th nerve, and 12th nerve. Schwannomas arising from the 9th, 10th, and 11th cranial nerves (also called jugular foramen schwannoma) without associated neurofibromatosis are relatively uncommon. We report a case of schwannoma of the jugular foramen with 12th cranial nerve palsy presenting as Collet-Sicard syndrome. The epidemiology, MRI findings, and differential diagnosis of this rare entity are reviewed.***

## Introduction

Tumours of the jugular foramen are uncommon, constituting approximately 0.3% of all intracranial tumours. Glomus jugulare tumours account for 60 – 80% of all such cases, while schwannomas – the second most common tumour type in this location are very rare with only a few reported cases[1]. The majority of jugular foramen schwannomas arise from the 9th cranial nerve, but they may also arise from the 10th or 11th cranial nerve. Because of this uncertainty, most authors prefer the term 'jugular foramen schwannoma'[2], and generally it is very difficult to determine the nerve of origin pre-operatively[3]. Jugular foramen schwannoma may also present with 12th cranial nerve palsy[4].

## Case report

A 30-year-old male patient presented with insidious onset, gradually progressive dysphagia, dysarthria, hoarseness of voice, and unilateral wasting of tongue muscles. There was no history of any long tract or cerebellar involvement, trauma, neck mass, or pulsatile tinnitus. On examination by the neurologist, there was strictly unilateral paralysis of soft palate and uvula, diminished pharyngeal, laryngeal sensations and vocal cord palsy on the same side. Atrophy and fasciculations of tongue muscles on the affected side were seen alongwith ipsilateral loss of gag reflex, weakness of contralateral head turning and ipsilateral shoulder elevation. In view of strictly unilateral involvement of lower cranial nerves 9th to 12th and absence of long tract/cerebellar signs and Horner's syndrome, a diagnosis of Collet- Sicard syndrome was considered. MRI of the brain with special emphasis on the skull base was advised.

MRI findings reveal a well-defined T1 isointense well-marginated lesion in the right jugular fossa extending along the course of the 9th – 11th cranial nerves into the parapharyngeal and carotid space, measuring 24 mm (sagittal) x 18 mm (antero-posterior) x 16 mm (transverse) in size. The lesion was homogeneously hyperintense on T2-weighted images without any significant flow voids. No cystic component was seen in relation to it. It showed homogeneous moderate contrast enhancement.

The patient was thereafter referred to a higher centre for further management.

## Discussion

Jugular foramen schwannoma becomes symptomatic either from dysfunction of the parent or neighbouring cranial nerves or from progressive distortion of the brainstem[2]. The clinical presentation of schwannomas arising in the jugular foramen appears to fit into one of three categories. First, tumours in this area can present either as Vernet syndrome (jugular foramen syndrome) or as Collet-Sicard syndrome. Vernet syndrome involves paralysis of cranial nerves 9th, 10th, and 11th due to tumour expansion within the foramen[5], characterised by loss of taste in the posterior third of the tongue (CN 9th); vocal cord paralysis, and dysphasia (CN 10th); and

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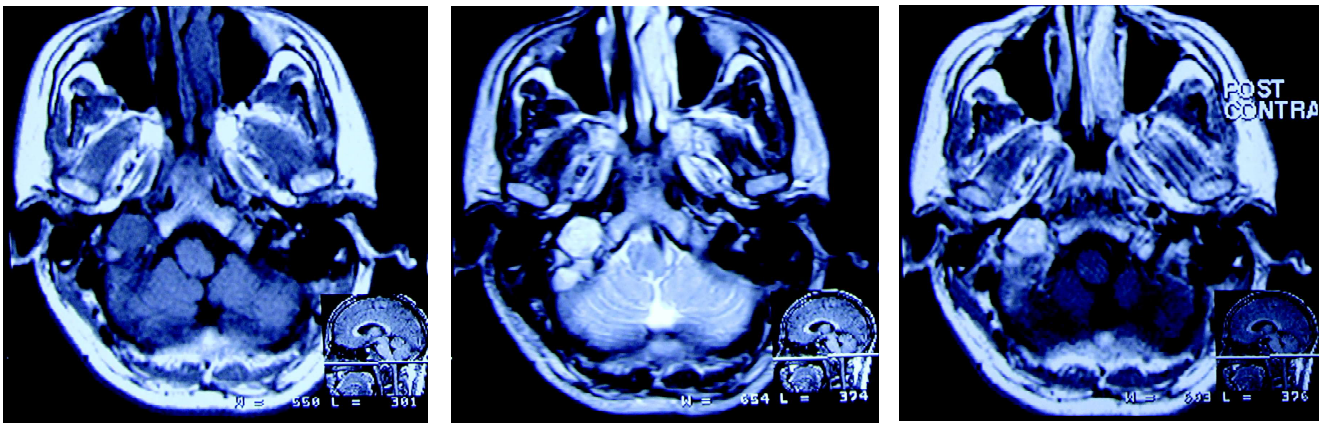


***Fig. 1a, b and c:*** *Axial images show T1 isointense (a) and T2 hyperintense (b) well-marginated lesion in the right jugular fossa without any significant flow voids. Post-contrast image shows moderate homogeneous enhancement (c).*

weakness of the sternocleidomastoid and trapezius (CN 11th)[6]. If in addition paralysis of hypoglossal nerve (CN 12th) characterised by paresis and atrophy of tongue is also present, it is called as Collet-Sicard syndrome[7]. This syndrome has been described in association with the Jefferson fracture, idiopathic cranial polyneuropathy, multiple myeloma, internal carotid artery dissection, Lyme disease, skull base tumours of primary and metastatic (prostate, lung, breast, and renal tumours) origin and occipital condyle fractures[8].

A second mode of presentation mimics that of a glomus jugulare neoplasm which can present with pulsatile tinnitus, a reddish mass behind the tympanic membrane and facial weakness. Finally, tumours arising within the foramen can give rise to the symptoms of hearing loss or disequilibrium and thus resemble an acoustic neuroma[5]. The characteristic physical examination finding is denervation atrophy of the trapezius and sternocleidomastoid muscles. In patients without phakomatosis, these lesions most often are encountered in the third to sixth decades of life[9]. There is a male predominance in the literature[3].

Accurate preoperative diagnosis can be done based on MR imaging[10]. Schwannomas cause smooth, well-demarcated enlargement of the jugular foramen[6]. Dumb-bell shaped tumours with both intra- and extra-cranial extension have been known[11]. Most schwannomas appear hypointense or isointense relative to gray matter on T1-weighted MR images, and hyperintense relative to gray matter on T2-weighted MR images[6] and show moderate contrast enhancement. On plain CT scan, the tumour is hypodense or isodense with the brain while it shows moderate enhancement on contrast administration[2]. The bony margins around the tumour are generally smoothly eroded. Usually, one can define the entire extent of the tumour, from the intracranial portion to that extending through the jugular foramen into the neck. One can also usually separate a neuroma arising in the jugular foramen from one arising from the acoustic nerve with a properly targeted MRI[5]. Calcification or haemorrhage is uncommon, but cystic or fatty degeneration are frequent[6].

