

C O N T E N T S

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Man, the known

BM Hegde*

“I regard consciousness as fundamental. I regard matter as derivative from consciousness. We cannot get behind consciousness. Everything that we talk about, everything that we regard as existing, postulates consciousness.”

– Max Planck.

Human body is immaterial-mental and spiritual (spirituality, defined as sharing and caring). In other words, the human body is a happy colony of 50-100 trillion individual human cells, which individually is capable of living independently as it is equipped with all that a normal human being is endowed with. In fact, they did live as independent individuals for millions of years before coming together as this colony called the human body today. Naturally, each one of those cells is capable of doing all that we, as human beings, can do. In keeping with the universal philosophy of sharing and caring, human body also is home to trillions of germs of all hues and shapes, which have become a part of us. It is predominantly they that keep our immune guard (security system) in top gear. The human meta-genome, therefore, consists of about twenty-five thousand human genes along with trillions of germs' genes-germinomes, virinomes, metabolomes and so on¹. Mind and body, consequently, are not separate entities. They are one and the same, hereinafter called the mind-body.

Every human body cell loves another cell of its own body as well as cells of other human beings because we are but the parts of the same whole, the universal energy, called universal consciousness. Thank God, we have an immune guard; as otherwise, we would have all become one large syncytium-cell mass! One must remember in this context that energy and matter are but the two faces of the same coin ($E=M$ or a-duality) as described by Hans Peter Durr². Anatomically, some cells have to look different from others; especially cells in different organs have different shapes but, physiologically they all work alike. Do not be surprised to know that even cancer cells work exactly like our normal body cells; cancer being, in that sense, a repair mechanism of the body following any injury, going astray not realising when to stop³!

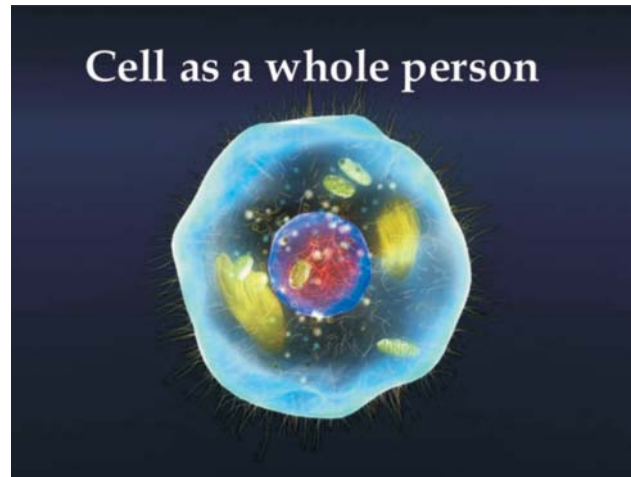


Fig.1: Plasma membrane structural components (Thanks to Google.com)

The dynamic human body runs on oxygen, food, and the electromagnetic energy from the Sun. The battery of every cell resides in the mitochondria of the cells and is being continuously charged by the Sun's electromagnetic energy. Curiously, the speed with which this energy signal travels is a whopping 186,000 miles per second while our chemical signals of therapeutic drugs travel at the rate of one cm per second! The body does not recognise the reductionist chemical molecules from outside. They are considered as *not self*. **The body tries to reject the chemical molecules by sending them to the liver for detoxification and excretion from the system, the so called first pass effect in pharmacology⁴.** It is not, therefore, surprising that the present day therapeutic drugs are one of the leading causes of liver damage and death!

Human life starts when the first cell, the zygote, the product of father's sperm and mother's ovum, gets its signal from the universal energy (consciousness) through its cell wall antenna. Death is when the same signal leaves the cell for good, may be to enter another new cell elsewhere! Human life, therefore, is like a picture in the TV screen. Whereas the picture in the screen can do all that it could while it is seen there but the person is not inside the TV box. It is the energy waves of the TV actor that are

* **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.**

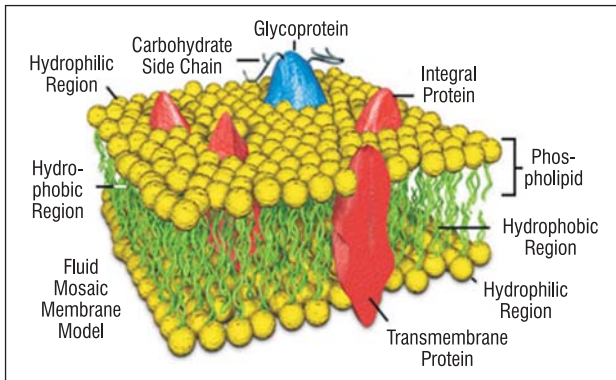


Fig. 2: (Thanks to Google.com)

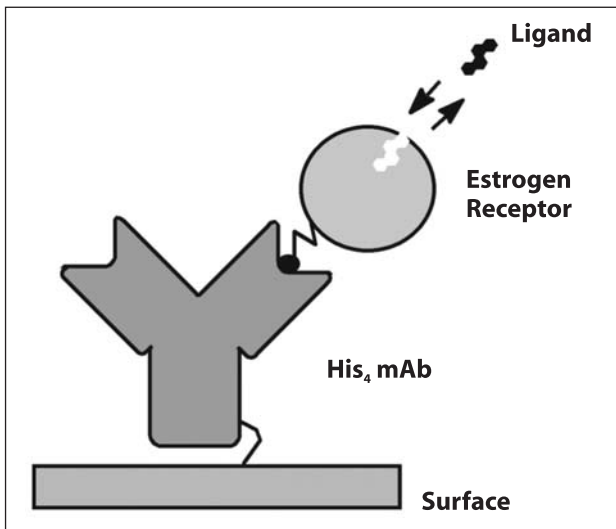


Fig. 3: (Thanks to Google.com)

producing the effect in the TV box⁵.

Similarly, this world is also a drama with changing scenes, called *Whirlicket* in German or *Maya* in Indian philosophy. When the universal energy leaves the cell wall antenna, the human being dies, may be the same energy enters another new cell elsewhere! Again, the TV analogy is very apt. When one switches off one TV the picture dies there, but if one switches on another TV immediately, the same picture will reappear there.

This new science of man makes us understand humans better than the old science of statistical reductionism, where we were looking at the bits and pieces of the body parts to make an assessment of the whole. The existing so-called science of modern medicine tries to understand the human body like a motor car engine with different parts doing different things. Little do we realise that in this dynamic universe the bits need not (do not) make the whole. Science of today, being just one of the *methods* of understanding nature, is only a poor depiction of what

happens in nature, thanks to its reductionist concept and the linear mathematical model. Science, after all, is making models, mostly mathematical constructs, which, with the verbal jargon, are supposed to work. But, they do not work that way in reality. That is why our present science of man does not understand man at all. "There is no science of man," wrote the Nobel Laureate Alexis Carrel, in his celebrated book, *Man the Unknown*⁶. The new science of man, which I have been propagating for the last one decade and more, described above, is the way forward⁷. I hope it will change the whole disease management strategy from chemical drugs to energy based therapeutics and herbal medicines of the East (these are accepted by the body as food).

Organ-based anatomical understanding, dividing doctors into specialists, has come in the way of progress. It is headed for disintegration as per the second law of thermodynamics which proclaims that anything that divides eventually disintegrates! Thinkers like Mary Tinetti of Yale and a few others feel that the present misunderstanding of man has resulted in over-treatment, under-treatment and/or, sometimes, even mistreatment of illnesses⁸. Illnesses are but altered energy patterns in the body which could now be set right using energy methods. The energy pattern, both normal and abnormal, could all be studied using the Bio-Photon Camera of Fritz-Albert Popp. *One is healthy when the body cells are in synch and one is unwell when they are out of synch*⁹. For clinical purposes, *health* could be defined as "enthusiasm to work and enthusiasm to be compassionate." Our aim in the future has to be *Whole Person Healing*, or WPH, which has been now accepted as official word for future healing by the Institute of Medicine in the USA in their February 2010 meeting. WPH was coined by the Late Professor Rustum Roy, a founder member of IOM, representing the American Academy of Science.

In our organisation, The World Academy of Authentic Healing Sciences, we have been developing various energy healing methods using both known energies and some occult energies as well with excellent results. Some of these are already published. Recent work has also clearly shown that faith in the doctor (may be in something superhuman – God if you will, also) works wonders in pain relief due to release of endorphins from the forebrain¹⁰. **Faith does heal!** More work needs to be done before we can sit back and relax. That said, I must hasten to add that we still need emergency trauma care and many other emergency situations along with some basic corrective surgical methods from the old medical armamentarium. Together, they will become the **post-modern medical system** of the future. Science is change and every new system needs to be refined on an ongoing basis as knowledge advances almost every day with

newer information coming in.

With the birth of this new science of man and better understanding of human physiology time is ripe now to refute all old dogmas in modern medicine to usher in a new era of the post-modern medicine, which I hope will make mankind happier and will become patient friendly. In addition to all these, it has to make illness care affordable to most people most of the time to do them most good. May mankind live in peace and happiness. Doctors will then get back their due respect in society with *post modern medicine*, described above, to become a Noble profession again. Homo altruisticus!

“New scientific ideas never spring from a communal body, however organised, but rather from the head of an individually inspired researcher who struggles with his problems in lonely thought and unites all his thought on one single point which is his whole world for the moment.”

– Max Planck.

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A DOCTOR'S PRAYER

*O Vidhaatha! Bless me with such an insight, intelligence and patience
That I may listen to my patient with a smile, compassion and tolerance.*

*O Merciful! Guide my mind, my hands, while I examine him, not to omit...
Any sign or symptom of his illness – not even a bit!*

*O Creator par excellence! Enthuse me with such a kind and loving attitude,
That as we depart, my patient is full of happiness and gratitude.*

*Grant me vision to relieve his misery and make him bold,
This shall fill me with thoughts pure and my coffers with gold!*

*Grant me! Grant me!! O, the Benevolent Unseen,
May I ever serve his prime need, not my own!*

– Dr. G.B. JAIN –
(1930 - 2009)

Prevalence of hyperhomocysteinaemia in type-2 diabetes mellitus and its correlation with its complications

Lakshman Ramachandran*, NS Negi**, B Gupta***

Abstract

Objective: Primary aim – To study the association of hyperhomocysteinaemia with diabetes mellitus and its complications in an Indian population. Secondary aim – To study the association of hyperhomocysteinaemia with increased levels of HbA1c and serum triglyceride (TG) levels in an Indian population.

Methods: This is a population-based study in which 50 diabetic patients and 30 healthy adults (non-diabetics) were recruited. The diabetic patients were further classified into two groups – diabetics with associated complications (DD), N=19, and diabetics with no associated complications (DC), N=31. Homocysteine levels along with the other conventional (HbA1c, lipid profile, urine for microalbuminuria) parameters for identifying complications of diabetes mellitus were measured and the levels were compared statistically.

Results: In our study, we have found that homocysteine levels are significantly higher in complicated diabetes (3.0095µg/ml Vs 2.3037µg/ml) than diabetes without complications. Significantly elevated homocysteine levels were found in type-2 diabetes mellitus with CAD ($p=0.002$), stroke ($p=0.000$) and neuropathy ($p=0.000$) as compared to control subjects. There was a positive correlation of HbA1c and serum TAG with homocysteine levels.

Conclusion: Higher homocysteine levels are found in diabetics who have developed micro-/macro-vascular complications and it is highly correlated with HbA1c and serum TG which are also indicators of poor diabetic control.

Keywords: Hyperhomocysteinaemia, Type-2 diabetes mellitus, Complications.

Introduction

Several studies have shown a positive correlation between glucose intolerance and cardiovascular disease with obesity, dyslipidaemia, hypertension, polycystic ovaries, smoking, sedentary lifestyle, certain ethnic groups, poorly regulated diabetes, and hyperinsulinaemia, due to any reason or risk factors. However, not all of these factors were able to explain the strong association of diabetes with premature atherosclerosis. Recently, it has been suggested that homocysteinaemia could be an important and independent predictor of complications in diabetes mellitus¹, especially atherothrombotic events.

The European Union Concerted Action Project, "homocysteinaemia and vascular disease", indicated that a plasma homocysteine level above 0.162 mg% accelerates the risk of myocardial infarction, cerebral or peripheral vascular disease in both men and women. There are studies suggesting that an elevated level of homocysteine in poorly controlled type-2 diabetes mellitus is related to increased risk of atherosclerosis and cardiovascular disease. The increased prevalence of elevated homocysteine levels in which macroangiopathy and nephropathy in type-2 diabetes mellitus was

demonstrated². Their data, however, should not be over-interpreted because the aetiological role of homocysteine in atherosclerosis in the presence of macroangiopathy is far from clear.

The precise relationship among hyperhomocysteinaemia, macroangiopathy and renal disease in type-2 diabetes mellitus has not yet been determined. One of the confounding factors among them is associated coronary vascular disease.

One study from India showed normal homocysteine levels in type-2 diabetes mellitus patients both with and without coronary artery disease³. However, another study from India reported higher total homocysteine levels in obese type-2 diabetes mellitus and not in lean diabetics.⁴ Hyperhomocysteinaemia, with treatment, is a modifiable risk factor to an extent. Therefore, correction of hyperhomocysteinaemia may have a beneficial effect in type-2 diabetes mellitus.

This study was undertaken with the aim to provide an insight on the association between type-2 diabetes mellitus and raised plasma homocysteine levels with increased risk for coronary artery disease and cerebral and peripheral vascular complications in an Indian population.

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

Primary aim – To study the association of hyperhomocysteinaemia with diabetes mellitus and its complications in an Indian population.

Secondary aim – To study the association of hyperhomocysteinaemia with increased levels of HbA1c and serum triglyceride levels in an Indian population.

Materials and methods

Study population

After screening 200 patients, a total of fifty patients of type-2 diabetes mellitus in the age group 35 - 65 years were included in the study. The study population was further separated by detailed clinical examination and relevant investigations into two groups:-

- **DC:** Diabetics without any associated complications (Diabetic Controls) and
- **DD:** Diabetics with complications (Diabetic Diseased).

Patients with a genetic disorder associated with elevated homocysteine levels or on medications known to increase the serum level of homocysteine like pregnancy, renal failure, stroke, and myocardial infarction (MI) within the last 3 months, malignancy, disease of ovary and pancreas, severe psoriasis, CHF, or any major invalidating disease and deficiency disorders like anaemia, hypothyroidism, etc. were excluded. Thirty asymptomatic healthy individuals were taken as healthy controls (HC). Informed written consents were obtained from all the patients and controls.

Laboratory Investigations

Blood samples were taken in the morning after subjects were kept fasting overnight. The tests included a complete haemogram, sugar profile, renal function tests, glycosylated haemoglobin (HbA1c), and lipid profile, apart from the plasma homocysteine (tHcy) levels. Urine was also collected to test for microalbuminuria. For tHcy estimation, the samples were processed within 60 minutes to prevent increase in homocysteine concentration due to ex-vivo generation. The serum was kept in ice (-20°C) till estimation of tHcy by High Performance Liquid Chromatography (HPLC).

