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*Editorial*

# THE EPIDEMIC OF CKD- ROLE OF HEAVY METALS IN DRINKING WATER

## Our consciousness, concern and commitment

**N. Mohapatra*, M.R. Behera****

India is experiencing a rapid health transition with large and rising burdens of chronic di-seases, which are estimated to account for 53% of all deaths and 44% of disability adjusted life years lost in 2005[1] Even in rural India, chro-nic non-communicable diseases are emerging as the leading cause of death[2] Chronic kidney disease (CKD) is a global threat to health in general and for developing countries in particular, because therapy is life-long and expensive. In India around 90% patients cannot afford the cost. According to World Health organization (WHO) Global Burden of Disease project, diseases of the kidney and urinary tract contribute to global burden with approximately 850,000 deaths every year and 115,010,107 disability adjusted life years[3]. The exact prevalence of chronic kidney disease in India is not clear in the absence of regular national registry data[4]. The prevalence of CKD was observed to be 17.2% with 6% have CKD stage 3 or worse[5]. In a community based study, diabetes, hypertension and chronic glo-merulonephritis accounted for 41%, 22%, and 16% of cases of CKD, respectively, other causes being chronic interstitial disease (5.4%), ischaemic nephropathy (5.4%), obstructive uropathy (2.7%), miscellaneous (2.7%) and unknown cause (5.4%)[6].

CKD has emerged as an epidemic in rural, agricultural communities of North Central Sri Lanka, Srikakulam District in Andhra Pradesh, India and Central America[7-10]. The three epidemics have crucial threads in common. The climate is tropical, the victims are relatively young and mostly farm workers, and few suffer from diabetes and high blood pressure, the usual risk factors for renal disease. A tubulointerstitial pattern of kidney injury predominates in these patients. So environment pollution particularly from hazardous heavy metals and minerals have been suggested.

Heavy metals are defined as those having a specific density of more than 5 g/cm$^3$. The main threats to human health from heavy metals are associated with exposure to lead, cadmium, mercury and arsenic (arsenic is a metalloid, but is usually classified as a heavy metal). Some elements like Fe, Zn, Cu, Co, Cr, Mn, Ni, are needed in small quantities for human metabolism, but may be toxic at higher levels. Lead (Pb), cadmium (Cd) and arsenic (As) have a direct effect on the kidneys and they are particularly nephrotoxic, even at "normal levels"[11,12]. In Sri Lanka, cadmium has been found to be one of the most troublesome toxic heavy metal which accumulates in the water reservoirs and agricultural soil . This is due to intensive use of Cd contaminated phosphate fertilizers. It is known that Cd is the heavy metal of most environmental concern in terms of adverse effects from long-term application of phosphate fertilizers. The kidney is the main organ affected by chronic Cd exposure and toxicity . Environmental exposure to Cd mainly occurs by contact with tobacco smoke, water and foodstuffs such as vegetables, grains and molluscs. The toxic effects of Pb have been known for more than 2000 years, since lead intake was a common problem among the Romans. At present, exposure to high concentrations of Pb is less common, due to better industrial management and the fact that Pb is no longer added to paint and petrol. However, Pb contamination is still a public health problem in many countries in Africa, Asia and Latin America due to domestic exposure through contaminated water and soil.

The renal pathology induced by high-level chronic exposure to either cadmium or lead is characterized by proximal tubular atrophy associated with interstitial fibrosis and vascular changes . The molecular mechanisms implicated in toxicity from these metals also share several similarities. Both metals are divalent cations that inhibit sulfhydryl group-containing enzymes. Substantial experimental evidence implicates oxidative stress via oxidation-reduction–inactive metal pathways for both lead and cadmium, resulting in increased

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reactive oxygen species that lead to depletion of nitric oxide and secondary upregulation of endothelial nitric oxide synthase[13]. Changes in intracellular calcium homeostasis and activation of protein kinase C may also be involved. Alterations in cell adhesion molecules in renal proximal tubules and endothelium appear to be important mechanisms for cadmium-related nephrotoxicity and may be involved in lead nephrotoxicity as well. This metal gradually accumulates in the body and levels increase with age given its long half-life, which is more than 20 years..

In the present issue "Study of Heavy Metals in drinking water of cases of Chronic Kidney Disease" conducted in the western part of Odisha showed that 56% (28/50) of CKD patients of unknown aetiology had their drinking water contaminated with heavy metals, predominantly lead and cadmium. Highest no. of samples of drinking water isolated Pb 18 (36%), followed by Cd in 8 (16%) and Cu in 02 (04%). Highest no. of positive samples were from Sonepur district i.e. 9 (Pb7, Cd02) followed by Jharsuguda 6 (Pb2, Cd3, Cu1), Bolangir 5 (Pb4, Cd1), Bargarh 4 (Pb3, Cd1), and Sambalpur 4 (Pb2, Cd1, Cu1). This alarming observations indicate need of large scale studies in western Odisha.

At present here is ample evidence of the renal damage associated with these heavy metals. In addition, the combination of different metals has been shown to have a cumulative nephrotoxic effect. Since these metals are commonly found in the environment and there are no treatment options that decrease their systemic effects, increased vigilance is needed in order to decrease environmental levels of Pb, Cd and As. Monitoring all drinking water sources for heavy metals should be considered throughout the world, and good test methods must be established, whereby measurement quality should include both sampling and analysis.

The World is currently facing critical water supply and drinking water quality problems, whereby drinking water quality policies, technologies, drinking water management strategies and human resources to satisfy water-quality standards are necessaries in many countries and cities throughout the world. A global effort to offer affordable and healthy drinking water must be launched around the globe, while various laws and regulations to protect and improve the utilization of drinking water resources should be updated or created throughout the world, including the low income countries. Political, industrial and public education programs are required on the awareness of health risks associated with heavy metal polluted drinking water. It is clear that treatment of chronic kidney disease and its advanced stage "end stage renal disease" (ESRD) is expensive and beyond the reach of average Indian. Thus it is crucial that prevention of chronic kidney disease has to be the goal of medical fraternity, the government and the general public. This needs an initiation of movement to ignite a sense of consciousness, concern and commitment for salution of the problem amongst public, industrialists and policy makers.

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*Original Article*

# STUDY OF HEAVY METALS IN DRINKING WATER OF CASES OF CHRONIC KIDNEY DISEASE

**D. Bhanja*, K.N. Padhiary**, M. Murmu***, A. Kar******


## ABSTRACT

***Introduction :*** *There is a relationship between chronic diseases and geologic environment. Geochemical environment is indeed a significant factor in the serious health problems. In the last 20 years, many people have suffered from these diseases that led to several studies to find out the relationship between drinking water and chronic diseases. The chemistry of drinking water commonly has been cited as an important factor in many diseases. Chronic kidney disease is apparently related to contaminated drinking water with heavy metals such as Pb, Cd, Cu, Mo, Ni, and Cr.* ***Aim :*** *The study of heavy metals in drinking water of cases of CKD was done from September 2011 to September 2013 in the Department of Medicine, V.S.S. Medical College, Burla to find out the possibility of metal toxicity in drinking water.* ***Materials & Methods*** *: Drinking water samples were collected from different villages of cases of CKD. Patients admitted to Department of Medicine, VSS Medical College, Burla, Sambalpur between September 2011 to September 2013. Samples were collected from tap water, tube well, river and other sources from where the patients take water and used for drinking purposes. Following heavy metal analysis was done : Lead (Pb), Cadmium (Cd), Mercury (Hg), Chromium (Cr), Copper (Cu), Arsenic (As).* ***Results****: 50 patients whose cause of chronic kidney disease could not be ascertained were included in this study, 28 patients (56%) showed heavy metals in their drinking water out of which Pb was found in 18, Cd in 8 and Cu in 2 samples of drinking water.* ***Conclusion*** *: Renal failure is related probably to contaminated drinking water with lead, cadmium and copper. Contaminated drinking water with these heavey metals may be one of the important cause for CKD in these patients. These metals if present at toxic levels should be removed from drinking water for human safety.*

***Keywords :*** *Heavy metals, drinking water, chronic kidney disease.*

## INTRODUCTION

Chronic kidney disease encompasses spectrum of pathophysiologic processes associated with abnormal kidney functions and progressive decline in glomerular filtration rate. It is a process of continous irreversible reduction in nephron number and typically corresponds to CKD stage 3 to 5[1].

There is a relationship between chronic kidney disease and geological environment in the last 20 years. Many people have been suffering from this disease in the western part of Odisha. This study is an effort to find out the relationship between drinking water contaminated with heavy metals and CKD.

Out of 45 heavy metals, six metals in water are mostly nephrotoxic. They are Lead, Cadmium, Mercury, Chromium, Copper and Arsenic. Pure water doesn't exist in nature. The contamination of water is directly related to the degree of contamination of our environment[2].

Rain water collects impurity while passing through air. Streams and rivers collect impurity from surface runoff and through the discharge of sewage and industrial affluent. These dangerous product from industries, agriculture and other human activities enter the rivers, lakes and underground water and contaminate our drinking water[3].

## AIMS AND OBJECTIVES

The present study was undertaken with an aim to study the heavy metals in drinking water of patients of CKD of the geographical area of western Odisha.

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## MATERIALS & METHODS

Drinking water samples were collected from different villages of cases of CKD patients admitted to the Department of Medicine, VSS Medical College, Burla, Sambalpur between September 2011 to September 2013.

Detailed history and physical examination of patients was done. Detailed blood examination like CBC, blood sugar, urea, creatinine, sodium, potassium, serum, uric acid, lipid profile, ANA (Hep.2) and other related tests were done. Urine analysis, imaging studies (e.g. USG abdomen and Pelvis) were done in all cases of established CKD to know the probable cause of CKD[4]. Those who had history of hypertension, DM, collagen disorder, drug history or other known causes of kidney disease were excluded from the study.

Samples were collected from tap water, tube well, river and other sources from where the patients take water for drinking purposes. Following heavy metal analysis were done : Lead (Pb), Cadmium (Cd), Mercury (Hg), Chromium (Cr), Copper (Cu), Arsenic (As)

They were analyzed in ICP emission instrument in Bhubaneswar under the guidance of Odisha Polution Board.