An important differential diagnosis is meningiomas, which usually have a lower T2 signal than do schwannomas, and higher pre-contrast CT attenuation than do schwannomas. In addition, they may show calcification and hyperostosis; growth is usually within the jugular foramen and extension below the skull base is unusual[12]. Another important differential diagnosis is tumour of the glomus jugulare. This is a highly vascular tumour, with intense contrast enhancement and typically multiple small flow voids[6]. Standard treatment is surgical resection and the target is total excision[2]. Gamma knife radiosurgery is a safe and effective primary or adjuvant treatment method for the control of jugular foramen schwannomas[10].

In conclusion, jugular foramen schwannomas are rare lesions that can mimic an acoustic neuroma or glomus jugulare tumour. Jugular foramen tumours must be considered in the aetiologic diagnosis of vocal fold paralysis, particularly in cases where signs or symptoms associated with the involvement of other cranial nerves are present.

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CASE REPORT

JIACM 2011; 12(3) : 230-33

# Fever of Unknown Origin – A Case of Secondarily Infected Teratoma

*Shakya Bhattacharjee*, Jaydip Deb***

## Abstract

***A 20-year-old female presented with persistent chest pain, low-to-moderate fever and cough for 8 weeks. She was investigated extensively and was ultimately found to harbour a neoplastic lesion – a secondarily infected benign mediastinal teratoma. Her symptoms responded to conservative therapy.***

***Key words: Chest pain, fever, infection, neoplastic.***

## Introduction

Benign mediastinal or intrathoracic germ cell tumours are relatively rare causing 3 – 12% of all mediastinal tumours according to a recent study[3]. A teratoma is a germ cell tumour composed of tissues arising from more than one of the three embryonic germ cell layers: ectoderm (e.g., teeth, skin, hair), mesoderm (e.g., cartilage and bone) and endoderm (e.g., bronchial, intestinal, and pancreatic tissue). Teratoma can be further divided into mature teratoma, immature teratoma, and malignant teratoma.

## Case report

A 20-year-old female presented with persistent right-sided localised chest pain, low-to-moderate grade fever, cough with minimal blood tinged expectoration for 8 weeks each. Her pain was persistent and was aggravated by cough or deep breathing. The pain had become severe since last 2 weeks and was disturbing her sleep. The fever was of intermittent variety, having no periodicity, around 37.8 °C and went up to a maximum of 39 °C, accompanied by chills and sweating during temperature decline following paracetamol administration. The patient had already taken some antibiotics and analgesics without consulting a doctor in this 8 weeks period. There was loss of appetite but no significant loss of body weight.

Intermittent cough with minimal blood-tinged expectoration was witnessed for 8 weeks . Cough had no periodicity, no aggravating and relieving factor.

Past history: insignificant; family history: insignificant; menstrual history: normal.

**General survey (prominent features)**

- Pallor°/J°/Cy°/Cl+/oe° no significant lymph node or venous prominence.
- Pulse rate: 82/m (R); blood pressure: 120/80 mmHg (supine); respiratory rate: 24/min; temperature: 38 °C.

## Systemic examination

Respiratory system

Diminished respiratory movements on the right-side (lower 2/3); decreased vocal fremitus over infraclavicular, mammary, axillary and infraaxillary areas. Percussion note was dull from right 3rd intercostal space downwards in mid-clavicular line, right 5th intercostal space downwards in mid-axillary region, posteriorly resonant, tenderness on percussion. Auscultation revealed reduced VBS on the right-side in the same distribution.

CVS: within normal limits

Nervous system: within normal limits

GI system including oral cavity and dental hygiene: within normal limits

Ophthalmological and otolaryngorhinological examination: no abnormality detected

## Investigations

- Hb: 11.65 gm/dl, WBC: 14,400/cu ml (N – 66, L – 28, E2 M2 B2), Hct: 42%, ESR: 64 mm/hr (1st), CRP: 24 mg/dl, platelet: 1,76,000/cu ml.
- FBS: 80 mg%, PPBS: 114 mg%

** Post-graduate Trainee, ** Associate Professor, Department of Chest Medicine, R. G. Kar Medical College and Hospital, Kolkata – 700 037, West Bengal.*

- LFT: total protein – 6 g%, albumin – 3.2 g%, bilirubin (T) – 0.8 mg%, conj – 0.5 mg%, SGOT – 44 U/l, SGPT – 30 U/l, ALP – 138 U/l, GGT – 310 U/l, PT – 14.3 sec, aPTT – 37.4 sec
- $Na^+$ – 130 meq/l, $K^+$ – 4 meq/l, $Ca^+$ – 8.8 mg/dl
- CPK-MB – 32/24 U/l, LDH – 290 U/l S. ACE – 36 U/ml
- Blood for culture: no organism detected
- Urine for RE/ME and C/S: no growth
- Sputum for AFB: negative
- Sputum for C/S study: no growth
- Chest X-ray: homogeneous opacity involving all the zones on the right-side, obliterating the right costophrenic and cardio phrenic angles, and lower mediastinum shifted to the opposite side (Figure 1 and 2)
- ECG: sinus tachycardia
- Echo (2D and M) : normal
- Pleural aspiration: dry tap
- FNAC of the aspirate: predominantly neutrophils
- C/S study of the aspirate: no growth
- USG whole abdomen: normal study
- Serological testing: ANA titre – 1/160, AMA, ANCA, dsDNA, anti-ENA: negative
- HbsAg, HCV and HIV: negative (anti-Hbs and anti-HBc were detectable)
- EBV and CMV: IgG – positive, IgM – negative