Estimation

The homocysteine in plasma is bound to protein. Bound homocysteine is first reduced to free homocysteine by tributylphosphine. The protein mass is precipitated with trichloroacetic acid and the supernatant is treated with thiol specific reagent: ammonium 7 fluorobenzo-2-oxa-

1, 3-diazole-4-sulphonate to produce fluorescence adduct. The adduct (sample size 15µ) is identified by isocratic using an ODS column, 5 µM, 4.5 x 250 mm with 0.1 M acetate buffer 2% methanol, plasma homocysteine 4.3 at a flow rate 1 ml/min fluorescence is intensity of the eluent was measured at 480 nm emission wavelength (at 375 nm excitation wavelength) by online fluorescence detector. A typical retention time for homocysteine was found to be 3.4 min. The integrated area under homocysteine peak from the sample was used to calculate its concentration by using calibration curve obtained with standard L-homocysteine. The integrated area under the peak concentration of homocysteine in the sample injected is converted to total plasma homocysteine.

Concentration of L-homocysteine =

$$\frac{\text{peak area of sample} \times \text{concentration of standard}}{\text{peak area of standard}}$$

Concentration of homocysteine = 2 × L-homocysteine.

Statistical analysis

Data were analysed using mean of plasma homocysteine levels, standard deviation in plasma homocysteine levels. To compare the mean of plasma homocysteine levels of two groups, the Student's 't' test was used and significance was assessed by 'p' value, labelled as significant if the value was < 0.05.

Observations and results

50 diabetic patients were further categorised according to the various associated complications: Hypertension – 9 cases, CAD – 4 cases (2 with past h/o MI and 2 with ECG changes s/o angina), ischemic stroke – 4 cases, neuropathy (peripheral and autonomic) – 3 cases, nephropathy (significant microalbuminuria > 30 mg/L with serum creatinine < 120 µmoles/L) – 16 cases, grade I diabetic retinopathy – 2 cases, peripheral vascular disease (PVD) – 0 cases.

In our study (Table I), we found that there was no significant difference between the patients of type 2 diabetes mellitus and the healthy control group (2.6886 µgm/ml Vs 2.3037 µgm/ml) with regard to plasma homocysteine levels. However, we found that homocysteine levels are significantly higher in complicated diabetes (3.0095 µg/ml Vs 2.3037 µg/ml) than diabetes without complications.

Table I: Plasma homocysteine levels in type-2 diabetes mellitus with complications (DD), without complications (DC), and in healthy controls (HC).

	N	Mean	SD	Std. error mean
DD	19	3.0095	1.0909	0.2503
DC	31	2.4919	0.7055	0.1267
Total	50	2.6886	0.8979	0.1270
HC	30	2.3037	0.8109	0.1481

Higher homocysteine levels (Table II) were also found in type-2 diabetes mellitus with hypertension ($p=0.098$) and type-2 diabetes mellitus with nephropathy ($p=0.126$) as compared to control subjects (i.e., type-2 diabetes mellitus with no complications) but the difference was not very significant. In contrast, significantly elevated homocysteine levels were found in type-2 diabetes mellitus with CAD ($p = 0.002$), stroke ($p = 0.000$), and neuropathy ($p = 0.000$) as compared to control subjects. In subjects with diabetic retinopathy, we found that homocysteine levels were higher than the control subjects ($p = 0.05$), although, not significant but much conclusion could not be drawn as the sample size was small.

Table II: Plasma homocysteine levels in diabetics without complications (DC) and diabetics with various complications.

	N	Mean	SD	Std. error mean	p value
DC	31	2.4919	0.7055	0.1267	
HTN	9	2.9756	0.8494	0.2831	0.098
CAD	4	3.7525	0.4542	0.2271	0.002*
CVA	4	4.3550	1.0082	0.5041	0.000*
Neuropathy	3	4.4267	1.2223	0.7057	0.000*
Nephropathy	16	2.9144	1.1542	0.2885	0.126
Retinopathy	2	3.6800	2.1920	1.5500	0.05

On correlating metabolic variables (Table III) like HbA1c and serum lipid studies in subjects with hyperhomocysteinaemia, we found that the only HbA1c and serum TG have a positive correlation with homocysteine levels.

Table III: Correlation of plasma homocysteine levels with glycosylated haemoglobin (HbA1C) and serum triglycerides (TG) in both the groups.

	HbA1C	HDL	LDL	T.Chol/HDL	T.Chol.	S.TG
Pearson correlation	0.325	0.078	0.174	0.039	0.147	0.254
Sig. (2-tailed)	0.003	0.492	0.122	0.731	0.192	0.023
N	50	50	50	50	50	50
p. value	0.003	NS	NS	NS	NS	0.023

Discussion

Pathogenicity of hyperhomocysteinaemia

Homocysteine is formed by demethylation of an essential amino acid, methionine, which so far has not been shown to have any metabolic function. Subjects with severe hyperhomocysteinaemia are at greatly increased risk of atherothrombotic events. Various studies have proposed that homocysteine induced endothelial injury exposes the sub-endothelial matrix, which in turn leads to platelet activation by various mechanisms such as impaired coagulant function, production of potent reactive oxygen species (ROS) including superoxide and hydrogen peroxide during the auto-oxidation of homocysteine⁵; also, by changing their phenotype from anticoagulant to procoagulant, modulating the expression of enzymes glutathione peroxidase and nitric oxide synthase, enhancing the binding of lipoprotein (a) to fibrin. they also enhance the coagulability by reducing protein c activation, inducing inhibition of antithrombin III, inhibiting the synthesis of anticoagulant heparin sulphate, suppressing thrombo-modulin. Homocysteine rapidly reacts with nitric oxide to form S-nitrosohomocysteine, which acts as a potent antiplatelet agent. Homocysteine is also a potent mitogen leading to a marked increase in vascular smooth muscle proliferation *in vitro*. Recently, patients with hyperhomocysteinaemia have documented an abnormal adenosylmethionine/denosylhomocysteine (adomet/adoHcy) ratio, which leads to impaired AdoMet-dependent methylation reactions leading to thrombosis and ageing.

To summarise, homocysteine promotes vascular disease primarily by inducing endothelial cell dysfunction by various mechanisms. The high prevalence of moderate hyperhomocysteinaemia, combined with acquired and genetic determinants, therefore, make it an ideal target for intervention in patients with CVD, as well as in the general population.

Prevalence of hyperhomocysteinaemia

The prevalence of hyperhomocysteinaemia has been estimated to be 5 per cent in the general population, and 13 - 47 among patients with symptomatic atherosclerotic vascular disease⁶.

Higher levels of homocysteine are particularly seen in patients with diabetic nephropathy (microalbuminuria)^{7,8,9}, early type1 diabetics¹⁰, patients with autonomic neuropathy¹¹, and those with chronic poor control of diabetes mellitus¹².

There have also been reports which concluded that

hyperhomocysteinaemia is an important risk factor for vascular disease, including stroke, independent of long recognised factors such as hyperlipidemia, hypertension, diabetes mellitus, and smoking^{13,14} as well as re-stenosis after coronary angioplasty^{15,16}.

Elevated homocysteine levels can often be normalised by supplementing the diet with folic acid (folate), pyridoxine hydrochloride (vitamin B₆), and cyanocobalamin (vitamin B₁₂). In its association with cerebrovascular disease, homocysteine may play a role in neurodegenerative disorders, even if only as a marker of functional vitamin B₁₂ deficiency. Homocysteine is also important to neurologists since most anticonvulsants raise homocysteine levels, an effect that may explain the teratogenic effects of these drugs.

Elevated plasma homocysteine concentration is considered an independent risk factor for atherosclerosis in subjects with normal glucose tolerance. Although type-2 diabetes is definitely associated with premature atherosclerosis, only a few studies have dealt with the association between hyperhomocysteinaemia and micro-/macro-angiopathy complications with contradictory results.

In our study, we compared homocysteine levels in healthy controls, type-2 diabetics with no complications, and type-2 diabetics with associated complications.

Previous studies from India had shown mixed results regarding the association of plasma homocysteine levels with the non diabetics, diabetics, and advanced diabetes with complications, but definite conclusion could not be drawn^{7,16,17}. In our study, plasma homocysteine level in patients of type-2 diabetes mellitus were similar to healthy control group (2.6886 µg/ml Vs 2.3037 µg/ml). However, when the cases were further divided into 2 groups, i.e., diabetes without complications (DC) and diabetes with associated complications (DD) and then comparing both the groups we have observed that homocysteine levels in diabetes with complications (3.0095 µg/ml Vs 2.3037 µg/ml) are higher than diabetes without complications. (*p* value = 0.013).

Earlier studies have shown that plasma homocysteine levels have been reported to be significantly higher in hypertensive patients with type 2 diabetes mellitus¹⁸ as well as in diabetic patients with albuminuria^{19,20}. In the Hoorn study (a population based survey of glucose tolerance and cardiovascular risk factors), higher levels of total homocysteine were associated with microalbuminuria independent of other determinants, including the presence of type-2 diabetes and serum creatinine. In our study, we have observed that though

the plasma homocysteine levels were higher in hypertensive type-2 diabetics (*p* = 0.098) and diabetes with albuminuria (*p* = 0.126) but it was not statistically significant.

Similarly, other studies have reported that hyperhomocysteinaemia as an independent risk factor for atherosclerotic vascular disease in patients of diabetes with stroke, CAD, or neuropathy^{11,13,17}. We notice that plasma homocysteine levels are higher in patients of type-2 diabetes mellitus with CAD (*p* = 0.002) than control subjects. The present study also suggests that plasma homocysteine levels are higher in Indian subjects with type-2 diabetes mellitus who suffered from ischaemic stroke (*p* = 0.000) against controls is significantly higher. Our result is unlikely to be due to direct effect of stroke since we had included only patients who had ischaemic stroke more than 3 months before the study, as recent stroke can itself elevate total homocysteine levels. Also, statistical significant difference (*p* = 0.000) of plasma homocysteine in patients with diabetic neuropathy (peripheral as well as autonomic) were observed compared to control subjects. Since in our study, all the three patients had autonomic and peripheral neuropathy, further studies are required to see the association of hyperhomocysteinaemia with autonomic and peripheral neuropathy separately.

Regarding retinopathy, in our study, we have found a significant association of homocysteine with diabetic retinopathy. The levels of homocysteine are higher in subjects with retinopathy (3.6800 Vs 2.4919 µg/ml) as compared to controls.

Though the results were statistically not significant but since the number of cases with retinopathy is few (2), many conclusions cannot be drawn from it. Moreover, patients with severe retinopathy could not be taken as these patients also had deranged kidney function and mostly presented in heart failure.

We found positive correlation of HbA1c and serum triglyceride with homocysteine levels in both the diabetic groups in our study.

Since elevated HbA1c and serum triglyceride levels are associated with poor glycaemic control in diabetics, their correlation with elevated homocysteine levels suggest that homocysteine levels could be another marker of poor glycaemic control and a predictor of complications in diabetic patients. Normalisation of homocysteine levels could be beneficial in reducing the risk of complications of diabetes. It will be interesting to see the effect of glycaemic control in homocysteine levels in patients after treatment, and the effect of vit. B₁₂ and folic acid therapy

in lowering homocysteine levels.

Though we excluded patients in whom any other cause of elevated total homocysteine could be present, studying serum B₁₂ and folic acid levels would have been more informative, as the deficiency could be the reason for elevated total homocysteine level. Also, follow-up after correction of deficiency could throw more light in reversing this important risk factor. Many subjects have more than one complication, therefore, it is difficult to analyse which associated complication is individually associated with elevated homocysteine levels and to what extent.

In a nutshell, higher homocysteine levels are found in diabetics who have developed micro-/macro-vascular complications and it is highly correlated with HbA1c and serum triglyceride levels which are also indicators of poor diabetic control. Therefore, hyperhomocysteinaemia could serve as another parameter of poor diabetic control and developing complications. Thus, homocysteine levels should be monitored in type-2 diabetes and therapy for lowering raised homocysteine may be administered to those having hyperhomocysteinaemia (B₁₂ and folic acid supplementation).

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Clinico-aetiological profile of pancytopenia in paediatric practice

Amieeleena Chhabra*, Vipin Chandar**, Anubhava Patel***, Harish Chandra****

Abstract

Objective: To study the profile of pancytopenia in hospitalised children.

Study Design: Prospective study. **Setting:** Tertiary care hospital in Uttarakhand.

Subjects: 111 children between 6 months and 14 years of age were studied for pancytopenia.

Result: 91 patients had pancytopenia and the rest had bicytopenias. Severe pancytopenia was seen in 25 patients. Megaloblastic anaemia was the most common cause (31.8%) followed by malignancies (25.2%), infectious diseases (19.7%), and aplastic anaemia (18.8%). The commonest clinical feature was bleeding manifestations in the form of petechiae, bruises, and ecchymosis seen in malignancies and aplastic anaemia.

Introduction

Bone marrow failure is characterised by a reduction in the effective production of mature erythrocytes, granulocytes and platelets by the bone marrow that leads to peripheral blood pancytopenia¹. Aetiology of pancytopenia is varied. It may be due to bone marrow failure syndromes and malignancies which are well recognised causes. However, a number of infections and vitamin deficiencies may also present as pancytopenia.

Pancytopenia in a patient with associated organomegaly and lymphadenopathy usually suggests the possibility of malignancies or bone marrow failure syndromes. There are a number of other causes which have a similar presentation but are more easily treatable. This study has been undertaken to identify easily treatable and reversible causes of pancytopenia.

Materials and methods

The study was conducted in a tertiary care hospital in Uttarakhand over a period of one year. Patients between 6 months and 14 years of age admitted with bicytopenia or pancytopenia were included in the study.

Pancytopenia was defined as haemoglobin <10 g%, absolute neutrophil count (ANC) < 1,500/ μ l, and platelet count < 100,000/ μ l. Bicytopenia was a decrease in any of the two cell lines. Severe pancytopenia was defined as haemoglobin < 7 g%, ANC < 500/ μ l, platelet count < 200,00/ μ l, and reticulocyte count < 1%².

A detailed history and physical examination was done at admission. Investigations at the time of admission included a complete haemogram using automated analyser, 3-part differential counter with recording of haemoglobin, total and differential leucocyte counts, red blood indices (MCV, MCH, MCHC), and platelets. Reticulocyte counts, blood picture, bone marrow examination, and other investigations were done to reach the diagnosis.

All those cases in which the diagnosis could be confirmed were included in the final analysis.

Results

111 children were evaluated, out of which 91 had pancytopenia and the remaining had bicytopenias. In the 91 patients of pancytopenia, 55 were males and 36 were females. Age of these patients was between 6 months and 14 years.

Table I shows the aetiology of cases with pancytopenia. Megaloblastic anaemia was seen in 29 (31.8%) cases – being the most common cause of pancytopenia. Malignancies which included acute lymphoblastic leukaemia, acute myeloid leukaemia, non-Hodgkin's lymphoma, Langerhans cell histiocytosis and myelodysplastic syndrome constituted 23 (25.2%) cases. Aplastic anaemia seen in 17 (18.68%) cases was another important causes of pancytopenia. Infections such as kala azar, malaria, enteric fever, bacterial septicaemia and others caused pancytopenia in 18 (19.7%) of the patients.

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Other infections included 2 cases of tuberculosis and one of dengue fever. The miscellaneous group included one case of Gaucher's disease presenting as hypersplenism, one of pure red cell aplasia, and two of idiopathic thrombocytopenic purpura.