## RESULTS

50 patients were included in this study, out of which 28 patients (56%) showed heavy metals in their drinking water. Normal reference range of heavy metals. (Table-1)

**TABLE-1 : NORMAL REFERENCE RANGE OF HEAVY METALS IN DRINKING WATER**

| Sl. No. | Parameters | Units | General standard for drinking water (IS:10500-2012) |
|---|---|---|---|
| 1 | Lead | mg/l | 0.01 |
| 2 | Cadmium | mg/l | 0.003 |
| 3 | Mercury | mg/l | 0.001 |
| 4 | Chromium | mg/l | 0.05 |
| 5 | Copper | mg/l | 0.05 |
| 6 | Arsenic | mg/l | 0.01 |

Out of 50 patients in our study, 15 patients were <40 years of age out of which in 9 patients (60%) drinking water samples showed heavy metals. The rest 35 patients were of >40 years of age, out of which 19 patients (54.0%) drinking water samples showed heavy metals. (Table-2)

**TABLE-2 : AGE DISTRIBUTION**

| Age | Total sample | Patients showing heavy metals (drinking water sample) | Percentage |
|---|---|---|---|
| < 40 years | 15 | 09 | 60% |
| > 40 years | 35 | 19 | 54% |

Out of 50 patients 34 were male (68%), and 16 (32%) were female. Male patients showing heavy metals in their drinking water were 20 (40%), and female patients showing heavy metals in their drinking water were 8 (16%).

Table-3 shows the geographical distribution of patients. Highest number of patients were from Sonepur District (17) followed by Jharsuguda (10), Bolangir (9), Bargarh and Sambalpur (7) each. The no. of patients showing heavy metals in their drinking water from different districts is as follows : Sonepur 9(18%), Jharsuguda 6(12%), Bolangir 5(10%), Bargarh and Sonepur 4(8%) each.

**TABLE-3 : GEOGRAPHICAL DISTRIBUTION**

| Name of district | No. of pts. (50) | Pts. Showing heavy metals (drinking water sample) | |
|---|---|---|---|
| | | No | (%) |
| Sonepure | 17 | 09 | 18 |
| Jharsuguda | 10 | 06 | 12 |
| Bargarh | 07 | 04 | 08 |
| Sambalpur | 07 | 04 | 08 |
| Bolangir | 09 | 05 | 10 |

Table-4 shows the percentage of patients having different heavy metals in their drinking water. Highest no. of samples isolated Pb 18 (36%) followed by Cd 8(16%) and Cu in 02 (04%) in the drinking water. None of the samples isolated Hg, Cr, As in the drinking water. Table-5 shows the districtwise heavy metal analysis in the drinking water. Out of 9 patients of Sonepur district Pb was found in 7 and Cd in 2 samples, 6 patients of Jharsuguda district Pb in 2, Cd in 3 and Cu in 1 sample, 4 patients of Bargarh district Pb in 3, and Cd in 1 samples, 4 patients of Sambalpur Dist. Pb in 2, Cd in 1 and Cu in 1 sample, 5 patients of Bolangir Pb in 4 and Cd in 1 sample were found.

**TABLE-4 : DISTRIBUTION OF METALS**

| Heavy Metals | No. of pts. (n=50) | Percentage |
|---|---|---|
| **Pb** | **18** | **36** |
| **Cd** | **08** | **16** |
| **Cu** | **02** | **04** |
| **Hg** | **0** | **0** |
| **Cr** | **0** | **0** |
| **As** | **0** | **0** |

**TABLE-5 : DISTRICTWISE METAL ANALYSIS**

| District | No. of pts. | Pb | (Cd) | (Cu) |
|---|---|---|---|---|
| **Sonepure** | **9** | **7** | **2** | **00** |
| **Jharsuguda** | **6** | **2** | **3** | **01** |
| **Bargarh** | **4** | **3** | **1** | **00** |
| **Sambalpur** | **4** | **2** | **1** | **01** |
| **Bolangir** | **5** | **4** | **1** | **00** |

## DISCUSSION

It is very important to identify the relationship between the presence of heavy metals in drinking water and the prevalence of renal failure.

The prevalence of these diseases were markedly increased in the last few years due to air pollution, water pollution, and hazardous over uses of pesticides in agriculture. Trace amounts of metals are common in water, and these are normally not harmful to our health. In fact, some metals are essential to sustain life. Calcium, magnesium, potassium, and sodium must be present for normal body functions. Cobalt, copper, iron, manganese, molybdenum, selenium, and zinc are needed at low levels as catalysts for enzyme

activities. Drinking water containing high levels of these essential metals, or toxic metals such as : arsenic, cadmium, chromium, lead, mercury, and silver, may be hazardous to our health[5].

Metals in our water supply may occur naturally or may be the result of contamination. Naturally occurring metals are dissolved in water when it comes into contact with rock or soil material. Other sources of metal contamination are corrosion of pipes and leakage from waste disposal sites.

One of the major consequences of chemical toxicity seems to be a breakdown of the immune system, which opens the gateway for all kinds of diseases in the body[6].

Toxic doses of chemicals cause either acute or chronic health effects. The levels of chemicals in drinking water, however, are seldom high enough to cause acute health effects. They are more likely to cause chronic health effects that occur long after exposure to small amounts of the presence of toxic element[7].

This study shows a strong relationship between heavy metals such as lead, copper, cadmium and renal failure.

Patients suffering from CKD were related to contaminant drinking water mainly with lead and cadmium. Lead is a dangerous element; it is harmful even in small amounts. Lead enters the human body in many ways. It can be inhaled in dust from lead paints, or waste gases from leaded gasoline. It is found in trace amounts in various foods, notably fish, which are heavily subject to industrial pollution. Some old homes may have lead water pipes, which can then contaminate drinking water. Most of the lead we take in is removed from our bodies in urine; however, there is still risk of buildup, particularly in children.

Exposure to lead is cumulative over time. High concentrations of lead in the body can cause death or permanent damage to the central nervous system, the brain, and kidneys (Jennings, et. al., 1996). Studies on lead are done in various part of the country because of its hazardous effect.

On the other hand, cadmium is generally classified as toxic trace element. It is found in very low concentration in most rocks, as well as in coal and petroleum and often in combination with zinc. Geologic deposits of cadmium can serve as sources to groundwater and surface water, especially when in contact with soft, acidic waters. There is no evidence indicating its essentiality to humans. Cd appears to accumulate with age, especially in the kidney and it is considered also as a risk factor for cancer and cardiovascular diseases[7].

Our results shows that patients suffering from CKD could be related to their contaminated drinking water with lead, cadmium and cupper[7].

The prevalence of CKD is increasing in western Odisha and its etiology in many patients remains unknown. The study showed that the people with lower socio-economic status and limited health care facilities have more prevalence of CKD with unknown aetiology that may be attributed to the environmental factors.

Drinking unsafe water mainly ground water at home or field was significantly higher among the patients.

## CONCLUSION

Renal failure is related to mostly contaminated drinking water with lead, cadmium and copper. These metal should be removed from drinking water if they are present at high levels for human safety. Law has to be done for prohibition of any kind of waste disposal into the rivers, canal or any reservoir for the safety of human health.

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*Original Article*

# EPIDEMIOLOGY OF HYPONATREMIA AND ITS OUTCOME IN THE INTENSIVE CARE UNIT OF A TEACHING MEDICAL COLLEGE OF EASTERN INDIA

**R. Padhi*, B.N. Panda**, S.C. Patra***, S Jagati******


## ABSTRACT

***Background:*** *Hyponatremia is a common electrolyte disturbance in critically ill patients that remains incompletely understood. This study was done to ascertain the frequency, predisposing conditions and outcome in critically ill patients admitted to the intensive care unit (ICU) with hyponatremia.* ***Materials and Methods:*** *This was an observational, prospective study of a series of ICU patients during a 12-month period.* ***Results:*** *The frequency of hyponatremia on ICU admission was 34.3%. Females comprised of 36.5%. The serum sodium was significantly lower in the hyponatremic group. The mean age of patients with hyponatremia was 60.4 $\pm$ 17.2. The hyponatremic group had significantly higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score when compared to those of the normal serum sodium group ($p < 0.01$). SIADH was diagnosed in 53% of the hyponatremic group. Patients with severe sepsis, pneumonia, subarachnoid haemorrhage and renal failure patients requiring renal replacement therapy and those who had undergone elective surgery were more likely to have low serum sodium ($p < 0.05$). Patients with low serum sodium values spent a longer time in the ICU ($p = 0.02$), had longer mechanical ventilator days ($p <0.05$) and had an increased mortality rate ($p = 0.01$) than patients in the normal serum sodium group.* ***Conclusio****n: Hyponatremia is a frequent finding in critically ill patients. SIADH is the most common cause of hyponatremia in critically ill., Severe sepsis, Pneumonia, subarachnoid haemorrhage, elective surgery, drugs and chronic medical conditions such as hypocortisolism, hypothyroidism, congestive heart failure, hepatic cirrhosis and renal failure are predisposing factors for hyponatremia. Patients with low sodium had longer ICU stay and longer mechanical ventilation days ($p=0.03$). Patients with hyponatremia had a higher APACHE II score and higher mortality rate than those with normal serum sodium.* ***Key Words****: Hyponatremia, critically ill, epidemiology*


## INTRODUCTION

Hyponatremia (serum sodium level less than 134 mmol/L) is a common electrolyte disturbance occurring in critically ill hospitalized patients. [1] However this common electrolyte abnormality remains incompletely understood due to its multiple aetiologies and varying underlying disease conditions. [2] The kidneys and the hypothalamus, by counter current mechanism and regulation of antidiuretic hormone (ADH, Vasopressin) respectively, maintain the water balance to keep the serum sodium within normal range (135 to 145 mmol/L) despite wide variations in water intake. Serum osmolality is calculated in mosmol/L, as: [2 x (serum sodium +serum potassium) + plasma glucose (mg/dL)/18 + BUN/2.8], all in mmmol/L. Hyponatremia can be classified on the basis of serum osmolality, volume status and urinary sodium into hypertonic, isotonic and hypotonic types. Hypotonic hyponatremia is further classified into hypervolemic, euvolemic and hypovolemic hyponatremia. [3] There is a wide variability

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in the clinical presentation of hyponatremia, ranging from asymptomatic hyponatremia to patients having coma and seizures. Symptoms depend on the level of hyponatraemia and the rate at which it develops. Above 125 mmol/L symptoms are rare; in the range 125–130 mmol/L, the predominant symptoms are gastrointestinal; neuropsychiatric symptoms dominate once the serum sodium falls below 125 mmol/L. The case fatality rate in untreated severe symptomatic hyponatraemia is high and neurological symptoms in any hyponatraemic patient call for immediate treatment. Signs and symptoms of hyponatraemia are: nausea and vomiting, muscular weakness, headache, lethargy, reversible ataxia, and psychosis and, in severe cerebral oedema, increased intracerebral pressure, seizures, coma, tentorial herniation, and respiratory depression. The treatment of hyponatremia depends on the duration of hyponatremia and volume status of the patients. There is serious neurologic sequel if hyponatremia is inappropriately treated. Limited data is available on whether the presence of hyponatremia on intensive care unit (ICU) admission is independently associated with excess mortality. This study was done to ascertain the frequency, aetiology and outcome in critically ill patients admitted to the intensive care unit (ICU) with hyponatremia.