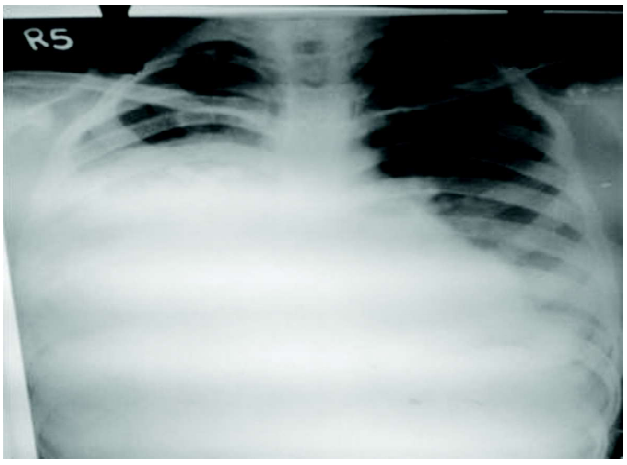


***Fig. 1:*** *Chest X-ray PA view showing opacity in right hemithorax.*

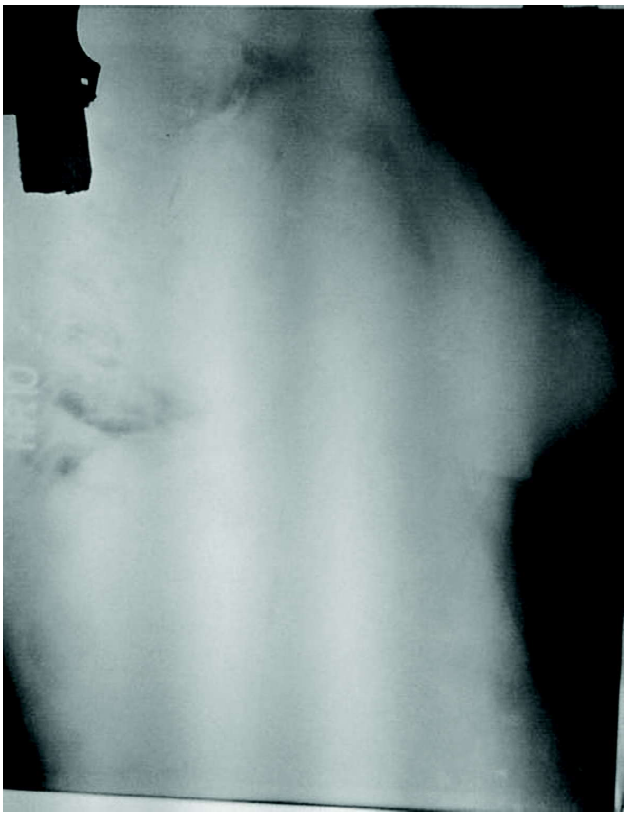

***Fig. 2:*** *Same patient showing right lateral view.*

USG of right hemithorax showed a solid mass of varying density, no fluid collection. CT thorax showed a predominantly cystic mass of varying density showing fluid, bony and fat densities in the anterior mediastinum, no consolidation, no obvious bony or great vessel involvement (Figures 3, 4, 5 and 6).

X-ray of facial cranium: no sinus cavity inflammation

CT brain and abdomen: Normal study

Serum AFP, hCG and CEA: within normal limits

Histopathology of the trucut biopsy of the specimen was suggestive of a mature teratoma (Figure 7, 8 and 9) and showed plenty of neutrophils.

Specimen sent for C/S study: no growth

The patient was given intravenous antibiotic Ceftriaxone (1 g) for 5 days and oral azithromycin (500 mg) for 3 days, and paracetamol (650 mg) four times daily.

Five days later, the fever, chest pain and cough started subsiding. WBC count dropped to 8,700, ESR to 20, and

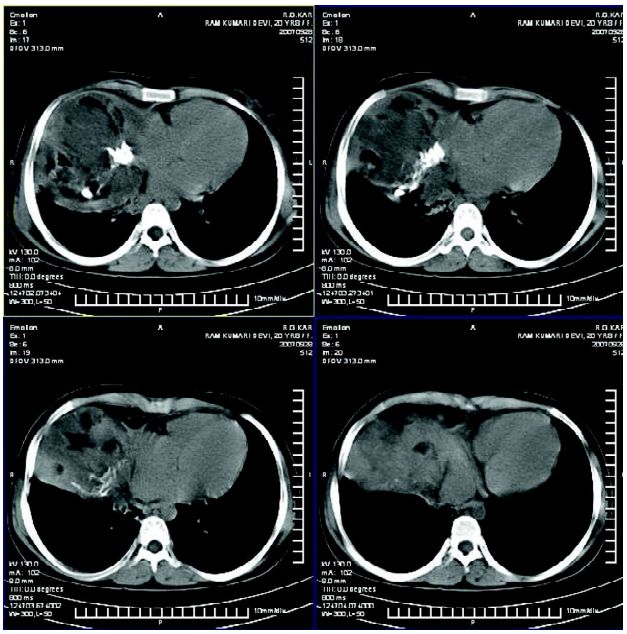

***Fig. 3:*** *CT thorax showing heterogeneous mass on the right-side.*

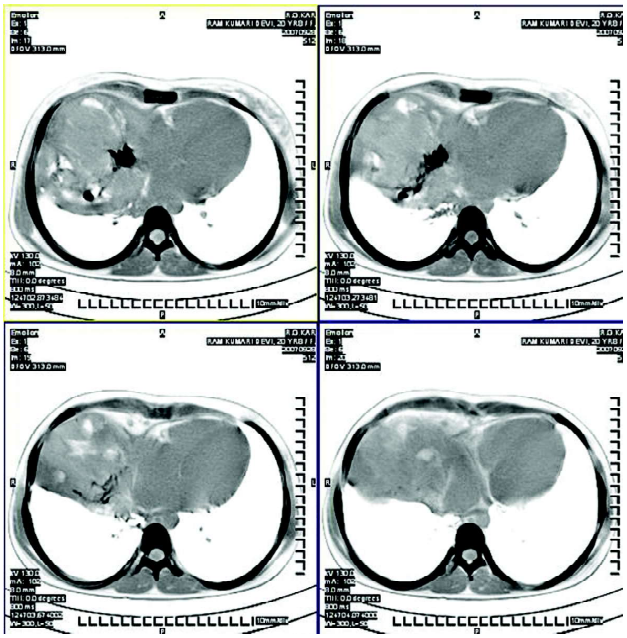

***Fig. 4:*** *Fat, fluid, bone density in the mass (teratoma).*

CRP to 8, and the lady felt a lot better. She was switched over to oral cefpodoxime 5 days later, and was transferred to the cardiothoracic surgery department. The mass was excised and biopsied, the same diagnosis was proved and no malignant focus could be detected.

Final diagnosis is intrathoracic benign cystic teratoma with secondary infection.

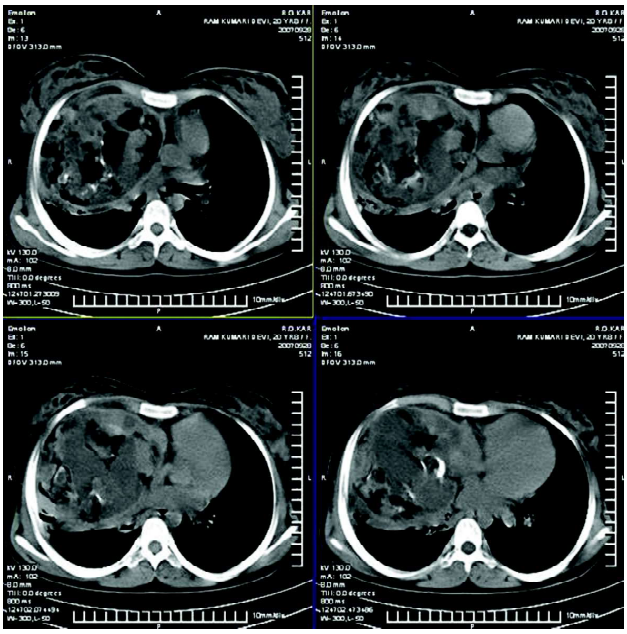

***Fig. 5:*** *Heterogeneity of the mass (teratoma) in CT of thorax.*

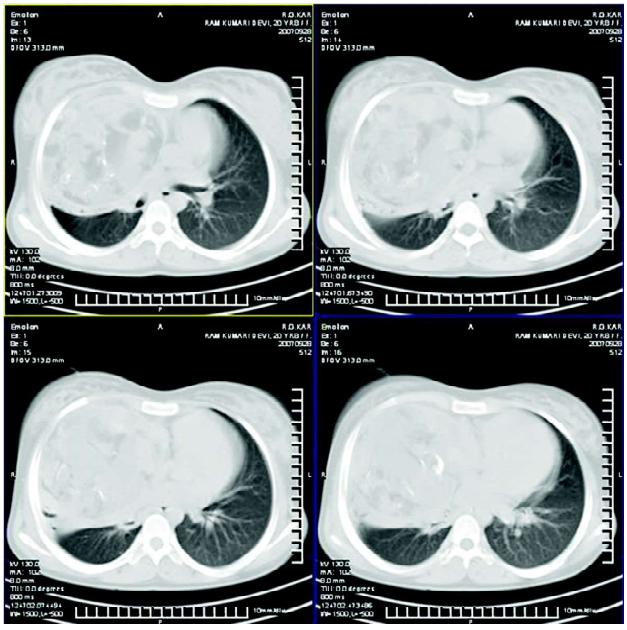

***Fig. 6:*** *Teratoma.*

## Discussion

A large percentage of mediastinal tumours and cysts produce no symptoms[2,7] and are found on an incidental chest radiograph or other imaging study of the thorax performed for an unrelated reason. In adults, asymptomatic masses are more likely to be benign. Constitutional symptoms (e.g., weight loss, fever, malaise, vague chest pain) commonly occur with malignant