Table I: Aetiology of pancytopenia (N = 91)

S. No.	Diagnosis	Number (%)
1.	Megaloblastic anaemia	29 (31.8)
2.	Malignancies	23 (25.2)
	• ALL	12
	• AML	4
	• MDS	3
	• Non-Hodgkin's	3
	• Langerhans cell histiocytosis	1
3.	Infections	18 (19.7)
	• Kala azar	6
	• Malaria	4
	• Enteric fever	3
	• Sepsis	2
	• Others	3
4.	Aplastic anaemia	17 (18.6)
5.	Miscellaneous	4 (4.3)

Figures in parenthesis indicate percentage.

Severe pancytopenia (Table II) was seen in 25 patients, Most of them had aplastic anaemia and acute leukaemias. However, a few cases of megaloblastic anaemia and infections also presented with the above.

Table II: Aetiology of severe pancytopenia (N = 25).

S. No.	Diagnosis	Number (%)
1.	Aplastic anaemia	12 (48)
2.	Acute leukaemia	7 (28)
3.	Megaloblastic anaemia	4 (16)
4.	Infections	2 (8)

Figures in parenthesis indicate percentage.

Bicytopenia (Hb < 7 g% and ANC < 500/ μ l, platelets < 200,00/ μ l) was seen in 7 (35%) patients of megaloblastic anaemia, 5 (25%) patients of acute leukaemia, 5 (25%) patients of aplastic anemia, and 3 (15%) cases of infections.

Table III: Clinical presentation of pancytopenia (N = 91).

Clinical presentation	Number (%)
Fever	58 (63.7)
Fatigue and lethargy	47 (51.6)
Bleeding manifestations	64 (70.3)
Pallor	59 (64.8)
Hepatomegaly	54 (59.3)
Splenomegaly	52 (57.1)
Lymphadenopathy	16 (17.5)
Weight loss	24 (26.3)

Figures in parenthesis indicate percentage.

The commonest clinical feature (Table III) was bleeding manifestations in the form of petechiae, bruises, and ecchymosis seen in malignancies and aplastic anaemia. Mucosal bleeds like epistaxis, gum bleeds, and malena were commonly associated with megaloblastic anaemia. 15 (51.7%) cases of megaloblastic anaemia had hepatomegaly and 13 (44.8%) had splenomegaly. All cases with splenomegaly also had hepatomegaly. There was significant association of lymphadenopathy in cases of malignancies ($p < 0.05$).

Bone marrow examination

Marrow was cellular in 65 (71.4%) cases, while it was hypocellular in 26 (28.5%) cases.

Table IV shows the bone marrow cellularity and aetiology of pancytopenia.

Table IV: Bone marrow cellularity and pancytopenia.

Cellular marrow (N=65)	
Aetiology	Number (%)
Megaloblastic anaemia	29 (44.6)
Malignancies	22 (33.8)
• ALL	11
• AML	4
• MDS	3
• Non-Hodgkin's	3
• Langerhans cell histiocytosis	1
Infections	10 (15.3)
• Kala azar	6
• Malaria	4
Miscellaneous	4 (6.1)
Hypocellular marrow (N=26)	
Aetiology	Number
Aplastic anaemia	17 (65.3)
ALL	1 (3.8)
Infections	8 (30.7)
• Enteric fever	3
• Sepsis	2
• Tuberculosis	2
• Dengue	1

Figures in parenthesis indicate percentage.

Discussion

Pancytopenia refers to a reduction below normal in values of all 3 peripheral blood lineages: leukocytes, platelets, and erythrocytes. Diagnosis of pancytopenia requires microscopic examination of a bone marrow biopsy specimen and a marrow aspirate to assess overall cellularity and morphology³.

In our study, it was seen that many conditions other than

malignancies and aplastic anaemia presented as pancytopenia, megaloblastic anaemia being the commonest (31.8%). Gomber *et al* in their study reported an incidence of 11%⁴ while Mukhbi *et al*⁵ had 47% cases of megaloblastic anaemia presenting as pancytopenia. Severe pancytopenia was seen in 4 cases of megaloblastic anaemia in our study while bicytopenia was seen in 7 patients. Other studies reveal an incidence of 44.8 and 80.5% respectively^{4,6}. Ineffective erythropoiesis, leukopoiesis and thrombopoiesis resulting from programmed cell death in the absence of vit B₁₂ or folic acid, and decreased survival of precursors in peripheral blood are causes of pancytopenia in megaloblastic anaemia¹. Bleeding manifestations in megaloblastic anaemia patients was seen in (44.8%) cases in our study in comparison to 3% and 20% in studies by Chandra *et al*⁷ and Khair *et al*⁸ respectively.

44.8% cases of megaloblastic anemia in our study had hepatosplenomegaly. This presentation along with bleeding manifestations can simulate acute leukaemias^{4,6,9}.

Many infections have also presented as cytopenias in our study accounting for 19.7% cases. 4 cases of malaria had pancytopenia. All were caused by *P. Vivax*. Haemophagocytic syndrome due to *P. Vivax* has been reported to cause pancytopenia¹⁰. The mechanisms in malaria reported are direct invasion by parasites, DIC, immune haemolysis, hypersplenism and haemophagocytosis^{11,12,13,14}. Leucopenia is rare; however, it has been reported by Bhatnagar *et al*¹⁵.

Kala azar presenting as pancytopenia has been seen in 6 patients in the study. Hypersplenism due to enlarged spleen causes pancytopenia in these patients¹⁶.

Enteric fever causing pancytopenia was seen in 3 cases in our study. In these cases bone marrow may undergo histiocytic hyperplasia with haemophagocytosis or complete necrosis. Immune-mediated haemolysis, hypersplenism, and DIC are other contributory factors¹⁷. Cytopenia with enteric fever has been reported in other studies^{18,19,20}.

Fulminant sepsis as cause of pancytopenia was seen in 2 cases in our study. Both had Klebsiella-positive cultures. Garewal *et al* has reported Gram-negative sepsis resulting in bone marrow necrosis in 2 cases²¹. One case of dengue fever has shown hypocellular marrow due to haemophagocytosis in our study.

Malignancies like ALL and aplastic anaemia are more common and dangerous causes of pancytopenia. In our study, 19.7% had aplastic anaemia and 25% had malignancies in comparison to 20 and 21% in a study by

Bhatnagar *et al*¹⁵.

Pancytopenia either has hypocellular or cellular morphology in bone marrow. There are few studies in literature which explore the aetiological factors with hypocellular and cellular marrow^{22,23,24,25}. The common causes vary in the different studies^{22,23,24,25}. In the present study, the marrow was cellular in 71.4% cases with megaloblastic anaemia being the most common cause while it was hypocellular in 28.5% cases where aplastic anaemia was the most common cause.

In our study, megaloblastic anaemia was found to be the most common cause of pancytopenia. These patients can present with severe bleeding and pancytopenia with organomegaly mimicking conditions like acute leukaemias and aplastic anaemia. This benign and easily treatable condition should be kept in mind while attending to such patients when they present to the hospital before the more serious conditions like leukaemias and aplastic anaemia are thought of. Early treatment with vit B₁₂ and folic acid can revert back the symptoms and result in speedy and complete recovery of such patients. In developing countries like ours, infections which are commonly encountered like malaria, enteric fever, kala azar, sepsis, and dengue fever should be kept in mind in addition to other serious conditions.

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Clinical profile of metabolic syndrome with reference to insulin resistance (HOMA-IR)

Sameer P Chaudhari*, MH Usmani**, PK Baghel**, MK Jain***

Abstract

Aims and objectives: To evaluate correlation between Hypertension and Obesity with Insulin Resistance (HOMA-IR) in patients with metabolic syndrome.

Methodology: In the present study, we have done a cross-sectional study of patients who fulfilled NCEP-ATPIII criteria of metabolic syndrome. 100 patients of metabolic syndrome were selected over a period of 21 months from November 2007 to July 2009. Routine investigations, fasting serum insulin levels, fasting blood glucose levels, and insulin resistance (HOMA-IR method) calculations were done. BMI and waist-hip ratios were calculated. Results were analysed statistically. p-value was taken to be significant if < 0.05.

Observations: Patients with systolic BP 130-150, 151-174, 175-200, > 200 mmHg had mean HOMA-IR 4, 5.3, 7.4, 8.9 respectively. Patients with diastolic BP 85-90, 91-95, 96-100, > 100 mmHg had mean HOMA-IR 3.6, 4.3, 5.7, 8.2 respectively. Patients with BMI \leq 33, 33.1-36, 36.1-39.9, \geq 40 kg/msq had mean HOMA-IR 2.7, 5.4, 10.2, 11.7 respectively. Male patients with waist:hip ratio 1-1.2, 1.21-1.39 \geq 1.4 had mean HOMA-IR 4.1, 9.2, 11.6 respectively. Female patients with waist:hip ratio 0.8-0.9, 0.91-0.99 \geq 1 had mean HOMA-IR 4.4, 9.1, 10.03 respectively.

Results: Patients with higher systolic BP (175-200, > 200 mmHg) had higher mean HOMA-IR (7.4, 8). Patients with higher diastolic BP (96-100, > 100 mmHg) had high mean HOMA-IR (5.7, 8.2). Patients with higher BMI (\geq 40, 36.1-39.9 kg/msq) had higher mean HOMA-IR (10.2, 11.7). Male patients with higher waist:hip ratio (1.21-1.39 \geq 1.4) had higher mean HOMA-IR (9.2, 11.6). Female patients with higher waist:hip ratio (0.91-0.99 \geq 1) had higher mean HOMA-IR (9.1, 10.03).

Conclusion: Hypertension correlates positively with insulin resistance (HOMA-IR). Increased waist:hip ratio and BMI are clinical parameters for insulin resistance (HOMA-IR).

Introduction

Ever since Reaven first described in 1988, in the Banting lecture, a clustering of interconnection of metabolic risk factors, subsequently labelled as metabolic syndrome (MS) has been appreciated. Metabolic syndrome has been provided a distinct code (9.277.7) under ICD nomenclature.

Metabolic syndrome comprises multiple features including obesity, hypertension, impaired glucose tolerance, dyslipidaemia. Insulin resistance is the primary link. Insulin resistance is responsible for future development of type-2 diabetes, and it has been seen that by the time glucose tolerance becomes impaired, appreciable β -cell destruction may have already occurred. So, prevention of type-2 diabetes will be possible only if intervention is commenced before this stage and this is possible by identifying cases of insulin resistance.

Greater industrialisation worldwide is associated with rising rates of obesity leading to a dramatically increased problem of metabolic syndrome and its cardiovascular morbidity and mortality. As India is an emerging

industrialised nation, this is a worrisome problem for all of us. At present, there is no single drug that targets metabolic syndrome directly. Rather, identifying patients early and taking preventive measures is an effective and practical way out.

The present study is a modest effort to correlate insulin resistance with hypertension and obesity using BMI and waist:hip ratio as clinical parameters.

Material and methods

The present study was undertaken at the Department of Medicine, S.S. Medical College and associated S.G.M. Hospital, Rewa, Madhya Pradesh, over a period of 21 months from November 2007 to July 2009. These patients were selected as follows:-

Inclusion criteria:

1. Blood pressure \geq 130/85 mmHg
2. HDL cholesterol < 40 mg/dl in males
< 50 mg/dl in females
3. Hypertriglyceridaemia \geq 150 mg/dl

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4. Fasting blood glucose ≥ 100 mg/dl
5. Waist circumference > 102 cm (Males) and > 88 cm (Females)

A patient should have three or more of the above-mentioned criteria to be considered as a metabolic syndrome patient.

Exclusion criteria:

1. Obese patients due to underlying endocrine diseases.
2. Pregnancy.
3. Old cases of hypertension due to congenital, renal, or metabolic abnormalities.
4. Diagnosed patients of type-2 diabetes mellitus.

Study design:

- The patients included in the study were either admitted in the medicine department of SGMH, Rewa, or were studied on an OPD basis.
- Detailed history was taken.
- Detailed clinical examination of each patient was done including waist:hip ratio and BMI calculation.
- Required investigations were done.
- If a patient fulfilled at least three criteria of metabolic syndrome, fasting serum insulin level was done and HOMA-IR was calculated.

Measurement of insulin resistance by HOMA-IR method

Homeostasis Model Assessment (HOMA) Model

The widely used HOMA model, developed by Matthews and colleagues (Matthews *et al*, 1985)¹, uses fasting measurements of blood glucose and insulin concentrations to calculate indices of both insulin resistance and beta-cell function. The principal of HOMA is that blood glucose and insulin concentrations are related by the feedback of glucose on beta-cells to increase insulin secretion. For a given level of blood glucose, prevailing insulin levels therefore reflect both insulin resistance and beta-cell function, although the relationship is complex. The model assumes that normal weight subjects aged less than 35 years have an insulin resistance (R) of 1 and 100% beta-cell function.

Using HOMA, insulin resistance (HOMA-IR) is calculated as follows:-

$$\text{HOMA-IR} = \frac{\text{Fasting serum insulin (mIU/L)} \times \text{Fasting blood glucose (mmol/L)}}{22.5}$$

Increase in HOMA-IR values indicate increase in insulin

resistance. HOMA measurements are clearly very easy to perform and correlate closely with EHC-derived measurements in insulin resistance (Hermans *et al*, 1999)².

Observations

Following were the observations of the study:-

1. Patients with systolic BP 130-150, 151-174, 175-200, >200 mmHg had mean HOMA-IR 4, 5.3, 7.4, 8.9 respectively.
2. Patients with diastolic BP 85-89, 91-95, 96-100, >100 mmHg had mean HOMA-IR 3.6, 4.3, 5.7, 8.2 respectively.
3. Patients with BMI ≤ 33 , 33.1-36, 36.1-39.9, ≥ 40 kg/msq had mean HOMA-IR 2.7, 5.4, 10.2, 11.7 respectively.
4. Male patients with waist: hip ratio 1-1.2, 1.21-1.39, ≥ 1.4 had mean HOMA-IR 4.1, 9.2, 11.6 respectively.
5. Female patients with waist: hip ratio 0.8-0.9, 0.91-0.99, ≥ 1 had mean HOMA-IR 4.4, 9.1, 10.03 respectively.

Table I: Distribution of patients according to systolic BP.

S.No.	Diastolic BP (mmHg)	Mean HOMA-IR (0.5-3.5)
1	85-90	3.6
2	91-95	4.3
3	96-100	5.7
4	>100	8.2

n = 100, *p* < 0.05

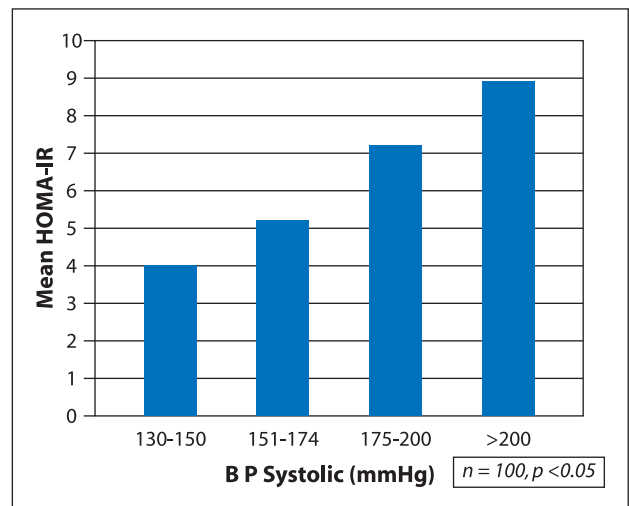


Table II: Distribution of patients according to diastolic BP.