## MATERIALS AND METHODS

This was an observational, prospective study of a series of ICU patients during a 12-month period. Patients with hypernatremia, hyperglycemia, hyperlipidemias, paraprotinemias, and those receiving mannitol were excluded. Hyponatremia was defined as a serum sodium level less than 135 mmol/L. The normal range for our institution is 135 to 145 mmol/L. To determine frequency of hyponatremia, patients were considered hyponatremic if they had a serum sodium level less than 135 mmol/L at any time a measurement was available during admission to the ICU for all the groups. The patients were divided into two groups: hyponatremic (serum sodium level less than 135 mmol/ L) and normal serum sodium (135 to 145 mmol/) groups. History and clinical examination was recorded in all the patients at the time of ICU admission. Detailed drug history was recorded, specially the use of thiazides diuretics and selective serotonin reuptake inhibitors (SSRIs). Patient characteristics included age, sex, admitting diagnosis, pre-existent chronic diseases and clinical evaluation of volume status, were recorded. Parameters for patients including mean arterial pressure, presence of acute renal failure (ARF) and need for renal replacement therapy, need for mechanical ventilator and ventilator days, duration of ICU and hospital stay (days) were recorded as observational data and other variables useful to calculate Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA) scores were also recorded [4]. The clinical criteria used to diagnose the Syndrome of inappropriate Antidiuretic Hormone (SIADH) remains the same as proposed by Bartter and Schwartz in 1967, [5] which include the following: Both hypoadrenalism and hypothyroidism must be ruled out, decreased effective plasma osmolality < 270 mOsm/kg water, inappropriately high urinary osmolality (in the presence of plasma hypoosmolality) > 100 mOsmol/ kg water, clinical euvolemia volume status, elevated urinary sodium excretion (>40 mmol/L) with normal salt and water intake.

This condition is occasionally referred to by the names of the authors of the first report as “Schwatz-Bartter syndrome”.

Laboratory data included values for complete blood count, fasting blood glucose, serum sodium (Na), serum potassium (K), serum urea, serum creatinine, serum uric acid, liver function tests (LFTs), lipid profile, morning serum cortisol, thyroid function tests, serum osmolality, urine osmolality and urine sodium. Serum osmolality, urine osmolality and urine sodium were analyzed with an ionic-specific electrode (Cobas b 121 POC system blood analyzer) using venous blood sample and urine.

### Statistical Analysis

The discriminative powers of admission and lowest serum sodium values regarding day-30 mortality

were evaluated by producing receiver operating curves (ROC). Binary end points were analyzed by means of a Fisher's exact test. Continuous variables were compared with the use of unpaired t-tests, Welch's tests, or Wilcoxon ranksum tests. All odds ratios and their corresponding 95% confidence intervals were calculated according to the profile-likelihood method. The time from inclusion to death in the two groups was compared with the use of the log-rank test, and the results are presented as Kaplan–Meier curves (Figure. 1). Hazard ratios for death from hyponatremia were calculated by logistic regression model. All p values were 2-tailed and p values of < 0.05 were considered statistically significant.

## RESULTS

A total of 730 patients were studied, out of which 27 patients were excluded due to presence of hypernatremia (serum sodium > 145 mmol/L), one patient had paraprotenemia and hence excluded and one patient was excluded due to presence of hypertriglyceredemia. Of the remaining 699 patients most had normal serum sodium (448, 66.9 %,). Table-1 shows the base line characteristics of patients of both hyponatremia and normal sodium group. The frequency of hyponatremia on ICU admission was 34.3% of all ICU admissions incidence rate ratio, 1.61; 95% confidence interval [CI], 1.15-2.25, P value < 0.01. Females comprised of 56.5% of hyponatremic patients and 39.9% of normal serum sodium group. The serum sodium was significantly lower in the hyponatremic group as compared to the normal serum sodium group ( 119 $\pm$ 6.5 vs 139 $\pm$ 6.9, P value < 0.01). The mean age of patients with hyponatremia was 60.4 $\pm$ 17.2. The hyponatremic group had significantly higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score when compared to those of the normal serum sodium group (p < 0.01). SIADH was diagnosed in 53% of the hyponatremic group. Severe sepsis, Pneumonia, subarachnoid haemorrhage, elective surgery, drugs (such as thiazide diuretics, selective serotonin re-uptake inhibitors (SSRIs) and carbamazepine) and chronic medical conditions such as hypocortisolism, hypothyroidism, congestive heart failure, hepatic cirrhosis and renal failure are predisposing factors for hyponatremia in the critically ill (p < 0.05) [Table 2]. Patients with low serum sodium values spent a longer time in the ICU (p = 0.02), had longer mechanical ventilator days (p <0.5) (Fig.2) and had an increased mortality rate (hazard ratio = 2.23; 95% confidence interval of ratio = 1.323 to 3.773, P = 0.01), than patients in the normal serum sodium group. (Table 3).

## DISCUSSION

The clinical expression of hyponatremia is dependent both on the severity and the acuteness of the decline in serum sodium concentration rather than its absolute value.

In our study the frequency of hyponatremia on ICU admission was 34.3% of all ICU admissions, incidence rate ratio, 1.61; 95% confidence interval [CI], 1.15-2.25, P value < 0.01. Females comprised of 56.5% of hyponatremic patients and 39.9% of normal serum sodium group.

Hyponatremia is the most common and probably the most poorly understood electrolyte disorder in the ICU and has recently been reported to occur in about 30 to 40% of ICU patients as observed by DeVita MV et al. [1] For hyponatremia to develop, a relative excess of water in conjunction with an underlying condition that impairs the kidney's ability to excrete water is required. Stimuli for the release of antidiuretic hormone and hence the impairment of water excretion are so frequent in critically ill patients, that virtually all patients are at risk of hyponatremia. [6] This is especially true in the postoperative period when non-osmotic stimuli such as nausea, pain, stress, and volume depletion lead to higher ADH levels compared with preoperative values. The risk of developing hyponatremia and its complications is higher in women and children compared with men, because of differences in respect of muscle mass and hormonal and anatomical factors .[6]

In our study SIADH is the most common cause of hyponatremia. Berghmans et al also found that

| Table 1. (Continued.) | | |
|---|---|---|
| Organ failure or dysfunction — no./total no. (%) | | |
| Respiratory | | |
| Dysfunction (SOFA score, 1–2) | 100/251 (39.8) | 170/448 (37.9) |
| Failure (SOFA score, 3–4) | 117/251 (46.6) | 206/448 (45.9) |
| Coagulatory | | |
| Dysfunction (SOFA score, 1–2) | 57/251 (22.7) | 80/448 (17.8) |
| Failure (SOFA score, 3–4) | 10/251 (3.9) | 13/448 (2.9) |
| Hepatic | | |
| Dysfunction (SOFA score, 1–2) | 72/251 (28.6) | 125/448 (25.6) |
| Failure (SOFA score, 3–4) | | |
| Cardiovascular | | |
| Dysfunction (SOFA score, 1–2) | 48/251 (19.1) | 85/448 (18.8) |
| Failure (SOFA score, 3–4) | 148/251 (58.9) | 255/448 (56.9) |
| Renal | | |
| Dysfunction (SOFA score, 1–2) | 87/251 (34.6) | 143/448 (31.9) |
| Failure (SOFA score, 3–4) | 47 /251 (18.7) | 40/448 (8.9) |
| Renal-replacement therapy — no./total no. (%) | 47 /251 (18.7) | 40/448 (8.9) |
| Mechanical ventilation — no./total no. (%) | 117/251 (46.61) | 207/448 (46.2) |
| | | |

* Plus–minus values are means +/- SD. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores can range from 0 to 71, with higher scores indicating more severe illness, and Sequential Organ Failure Assessment (SOFA) scores can range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction. † The body-mass index is the weight in kilograms divided by the square of the height in meters.

* Plus–minus values are means +/- SD. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores can range from 0 to 71, with higher scores indicating more severe illness, and Sequential Organ Failure Assessment (SOFA) scores can range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction. Severe sepsis was defined according to the consensus-conference criteria of the American College of Chest Physicians–Society of Critical Care Medicine.[6]. ICU denotes intensive care unit.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

**Table 2 : Subgroup Classification**

| Table 2. Subgroup Classification | | | |
|---|---|---|---|
| Subgroup classification — no./total no. (%) | | | P value (two tailed) Fisher's extract test |
| Severe sepsis at admission | 54/251 (21.51) | 59/448 (13.16) | 0.0052 |
| Pneumonia at admission | 39/251 (15.53) | 28/448 (6.25) | 0.0001 |
| Subarachnoid Haemorrhage | 5/251(2.01) | 1/448(0.22) | 0.0246 |
| Trauma | 53/251 (21.51) | 39/448 (8.70 ) | <0.0001 |
| Heart Failure | 13/251 (5.17) | 3/448 (0.67) | |
| Liver Cirrhosis | 9 | 0 | |
| Renal Failure | 15 | 0 | |
| Hypothyroidism | 3 | 0 | |
| Hypocortisolism | 1 | 0 | |
| Thiazide diuretics | 15/251 | 6/448 | |
| SSRIs | 6/251 | 2/448 | |
| Carbamazepine | 9/251 | 3/448 | |
| Surgery | | | |
| *After emergency surgery* | 13/251 (5.17) | 30/448 (6.69) | 0.2429 |
| *After elective surgery* | 19/251 (7.56) | 12/448 (2.67) | 0.0037 |
| APACHE II score ≥25 | 155/251 (61.75) | 198/448 (44.19) | <0.0001 |

* Severe sepsis was defined according to the consensus-conference criteria of the American College of Chest Physicians–Society of Critical Care Medicine. ICU denotes intensive care unit. SIADH denotes Syndrome of inappropriate Antidiuretic Hormone. SSRIs denotes selective serotonin re-uptake inhibitors.