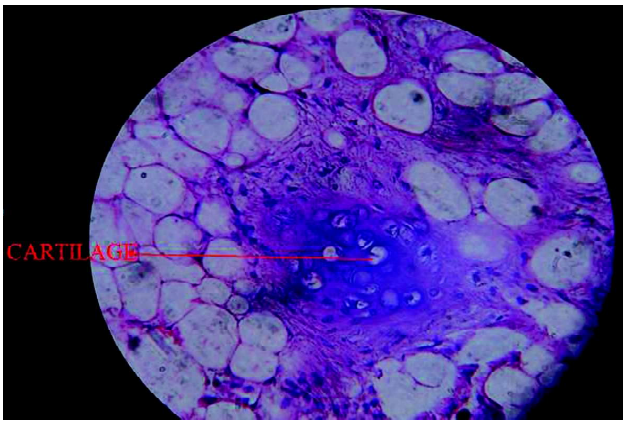


***Fig. 7:*** *Histopathology of the mass showing cartilage.*

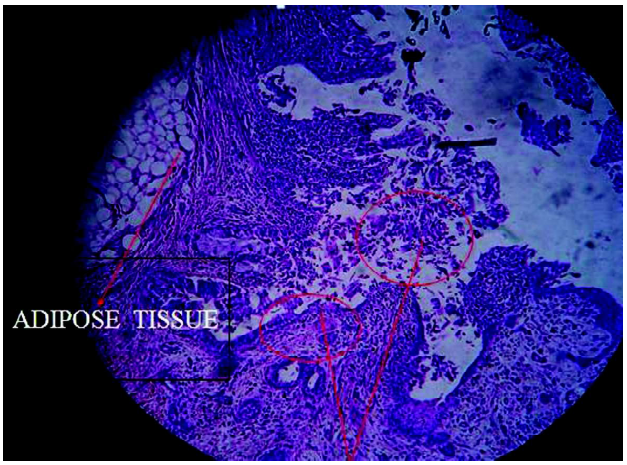


***Fig. 8:*** *Histopathology showing adipose tissue.*

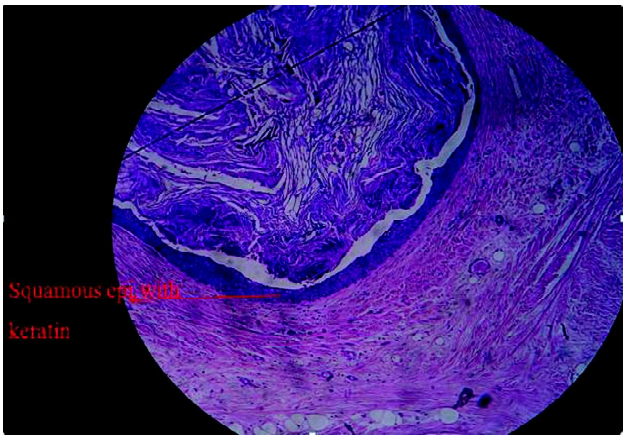


***Fig. 9:*** *Histopathology showing squamous epithelium.*

tumours, but can be rarely observed in some benign tumours as well. There is a case report of massive haemoptysis[5,6] in a benign mediastinal teratoma and a case of heart failure[8] in an adult. One series on 8 giant mediastinal teratomas reported secondary bacterial infection of the teratoma tissue components as the cause of fever and chest pain[4]. Shields reported that benign mediastinal teratomas secrete pancreatic enzymes causing tissue inflammation, secondary bacterial infection, fever, and chest pain[1,7]. Teratomas can get infected from contiguous foci in the lung parenchyma or via the bloodstream[3]. No obvious cause of fever or chest pain prompted us to consider secondary bacterial infection of the giant teratoma. Though C/S study of the aspirate could not find any organism (probably due to previous antibiotic use), antibiotics reduced the WBC count, high CRP, ESR, the pain and fever. With onset of infection, there is a rapid influx of fluid and sudden increase in size of the mass, turning it symptomatic. The disappearance of the pain and fever after antibiotic administration was due to the reduction of the tumour in size with the clearance of the inflammatory exudate[3].

## Conclusion

A benign teratoma may masquerade as an empyema or pneumonia and sometimes clinically behaves like its malignant counterpart. Often the X-ray is misleading and if someone is not watchful enough he or she can miss the heterogeneous nature of the X- ray lesion.

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CASE REPORT

JIACM 2011; 12(3) : 234-5

# Gatifloxacin and Hyperglycaemia

*Nagina Agarwal**

## Abstract

***A diabetic female presented with urinary tract infection. She was prescribed gatifloxacin 400 mg per day. Symptoms of UTI improved but hyperglycaemia occurred on two separate occasions with gatifloxacin which required short-term increase in dose of oral hypoglycaemic agent.***

***Key words: Dysglycaemia, quinolones.***

## Introduction

Flouroquinolones are frequently prescribed antibiotics. Common side-effects are dizziness, tinnitus, psychiatric symptoms, phototoxicity, toxic epidermal necrolysis, prolongation of QT interval, and hepatotoxicity. But reports of hyperglycaemia are rare. Here we report a case of gatifloxacin associated hyperglycaemia in a diabetic patient with urinary tract infection (UTI).

## Case report

A 75-year-old patient presented in our hospital's out-patient department with complaint of burning micturition for five days. She was a diabetic since the last two years and was well-controlled on tablet voglibose 0.2 mg twice a day. On examination, her vitals were stable. General physical and systemic examinations were normal. Investigations revealed haemoglobin - 11 gm%, total leukocyte count - 6,800 per cu mm, differential leukocyte count - P-60, L-37, M2 E1, erythrocyte sedimentation rate - 40 mm in first hour, blood urea 36 mg%, serum creatinine 0.6 mg%, serum bilirubin 0.8 mg%, serum aspartate transaminase - 24 IU/ml, serum oxaloacetate transaminase - 30 IU/ml, blood sugar fasting - 92 mg% and post-prandial - 110 mg%. Urine microscopy showed 20 pus cells per high power field and urine culture grew *E. coli* more than $10^5$ per ml sensitive to gatifloxacin. The patient was prescribed gatifloxacin 400 mg once daily for five days. She became asymptomatic and urine culture was sterile after five days. However, her blood sugar post-prandial was 254 mg%. Dose of voglibose was inceased to 0.2 mg thrice daily and repeat blood sugar (random) on day 12 was 158 mg%, and on day 15 it was 60 mg%. Therefore, voglibose was decreased to the previous dose of 0.2 mg twice daily, and blood sugar random became 110 mg%.