S.No.	Systolic BP (mmHg)	Mean HOMA-IR (0.5-3.5)
1	130-150	4
2	151-174	5.3
3	175-200	7.4
4	>200	8.9

n = 100, *p* < 0.05

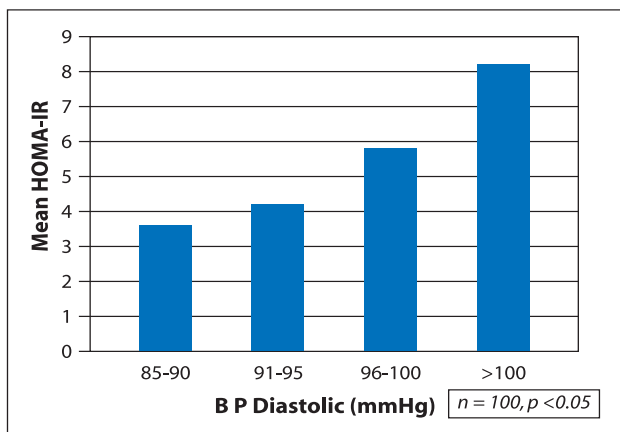


Table III: Distribution of patients according to BMI.

S. No.	BMI (kg/msq)	Mean HOMA-IR (0.5-3.5)
1	≤ 33	2.7
2	33.1-36	5.4
3	36.1-39.9	10.2
4	≥ 40	11.7

n = 100, p < 0.05

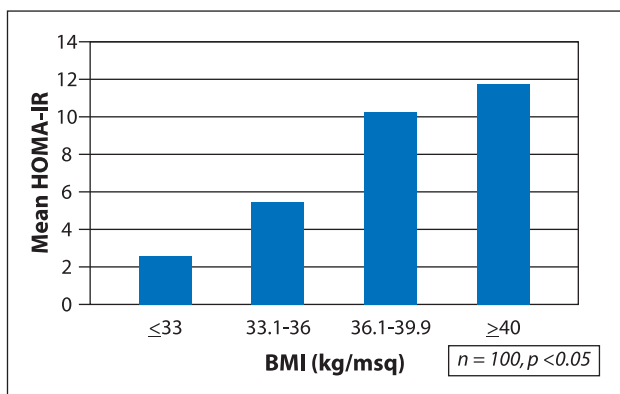


Table IV: Distribution of patients according to waist:hip ratio (Males).

S. No.	Waist:hip ratio	Mean HOMA-IR (0.5-3.5)
1	1-1.2	4.1
2	1.21-1.39	9.2
3	≥ 1.4	11.6

n = 100, p < 0.05

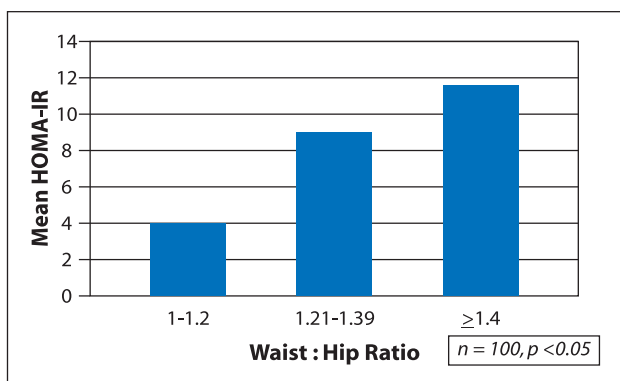
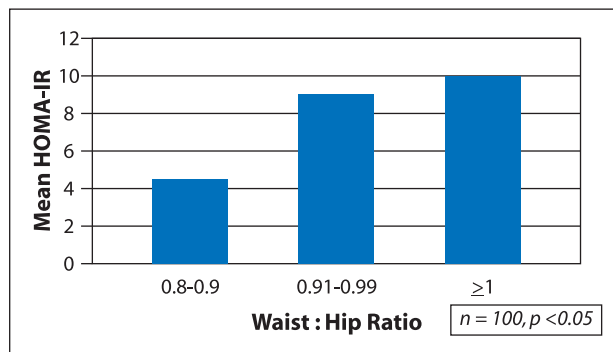


Table V: Distribution of patients according to waist:hip ratio (Females).

S. No.	Waist:hip ratio	Mean HOMA-IR (0.5-3.5)
1	0.8-0.9	4.4
2	0.91-0.99	9.1
3	≥ 1	10.03

n=100, p < 0.05



Discussion

Metabolic syndrome is a clinico-biochemically defined entity. Determination of insulin resistance is of utmost importance, as it is the root factor associated with clinical and metabolic abnormalities in metabolic syndrome.

In the present study, HOMA-IR has been taken as the standard method for measuring insulin resistance. We have compared HOMA-IR in metabolic syndrome patients in relation to their clinical presentation.

Correlation of HOMA-IR with blood pressure (BP)

Hypertension itself, independent of other risk factors, has been associated with the propensity to progress to diabetes. A possible mechanism is that an intrinsic defect in vasodilatation may contribute to insulin resistance by decreasing the surface area of the vasculature perfusing skeletal muscle, decreasing the efficiency of glucose uptake. Two other mechanisms have been proposed to explain the linkage between insulin resistance and hypertension: increased activity of the adrenergic nervous system, and increased renal sodium retention (Anderson *et al.* 1991)³.

Under normal physiologic conditions, insulin is a vasodilator with secondary effect on sodium reabsorption in the kidney. However, in the setting of insulin resistance, the vasodilatory effect of insulin is lost, but that renal effect on sodium re-absorption is preserved. Insulin also increases the activity of the sympathetic nervous system, an effect that may also be preserved in the setting of the insulin resistance. Finally, insulin resistance is characterised by pathway-specific impairment in phosphatidylinositol-

3-kinase signalling. In the endothelium, this may cause an imbalance between the production of nitric oxide and secretion of endothelin-1, leading to decreased blood flow (Kim *et al*, 1999)⁴.

Insulin directly stimulates the calcium pump in insulin-sensitive tissues and promotes calcium loss from the cell, and raising cytosolic calcium levels. If a cell is resistant to insulin, the insulin-induced calcium loss from the cells would be decreased, and in vascular smooth muscle cells the resultant increase in intracellular calcium would enhance responsiveness to vasoconstrictors and increase blood pressure.

It is reasonable to postulate that sympathetic nervous system overrides normal vasodilatory effects of insulin under more extreme conditions such as sucrose feeding, in obesity, and with hypertension (Landsberg *et al*, 1990)⁵. Hyperinsulinaemia has been proposed as a link between hypertension, obesity, and IGT (Mohan *et al*, 1997)⁶.

In our study, we have tried to correlate insulin resistance (HOMA-IR) with hypertension.

In the present study, we have considered patients with systolic BP > 130 and diastolic BP > 85 mmHg. Mean HOMA-IR was 4 for systolic BP 131-150 mmHg, 5.3 for systolic BP 151-174 mmHg, and 7.4 for systolic BP 175-200 mmHg, 8.9 for systolic BP > 200 mmHg. Difference in HOMA-IR of these groups was statistically significant ($p < 0.05$). Thus, as systolic blood pressure increases, HOMA-IR shows positive correlation.

Similar was the observation in case of diastolic BP. HOMA-IR being 3.6, 4.3 for diastolic BP 85-90 mmHg, 91-95 mmHg and 5.7, 8.2 for diastolic BP 96-100 mmHg, > 100 mmHg respectively. Thus, as diastolic blood pressure increases, HOMA-IR shows positive correlative rise. Difference in HOMA-IR of these groups was statistically significant ($p < 0.05$).

Correlation of HOMA-IR with BMI

There is a strong curvilinear relationship between BMI and relative body fat mass. Large epidemiologic studies by Troiano (1996)⁷ and Calle (1999)⁸ have established that there is a strong inverse relationship between BMI and mortality. A study by Assali (2001)⁹ in Israel demonstrated similar positive correlation between BMI and serum insulin.

In our study, we have studied the correlation of BMI with HOMA-IR.

For patients with BMI ≤ 33 kg/msq and 33.1-36 kg/msq, mean HOMA-IR was 2.7 and 5.4, respectively. For patients

with BMI 36.1-39.9 kg/msq and ≥ 40 kg/msq, mean HOMA-IR was 10.2 and 11.7, respectively. The difference between these groups was statistically significant ($p < 0.05$).

In our study, it was seen that mean HOMA-IR increases with increase in BMI.

Correlation of HOMA-IR with waist:hip ratio

Central obesity is strongly related to insulin response. (Arner *et al*, 1990¹⁰, Nicklas *et al*, 1996¹¹). This is because abdominal fat is lipolytically more active, resistant to antilipolytic effects of insulin. Also, it bears greater complement of adrenergic receptors. Tabata *et al*, 2008¹² in Japan showed positive correlation of HOMA-IR with waist:hip ratio. In our study also, waist:hip ratio shows positive correlation with HOMA-IR.

Mean HOMA-IR was 4.1 for waist:hip ratio 1-1.2, 9.2 for waist:hip ratio 1.21-1.39 and 11.6 for waist:hip ratio ≥ 1.4 in males and similarly in females, mean HOMA-IR was 4.4 for waist:hip ratio 0.8-0.9, mean HOMA-IR 9.1 for waist:hip ratio 0.91-0.99, and 10.03 for waist:hip ratio ≥ 1 .

It is obvious that male patients with higher waist:hip ratio (1.21-1.39, ≥ 1.4) had higher mean HOMA-IR (9.2, 11.6), and similarly female patients with higher waist:hip ratio (0.91-0.99, ≥ 1) had higher mean HOMA-IR (9.1, 10.03). These values were found statistically significant ($p < 0.05$) and suggests waist:hip ratio as a clinical parameter of insulin resistance.

Results

Following inferences were drawn from the study:-

1. Patients with higher systolic BP (175-200, >200 mmHg) had higher mean HOMA-IR (7.4, 8.9).
2. Patients with higher diastolic BP (96-100, >100 mmHg) had higher mean HOMA-IR (5.7, 8.2).
3. Patients with higher BMI (≥ 40 , 36.1-39.9 kg/msq) had higher mean HOMA-IR (10.2, 11.7).
4. Male patients with higher waist:hip ratio (1.21-1.39, ≥ 1.4) had higher mean HOMA-IR (9.2, 11.6).
5. Female patients with higher waist:hip ratio (0.91-0.99, ≥ 1) had higher mean HOMA-IR (9.1, 10.03).

Conclusion

Observations of present study show that in patients of metabolic syndrome:-

1. Hypertension correlates positively with insulin

resistance (HOMA-IR).

2. Increased BMI and waist:hip ratio are clinical parameters for insulin resistance (HOMA-IR).

Limitations

We did not study the correlation of lipid profile and dysglycaemia with insulin resistance.

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Survival trend and prognostic outcome of AIDS patients according to age, sex, stages, and mode of transmission – A retrospective study at ART centre of a tertiary care hospital

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Abstract

Background: The rate of progression of HIV infection is variable among different individuals, a fact that is known from the early period of the HIV epidemic. The progression of HIV-AIDS and the ultimate survival depends not only on the quality of care and highly active anti-retroviral therapy (HAART), but also on a host of other demographic factors such as age at seroconversion, mode of infection, and sex of the individuals. Earlier studies done primarily in the pre-HAART era have looked into these issues. The present study was undertaken to estimate survival function of AIDS patient who were diagnosed at an ART centre and whether age, gender, stages, and mode of transmission affect survival of AIDS patients on HAART.

Material and methods: We analysed the data of 344 AIDS patients who were followed-up at an anti-retroviral therapy centre (ART) of a teaching hospital. The records of the patients undergoing treatment were retrospectively analysed for various demographic variables, survival and mortality rate over a period of 6 years. The study included a cohesive treatment of censored observations based on lost to follow-up or deaths till the end of study as well as uncensored observations. The trend of survivability with respect to age, sex, stages, and mode of transmission was studied across these 6 years. Kaplan Meier method was used to estimate survival function with respect to gender and mode of transmission. Cox proportional hazard model was applied for the prediction of significant prognostic factors related to survival time.

Results: Age at the time of diagnosis was inversely correlated to survival in AIDS patients: median survival time was 5.66 ± 1.38 , 5.1 ± 1.76 and 4.59 ± 1.73 years for children (0 - 14 years), youth (15 - 35 years), and adults (> 35 years) respectively. Sex of the patient had no significant effect on the survival of the patients. AIDS patients who were intravenous drug users and were in stage IV of disease had the worst survival rates amongst all groups.

Conclusion: Even in the HAART era, age of the patient and mode of transmission are important prognostic factors in predicting the survival of AIDS patients. These findings could have significant impact on the management and treatment in AIDS patients as older patients and intravenous drug abusers need more aggressive management and close monitoring.

Keywords: HIV, AIDS, anti-retroviral therapy (ART), survival period, age, sex, stages, mode of transmission, HETERO, HOMO-MSM, MTCT, BLOOD, IDU, Kaplan-Meier, Cox proportional hazard model, relative risk.

Introduction

The longevity of an HIV infected individual is influenced by the numbers of variables – factors like social, biological, economic and medical – which either prolong or shorten the lifespan. It has been proven in studies that anti-retroviral therapy (ART) has significantly reduced mortality and improved life expectancy of individuals suffering from HIV infection^{1,2}. Apart from ART, other factors affecting survival have also been studied in the past: poor prognosis has been seen for male patients in comparison to females (Ward *et al*³, Frienlandet *et al*⁴); IDUs (Rothenberg *et al*⁵) and persons infected early in the epidemic (Rutherford *et al*⁶). However, some other researches (Remafedi⁷) have shown that there were no significant differences between deceased and other

subjects in relation to mode of transmission, gender, age at the time of the diagnosis of HIV infection, number of years from the diagnosis to death or to the end of study.

The incubation period may vary from person to person and place to place^{8,10}. Distribution of incubation period is very difficult to estimate, as exact time of infection in any of the risk groups is usually unknown. Moreover, in India, the exact time of HIV infection is difficult to know because of unawareness about the disease and lack of medical facilities. Hence new infections of HIV/AIDS are usually underestimated. Studies of the natural history of the HIV infection have generally focused on time from sero-conversion to AIDS rather than the time from entering into the stage of AIDS to the stage of death of the patients, as the latter requires longer duration of

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follow-up^{8,9}. However, death of AIDS patients when considered as end-point is more meaningful while finding the actual survivability of an individual for future planning and economic evaluation⁸. Therefore, in our study, instead of the time of seroconversion we estimated the survival of patients from the time they were diagnosed with AIDS and began HAART at the ART centre. The goal was to estimate the prognosis and survival function of AIDS, and to look whether age, gender, stages and mode of transmission act as a risk factor of death in AIDS patients.