**Table 3. Outcomes and Adverse Events.***

| Table 3. Outcomes and Adverse Events.* | | | | | |
|---|---|---|---|---|---|
| Outcome Measure | Hyponatremia group (n=251) (Serum sodium <135mmol/L) | Normal Serum Sodium Group (n=448) | Odds Ratio or Absolute Difference (95% CI)† | Statistical Test | P Value |
| Death — no. of patients/total no. (%) ; all cause 30-day | 49/251 (19.5) | 74/448 (16.5) | 0.4474(0.3102 to 0.6454 | Mantel-Haenszel | 0.0006 |
| Days in hospital — median (IQR) | 23 (15 to 23.5) | 21 (14 to 23) | 0 | Log-rank test | 0.15 |
| Mechanical ventilation — no. of patients/ total no. (%) | 94/251 (37.45) | 37/448 (8.25) | 0.99 (0.62 to1.58) | Pearson's test | <0.01 |
| Days of mechanical ventilation | 9.52+/-5.99 | 6.48+/-5.21 | 0 | Wilcoxon rank-sum test | 0.03 |
| Renal-replacement therapy — no. of patients/ total no. (%) | 47 /251 (18.7) | 28/448 (6.3) | 0.33 (0.12 to0.87) | Pearson's test | 0.03 |
| Days of renal-replacement therapy | 0.8 +/-2.3 | 0.7 +/- 2.1 | 0 | Wilcoxon rank-sum test | 0.34 |

* Plus–minus values are means +/- SD. CPR denotes cardiopulmonary resuscitation, ICU intensive care unit, and IQR interquartile range. † Absolute differences (percentage points) are given for median days in the ICU or hospital, and mean +/- SD days of mechanical ventilation or renal-replacement therapy; for all other measures, odds ratios are given. ‡ Organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score of 3 or 4 for any individual organ system.

SIADH to be the most frequent cause of hyponatremia, although hyponatremia associated with volume depletion of the extracellular fluid also occurs commonly. [7]

In our study Severe sepsis, Pneumonia subarachnoid haemorrhage, emergency surgery, drugs (such as thiazide diuretics, selective serotonin re-uptake inhibitors (SSRIs) and carbamazepine) and chronic medical conditions such as hypocortisolism, hypothyroidism, congestive heart failure, hepatic cirrhosis and renal failure are predisposing factors for hyponatremia (Table.2).

In our study severe sepsis is the most common predisposing factor for hyponatremia. Hannon et al observed that hyponatraemia associated with sepsis is known to have an increased morbidity and mortality. The cause of this phenomenon is unknown, but may be

Figure 1. The time from inclusion to death in the two groups

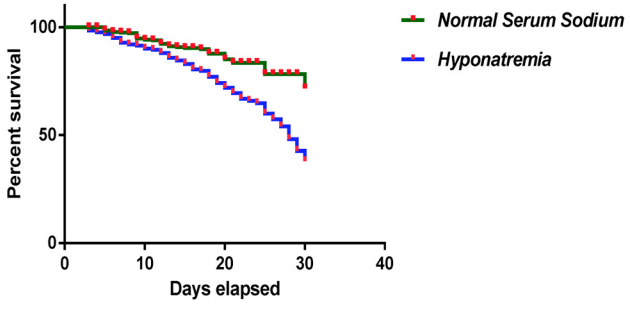
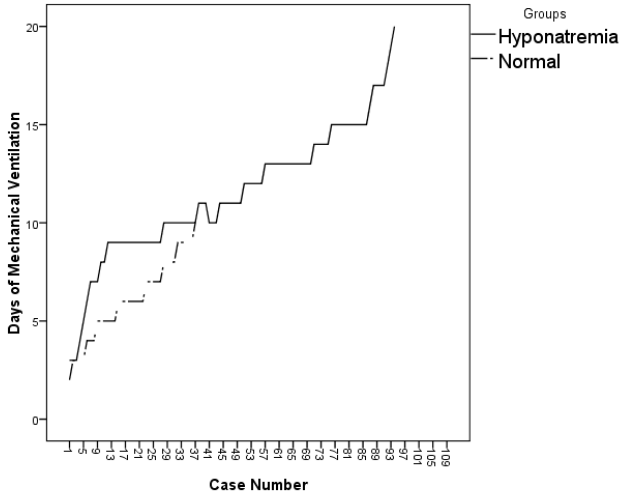


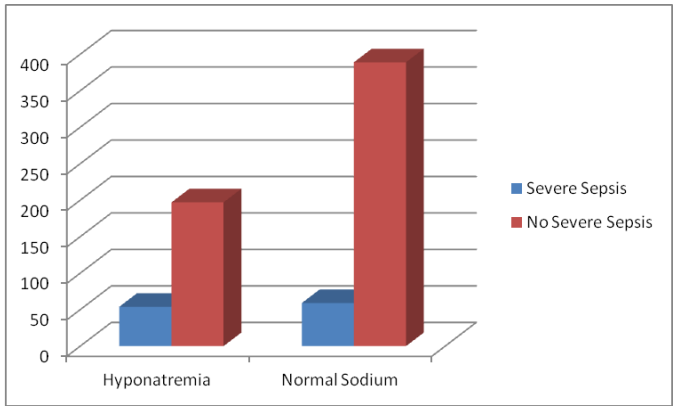

Figure 2. Days of Mechanical Ventilation in the two groups.




related to dilution of the extracellular space with retained exogenous fluid.[8] Pneumonia is known to be associated with hyponatremia at the time of admission and it is associated with more severe illness, increased risk of mortality and prolonged hospital stays as reported by Nair et al..[9] In our study pneumonia at the time of ICU admission was the second most common predisposing factor for hyponatremia.

In the present study patients who were taken up for elective surgery were more likely to have hyponatremia than emergency surgery patients. Like

Figure 3. Severe Sepsis At the time of admission*.




our study Alexander et al [10] found that preoperative hyponatremia association was particularly marked in patients undergoing nonemergency (elective) surgery: adjusted odds ratio (aOR) 1.59; 95% CI, 1.50-1.69; *P* < .001 for interaction), and as per the American Society of Anesthesiologists patients with hyponatremia have a higher risk of 30-day mortality (5.2% vs 1.3%; [aOR], 1.44; 95% CI, 1.38-1.50), and this finding was consistent in all the subgroups. Also, hyponatremia was associated with a greater risk of perioperative major coronary events (1.8% vs 0.7%; aOR, 1.21; 95% CI, 1.14-1.29), wound infections (7.4% vs 4.6%; 1.24; 1.20-1.28), and pneumonia (3.7% vs 1.5%; 1.17; 1.12-1.22) and prolonged median lengths of stay by approximately 1 day.[10]

Like our study, Bissram et al found that symptomatic hyponatraemia was associated with volume depletion (32.6%), congestive heart failure (26%), syndrome of inappropriate antidiuretic hormone (26%), thiazide diuretic use (26%) and selective serotonin re-uptake inhibitor use (26%). In 21.7% of cases, the cause was multifactorial (congestive heart failure, syndrome of inappropriate antidiuretic hormone or medication use with volume depletion). [11]

In our study patients with low serum sodium values spent a longer time in the ICU, had longer mechanical ventilator days and had an increased mortality rate than patients in the normal serum sodium group. In a large a retrospective study in 77 medical,

surgical, and mixed ICUs in Austria, with a database of 151,486 adults admitted consecutively over a period of 10 years Funk et al demonstrated that all types and grades of dysnatremia were associated with increased mortality. [12] However, taking into account all comorbidities, and relative severity of illness mortality comparison would require a large scale regression analysis for a definitive comment on prognosis.

## CONCLUSION

Hyponatremia is a frequent finding in critically ill patients (34.3% of all ICU admissions incidence ratio, 1.61; 95% confidence interval [CI], 1.15-2.25, and p value < 0.01). SIADH is the most common cause of hyponatremia in critically ill. Severe sepsis, Pneumonia subarachnoid haemorrhage, elective surgery, drugs (such as thiazide diuretics, selective serotonin re-uptake inhibitors (SSRIs) and carbamazepine) and chronic medical conditions such as hypocortisolism, hypothyroidism, congestive heart failure, hepatic cirrhosis and renal failure are predisposing factors for hyponatremia ($p < 0.05$). Patients with low sodium had longer ICU stay and longer mechanical ventilation days (p=0.03). Patients with hyponatremia had a higher APACHE II score and higher mortality rate than those with normal serum sodium; however, because the former are more severely ill, no causality is apparent or suggested.

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*Original Article*

# CARDIAC MANIFESTATIONS IN HIV/AIDS

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## ABSTRACT

***Introduction:*** *With the introduction of HAART in patients with HIV and AIDS, survival has increased and so does the manifestations of late stage HIV Infection including cardiovascular complications which often remains quiescent clinically and may be fatal.* ***Aim:****To study Cardiac manifestations in HIV/AIDS patients and its correlation with CD4 count.* ***Methods and Materials:*** *A total of 62 consecutive patients with HIV infection admitted to Medicine department of MKCG medical college hospital Berhampur between march 2011 to july 2012 were taken into study. All the patients underwent clinical examination, 2D and M mode,Doppler echocardiography, CD4 count and routine investigations.* ***Results:*** *Echocardiographic abnormalities were detected in 51.6% of patients. Most common cardiac abnormality detected was reduced fractional shortening(<28%) which was found in 24 patients(38.7%) followed by reduced ejection fraction (<50% ) in 13patients(20%), dilated cardiomyopathy in 6 patients(9.67%) , left ventricular diastolic dysfunction in 8 patients(12.9%), pericardial effusion in 9 patients(14.5%)of which one case had constrictive pericarditis with moderate pleural effusion. Significant statistical correlation was observed between low CD4 count and echocardiographic abnormality.* ***Conclusion****: Cardiovascular abnormalities were detected in 51.6% of HIV infected patients. The main abnormality found was systolic dysfunction (ie reduced fractional shortening, reduced ejection fraction) in 38.7%patients, Out of which 6 patients(25%) had dilated cardiomyopathy. Diastolic dysfunction was seen in 12.9% patients and pericardial effusion in 14.5% patients. One patient presented with constrictive pericarditis which is rare.* ***Keywords :*** *HIV, AIDS, Cardiac manifestations.*

## INTRODUCTION

HIV infection is a leading health problem across the entire world. The Introduction of HAART has resulted in a significant decline in mortality associated with HIV infection and hence increased survival. Cardiovascular complications are an important health concern in HIV infected population especially after introduction of anti-retroviral therapy whether it is due to virus itself, the effects of antiretroviral medications or altered immune mechanisms associated with the infection is not well established.[1]Approximately 34 million people were infected with HIV worldwide by the end of 2010 (range 31.6-35.2 million) as per UNAIDS Worlds Aids Day Report 2011, this reflects the continued large number of new HIV infections and a significant expansion of access to antiretroviral therapy, which has helped reduce AIDS-related deaths, especially in more recent years.[2]In India 23.9 lakh people are estimated to be infected with HIV, with adult HIV prevalence of 0.31% as per NACO 2009.[3]The prevalence of cardiac involvement in AIDS patients has been reported in the range of 28% to 73%.[4]Heart disease is a relatively common post-mortem finding in HIV infected patients(25-75% in autopsy series).[5] The patients with HIV infection can have a variety of cardiovascular manifestations, the most common being pericardial effusion, myocarditis, endocarditis, pulmonary