Surprisingly, this patient had another episode of UTI when urine culture grew *E. coli* more than $10^5$ per ml sensitive to gatifloxacin. Patient was again prescribed gatifloxacin 400 mg once daily for five days. Random blood sugar increased on day five to 260 mg%, became 130 mg% on day 11 on tablet voglibose 0.2 mg thrice daily and 50 mg% on day 17. Again voglibose was decreased to its previous dose of 0.2 mg twice daily and blood sugar random came up to 100 mg%.

## Discussion

It is an interesting case of recurrent hyperglycaemia due to gatifloxacin in a seventy-five-year-old female with diabetes and UTI. On review of literature, it has been found that among quinolones, dysglycaemia is more common with gatifloxacin and levofloxacin. In a single largest study by LePlante *et al*, out of 1,573 patients studied, dysglycaemia occurred in 33 patients, of which 13 were receiving gaitifloxacin and among these 13 patients, 11 had diabetes[1]. Various risk factors predisposing to dysglycaemia with gatifloxacin are age more than 65 years[2], diabetes[1,3], lack of adjustment of dose for renal function[3] and patient receiving insulin or sulphonylurea for diabetes[1].

However, in another study, severe hyperglycaemia occurred with gatifloxacin in non-diabetic patients despite adjustment of dose for renal function[4]. Lodise *et al* observed that gatifloxacin is independently associated with hypoglycaemia and hyperglycemia (adjusted odds

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ratio 2.5 and 2.4 respectively) even after dose adjustment for renal function[5].

In the present case, the only risk factors were age and diabetes. This is in contrast to the study of Onyenwenyi *et al* in 1,504 patients where gatifloxacin was not associated with increased risk of hyperglycaemia (adjusted odds ratio: 1.06) and stratification by diagnosis of diabetes, gatifloxacin treated patients appeared to have decreased risk of hyperglycaemia as compared to non-diabetics (adjusted odds ratio: 0.4 and 1.64 respectively)[6].

The exact mechanism of gatifloxacin-induced hyperglycaemia is unknown, but possibly may be related to vacuolation of pancreatic beta cells leading to decrease in insulin secretion[2].

Another interesting feature in this patient is that hyperglycaemia is mild which responded to increased dose of voglibose. This is in contrast to previous reports of severe hyperglycaemia occurring after three days of gatifloxacin requiring insulin infusion in non-diabetic patients[7].

## Conclusion

The present case is a case of an elderly diabetic female with normal renal function requiring gatifloxacin for urinary tract infection who responds to treatment but develops mild hyperglycaemia which gets controlled with slight increase in dose of oral hypoglycaemic agent on two separate occasions. The case stresses the importance of gatifloxacin producing hyperglycaemia emphasising the need to monitor blood sugar in every patient requiring gatifloxacin or a switch-over to another antibiotic if possible.

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CASE REPORT

JIACM 2011; 12(3) : 236-8

# Ruptured Sinus of Valsalva with Complete Heart Block

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## Abstract

***Complete heart block due to ruptured sinus of Valsalva is a very rare complication and to the best of our knowledge no such case has been reported in the literature. Here, we describe a case of ruptured aneurysm of the right coronary sinus of Valsalva with complete heart block diagnosed by transthoracic two-dimensional echocardiography and electrocardiography in a patient with recent onset of giddiness, continuous murmur, and acute right congestive heart failure.***

***Key words:** Transthoracic echocardiography, sinus of Valsalva aneurysm, complete heart block.*

## Introduction

Ruptured sinus of Valsalva (RSOV) is an uncommon condition with protean manifestations. The presentation may range from an asymptomatic murmur to acute cardiogenic shock and death. Echocardiography has become the definitive investigative tool not only to diagnose the lesion, but also to quantify its severity. In the literature, complete heart block has been reported with unruptured sinus of Valsalva aneurysm. However, it is a very rare complication of RSOV. Thus, we report a case of ruptured sinus of Valsalva with complete heart block.

## Case report

A 27-year-old man presented with a history of giddiness and acute dyspnoea of six hours duration. Physical examination of the patient on admission revealed a normal stature (height 170.2 cm and weight 72 kg). Body temperature was 36.5°C. Blood pressure was 110/64 mmHg and the pulse was 44/min, regular, and of good volume. The neck veins were distended and the liver was palpable 2 cm below the right costal margin and it was non-pulsatile. There was no ankle oedema, and the lungs were clear. A broad cardiac impulse was located on the precordium, and both systolic as well as diastolic thrills were palpable. A grade VI continuous, harsh murmur, maximal in the 4th intercostal space along the left sternal border, was audible over a wide area. The first and second sounds were of normal intensity, whereas the third and fourth sounds were not audible. Laboratory examination revealed haemoglobin of 13 gm%, serum sodium of 143 meq/l, serum potassium of 4.1 meq/l, SGOT of 36 IU/l, SGPT of 43 IU/l, serum alkaline phosphatase of 83 IU/l, serum bilirubin of 0.8 mg/dl and serum creatinine of 0.8 mg/dl. All investigations were within the normal range. Tests for C-reactive protein and rheumatoid arthritis factor were negative and the antistreptolysin-O titre was 100 Todd units. Chest skiagram demonstrated moderate cardiomegaly. Ultrasound abdomen revealed hepatomegaly with prominent intrahepatic veins.

Electrocardiogram revealed complete heart block with an atrial rate of 120/min and ventricular rate of 44/min (Fig. 1). Transthoracic two-dimensional echocardiography (TTE) demonstrated an aorta-to-right ventricle fistula through a ruptured right coronary sinus of Valsalva with enlarged right chambers of heart (Fig. 2). Both contrast and colour-Doppler techniques showed shunting of blood from the sinus of Valsalva into the right ventricle (Fig. 3).

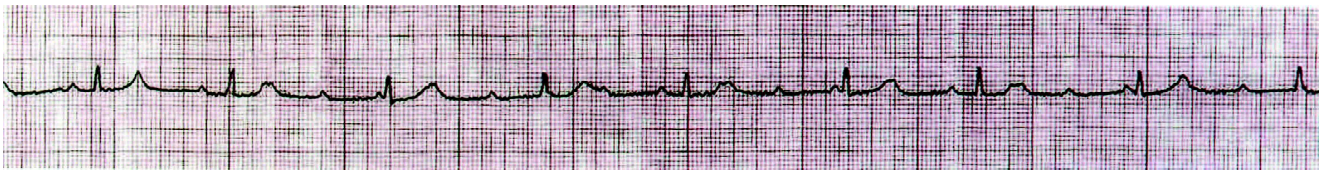

***Fig. 1:** Electrocardiogram showing complete heart block with atrial rate of 120/min and ventricular rate of 44/min.*

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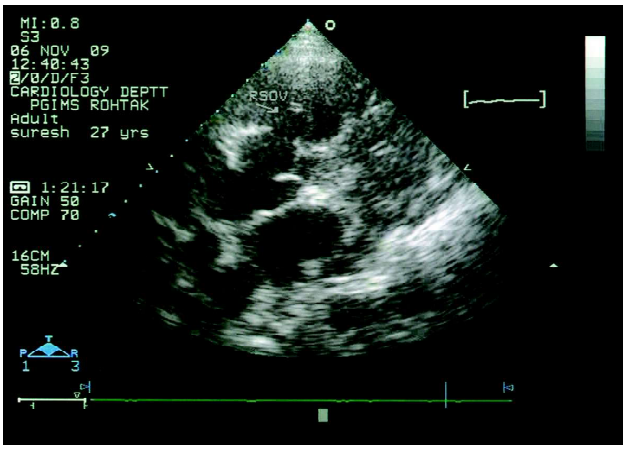