Material and methods

We collected data of AIDS patients who reported in the anti-retroviral therapy (ART) centre at PGIMER and Dr. Ram Manohar Lohia Hospital, New Delhi, India. A cohort of 343 AIDS cases in the year 2004 were considered and followed-up for a period of 6 years (i.e., up to 2009) with the variations noted according to age, sex, stages, and modes of transmission. The patients who had a CD4 count less than 200 or were having AIDS-defining illness according to the WHO were selected. The patients who were lost either to death due to AIDS or to follow-up against medical advice were also included. For these six years' follow-up study, we have categorised the data into six groups: **Group-1** consists of HOMO-MSM (sex with men to men) who were infected through sex from male with male; **Group-2** consists of HETEROs who had been infected through sex; **Group-3** consists of MTCTs (mother to child transmission) who were infected through mother to child; **Group-4** consists of BLOOD who were infected through blood transfusion; **Group-5** consists of IDUs (injection drug users) who were infected through contaminated needles/syringes; **Group-6** consists of UNKNOWNs who were infected through unknown modes of transmission.

For the reported AIDS patients, we have considered survival and censored time in a random manner. The estimation of survival functions for AIDS patients were done using both parametric and nonparametric methods, subcategorising with respect to different variables of interest: mode of transmission, gender, age at the time of diagnosis, stage of AIDS (defined by WHO), and year of AIDS diagnosis. Kaplan Meier method was used to estimate the cumulative survival function for AIDS patients with respect to gender and mode of transmission. Cox proportional hazard model was used for the prediction of significant prognostic factors related to survival time. We confirmed our assumption about the proportionality of the hazard ratio by graphically plotting the log-normal of the time against the log-normal of the survival probability. All the analysis was performed on

SPSS version 15.

Results

The gender distribution in our study was: 73.2% males, 26.5% females, and 0.3% eunuchs (Table I). The most common mode of transmission was HETEROSEXUAL (63.48%) followed by BLOOD (14.9%) (Table I, Figure 1). IDU cases were observed in the male gender only. Out of 219 in the heterosexual groups, 137 were observed in the age group of 15 - 35 yrs and 81 were in the above 35 years age group. In HOMO-MSM groups more patients fell in the above 35 years of age group (Table IV).

Table I: Frequency distribution and percentage of reported AIDS patients with mode of transmission.

Mode of transmission	Sex			Total	Percentage (%)
	Eunuch	Female	Male		
Hetero	0	44	175	219	63.48
Homo-MSM	1	0	11	12	3.5
MTCT	0	6	17	23	6.7
Blood	0	19	32	51	14.9
IDU	0	0	14	14	4.1
Unknown	0	22	2	24	6.7
Total	1 (0.3%)	91 (26.5%)	251 (73.2%)	343	

Out of 343 patients, 98 patients (28.6%) died in the six years of follow-up (Table II). Maximum death rate was reported in IDU users; 9 out of 14 (64.3%) expired during

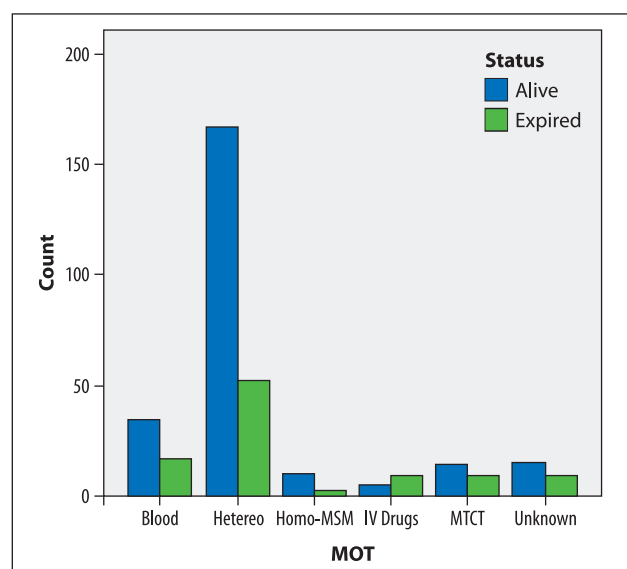


Fig. 1: Alive and expired cases with mode of transmission.

this period (Table II, Figure 1). The total numbers of withdrawal cases were 81 during this period.

Table II: Frequency of “deaths and alive” AIDS patients with respect to mode of transmission (2004-2009).

Mode of transmission	Status		Total
	Alive	Expired	
Blood	34 (66.7%)	17 (33.3%)	51
Hetero	167 (76.3%)	52 (23.7%)	219
Homo-MSM	10 (83.3%)	2 (16.7%)	12
IDU	5 (35.7%)	9 (64.3%)	14
MTCT	14 (60.9%)	9 (39.1%)	23
Unknown	15 (62.5%)	9 (37.5%)	24
Total	245 (71.4%)	98 (28.6%)	343

We segregated the patients into three age groups: children (1 - 14 years), youth (15 - 35 years), and adults (36 - 80 years). For these age groups, the median age at the time of the diagnosis was 5, 31, 42 years and median (\pm standard deviation) survival time was 5.66 (\pm 1.38), 5.1 (\pm 1.76), and 4.59 (\pm 1.73) years respectively, which was significant ($p = 0.032$).

When we analysed difference in mean ages of alive and expired patients with respect to mode of transmission, except for BLOOD and IDU, it was not significant (Table III). In patients with BLOOD as a mode of transmission, the risk of death was significantly more in the younger age group ($p\text{-value} = 0.014$). The finding was opposite for IDU as mode of transmission: those with older age expired early ($p\text{-value} = 0.04$). We also note that the average age for various modes of transmissions for alive as well as expired patients was highly significant (ANOVA, $p\text{-value} < 0.01$). Further analysis using Tukey's test revealed that for the alive patients, the average age of the MTCT is significantly lower than that of other modes of transmission. Also, for expired patients the average ages of MTCT and BLOOD are significantly lower than that of other categories.

Table III: Mean age of deaths and alive cases with respect to mode of transmission (2004-2009).

Mode of transmission	Alive (Mean \pm S.D.)	Deaths (Mean \pm S.D.)	p-value
Hetero	34.353 \pm 8.26	34.538 \pm 8.56	0.889
homo-MSM	38.2 \pm 5.432	46.5 \pm 9.192	0.100
MTCT	5.286 \pm 2.84	4.0 \pm 2.179	0.262
BLOOD	25.471 \pm 12.488	16.176 \pm 11.786	0.014
IDU	31 \pm 1.581	37.333 \pm 7.45	0.04
Unknown	29.4 \pm 7.268	35.111 \pm 9.4	0.109
ANOVA p-value	< 0.01	< 0.01	

The average age of males was higher than that of females for all modes of transmission; however the difference was significant only for HETERO as mode of transmission (t-test, $p\text{-value} = 0.012$) (Table IV).

Table IV: Mean age of males and females with respect to mode of transmission at the time of entering in ART centre (2004-2009).

Mode of transmission	Male (Mean \pm S.D.)	Female (Mean \pm S.D.)	p-value
Hetero	35.103 \pm 8.361	31.591 \pm 7.574	0.012
Homo-MSM	39.545 \pm 6.817	NA	-
MTCT	5.118 \pm 2.848	3.833 \pm 1.722	0.314
Blood	23.344 \pm 13.319	20.737 \pm 12.4	0.492
IDU	35.071 \pm 6.696	NA	-
Unknown	38 \pm 11.314	30.955 \pm 8.197	0.266
p-value	< 0.01	< 0.01	

We analysed the average length of survival from getting treatment in ART centre till death or to the end of the study in different modes of transmission (Table V). The t-test shows that mean length of survival of alive was significantly more than the deceased AIDS patients with HETERO ($p\text{-value} = 0.001$), MTCT ($p\text{-value} = 0.031$) and UNKNOWN (p-value = 0.034) as the mode of transmission. Moreover there was no significant difference in the length of survival across various modes of transmission for both ALIVE (ANOVA, $p\text{-value} = 0.315$) and EXPIRED cases ($p\text{-value} = 0.204$) (Table 5).

Table V: Mean length of survival of AIDS patients from diagnosis to death or the end of study for death and alive cases with respect to mode of transmission (2004-09).

Mode of transmission	Alive (Mean \pm S.D.)	Deaths (Mean \pm S.D.)	p-value
Hetero	4.601 \pm 1.339	3.481 \pm 1.388	0.001
Homo-MSM	4.028 \pm 1.782	4.63 \pm 1.004	0.661
MTCT	5.078 \pm 0.986	4.059 \pm 1.108	0.031
Blood	4.583 \pm 1.2	3.871 \pm 1.413	0.066
IV drugs	5.336 \pm 0.285	4.134 \pm 1.243	0.058
Unknown	4.313 \pm 1.519	2.806 \pm 1.697	0.034
p-value	0.315	0.204	

Using Kaplan Meier estimation method, the median survival time for the AIDS patients with these modes of transmission viz. HETERO, HOMO-MSM, MTCT, BLOOD, IDU and UNKNOWN were 5.68, 5.01, 5.87, 5.11, 4.48, and 5.23 years respectively (Table VI). As illustrated in Figure 2, the survival curves are falling gradually for HETERO and

HOMO-MSM mode of transmission, whereas for the others the decline is very steep.

Table VI: Kaplan-Meier estimates of survival function of AIDS patients with mode of transmission (2004-2009).

Mode of transmission	Starting time (Years)	Number entering interval	Number withdrawn	Number of deaths	Cumulative survival function	S.E. of cumulative survival function
Hetero	0-1	219	2	1	1.00	0.00
	1-2	216	7	3	0.98	0.01
	2-3	206	10	8	0.94	0.02
	3-4	188	6	10	0.89	0.02
	4-5	172	9	15	0.81	0.03
	5-6	148	22	15	0.72	0.03
Homo-MSM	0-1	12	0	0	1.00	0.00
	1-2	12	2	0	0.98	0.01
	2-3	10	0	0	0.96	0.02
	3-4	10	1	0	0.92	0.04
	4-5	9	1	1	0.88	0.08
	5-6	7	0	1	0.76	0.11
MTCT	0-1	23	0	0	1.00	0.00
	1-2	23	0	0	0.99	0.01
	2-3	23	1	1	0.94	0.04
	3-4	21	0	2	0.86	0.07
	4-5	19	0	2	0.77	0.09
	5-6	17	3	4	0.57	0.11
Blood	0-1	51	1	0	1.00	0.00
	1-2	50	0	2	0.96	0.03
	2-3	48	0	1	0.94	0.03
	3-4	47	5	2	0.90	0.04
	4-5	40	3	5	0.78	0.06
	5-6	32	2	6	0.63	0.07
Drugs	0-1	14	0	0	1.00	0.00
	1-2	14	0	0	0.98	0.01
	2-3	14	0	1	0.93	0.07
	3-4	13	0	2	0.79	0.11
	4-5	11	0	1	0.71	0.12
	5-6	10	0	5	0.36	0.13
Unknowns	0-1	24	0	1	0.96	0.04
	1-2	23	1	1	0.91	0.05
	2-3	21	2	2	0.82	0.08
	3-4	17	0	2	0.73	0.10
	4-5	15	3	1	0.67	0.10

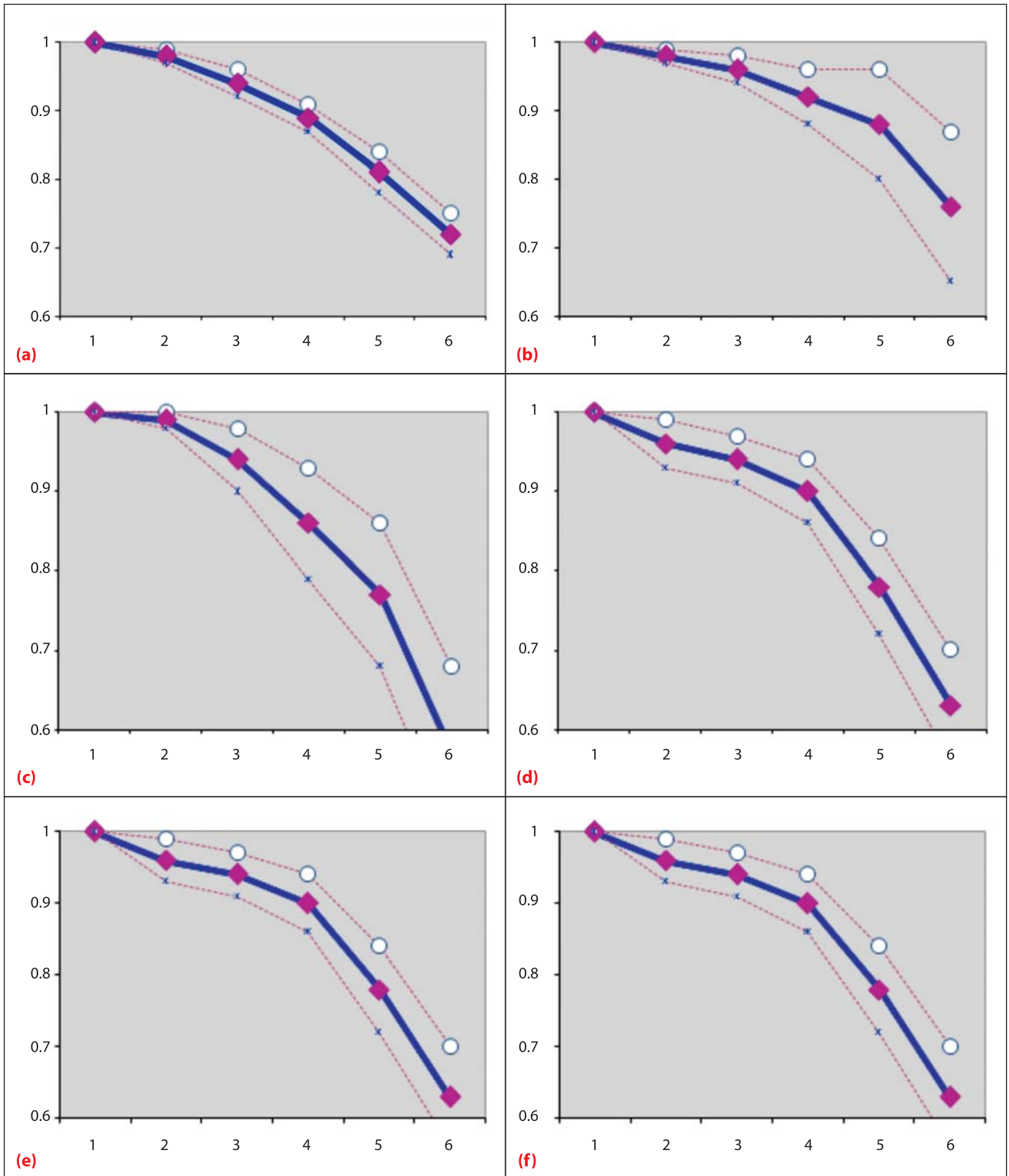


Fig. 2: Survival function of AIDS patients and 95% confidence interval with respect to year from diagnosis with mode of transmission (a) HETERO, (b) HOMO-MSM, (c) MTCT, (d) BLOOD, (e) IDU, (f) UNKNOWN. (x - duration of study, 6 yrs ; y - CSF, Table VI).

	5-6	11	0
2	0.55	0.11	

Applying nonparametric Wilcoxon-test, there was no significant difference between male and female survival time for the patients at the ART centre (p-value =0.343) (Table VII; Figure 3).

Table VII: Comparison of Kaplan Meier estimates of survival function with respect to gender among AIDS patients and its graphical representation.