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hypertension, cardiac neoplasm like Kaposi sarcoma and lymphoma, coronary artery disease, and drug induced cardiotoxicity.[5] As clinical signs are inadequate for the diagnosis of cardiac involvement, a more direct assessment of cardiac function is needed, early screening of HIV infected patients will identify potentially fatal complications of HIV disease and permit efficient treatment strategy.[6] Echocardiography is very helpful in detecting cardiac dysfunction at an early stage, much before overt clinical manifestations develop.[7] Early recognition and prompt treatment are important to prevent significant morbidity from cardiovascular involvement.[8]

## MATERIALS AND METHODS

In this cross-sectional hospital based study sixty two HIV infected patients admitted to the medicine department of MKCG Medical college between July 2011 to July 2012 were studied.Patients having congenital heart disease, pre-existing cardiovascular disease, hypertension and diabetes mellitus were excluded from the study.The patients were diagnosed as HIV positive after 3 rapid kit test supplied by the National AIDS Control Organisation, the three rapid kit test supplied included COMBAIDS test, Pareekshak HIV ½ trilene card test and HIV ½ Trispot test.The patients were assessed clinically by relevant history,general and systemic examination with special emphasis on cardiovascular and respiratory system,specific investigations were undertaken to establish the diagnosis and screening for oppurtunistic infections.CD4 count was done by BD FACS CALIBUR automated machine using flow cytometry.All patients were studied using M mode, two dimensional transthoracic echocardiography and colour flow Doppler examination with Philips machine HD7XE. Right ventricle dimensions, left ventricular end systolic diameter, left ventricular end diastolic diameter, interventricular septum were measured using M Mode. The conventions of the American society of echocardiography were followed in obtaining these measurements. Left ventricular systolic function was determined by the left ventricular fractional shortening computed from the formula : LVFS =(LVEDD-LVESD) / LVEDD x 100. Ejection fraction was automatically calculated by the existing software in the equipment, using the Teichholz formula.

Systolic dysfunction was diagnosed when left ventricular fractional shortening is $\leq$ 28%.[9] Reduced Ejection fraction was taken as ejection fraction <50%. Dilated Cardiomyopathy was diagnosed using three criteria: left ventricular end diastolic diameter $\geq$ 60mm with a ejection fraction <45% and global hypokinesia.[10,11] Diastolic function was analysed using E/A ratio and DT.[10] The presence of pericardial effusion,any valvular regurgitation and any regional wall motion abnormalities was looked for.

All results are reported as the percentage of patients found to have the given abnormality or as mean ± standard deviation. Statistical analysis of the data was done using SPSS 16 software.For all analysis a p value <0.05 as considered significant.

## RESULTS

A total of sixty two HIV positive patients were taken for study, out of which 41 were males (66.2%) and 21 were females (33.8%). In this study 91% of the patients were in the age group 15-49 years and 8.06% in the age group $\geq$ 50 years.The mean age was 34.19(±8.72) years for males ranging between 21 and 53years and mean age for female was 29.47(±4.97) years ranging between 22 and 43years.Maximum number of patients (80%) were young in the age group 25 to 44 years. All patients were heterosexual and none had history of intravenous drug use. There were no haemophiliacs. Multiple heterosexual behaviour was the most common risk behaviour admitted by the HIV patients.

The clinical features of the patients studied with relevance to cardiovascular system was fever(72.5%), cough(30.6%), breathlessness(20%), chest pain(14.5%) and pedal oedema(4.8%). The maximum number of patients studied were in clinical stage 3(45.16%) followed by clinical stage 4(27.41%), clinical stage 2(16.12%) and 11.2% patients were in clinical stage 1. Most of the patients(35.48%) in the study population had CD4 count less than 200/microl.

The mean CD4 count of study population was 249.7±140.52.

Echocardiographic abnormalities were noted in 32(51.6%) patients with some patients having multiple abnormalities.Reduced FS(<28%) was seen in 24 patients(38.7%), reduced EF(<50%) in 13 patients(20%), DCM in 6 patients(9.67%), left ventricular diastolic dysfunction in 8 patients(12.9%), pericardial effusion in 9 patients(14.5%) respectively as shown in table 1. Pericardial effusion was seen in 9(14.5%)patients out of which 6 patients(66.66%) had mild, 2patients(22.22%) had moderate, 1patient(11.11%) had severe pericardial effusion and one patient with moderate effusion had constrictive pericarditis. In patients with pericardial effusion 60% of patients had evidence of tuberculosis and were put on antitubercular drugs following which there was disappearance of pericardial effusion.

Echocardiographic abnormalities was seen in maximum number in patients who were in clinical stage 4.Out of 24 patients with reduced FS, 12 patients(50%) were in clinical stage 4,11 patients(45%) in stage 3 and 1 patent(4.16%) in stage1, 8(61.5%) out of 13 patients of reduced EF were in clinical stage 4 , 4 patients(30.7%) in stage 3 and 1(7.69%) in stage 1. 5 patients(55.55%) with pericardial effusion were in stage 4 and 4 patients(44.44%) were in stage 3. Out of 6 patients of Dilated cardiomyopathy 4 patients(66.66%) were in stage 4 and 2 patients(33.33%) were in stage 3. 3 patients(37.5%) of diastolic dysfunction were in clinical stage 4, 4 patients(50%) were in stage 3 and 1 patient(12.5%) in clinical stage 1,The lone case of constrictive pericarditis was in clinical stage 4 as shown in Table 2.

Maximum number of echocardiographic findings were seen in patients with CD4 count less than 200/microlitre. Out of total 24 patients of reduced fractional shortening 15 patients(62.5%) had CD4 count less than 200 and 9 patients(37.5%) had CD4 count between 200 and 499. Out of 13 patients, 8 patients(61.5%) had CD4 count less than 200/microl and 5 patients(38.46%) had CD4 count between 200 and 499. 4 patients(66.66%) of Dilated cardiomyopathy had CD4 count less than 200/microl and 2 patients(33.33%) had CD4 count between 200 and 499. 9 patients(100%) of pericardial effusion had CD4 count less than 200/microl of which 4patients(44.44%) had CD4 count less than 50/microl and 5patients(55.55%) had CD4 count less than 200/microl. 7 patients(87.5%) of diastolic dysfunction had CD4 count less than 200/ microl and 1 patient had CD4 count between 200-499 as shown in Table 3. Lower CD4 count was significantly associated with cardiac disorder p<0.001.

Reduced FS was seen in 24 patients(38.7%). Mean CD4 count with reduced FS was 159±55.17 and mean CD4 count without reduced FS was 306.5±148.6.p<0.001 the correlation has been shown in Figure 1.Reduced EF was seen in 13(20%) patients with mean CD4 count 158±59.3 and mean CD4 count without reduced EF was 273.8±146.24. p<0.001 the correlation has been shown in Figure 2.Pericardial effusion was seen in 9(14.5% )patients. The mean CD4 count with pericardial effusion was 79.5±59.45 and mean CD4 count without pericardial effusion was 278.64±129.p<0.001.

Chest radiography was normal in 28 patients(45.16%), abnormalities in lung field was seen in 26 patients(41.9%) and 8 patients(12.9%) had cardiomegaly . Among patients showing abnormalities in lung field 16 patients(61.53%) had infiltrates and fluffy shadows,7 patients(26.92%) had pleural effusion and 3 patients(10.71%) had consolidation. Electrocardiography was normal in 49 patients (79%), 7 patients (11.2%) had sinus tachycardia and 6 patients (9.6%) had low voltage complexes. None of the patients had PAH, CAD or Valvular regurgitation.There was no statistically significant difference in Haemoglobin, total leucocyte count, FBS and lipid profile in patients with or without echocardiographic abnormality.

## DISCUSSION

Men were affected more than females by a ratio of 2:1. 41patients(66.2%) were males and 21patients(33.8%) were females which is same as NACO report[3] where 39% of the total HIV patients in India are females,3.5% are children and 57.5% are males.In this study 91% of patients were in the age

group 15-49 years and only 8.06% patients were of 50years and above which is in accordance with NACO[3] in which 83% of PLHIV are in age group 15-49 years. The majority of patients(80%) were young and belonged to age group 25 to 44years.The NACO report[3] has shown that most PLHA in India were young adults.

All the patients in our study were heterosexual with multiple sexual partners. According to NACO[3] heterosexual mode of transmission accounts for 88.2% of HIV positive cases detected, mother to child transmission accounts for 5%, infected needle and syringe 1.7%, homosexual 1.5% and contaminated blood and blood products account for 1% of HIV infections. Globally sexual contact is the commonest mode of transmission. In the West ,75% of the newly affected males are due to homosexuality, 14% consequent to heterosexual contact, 8% due to injection drug use and a meagre 3% due to other modes of transmission. There is wide difference in the mode of transmission of HIV in different population.

Clinical features such as fever (72.5%), cough(30.6%), breathlessness (20%), chest pain(14.5%), pedal edema (4.8%) is similar to other studies but it is non specific and can be attributable to pulmonary disease. Patients wih HIV infection is known to develop multiple pulmonary opportunistic infections, which were present in many of our patients.

Most of the cases studied had CD4 count less than 200/microl, the reason behind low CD4 count is that the patients studied were hospitalised case and presented at an advanced stage of disease. Most of the cardiac manifestations are seen in patients with low CD4 count.

Most of the cardiac manifestations were seen in patients in WHO clinical stage 4 as par Khunnawat et al[12], lipshultz SE et al[13] who have shown that cardiac manifestations occur late in the course of the disease.

The study showed that echocardiographic abnormalities was common in HIV infected patients. In present study echocardiographic abnormalities were seen in 51.6% patients while it was 42.3% in study by Aggarwal et al[8], and 58% in study done by Singh et al in India.[14] It is consistent with studies done in Zimbabwe by Hakim et al[15] in which cardiac manifestations was seen in 50% patients.

Most common manifestation in our study is reduction in fractional shortening seen in 38.7% patients. This was consistent with studies done in Europe by Corralo et al[16] as well as from India by Aggarwal et al[8] and Singh et al.[14] Left ventricular fractional shortening was lower in patients with low CD4 count which was statistically significant ($p<.0001$) which is same as study done by Mirri et al.[17]

Reduction in ejection fraction was seen in 20% of patients in the present study which is as par study done by Singh et al.[14] Reduction in ejection fraction without global hypokinesia or chamber enlargement or without any symptoms represented a mild form of cardiac disease that will progress to a clinically evident form of Dilated cardiomyopathy later.

Dilated cardomyopathy was seen in 9.67% of patients which is consistent with studies done in Zimbabwe by Hakim e al.[15] (9%), and in United states by Himelman and Chung et al.[18] (11%).