***Fig. 2:*** *Echocardiogram showing ruptured sinus of Valsalva.*

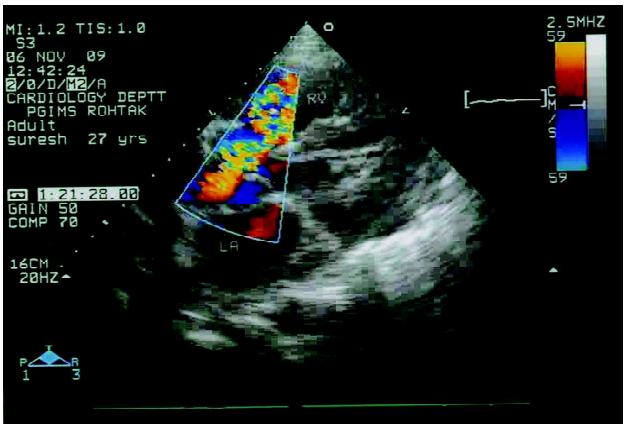


***Fig. 3:*** *The typical mosaic colour jet showing the blood flow across a ruptured sinus of Valsalva.*

There was no evidence of infective endocarditis, rheumatic fever or syphilis on the basis of the patient's history and relevant laboratory analysis. Patient was diagnosed as a case of ruptured sinus of Valsalva with complete heart block, which had presented with right congestive heart failure and bradycardia. He was put on diuretics and oxygen inhalation. Complete heart block was transient and atrio-ventricular conduction reverted to normal after two hours. The patient was thereafter referred to the cardio-thoracic surgeon for repair of ruptured sinus of Valsalva aneurysm.

## Discussion

Aneurysms of the sinus of Valsalva account for less than 1% of congenital cardiac anomalies[1]. The pathology of this condition is thought to be due to a failure of the fusion between the aortic media and the heart at the level of the annulus fibrosus of the aortic valve, with subsequent aneurysmal enlargement at this weak point due to the high head of pressure at the root of the aorta. In most of the cases, these aneurysms rupture in the second or third decade of life. 90% to 95% of these congenital aneurysms originate in the right or non-coronary sinus and project into the right ventricle or into the right atrium. Aneurysms arising in the non-coronary sinus almost always rupture into the right atrium, and those arising in the right coronary sinus generally communicate with the right ventricle and occasionally with the right atrium. Aneurysms of left coronary sinus rupture into the pericardial space beneath the left coronary artery[2].

Before the introduction of echocardiography, the diagnosis of a ruptured sinus of Valsalva aneurysm in the living patient was rare, with most of the reports coming from autopsy or surgery. Nowadays, the diagnosis is possible with both TTE and transoesophageal echocardiography (TEE). In the patient presented herein, TTE provided very detailed information to us[3].

Complications of sinus of Valsalva aneurysms include aortic regurgitation, decrease in coronary artery blood flow, arrhythmias, endocarditis, and rupture[4]. Cardiac conduction disturbances due to sinus of Valsalva aneurysms occur because of protrusion of aneurysm into the interventricular septum. These conduction abnormalities include sinoatrial conduction disruption, transient or persistent complete atrio-ventricular block, and bundle branch block[5,6]. In the literature, complete heart block has been reported with unruptured sinus of Valsalva aneurysm; but no case of complete heart block with ruptured sinus of Valsalva aneurysm has been reported.

It is concluded that RSOV with complete heart block is a rare condition with a varied presentation that sometimes can be fatal, if not diagnosed quickly. Echocardiography is a useful tool to accurately diagnose the ruptured sinus of Valsalva aneurysm. Electrocardiogram must be recorded in every patient to preclude fatal arrhythmias.

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CASE REPORT

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# CMV Encephalitis with Bilateral Thalamic Involvement in an Immunocompetent Young Female

*S Prasad*, R Chandel**, R Manocha**, A Jain**, A Pandey**, R Kumar**, V Goel**, B Gupta***

## Abstract

***We report a case of CMV encephalitis in an immunocompetent female with bilateral thalamic involvement (alongwith ventral midbrain and periventricular white matter hyperintensities on T2W and FLAIR sequences in MRI).***

***Key words: Cytomegalovirus (CMV) encephalitis, bilateral thalamic involvement, MRI, immunocompetent.***

## Introduction

Cytomegalovirus (CMV) can cause severe disease in immunocompromised patients, due either to reactivation of latent CMV infection or by acquisition of primary CMV infection. Clinical syndromes that may be observed include encephalitis, pneumonitis, hepatitis, uveitis, retinitis, colitis, and graft rejection. CMV encephalitis primarily affects immunocompromised patients, and is less commonly encountered in immunocompetent hosts. Magnetic resonance imaging usually reveals meningeal enhancement, ependymal enhancement or periventricular enhancement. We report a case of CMV encephalitis in an immunocompetent female with bilateral thalamic involvement (alongwith ventral midbrain and periventricular white matter hyperintensities on T2W and FLAIR sequences).

## Case report

A 35-year-old female, resident of Faridabad, Haryana was referred to our casualty on 12th December 2010, with complaints of low-to-moderate grade fever for 5 to 6 days, one and an half month back, followed by altered sensorium for one month. There were no preceding complaints of nausea, vomiting, loose motions, or any history of hypertension, diabetes mellitus, or tuberculosis. The patient was absolutely healthy before these symptoms appeared.

She was under treatment for this in a private hospital and a perusal of the previous records showed that her CSF examination had revealed 75 cells (of which 85% were lymphocytes and the remaining 15% were neutrophils), glucose level of 49 mg% (normal range: 40 - 70 mg/dl), and protein level of 68 mg% (normal range: 15 - 50 mg/dl). She was being managed as a case of post-encephalitic syndrome with supportive management.

On examination at the time of presentation, the patient was pale, acyanotic, nonicteric, with no evidence of oedema or clubbing. She was conscious but in a state of akinetic mutism (she remained immobile, made no sounds, and followed movements slowly with her eyes). Her vitals were stable. Cardiac examination was unremarkable with normal first and second heart sounds and no added murmur. Chest auscultation revealed bilateral vesicular breath sounds. There was no organomegaly and normal bowel sounds were present on abdominal examination. Pupils were of normal size and displayed normal reaction bilaterally. Fundus examination was normal. Deep tendon reflexes were absent. Plantars were flexor bilaterally and there was no neck rigidity. There were bed sores in the lumbo-sacral region, and she had developed contractures (due to poor nursing care and lack of physiotherapy).

Laboratory investigations revealed a haemoglobin of 11.5 gm%, leucocyte count of 11,600/dl (P-70, L-26, M-2, E-2), and a platelet count of 1,64,000/dl. Her KFT, LFT, and serum electrolytes were within normal limits. Serological tests for HIV, hepatitis B and C were negative. NCCT head done elsewhere had revealed a left thalamic infarct. To strengthen the diagnosis and to rule-out any other cause for the altered sensorium, an MRI was done, which showed

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bilateral thalamic, ventral, midbrain, and periventricular white matter hyperintensities on T2W and FLAIR sequences suggestive of viral encephalitis (Fig. 1).