Years of study	Male	Female
0-1	1.00	0.99
1-2	0.98	0.97
2-3	0.94	0.92
3-4	0.89	0.84

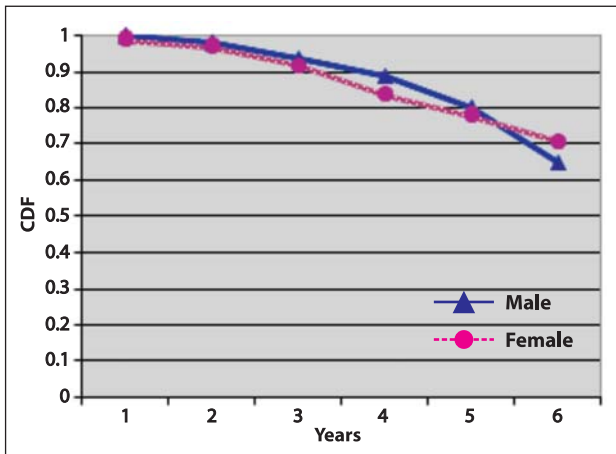


Fig. 3: Comparison of Kaplan Meier estimates of survival function with respect to gender among AIDS patients and its graphical representation.

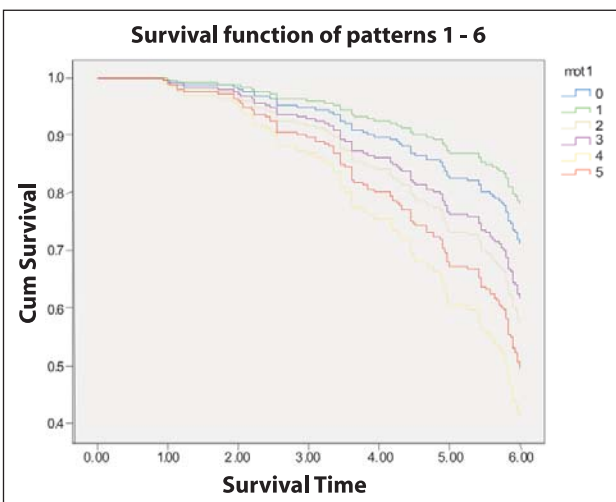


Fig. 4: Survival function of AIDS patients estimated by Cox proportional hazard model with respect to years from diagnosis for different age groups: child (0), youth (1), adult (2) (2004-2009).

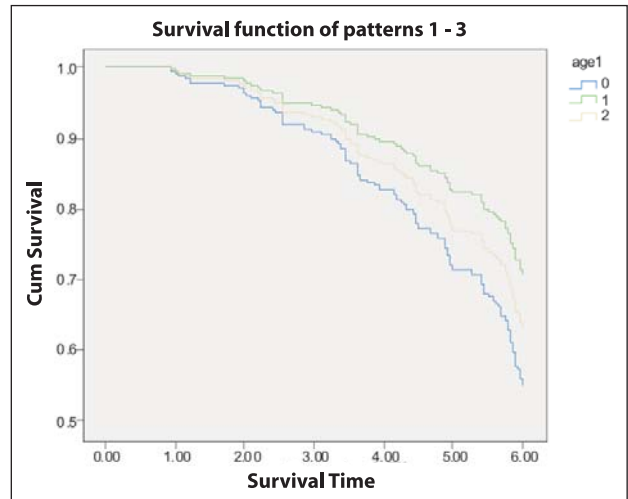


Fig. 5: Survival function of AIDS patients estimated by Cox proportional hazard model with respect to years from diagnosis for different age groups: child (0), youth (1), adult (2) (2004-2009).

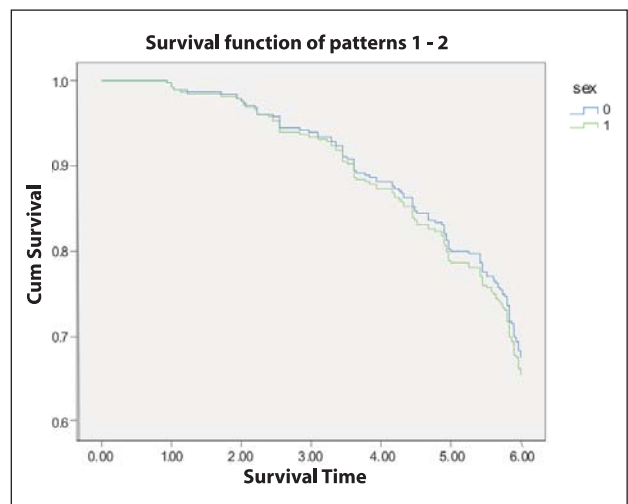


Fig. 6: Survival function of AIDS patients estimated by Cox proportional hazard model with respect to years from diagnosis for male (1) and female (0) groups (2004-2009).

4-5	0.80	0.78
5-6	0.65	0.71

We applied Cox proportional hazard model for the prediction of significant prognostic factors related to survival time; figures 4, 5, 6, and 7 show survival function with respect to mode of transmission, age, gender, and stages respectively.

It reveals that except for gender, other factors were significant prognostic factors related to survival of AIDS patients. With respect to mode of transmission, survival was worst for IV drug abusers and best for heterosexual mode of transmission. Similarly, survival was better for younger patients (age < 35 years) as compared to older

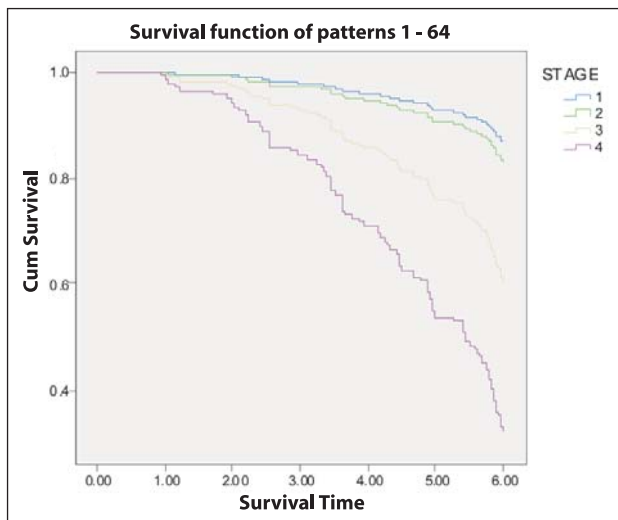


Fig. 7: Survival function of AIDS patients estimated by Cox proportional hazard model with respect to years from diagnosis Stage-wise (I-IV) (2004-2009).

patients (age > 35 years). We also observed that as the disease progressed to a higher stage, survival was the worst. However, compared to transition from stage 1 to 2, survival duration fall very rapidly from stage 2 to 3, and 3 to 4.

Discussion

In this paper, we have tried to provide a comprehensive study about the survival trend of AIDS patients. The analysis has been performed to determine association between survival time and mode of transmission, age, sex, and stage of the disease.

The distribution of the modes of transmission of HIV infection varies in different countries. In western countries such as the United States, the most common mode of transmission, particularly among males, is male to male homosexual contact accounting for more than 50% of the new cases among them¹⁰. In contrast, in resource-limited areas, high risk heterosexual contact is responsible for 70 - 80% of AIDS cases followed by perinatal transmission and injection drug use (IDU) which account for 5 - 10% of the cases¹¹. In our study too, the most common mode of transmission was heterosexual contact accounting for 63.48% of the cases (Table I). The possible reasons of low incidence of homosexual AIDS cases is the taboo associated with homosexuality resulting in incorrect history and underestimation of the prevalence of cases.

We observed that, number of years for alive cases with respect to HETERO, MTCT, and UNKNOWN mode of transmission are significantly greater than that of deaths

cases respectively (Table V). In our study, IV drug abusers have fared poorly as compared to other modes of transmission; 64.3% of patients in this group had expired by the end of the study period (Table II), and median survival time was just 4.48 years. Moreover, IDU with old age is a more deadly combination as they expired more rapidly than younger patients (Table III). There are theoretical concerns that injection drug use could affect HIV disease progression. Drugs, such as opioids, may increase HIV replication *in vitro*^{12,13}. Furthermore, drug use may negatively impact on medication adherence and access to care¹⁴. In spite of these theoretical reasons, clinical studies on this subject have found conflicting results. Wood *et al* found that after 84 months of HAART, all-cause mortality rate was similar between the 915 IDUs (26.5%; 95% CI, 23.2% - 29.8%) and 2,201 non-IDUs (21.6%; 95% CI, 16.9% - 26.2%) (Wilcoxon P = .47)¹⁵. The Anti-retroviral Therapy Cohort Collaboration had significantly different results; in their cohort of more than 40,000 patients spread over Europe and North America, patients with presumed transmission via injecting drug use had lower life expectancies than did those from other transmission groups (32.6 years vs 44.7 years in 2003 - 05)¹⁶.

Age is one of the most important demographic factor that influences the prognosis of AIDS. Multiple studies have demonstrated that increasing age at the time of HIV infection is associated with more rapid progression to AIDS in the absence of anti-retroviral therapy. Old age is associated with immunologic vulnerability, exposure to infectious diseases, psychosocial co-morbidities and the other factors of disease progression. The Collaborative Group on AIDS Incubation and HIV Survival reported that following HIV seroconversion, the incidence of AIDS increased and survival time decreased with age¹⁷. They found that individuals who seroconverted at ages 15 - 24 years had median survival of 12.5 years compared to 7.9 years for individuals aged 45 - 54 years; for development of AIDS, the corresponding values were 11 and 7.7 years respectively. May *et al* found that among patients on ART, high mortality was associated with advanced age and advanced stage of clinical disease¹⁸. In our study, for the three age groups, children (1 - 14 years), youth (15 - 35 years), and adults (36 - 80 years), mean (\pm standard deviation) survival time following development of AIDS was 5.66 (\pm 1.38), 5.1 (\pm 1.76), and 4.59 (\pm 1.73) years respectively. Patients younger than 35 years had significantly better survival as compared to patients older than 35 years of age (Fig. 5).

The natural history of HIV infection in children is different from that of adults and also depends on mode of

transmission. Children who acquire HIV vertically through maternal-to-foetal transmission, have a bi-modal disease progression depending on the timing of infection. Those who are infected *in utero* have a more rapid progression of disease in which children reach severe clinical and/or immunologic stages within the first year of life and often die by the second year of life¹⁹. This is seen in 10 - 25% of children infected with HIV. The other 75% or majority of children have a more typical, slower progression, with clinical and immunologic deterioration by five to six years of life²⁰. In our study, most of the children were of this second group as the mean age at the time of entry was 5.118 ± 2.848 yrs for males and 3.833 ± 1.722 years for females (Table IV). We observed that survivability of AIDS patients was highest in MTCT mode of transmission (mean length of survival: 5.078 years), and in age group of 1 to 14 years (median survival time: 5.66 ± 1.38 years). However, the Cox proportional hazard model to assess survival indicates that over the follow-up period, the risk of death was highest in children (Figure V). It could be presumably because of acquisition of infection at a time of immunological immaturity and/or availability of increased number of susceptible cells. On the other hand, older children who are infected horizontally may have a course more similar to adults with HIV infection.

Sex of the patient may also be an important prognostic factor in AIDS. Again, the results of various studies are conflicting. While the Antiretroviral Therapy Cohort Collaboration¹⁶ found that women had higher life expectancies than men, others (Remafedi⁷) have found that sex of the patient does not significantly alter the prognosis and survival in AIDS patients. In our study, although females had a slightly better survival than males, this was not statistically significant (Table VII, Figures 3, 6).

Cox regression model for survival indicates that stages III and IV disease has a significant effect as compared to stage I and II on survival time. Similar conclusions were drawn by May *et al*¹⁸.

Conclusion

Besides the laboratory parameters such as CD4 cell count and viral load, several other factors play an important role in the progression of AIDS. Age as a factor had a significant difference in survival; patients < 35 years at time of seroconversion had significantly better survival as compared to > 35 years of age. Again, risk of death was high among the very young, i.e., children. Intravenous drug abuse was mode of transmission with worst survival; IDU with old age is a more deadly combination. However, sex of the patients was not associated with survival of

patients. It can be safely assumed that even in HAART-treated population, these demographic factors have significant impact on prognosis.

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Dynamic auscultation – A lost art which needs to be revived

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Abstract

The rate at which technological advances in cardiology have emerged and subsequently integrated into common practices has continually accelerated during the past few decades. Although many paradigms are shifting, some remain foundational and change less, the most important of which is the bedside clinical examination. There has been a perceptible reduction in the skills and abilities of medical students and residents in diagnosing and interpreting heart sounds and murmurs. In experienced hands, the cardiac physical examination is a sensitive and specific instrument for detecting cardiac pathology. The term dynamic auscultation refers to a technique of altering circulatory dynamics by means of respiration and a variety of physiological and pharmacological manoeuvres and determining the effect of these manoeuvres on heart sounds and murmurs.

Key words: Dynamic auscultation, heart sounds, murmurs.

Introduction

The French physician René Théophile Hyacinthe Laënnec (1781-1826) introduced the medical world to auscultation by inventing the stethoscope. Despite the fact that it has been a part of the doctors' paraphernalia for over a century, the stethoscope is not being put to its best use by the medical profession as noted by Drs. Levine and Harvey more than 50 years ago. This loss has occurred despite new and sophisticated teaching modalities including graphic instructions, digital recordings, and computer-enhanced simulation. Although the reason for reduction in these clinical skills is not entirely clear, the increased availability and promotion of newer diagnostic techniques, a reduction in emphasis on auscultation instructions, a lack of physician confidence, and increased concern about litigation may be involved in the increased frequency of ordering of additional imaging modalities. Assessment studies of internal medicine and family practice residents have shown less than adequate proficiency in cardiac auscultation. The literature also indicates that the formal teaching of cardiac auscultation has waned considerably despite positive attitudes about its importance as a useful clinical skill¹⁻³.

Effect of echocardiography on the utility of cardiac auscultation

The availability of echocardiography does not eliminate the need for properly performed auscultation of the heart. Although echocardiography provides additional information in many patients and can even provide the correct aetiology of various systolic and diastolic murmurs, it is an unnecessary step in many patients with innocent

murmurs. Echocardiography can even lead to a false diagnosis of echocardiographic heart disease.

Often, a mild valvular regurgitant jet, detected by color-flow Doppler techniques, is not associated with an audible murmur despite optimal auscultation. Such regurgitant jets usually do not indicate clinical heart disease. Trivial mitral regurgitation can be detected by Doppler in up to 45 per cent of normal individuals; tricuspid regurgitation in up to 70 per cent; and pulmonary regurgitation in up to 88 per cent. Normal aortic regurgitation is encountered much less frequently, and its incidence increases with advancing age. Newly developed, small, handheld echocardiographic detectors are highly unlikely to replace the stethoscope as the presence of a fourth heart sound during carefully performed cardiac auscultation gives additional information regarding the atrial contribution to ventricular filling. Beside that, the presence of a third heart sound is, in an elderly person, in itself considered an independent predictor regarding the long-term prognosis. Echocardiographic finding of mitral valve prolapse in the absence of any auscultatory abnormality should be considered as a benign condition. Again, the most difficult decision during a cardiac examination is the differentiation of constrictive pathology from restrictive pathologies. Even using the most sophisticated modalities like echocardiography and cardiac catheterisation, differentiation between the two is sometimes impossible; but sometimes the presence of a diastolic sound like pericardial knock on cardiac auscultation gives a useful clue regarding constrictive pathology.