Diastolic dysfunction was seen in 12.9% patients in our study while it is 18% in study done in Kolkata by Guha et al.[19]and 19.2% in study done by Aggarwal et al.[8]

There is wide spectrum of pericardial involvement in HIV infection ranging from asymptomatic effusions detected on routine echo-cardiography to fatal tamponade and constrictive pericarditis. Present study showed 14.5% patients with pericardial effusion where as studies published by Aggarwal et al[8], Himelman et al[18], Guha et al[19] showed 11.5%,10% and 13% respectively. In our study there was one case of constrictive pericarditis which is rare and only few cases have been reported . Pericardial effusion in HIV patients may be a marker of end stage HIV infection because it is associated with low CD4 count as seen in our study and also in study done by Guha et al**[19]** and Singh et al.[14] In our study most of the patients with pericardial effusion were suffering from pulmonary tuberculosis.

**TABLE 1.DISTRIUTON OF CASES WITH ECHOCARDIOGRAPHIC ABNORMALITIES**

| CARDIAC MANIFESTATION | NUMBER | PERCENTAGE |
|---|---|---|
| Reduced FS | 24 | 38.7 |
| Reduced EF | 13 | 20 |
| Dilated cardiomyopathy | 6 | 9.67 |
| Pericardial effusion | 9 | 14.5 |
| Diastolic Dysfunction | 8 | 12.9 |
| Total | 32 | 100 |

**TABLE 2:ASSOCIATION OF ECHOCARDIOGRAPHIC ABNORMALITY WITH CLINICAL STAGING ACCORDING TO WHO**

| CARDIAC MANIFESTATION | I | II | III | IV |
|---|---|---|---|---|
| Reduced FS | 1(4.16%) | 0 | 11(45%) | 12(50%) |
| Reduced EF | 0 | 1(7.69%) | 4(30.7%) | 8(61.5%) |
| Dilated cardiomyopathy | 0 | 0 | 2(33.33%) | 4(66.66%) |
| Pericardial effusion | 0 | 0 | 4(44.44%) | 5(55.55%) |
| Diastolic dysfunction | 1(12.5%) | 0 | 4(50%) | 3(37.5%) |

**TABLE 3:**
**ASSOCIATION OF ECHOCARDIOGRAPHIC ABNORMALITIES WITH CD4 COUNT**

| CARDIAC MANIFESTATION | CD4 in µl <50 | 50-199 | 200-499 | Mean CD4 Count |
|---|---|---|---|---|
| Reduced FS | 0 | 15(62.5%) | 9(37.5%) | 159±55.7 |
| Reduced EF | 0 | 8(61.5%) | 5(38.5%) | 158±59.3 |
| Dilated cardiomyopathy | 0 | 4(66.66%) | 2(33.33%) | 143±49.5 |
| Diastolic dysfunction | 1(12.5%) | 6(75%) | 1(12.5%) | 114.7±53.73 |
| Pericardial effusion | 4(44.44%) | 4(44.44%) | 1(11.11%) | 79.5±59.5 |

FIGURE:1

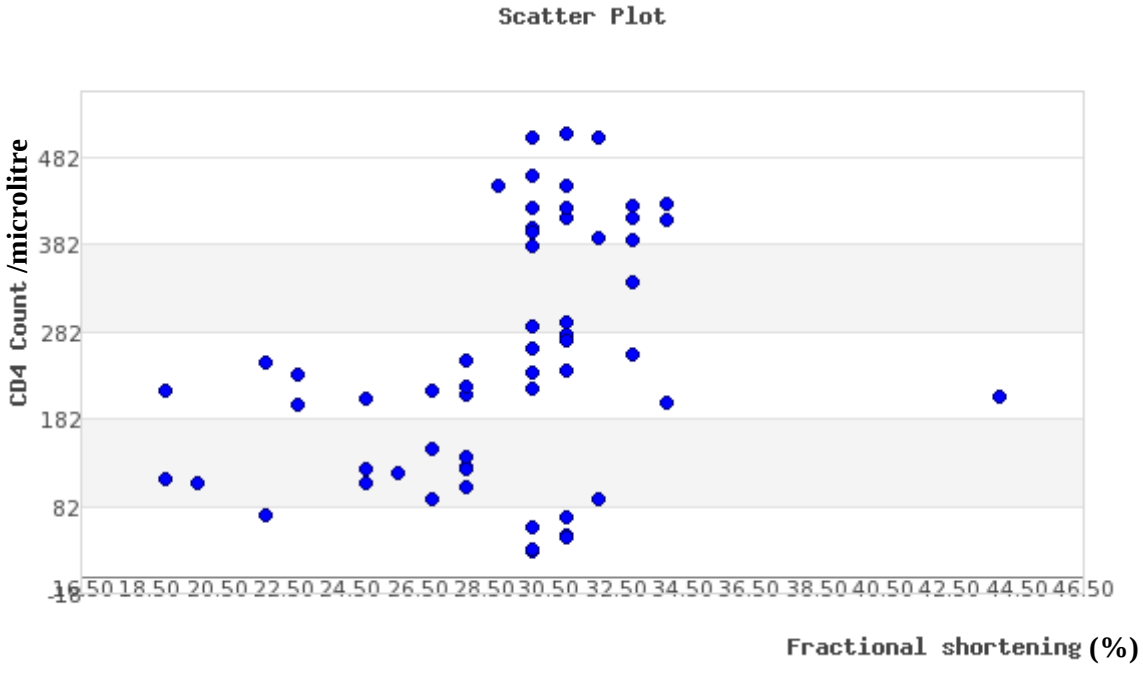
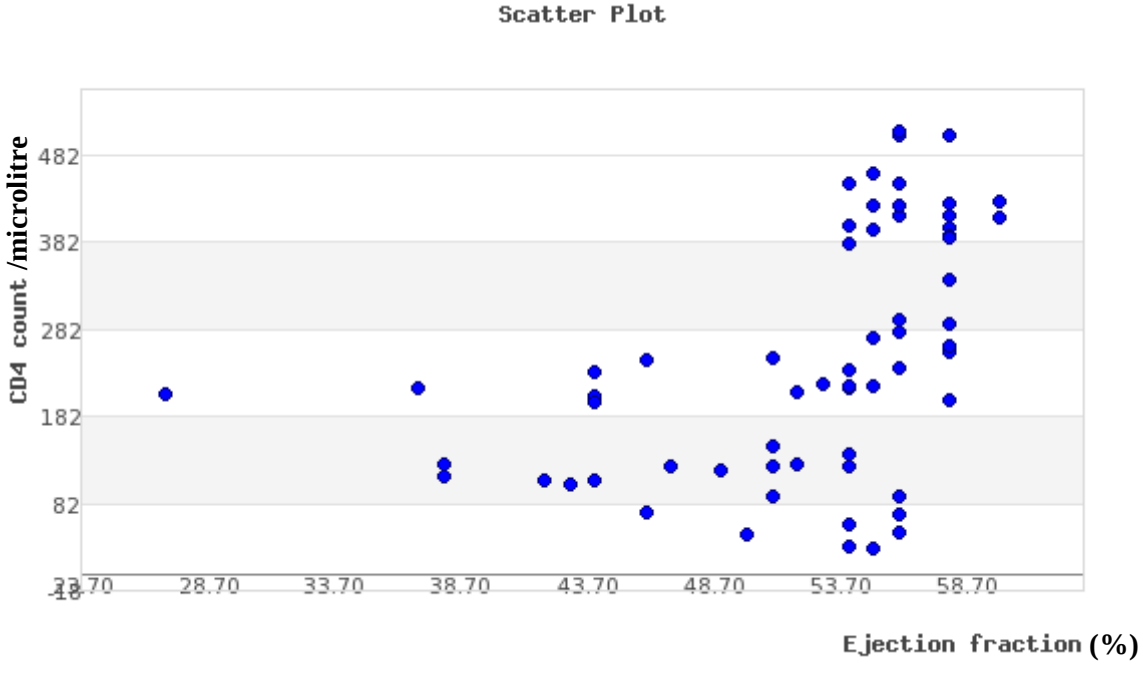



FIGURE:2



Studies done before have shown that cardiovascular manifestations are often seen in a state of severe immunosuppression with low CD4 counts. This study showed that patients with CD4 count less than 200/microl had a high prevalance of echocardiographic abnormalities as compared to those with CD4 count more than 200/micol. CD4 count has a significant positive correlation with reduction in fractional shortening, ejection fraction and pericardial effusion ($p<0.001$) as seen in our study.

Infective endocarditis has been described in HIV infection, especially in context of intravenous drug use. However none of our patients admitted to intravenous drug use and no case of infective endocarditis was found. The marantic endocarditis seen in chronic and wasted patients was also not seen in our study. There was also no case of Pulmonary arterial hypertension, coronary artery disease or any valvular regurgitation.

**CONCLUSION**:

Heart involvement is common in HIV infected patients but is obscured by oppurtinistic infections, as management of oppurtinistic infections continues to improve, cardiac abnormalities are likely to be manifestated with increased frequency. The most common echocardiographic abnormality found is systolic dysfunction(38.7%) out of which 25% patients had dilated left ventricle with global hypokinesia(DCM). Pericardial effusion was seen in 14.5% patients and 12.9% patients had diastolic dysfunction.Low CD4 count is associated with echocardiographic abnormalities.

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*Original Article*

# STUDY OF DIABETES MELLITUS AND GLUCOSE INTOLERANCE IN PATIENTS OF HIV/AIDS WITH SPECIAL REFERENCE TO PATIENTS ON HAART THERAPY

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## ABSTRACT

***Objectives**:- To find out patients of HIV/AIDS who developed Diabetes/ Impaired glucose tolerance during treatment with HAART, Follow up of the HIV/AIDS patients having IGT/Diabetes mellitus for the period of 1 year and studying the course of the IGT/Diabetes mellitus in this group of patients. **Materials And Methods** -108 HIV infected patients attending ART centre of SCB medical college, Cuttack were included in the study. Known cases of Diabetes mellitus, patients on drugs causing hyperglycemia like beta blockers, corticosteroids and patients having first degree relatives of diabetes were excluded. They were subjected to detailed clinical examination, Hb%, TLC, DLC ,urine routine ,Fasting plasma glucose, 2 Hr Post glucose plasma glucose, HbA1C, Serum fasting insulin. HOMA-IR was calculated as FPG x Serum fasting insulin/405, HOMA-B was calculated as 360 x serum fasting insulin / FPG-63.All the patients were followed up and their glycemic status and insulin resistance were studied. **Results** -Total number of patients studied-108, Males-66(61.1%), Females-42(38.9%) Most of the patients were in age group of 21-30yrs (52%) and 31-40yrs(41%). 56 patients were on HAART and 52 were not treated, Mean duration of treatment was 16.9 months. Mean FBS in patients on HAART was 104mg/dl, and in untreated patients was 87mg/dl (p=0.0468), Mean 2Hr PGBS in patients on HAART was 162.9mg/dl, in untreated patients 121.9mg/dl(p=0.014),Mean fasting serum insulin levels were 12.783microIU/ml in patients on HAART and 7.80micro IU/ml in untreated patients (p<0.001) Mean HOMA-IR in patients on HAART was 2.76 and in untreated patients was 1.53mg/dl. (p=0.002) was statistically significant. Mean HOMA-B levels were 144.7 in patients on HAART and 102.2 in untreated patients. (p=0.276). Among the patients who were treated with HAART, 15(26.8%) of the patients developed IGT, 4(7.1%) developed impaired fasting glucose and 04(07.1%) developed Diabetes mellitus. **Conclusion**- The above study shows that there is an increased incidence of glucose intolerance and Diabetes mellitus in patients of HIV/AIDS treated with HAART therapy. Diabetes mellitus and glucose intolerance is due to insulin resistance caused by antiretroviral agents. Hence glycemic status of HIV/AIDS patients taking HAART therapy should be regularly monitored and followed up. **Key words :** HIV, AIDS, HAART Therapy, Diabetes Mellitus, Glucose intolerance.*


## INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is characterized by an acquired, profound, irreversible, immune suppression that predisposes the patient to multiple opportunistic infections, malignant neoplasms and a progressive dysfunction of multiple organ systems There have been major advances in the management of HIV disease. Highly active Anti-retroviral therapy (HAART) is now widely available and has led to major improvements in morbidity and mortality among persons with HIV/AIDS. However the use of HAART is associated with a number of adverse effects which range from nausea, vomiting to metabolic abnormalities like fat redistribution, glucose intolerance, dyslipidemia. [(1,2)] Several studies have reported an increased

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prevalence of glucose intolerance and diabetes among HIV infected individuals during treatment.[2,3] These disorders have been largely attributed to protease inhibitors, however other ART agents and classical risk factors may have a contributory role.[3] The mechanism by which HIV infected patients develop glucose intolerance is not completely understood. Possible mechanisms are [4,5,6] reduced activity of GLUT-4 by protease inhibitors, mitochondrial damage caused by NRTI agents,[7], fat redistribution, chronic inflammatory changes caused by HIV infection. Impaired insulin secretion in HIV infected patients has been less well studied although some data suggest an association between protease inhibitor use and defects in beta cell function.[5] According to study by Micheal Dube the prevalence of impaired glucose tolerance is 15-25%, and frank diabetes is 0.5-1.5 % in patients of HIV on HAART.[10]

## OBJECTIVES

The present study was carried out in the Department of Medicine, SCB Medical College, Cuttack with an objective to find out patients of HIV/AIDS who developed Diabetes/ Impaired glucose tolerance during treatment with HAART, follow up of the HIV/ AIDS patients having IGT/Diabetes mellitus for the period of 1 year and studying the course of the IGT/ Diabetes mellitus in this group of patients.

## MATERIALS AND METHODS

108 HIV infected patients attending ART centre of SCB Medical College, Cuttack were included in the study. Both naïve patients and patients on HAART therapy were included in the study. Patients of Diabetes mellitus prior to detection of HIV infection, patients on drugs that can alter the glycemic status like corticosteroids, beta blockers, patients having first degree relative of Diabetes mellitus were excluded. They were subjected to detailed clinical examination, routine investigations, fasting plasma glucose, 2 Hr post glucose plasma glucose was done and patients were classified as euglycemic, impaired glucose tolerance, impaired fasting glucose and Diabetes mellitus based on American Diabetes association guidelines[11] . Oral glucose tolerance test (75grams) (OGTT) was done and patients were classified as normal glucose tolerance (<140mg/dl), impaired glucose tolerance(140-199mg/dl), Diabetes mellitus(>200mg/dl), Serum fasting insulin levels were done. Insulin resistance was calculated by the formula HOMA-IR= Fasting insulin (microunit/ml) X Fasting glucose/405 (HOMA-IR is homeostasis model for assessment of insulin resistance) HOMA B= 360 X serum insulin/ fasting plasma glucose-63(HOMA-B is homeostasis model for assessment of Beta cell function),HbA1C, Serum total cholesterol, Triglycerides, HDL, LDL,VLDL were done. Patients who developed IGT/Diabetes mellitus on HAART therapy were followed up after a period of 6 months FPG, 2Hr PGPG, serum insulin were done. HOMA-IR and HOMA-B were calculated. The normal value of fasting serum insulin in an adult as per the kit was 2.6 – 12 microIU/ml. Insulin resistance was calculated by HOMA method developed in 1985 by Mathew & co-workers as it is simple and appropriate to developing countries. Since, HOMA-IR score of greater than 1 implies insulin sensitivity of less than 100%, this could mean insulin resistance. However, although a HOMA score of 1.0 is the ideal, the study of Bonora et al, 2000 found a mean HOMA-IR score of 2.06 ± 0.14 in the normal non-diabetic population. The normal value of insulin resistance as assessed by HOMA-IR in our population is less than 2 (Das. S et al.2007)[19].HOMA-IR value above 2 was considered as insulin resistance in our study. In normal weight subjects beta cell function is assumed to be 100 (Mathew DR et al 1985) [21]

### Statistics

The data were analyzed using SPSS software (version 16; SPSS Inc., Chicago, IL). Student's *t*-test was done to compare numerical variables in the two groups.

## OBSERVATION

Total number of cases were 108, Males were 66 (61.11%), Females were (38.89%). 88% of the patients studied were in younger age group of 21-40 yrs. Of all the patients 56 patients (51.85%) of the patients were on HAART and 52 patients (48.15%) were not treated with any anti-retroviral drug. AZT+3TC+NVP (Zidovudine +Lamivudine+Nevirapine) was the most common ART regimen given (27.77%) (Table No-1). Mean duration of treatment with HAART

**TABLE: 1**

**DISTRIBUTION OF PATIENTS ACCORDING TO HAART THERAPY**

| | | Number | Percentage |
|---|---|---|---|
| Not on ART | | 52 | 48.14 |
| On ART | AZT+3TC+NVP | 30 | 27.77 |
| | AZT+3TC+EFV | 12 | 11.11 |
| | d4T+3TC+NVP | 10 | 9.25 |
| | d4T+3TC+EFV | 4 | 3.7 |

**TABLE-2**

**PHYSICAL PARAMETERS AND MEANS OF GLYCEMIC PARAMETERS OF PATIENTS ON HAART AND PATIENTS NOT RECEIVING ART**

| | PATIENT ON HAART | PATIENT NOT RECEIVING ART | P VALUE |
|---|---|---|---|
| **Number of patients** | **56** | **54** | |
| **BMI** | **19.390+3.5** | **18.735+1.822** | **0.1977** |
| **WAIST-HIP RATIO** | **0.947+0.11** | **0.885+0.04** | **0.0006** |
| **FASTING PLASMA GLUCOSE** | **104.03+18.2mg/dl** | **87.15+9.93** | **0.0468** |
| **2 Hr POST GLUCOSE PLASMA GLUCOSE** | **162.11+51.69** | **121.9+26.11** | **0.0146** |
| **HBA1C** | **6.781** | **6.011** | **0.0277** |
| **SERUM FASTING INSULIN** | **12.783microIU/ml** | **7.07microIU/ml** | **<0.001** |
| **HOMA-IR** | **2.76** | **1.53** | **0.0002** |
| **HOMA-B** | **147.6** | **102.5** | **0.276** |

**TABLE-3**

**GLYCEMIC STATUS OF PATIENTS ON HAART AND PATIENTS NOT ON ART**

| GLYCEMIC STATUS | PATIENTS ON HAART | PATIENTS NOT ON ART |
|---|---|---|
| **EUGLYCEMIC** | **32 (57.2%)** | **46 (88.4%)** |
| **IMPAIRED GLUCOSE TOLERANCE** | **15 (26.8%)** | **06 (11.6%)** |
| **IMPAIRED FASTING GLUCOSE** | **05 (8.9%)** | **NIL** |
| **DIABETES MELLITUS** | **04 (7.1%)** | **NIL** |

was 16.9months. Mean BMI of the patients on HAART was 19.390±1.732, and in patients not on ART was 18.735±1.822 (p=0.1977), Waist-hip ratio was 0.947±0.11 and 0.885±0.04(p=0.0006). The mean fasting plasma glucose levels in patients on HAART was 104.03+14.2mg/dl, and 87.15+9.93 mg/dl in patients not taking ART (p=0.0468). Mean 2 Hr post glucose plasma glucose in patients on HAART was 162.11±51.69mg/dl and 121.9 ± 26.11 mg/dl in patients not receiving ART (p=0.0146). The mean HbA1C in patients taking HAART was 6.781±1.083 and in patients not receiving ART was 6.011±0.72 (p=0.0277). The mean serum fasting Insulin levels were 12.783micrIU/ml in patients on HAART and 7.07microIU/ml in patients not on ART (p<0.001). Mean HOMA-IR in patients on HAART was 2.76 and 1.53 in patients not on ART. (p=0.0002). Mean HOMA-B of the patients on HAART IS 147.6±74.3 and in patients not taking ART was 102.5±23.5 (P=0.276) (Table No-2). Out of patients who were not on ART 46 patients (88.4%) euglycemic and 6 patients (11.6%) were having impaired glucose tolerance. Among the patients who were on HAART 32(57.2%) were euglycemic, 5 patients (8.9%) developed impaired fasting glucose, 15 (26.8%) developed impaired glucose tolerance and 4 patients(7.1%) developed diabetes mellitus. (Table-3). Patients who had developed IGT on HAART therapy were followed up after 6 months. FPG was 104±17.86mg/dl initially , 112±16.44mg/dl after 6 months (p=0.03), 2 Hr PGPG was 166.8±20.07 initially, 186.2±16.74 after 6 months (p=0.003), Mean serum fasting insulin was 13.945±6.7 at the time of detection, 19.542 after 6 months(p=0.0319), Mean HOMA-IR was 3.367±1.467 at first visit, 3.850±1.368 after 6 months (p=0.019), HOMA-B level were 143±73.20 and 148.77±74.94 after 6 months.