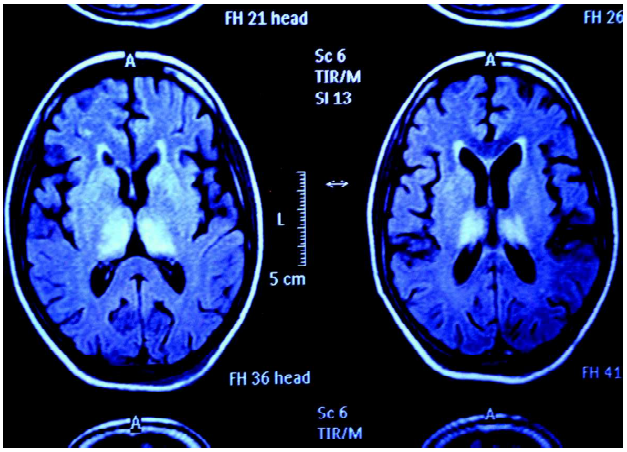


***Fig. 1:*** *MRI showing bilateral thalamic hyperintensities on T2-W sequences suggestive of viral encephalitis.*

In the quest for the aetiological agent, serological tests for HSV1 and 2, Japanese encephalitis (JE) and cytomegalovirus (CMV) from blood and serum were conducted (lumbar puncture was not possible due to the decubitus ulcer in the lumbo-sacral region). While serum was nonreactive for HSV 1 and 2 and JE, serology for CMV was positive.

She was initiated on Ganciclovir and Foscarnet. Along with this, she was managed conservatively with empirical antibiotics, regular dressings, and physiotherapy. The lymphocyte counts returned to normal. The decubitus ulcer showed healthy granulation tissue and swab for culture failed to isolate any organism. The patient was later discharged on request, advised to come for regular follow-up, but was lost to follow-up.

## Discussion

Cytomegalovirus (CMV) infection is the most common opportunistic viral infection associated with HIV infection: it is recognised before death in up to 40% of patients with end-stage AIDS, and in up to 90% at autopsy[1, 2]. CMV causes retinitis and gastrointestinal disease, and both the peripheral nervous system and the CNS are vulnerable to CMV infection. Cytomegalovirus (CMV) infection of the central nervous system may affect the brain (i.e., diffuse encephalitis, ventriculoencephalitis, cerebral mass lesion) or the spinal cord (i.e., transverse myelitis, polyradiculomyelitis). CMV encephalitis primarily affects immunocompromised patients, and is less commonly encountered in immunocompetent hosts. In a review of 676 patients with CMV encephalitis, Arribas *et al*[3], found that 85% of the patients were infected with HIV, 12% had other causes of immunosuppression (usually organ transplantation), and only 3% were otherwise healthy. Most patients with neurological CMV disease previously had CMV disease diagnosed at another site, such as retina[3]. However, our patient had no evidence of CMV disease at other sites.

Most patients with CMV disease of the brain present with either diffuse micronodular encephalitis or ventriculoencephalitis. The former is characterised by multifocal, diffusely scattered micronodules, which are aggregates of macrophages and glial cells[4, 5]. Nodules and inclusions bearing cytomegalic cells are concentrated in gray matter and widely distributed in the cortex, basal ganglia, brainstem, and cerebellum[6]. Although these are frequently found on histopathologic examination, the clinical significance is not always clear.

Clinically, ventriculoencephalitis presents as a rapidly progressive delirium, cranial nerve deficits, nystagmus, and ataxia. The CSF usually has an elevated protein level, pleocytosis, and/or hypoglycorrhachia[7, 5]. In patients with isolated ventriculoencephalitis, the CSF pleocytosis consists mostly of mononuclear cells. In patients with concomitant radiculomyelitis, neutrophil predominance is seen[3]. The initial CSF report in our case was in consonance with these.

Our case had presented with akinetic mutism. The causes of akinetic mutism include damage in the regions of medial thalamic nuclei or the frontal lobe (particularly lesions situated deeply or on the orbitofrontal surface), or from hydrocephalus. We had performed the MRI since the NCCT showed only left thalamic infarct and failed to provide reasons to explain the akinetic mutism.

Neuroimaging is fundamental in recognising CNS alterations and it also provides some distinction between the different viral encephalitis. MRI reveals progressive ventricular enlargement, periventricular enhancement, and increased periventricular signal on T2-weighted

images in CMV encephalitis. However, diagnosis of CNS CMV infection is difficult because radiological findings may be normal and CMV is rarely cultured from CSF[1, 8]. In some cases, diffuse and irregular increased signal intensities through the long segment of the spinal cord and cauda equina on T2-weighted MRI[9] or periventricular enhancement after contrast infusion[5] provides diagnostic clues. The usual imaging pattern consists of periventricular inflammation that is not always related to the severity of pathologic changes[7]. There is a case report of CMV encephalitis presenting with clinical and radiologic brainstem and cerebellar involvement[10]. However, to our knowledge, ours is the first case of CMV encephalitis presenting with bilateral thalamic involvement.

MRI finding of bilateral T2 thalamic hyperintensity is most characteristic of Japanese encephalitis[11]. Unilateral involvement has also been reported but is less common. Other common sites of involvement include basal ganglia, substantia nigra, red nucleus, pons, hippocampus, cerebral cortex, and cerebellum. Subcortical white matter involvement is also reported in some patients, but this has always been in combination with the more characteristic gray matter lesions[12-14]. Some lesions, especially those in the thalamus, may be haemorrhagic[11]. Serological examination for Japanese encephalitis was non-reactive in our case.

The predilection of herpesviruses for limbic-related areas (e.g., hippocampal complex, medial temporal cortex, insula, cingulated cortex) can help to distinguish herpes encephalitis from other aetiologies (e.g., Japanese encephalitis)[15]. Our patient's serology was negative for HSV 1 and HSV 2 also.

Ganciclovir is a guanarine derivative and the mainstay of treatment for CMV retinitis, but ganciclovir-resistant strains have been reported[16]. Ganciclovir also reaches lower concentrations in the CSF and brain than it does in serum[6, 17], and is associated with poor responses[7, 18]. Foscarnet, a pyrophosphate analogue with better CSF penetration, is an alternative therapeutic approach because it does not require phosphorylation to be active (as does ganciclovir). Synergism between ganciclovir and foscarnet has been reported *in vitro*, and some clinical data are supportive of a similar phenomenon *in vivo*, in CMV retinitis and in encephalitis[19, 16].

Due to the lack of controlled, randomised, double-blinded studies, the optimal antiviral treatment for CMV encephalitis has yet to be determined. In patients with AIDS and CMV neurological diseases, the International AIDS Society-USA[20] recommends therapy with intravenous ganciclovir or intravenous foscarnet or a combination of the two drugs. The poor general condition in this case, the above-mentioned findings, and the high mortality associated with CMV encephalitis – even in the immunocompetent host – led us to combine the two drugs. In contrast to AIDS patients with CMV encephalitis and retinitis, there is no consensus about maintenance antiviral therapy in the non-HIV population[21, 19].

In conclusion, while MRI provides useful clues to the aetiology, serology – and if possible, isolation of the virus – is needed to confirm the diagnosis and initiate appropriate treatment.