Dynamic auscultation

Auscultation of the heart should be considered a

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dynamic exercise. In addition to being auscultated in the left lateral decubitus position, the patient should, when possible, also be examined while standing, squatting, and during Valsalva manoeuvre and following its release. This type of dynamic auscultation changes the pre-load and after-loading conditions of the heart and might yield diagnostic information because of the typical response of heart sounds and murmurs to these manoeuvres. There are, basically, seven manoeuvres in dynamic auscultation that may be easily and rapidly used at the bedside: 1) Valsalva manoeuvre, 2) exercise, 3) respiration, 4) postural changes, 5) transient arterial occlusion, 6) response after premature ventricular contraction (PVC), 7) amyl nitrite inhalation⁵⁻⁸.

1. **Valsalva manoeuvre:** Valsalva, a manoeuvre, was described in 1704 as a method of clearing pus from the middle ear by straining with the mouth and nose closed. The Valsalva manoeuvre is easily performed at the bedside and consists of a relatively deep inspiration followed by forced expiration against a closed glottis for 10 - 12 seconds. The examiner places the flat of the hand upon the abdomen to provide the patient with a force against which to strain and permit assessment of the degree and duration of the straining effort. The amount of expiratory effort should be adequate to cause physiological changes⁷.

The Valsalva manoeuvre has 4 phases:-

Phase 1 - is associated with a transient rise in systemic BP and intrathoracic pressure as straining commences. This phase is approximately of 1 - 3 seconds and is usually undetectable at bedside.

Phase 2 - is accompanied and readily detected by reflex tachycardia.

Phase 3 - begins promptly with the cessation of straining, is associated with a perceptible decrease in systemic venous return, blood pressure and pulse pressure, is associated with a transient decrease in blood pressure and systemic venous return, lasts for 1 - 3 seconds, and is usually undetectable at the bedside.

Phase 4 - the venous return exceeds its level before the performance of Valsalva manoeuvre, thereby augmenting the right ventricle, and left ventricle stroke volume⁷.

The Valsalva manoeuvre strain phase decreases the intensity or duration of all left-sided murmurs except mitral valve prolapse (MVP) and hypertrophic cardiomyopathy (HOCM) (Table I)⁷.

Table I: Various phases of Valsalva manoeuvre: their physiology and effect on murmurs.

Phases	Physiology	Murmur
Strain phase	↑ HR	↑ MVP, ↑ HOCM
	↑ intra-thoracic pressure,	↓ AS, ↓ PS, ↓ MS, ↓ AR, ↓ MR,
	↑ ventricular volume,	↓ VSD, ↓ PDA
	↓ VR, ↓ CO	
Release phase	↑ VR, ↑ CO	↓ MVP, ↓ HOCM
		↑ AS, ↑ PS, ↑ MS, ↑ AR, ↑ MR,
		↑ VSD, ↑ PDA

2. **Mullers manoeuvres:** This is a converse of the Valsalva manoeuvre. In this, the patient forcefully inspires – with nose and mouth firmly sealed – for 10 seconds. This method widely splits S2, and augments murmurs and filling sounds originating in the right side of the heart⁸.
3. **Isometric exercises:** Exercise is a simple manoeuvre for the evaluation of the specific cardiac findings while the patient is at rest, the easiest exercise being the sustained handgrip. Physiologically, the haemodynamic effects are related to a withdrawal of a vagal tone and an increase in sympathetic tone. In a normal individual patient, the isometric hand grip produces tachycardia, elevates systolic and diastolic BP, and elevates cardiac output. Effect of hand grip on systemic vascular resistance varies with the amount of effort produced. All left-sided regurgitant murmurs are increased by isometric exercises. LV outflow lesions like valvular and sub-valvular AS, may be decreased by hand grip as a result of increased SVR⁹⁻¹¹.
4. **Respiration:** Changes in cardiac sounds and murmurs with respiration are helpful in differentiating cardiac pathology from normal variation. During inspiration, the intrathoracic pressure decreases to subatmospheric levels. From a haemodynamic standpoint, inspiration increases VR, which augments RA & RV pre-load. Resistance to RV outflow also decreases as a result of dilatation of the pulmonary vasculature. The net effect is increased RV stroke volume. Reciprocally, during expiration there is decrease in lung volume. Pulmonary vein flow into the LA increases as a result of increased intrathoracic pressure transmitted to the pulmonary capillary bed that augments the flow out of the pulmonary bed into the LA & LV. Respiratory changes in cardiac sounds and murmurs may be divided into two categories: those which increase with inspiration

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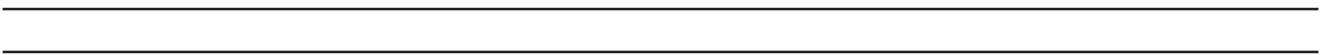


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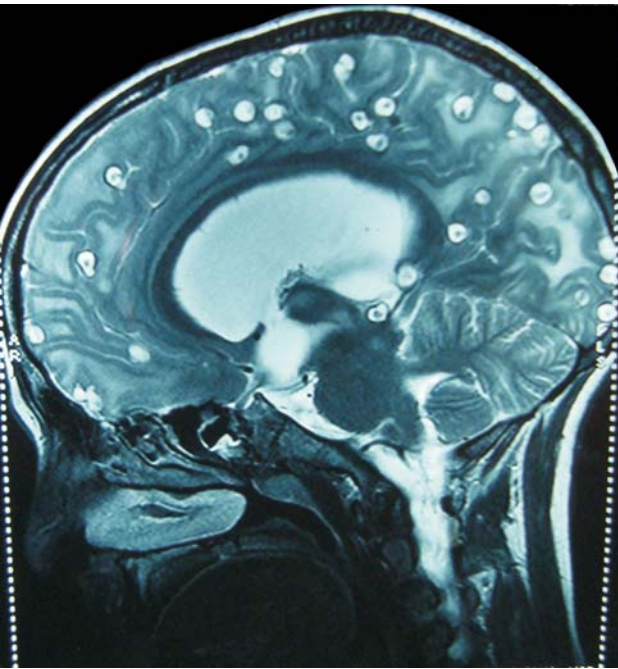
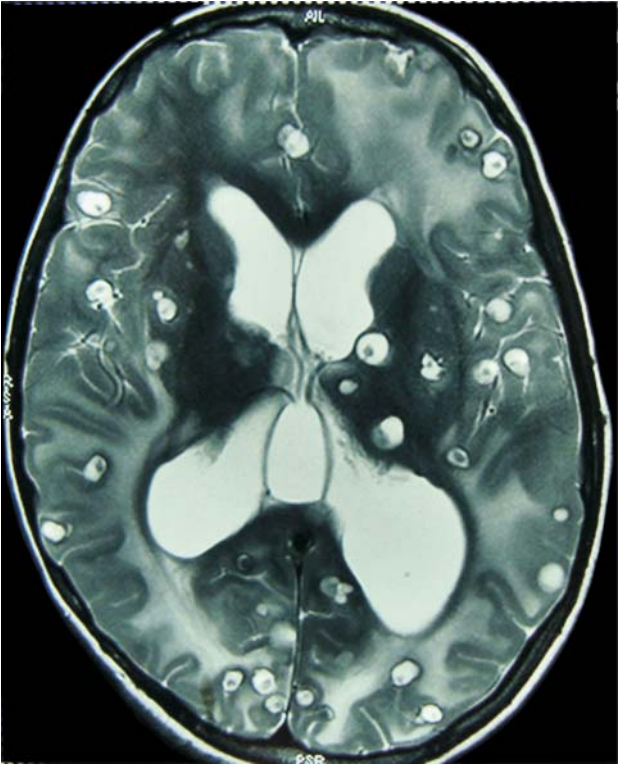
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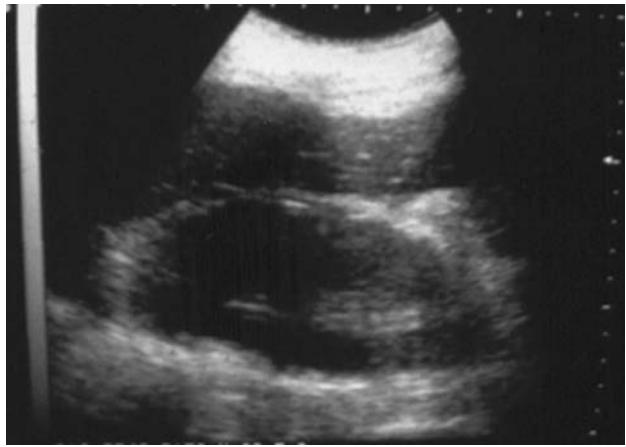


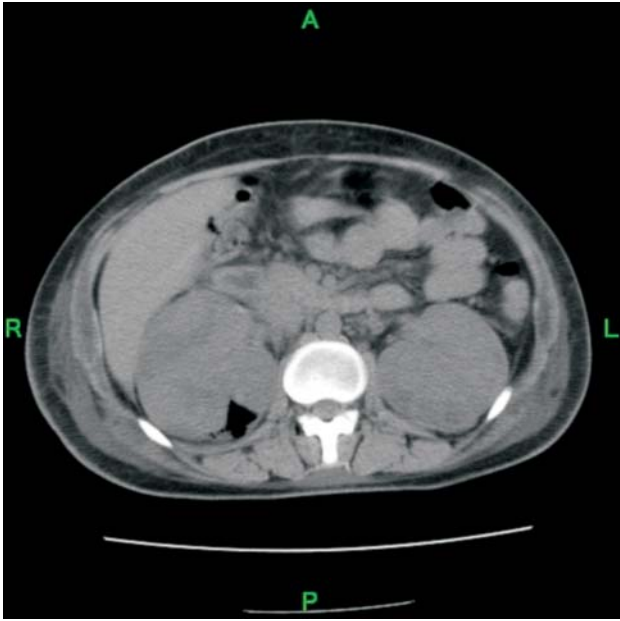






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- For soybean oil seeds and pulses, one spray after 25 days interval.
- For flower plants like-rose, jasmine, chrysanda, chrysanthemum etc once in 20 days.
- For fruits and horticultural crops once in 20 days.

DOSE: 2-3 ml in 1 liter of water to spray on crops. **STORAGE:** Store in a cool & dry place. Keep away from children. Shake the bottle well before use.

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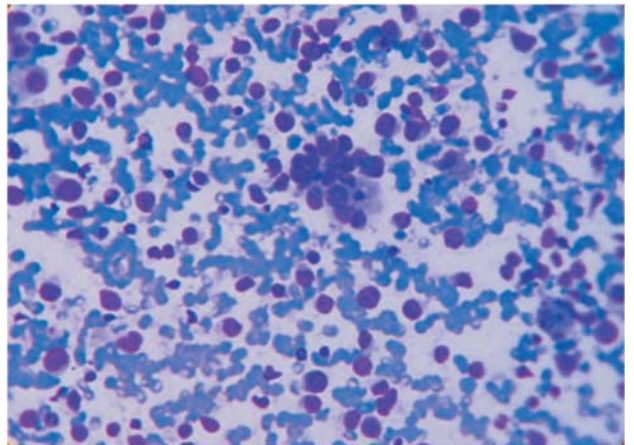
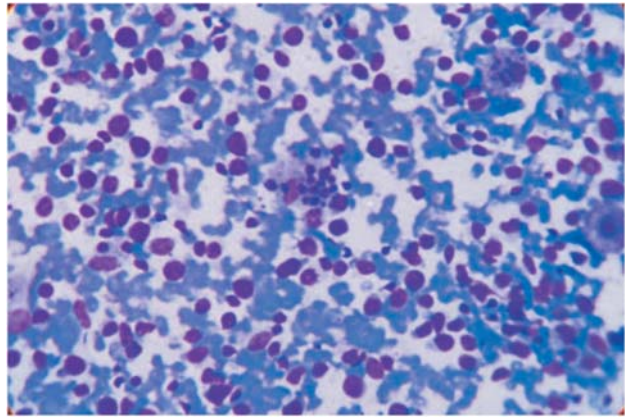
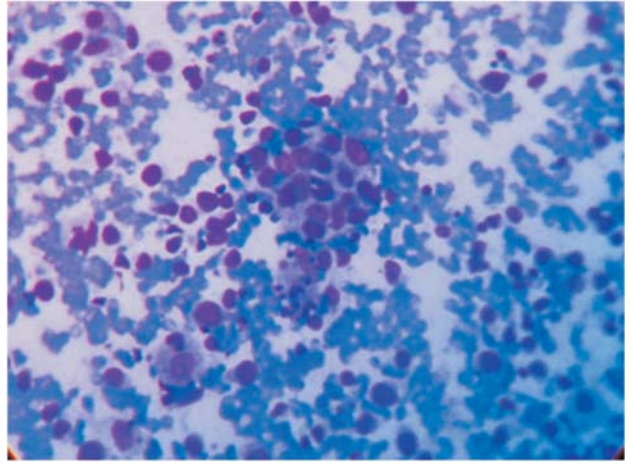
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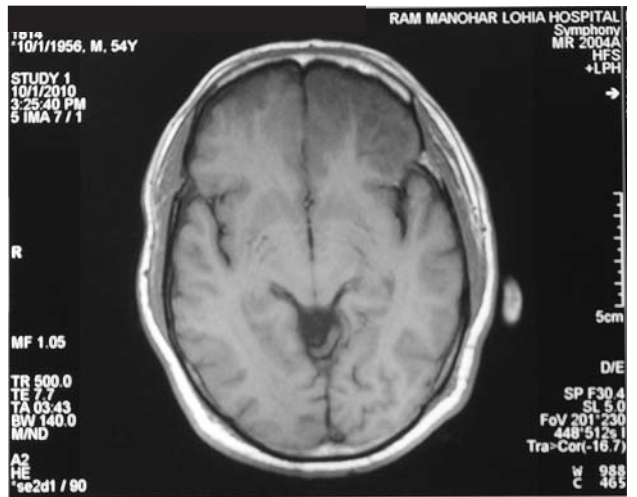
- कपास, बैंगन, टमाटर के लिये हर २५ दिनों के अंतराल से छिड़काव करें. सोयाबीन, दलहनी फसलें व अन्य तेल वनीय फसलों के लिये २५ दिनों के अंतराल से छिड़काव करें.
- चमेली, गुलाब, गेंदा तथा अन्य फूलों पर २० दिन के अंतराल से छिड़काव करें.
- फल व बागवत खेती के लिये २० दिनों के अंतराल से छिड़काव किया जा सकता है.

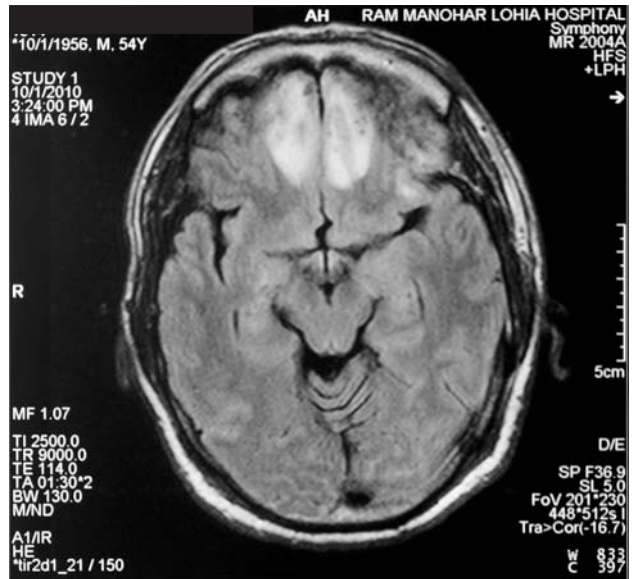
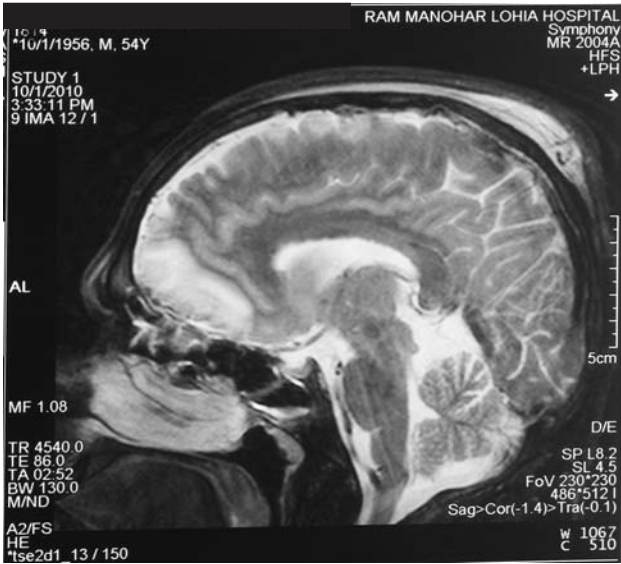
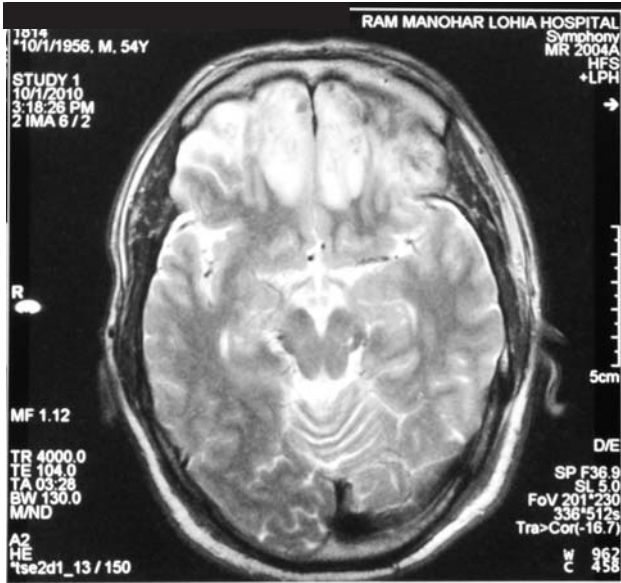
Formulated & Marketed By:
Pratham Biotech Private Limited
C/o R.K. Business Centre, 194, Cement Road, Shivaji Nagar,
Nagpur 440 010. email: prathambiotech@indiatimes.com
CUSTOMER CARE PHONE: 0712- 2547295

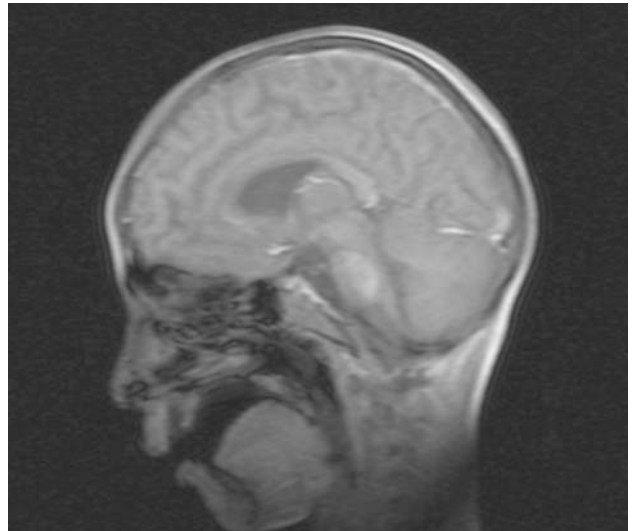
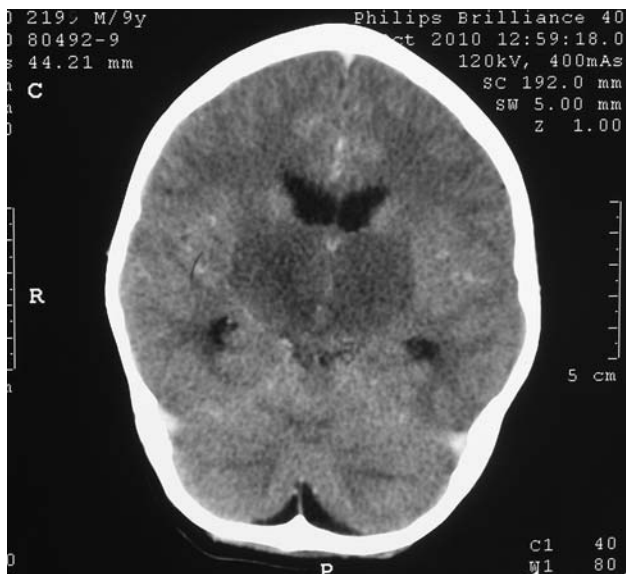
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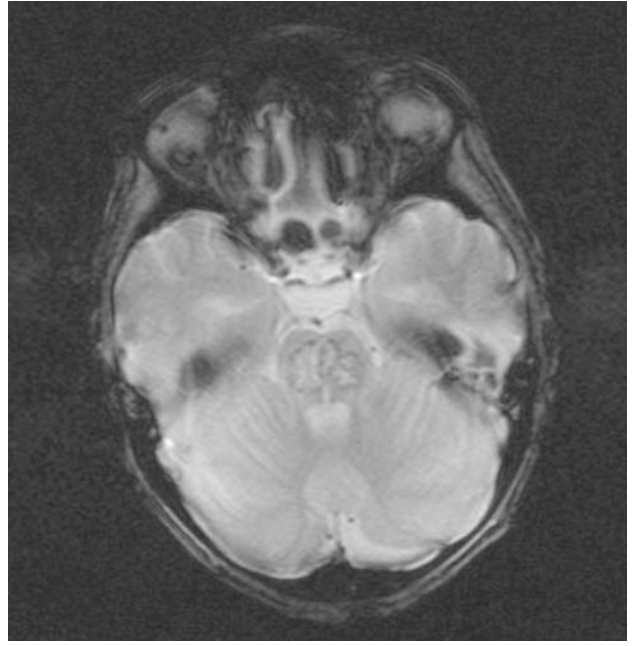
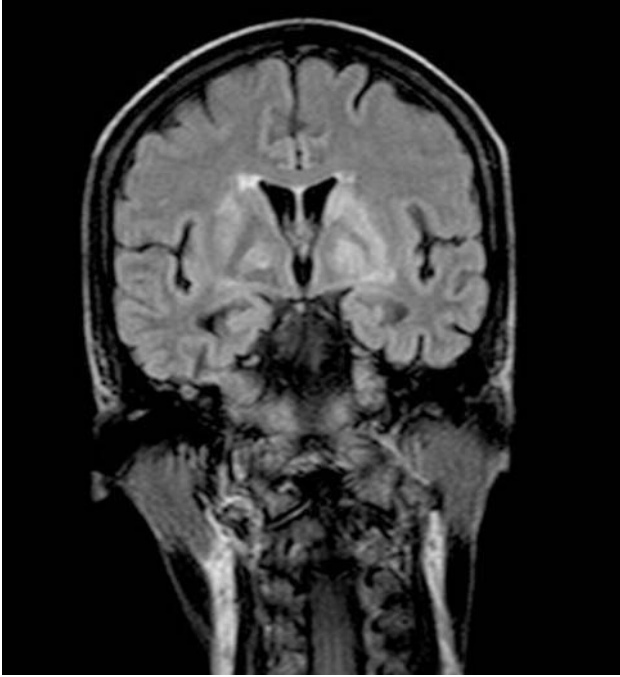








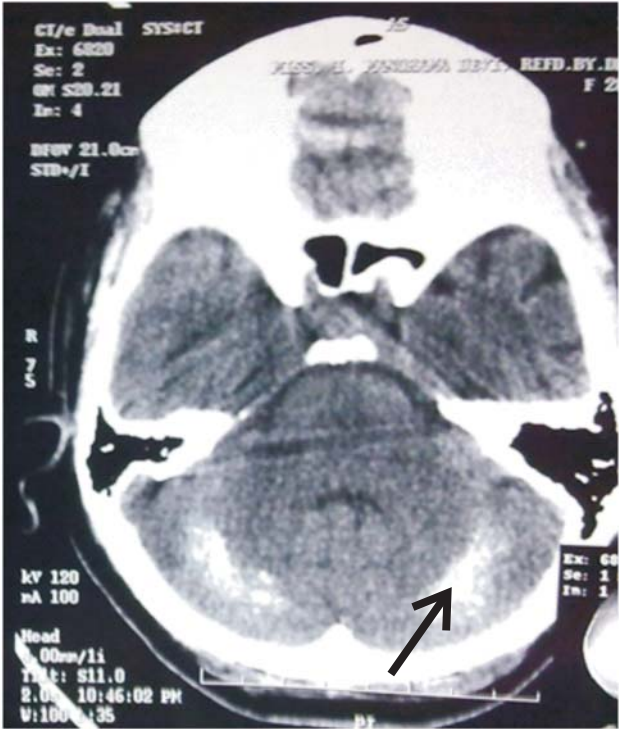


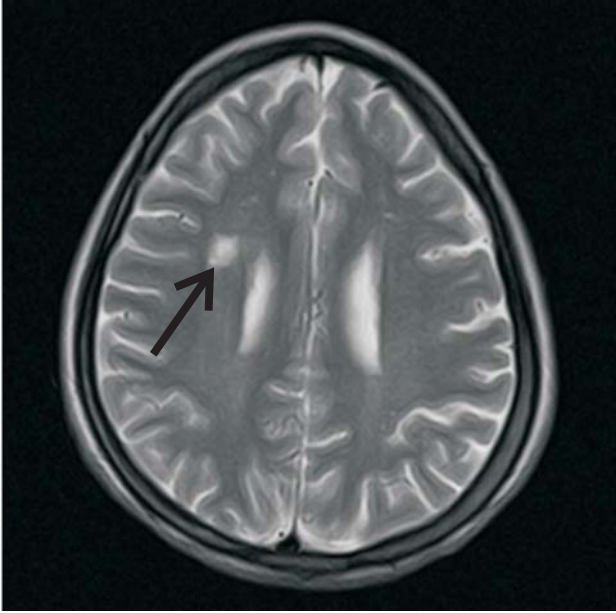


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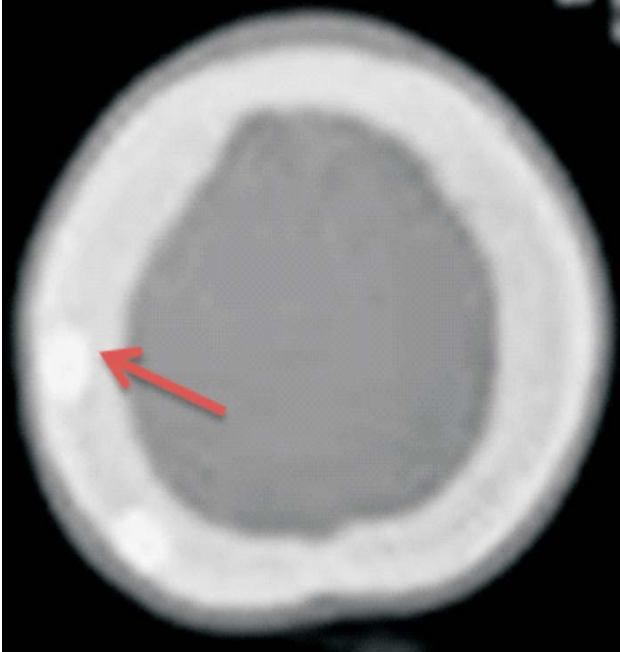
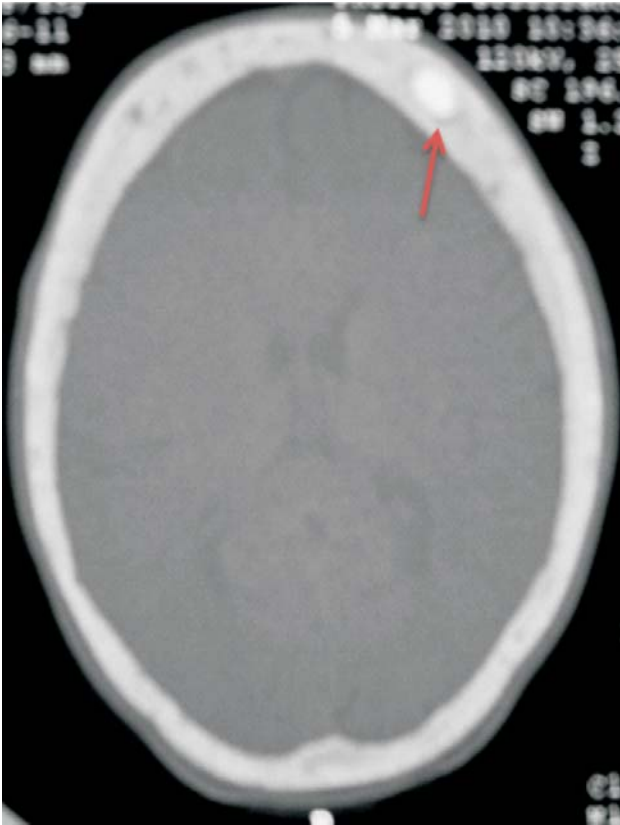




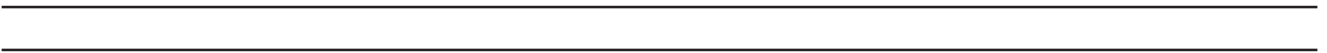


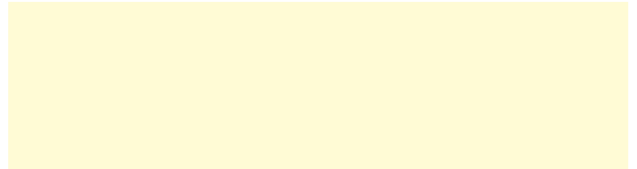
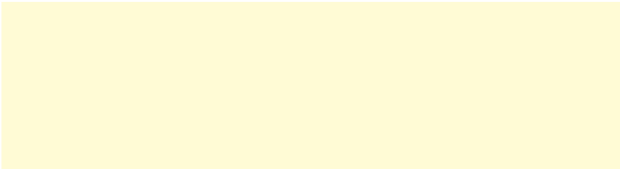
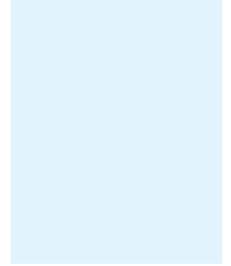
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