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CASE REPORT

JIACM 2011; 12(3) : 243-5

# Cardiac Failure following Imatinib Treatment – A Rare But Fatal Complication

*VV Jain*, H Pawade**, OP Gupta****

## Abstract

***Tyrosine kinase inhibitors like imatinib are used in treatment of Philadelphia chromosome-positive leukaemia and may induce a potential cardiotoxicity leading to congestive cardiac failure, acute coronary syndromes or arrhythmias. We present one such case of fatal congestive cardiac failure following Imatinib therapy.***

## Introduction

CML is a myeloproliferative disorder and advent of tyrosine kinase (TK) inhibitors has revolutionised its treatment. Cardiac toxicity can be caused by the tyrosine kinase inhibitors and these range from asymptomatic subclinical abnormalities to life-threatening cardiac failure and arrhythmias.

## Case report

An elderly female was admitted with complaints of easy fatigability and weakness since 1 month. There was no h/o chest pain, fever, cough, swelling over feet, chronic blood loss. She had no past h/o ischaemic heart disease, chronic obstructive airway disease, asthma, hypertension, and diabetes mellitus. On examination she was afebrile, pulse of 100/min, BP – 120/60 mmHg, markedly pale, anicteric, Jugular venous pressure (JVP) not raised and no pedal oedema. Left submandibular lymphadenopathy was present, 2 x 2 cm, and firm, non-tender, not fixed to underlying structure or skin. Abdominal examination revealed mild, non-tender hepatomegaly (2 cm below costal margin) with grade II splenomegaly (4 cm below subcostal margin), firm, and non-tender with smooth surface. On investigation she was found to have haemoglobin (Hb) of 6.7 gm/dl, mean corpuscular volume (MCV) – 88.2 fl, total leucocyte count (TLC) of 1, 85,000/cumm, platelets of 1, 76,000/cumm. Peripheral smear revealed marked leukocytosis, differential counts suggestive of mature and immature cells of myeloid series (75%) and lymphoid cells (5%) which was suggestive of chronic myeloid leukaemia (CML) with blast crisis. Ultrasound imaging (USG) of abdomen and pelvis were done which revealed splenomegaly and periportal lymphadenopathy. Fine needle aspiration cytology (FNAC) was done from left submandibular lymph node to look for any extramedullary leukaemic infiltrate but it revealed only reactive inflammatory reaction. Genetic studies for Philadelphia chromosome could not be done. After much discussion and deliberation with relatives, patient was started on tablet imatinib 600 mg daily.

After 10 days she presented to us in emergency with history of swelling all over body since 2 days and acute onset breathlessness since a night before admission. There was no h/o chest pain, cough, decreased urine output, itching/rash over the body. On examination she was afebrile, pulse of 124/min, BP – 130/70 mmHg, pale, anicteric, puffy face, JVP raised, multiple cervical lymphadenopathy, non-matted, largest being left submandibular 3 x 3 cm, slightly tender, mobile, no cyanosis, anasarca present. On cardiovascular examination tachycardia present, S3 gallop present, no murmur. On respiratory system examination bilateral coarse crackles were present, bilateral wheeze present. Per abdomen examination revealed hepatomegaly 4 cm below subcostal margin, firm, tender, splenomegaly 5 cm below subcostal margin, firm, and non-tender. There was no e/o ascites. Her ECG did not reveal any abnormality. Chest X-ray (CXR) revealed pulmonary oedema. Complete blood count (CBC) revealed Hb of 6.4 g/dl, TLC of 2, 74,000/cumm. She was started on diuretics and was given continuous positive airway pressure (CPAP)

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ventilatory support. However, she succumbed to her illness within 12 hours.

## Discussion

CML is a myeloproliferative disorder with unique abnormality, i.e., t (9:22) also known as Philadelphia chromosome. It usually presents in chronic stable phase (85 – 90% cases) and rarely, as in our case, it presents either as accelerated phase or blast crisis. Prognosis of blast crisis phase is poor even with treatment.

The advent of tyrosine kinase (TK) inhibitors has revolutionised the treatment of CML. With imatinib therapy the median survival in patients of CML has been found to be 17 months for those who show complete remission, and 6 and 3 months for those with partial and no response respectively[1].

Targeted therapies are considered less toxic and better tolerated by patients compared with classic chemotherapy drugs[1]. But these targeted therapies have been in use only since a limited period and hence the spectrum and severity of their complications is not yet completely known.

Imatinib mesylate is a small-molecule inhibitor, which blocks selectively the tyrosine kinase activity of c-abl, bcr-abl, platelet-derived growth factor receptor, c-fms and c-kit. It is widely used for the treatment of Philadelphia chromosome-positive leukaemia[1].

Kerkelä *et al* reported 10 patients who developed congestive heart failure after taking imatinib mesylate. On histological examination the cardiac cells of these patients showed evidence of toxic cardiomyopathy. It was found that most of the patients with congestive cardiac failure had pre existing heart disease or cardiovascular risk factors. So it is postulated that may be imatinib might have precipitated these pre existing cardiac disease rather than causing new cardiotoxicity[2].

It has also been found that, traztuzumab and altemtuzumab, antibody based TK inhibitors, induce heart failure or asymptomatic LV dysfunction in 1 – 4% and 10%, respectively[3]. In patients treated with sunitinib, a recently-approved, multi-targeted TKI, 11% of subjects suffered a cardiovascular event with congestive heart failure (CHF) occurring in 8% of the population. Twenty-eight per cent of patients treated at the FDA-approved dose had LVEF declines of ≥ 10 EF%, and 19% experienced LVEF declines of ≥ 15 EF%. In mice models sunitinib has been found to induce mitochondrial swelling, degenerative changes and apoptosis in cardiac myocytes[2].

Cardiac toxicity can be caused by the tyrosine kinase inhibitors imatinib mesylate, dasatinib, nilotinib, sunitinib, sorafenib and lapatinib, while gefitinib and erlotinib have not been related to toxic effect on the heart. The spectrum of cardiac toxicity may range from asymptomatic subclinical abnormalities and decline in left ventricular ejection fraction to life-threatening events like CHF and acute coronary syndromes (ACS). For patients with severe side-effects, discontinuation of treatment is warranted[4].

In literature there are documented cases of CHF occurring with imatinib mesylate therapy for GIST and idiopathic hypereosinophilic syndrome[5, 6]. In a recent article the occurrence of grade 3 or 4 potentially cardiotoxic adverse events (mostly oedema and effusions) was only seen in 8.2% of patients and was effectively managed by medical therapy and did not warrant discontinuation or reduction in imatinib dose. Less than 1% of patients suffered with arrhythmias, CHF or ACS[7].

Ehab Atallah *et al* reviewed all reported cardiac adverse events in patients on clinical trials involving imatinib. Out of total 1.7% (22) patients with systolic heart failure, 0.6% were considered possibly or probably related to imatinib. Of the 22 patients, 11 continued imatinib therapy with dose adjustments and management for the CHF symptoms without further complications.

To conclude, imatinib and also other ablkinase inhibitors might induce congestive heart failure. This side-effect may prove and hence requires careful monitoring especially in the first few weeks of treatment. But cardiotoxiticity is usually seen in patients with pre existing heart disease and the overall incidence of this complication is low. Thus imatinib and related drugs still prove to be very useful drugs in treatment of Philadelphia chromosome-positive leukaemia[2].

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