## DISCUSSION

One hundred and eight patients who were sero-positive for HIV infection, attending ART centre of S.C.B medical college and hospital were taken up for present study. The mean duration of treatment with HAART was 16.8±9.5 months. Mean fasting plasma glucose in patients on HAART was 104.03±14.2mg/dl, and 87.15±9.93 mg/dl in patients not taking ART (p=0.0468). The difference in FPG was statistically significant. This is in concordance with study by Jyoti et al [17] where FPG of patients on ART was 96mg/dl and in ART naïve patients was 78mg/dl. Mean 2 Hr post glucose plasma glucose in patients on HAART was 162.11±31.69mg/dl and 121.9 ± 26.11 mg/dl in patients not receiving ART (p=0.0146). This difference was statistically significant. This was at par with the study of jyoti et al [17]. where 2 hr PGPG was 144mg/dl in patients on HAART and 111 mg/dl in ART naïve patients. Mean serum fasting Insulin levels were 12.783±5.7micrIU/ml in patients on HAART and 7.07±3.14microIU/ml in patients not on ART (p<0.001). This difference in serum fasting Insulin level was highly significant suggesting that patients on HAART had significant hyper-insulinemia. This is in concordance with study of Andrew Carr et al [15]. where patients on ART had mean fasting serum insulin levels of 9.1±0.6 and ART naïve patients had 7.2±0.8 (p<0.01). Mean HOMA-IR in patients on HAART was 2.76 and 1.53 in patients not on ART. (p=0.0002). This difference is statistically significant. The normal value of insulin resistance as assessed by HOMA-IR in our population is less than 2 (Das .S et al.2007) [19].Hence HOMA-IR>2 indicates insulin resistance. This shows that patient on HAART had significant insulin resistance which was the cause of impaired glucose tolerance and Diabetes mellitus. Insulin resistance is due to decreased utilization of glucose in peripheral tissues due to mitochondrial toxicity caused by NRTI agents. This was in concordance with study of Andrew Carr et al [15] where HOMA-IR of patients on HAART was 2.00± 0.15 and 1.13± 0.10 in patients not on ART(p<0.01). Mean HOMA-B levels in the study Mean HOMA-B of the patients on HAART is 147.6±74.3 and in patients not taking ART WAS 102.5±23.5 (P=0.276) . In normal weight normal subjects aged beta-cell function is assumed to be 100% (Mathew DR et al, 1985)[21]. This shows that beta cell function among these two groups was not effected significantly indicating that beta cell function was not affected by drugs used in HAART therapy in our study in which NRTI and NNRTI were used, Protease inhibitors which cause beta cell dysfunction were not used in our study. 46 patients (88.4%) of the patients who were not on ART were euglycemic and 6 patients (11.6%) were having impaired glucose tolerance. Among the patients

who were on HAART 32 (58%) were euglycemic, 15 (26.8%) developed impaired glucose tolerance, 05 developed impaired fasting glucose and 4 patients (7%) developed diabetes mellitus (Graph-1). This was at par with other studies like- Jyoti ediculla et al[17] study in which 37% patients on ART developed Impaired glucose tolerance and Diabetes mellitus. Micheal Dube et al[10] concluded that the prevalence of impaired glucose tolerance is 15-25%, and frank diabetes is 0.5-1.5 % in patients of HIV on HAART. Friess Moller N et al study[13] had 33,389 patients, 952 had diabetes at baseline, for a prevalence of 2.85%. During the follow-up period, 744 patients were diagnosed with diabetes, an incidence of 5.72 per 1,000 PY of follow up. Brown et al study[7]-Of 1,278 men from the Multicenter AIDS Cohort Study (MACS), 47 of 411 men with HIV using HAART (14%) had diabetes at baseline compared with 33 of 710 men without HIV(5%). Of the 680 study participants who were followed prospectively, men on HAART had an incidence rate of diabetes of 4.7 per 100 person-years (PY), compared with 1.4 cases per 100 PY in men without HIV, indicating a four-fold increased risk of developing diabetes for men on HAART, adjusted for age and body mass index . Follow up of patients who had developed IGT on HAART after 6 months it is seen that the glycemic parameters and insulin resistance increased on continuation of treatment.

## CONCLUSION

The above study shows that there is an increased incidence of glucose intolerance and Diabetes mellitus in patients of HIV/AIDS treated with HAART therapy. Diabetes mellitus and glucose intolerance is due to insulin resistance caused by antiretroviral agents. The incidence of insulin resistance, glucose intolerance increases with the duration of HAART therapy and with age of the patient. Hence glycemic status of HIV/AIDS patients taking HAART therapy should be regularly monitored and followed up.

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*Original Article*

# STUDY OF COAGULATION PROFILE IN ACUTE MYELOID LEUKEMIA

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## ABSTRACT

***Introduction:*** *Disseminated Intravascular Coagulation (DIC) is an important complication in Acute Myeloid Leukemia(AML). While Acute Promyelocytic Leukemia (APL) is a well established risk factor for DIC, bleeding is also seen in other types of AML(non-APL AML).* ***Objectives:*** *The present study was designed to study the coagulation profile abnormalities in Acute Promyelocytic Leukemia (APL) and non-APL Acute Myeloid Leukemia (non-APL AML) and their predictive value in clinical bleeding events.* ***Methods:*** *55 naïve consecutive cases of adult AML (age > 15 years) were taken up for the study. Detailed history taking and clinical examination, hematological parameters, bone marrow study and immunophenotyping were done in all cases. Coagulation profile, including PT, APTT, serum Fibrinogen and FDP were done in every patient. The cases were divided into 2 groups as APL and non-APL AML. The coagulation profile abnormalities and the haematological parameters in the 2 groups were studied, analysed and correlated with bleeding events using SPSS.* ***Results:*** *In APL group 11 out of 17 patients (64.7%) and in non-APL AML group 10 out of 38 patients (26.3%) presented with bleeding manifestations. In both the groups significant difference was found in mean PT prolongation in patients with bleeding and patients without bleeding (p value - 0.027 in both APL and non-APL AML group). Similarly there was significant difference in mean FDP in patients with bleeding and those without bleeding in both the groups (p value 0.0041 in APL and 0.0001 in non-APL AML). But the difference in mean APTT prolongation and Fibrinogen in patients with bleeding and patients without bleeding were not significant in any group. In APL group, TPC had significant correlation with clinical bleeding (p value - 0.016 ) whereas in non-APL AML group, TLC had significant correlation with clinical bleeding (p value - 0.001). DIC score significantly correlated with bleeding events in both APL and non-APL AML groups (p value-0.002 and 0.0001) respectively.* ***Conclusion****: Though bleeding is a major complication in APL patients, it also occurs in a significant number of patients in non-APL AML patients. DIC is the major cause of bleeding in both APL and non-APL AML group with hyperleucocytosis additionally contributing to the cause of bleeding in non-APL AML patients. PT prolongation and FDP are good indicators of DIC.* ***Key words :*** *Acute Myeloid Leukemia, Coagulation, DIC, Acute promyelocytic leukemia.*


## INTRODUCTION

Acute myeloid leukemia (AML) is a clonal, malignant disease of hematopoietic tissues that is characterized by accumulation of abnormal (leukemic) blast cells, principally in the marrow and impaired production of normal blood cells.[1] AML has a very wide variety of presentations including fatigue, loss of appetite, loss of weight fever, gum bleeding, bone pain etc[2] .Many a times patients present with features of Disseminated Intravascular Coagulation (DIC) which is a medical emergency with life threatening complications[3,4].Acute promyelocytic leukemia(APL) is a well-established risk factor for DIC. In patients with

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other types of AML (non-APL AML), DIC also occurs as a devastating complication, although it develops less frequently. The prevalence of DIC and its clinical association in patients with non-APL AML have not yet been fully elucidated. It would be valuable if we could predict the development of DIC in these patients and prevent the complications. Coagulation profile is the test which helps the physician in the early detection of DIC. Hence this study was undertaken to analyse the coagulation profile abnormalities and their predictive value in clinical bleeding events in patients of AML, that would help in decreasing their mortality and morbidity .

## MATERIALS AND METHODS

The study was undertaken in the Department of Medicine and Clinical Hematology of S.C.B. Medical College, Cuttack during the period September 2011 to September 2012. All newly diagnosed adult patients (age>14 years) with AML were included in the study. Patients with secondary AML and relapse AML were excluded from the study.

Detailed history taking and clinical examination was done in all the cases. Laboratory tests for hematological parameters (Hb, DC, TLC, TPC, ESR, Peripheral smear comment) was done by Automated 5 part cell counter(SYSMEX XT 2000-I).Biochemical parameters (RBS, LFT, Serum Urea & Creatinine, Serum $Na^+$ & $K^+$, serum Uric acid, serum LDH) and Urine examination (Routine & Microscopic) were done. Bone Marrow aspiration was performed and smears were routinely stained with Leishman stain and Myeloperoxidase(MPO). 3ml of marrow aspirate was collected at the same setup in heparinised vials for immunophenotyping. Coagulation profile including PT, APTT, Serum Fibrinogen (by fully automated coagulometer-SYSMEX 500) and FDP (D-dimer) was done for every patient. DIC Score was calculated as per the ISTH (International Society on Thrombosis and Hemostasis) guidelines . Diagnosis was based on the morphology, histopathology and confirmed by Immunophenotyping by Flow cytometer (BD FACS CALIBUR).

All the patients were categorized into M0, M1, M2, M3, M4, M5, M6, M7 using the French- American - British classification. The cases were then divided into two groups, APL(M3) and non-APL AML. Each of these two groups were further categorized into those with and those without bleeding manifestatioins. The coagulation profile was then compared between the groups.

## RESULTS

55 patients of AML were diagnosed and classified as M0-0 , M1- 6 ,M2- 23 ,M3-17 ,M4- 4, M5- 5,M6- 0 ,M7- 0 .In the M3 or the APL group there were 17 patients and the rest 38 were put together in the non-APL AML group. Bleeding manifestations were seen in 11 out of the 17(64.7%) APL patients and in 10 out of 38 (26.3%) patients in the non-APL group. (Figure-1)

Significant difference was found in mean PT prolongation (p value-0.027) and mean FDP (p value-0.0041) between patients with bleeding and patients without bleeding in APL group (Table-1). Similarly there was significant difference in mean PT prolongation (p value-0.027) and mean FDP (p value-0.0001) between patients with bleeding and patients without bleeding in Non APL AML group (Table-2). But the difference in mean APTT prolongation and Fibrinogen in patients with bleeding and patients without bleeding were not significant in any group (Table-1 & Table-2). In APL group, TPC and DIC score had significant correlation with clinical bleeding (p value - 0.016 & 0.002 respectively) (Table-3) whereas in non-APL AML group, TLC and DIC score had significant correlation with clinical bleeding (p value-0.001 & 0.0001 respectively)(Table-4).

## DISCUSSION

In APL group, 11 (64.7%) out of 17 and in Non APL AML group, 10(26.3%) out of 38 presented with haemorrhagic manifestations. Study by Catherine C et al[5], Zuazu et al[6], Hung C et al[4] found 63%,70%,77.6% bleeding manifestations respectively in APL patients. In Non APL AML patients, Uchimi H

**TABLE-1. CORRELATION OF COAGULATION PROFILE WITH CLINICAL BLEEDING IN APL PATIENTS.**

| | WITH BLEEDING (n=11) (MEAN ± SE) | WITHOUT BLEEDING (n=7) (MEAN ± SE) | p VALUE |
|---|---|---|---|
| PT PROLONGATION | 5.3 ± 0.599 | 3.05 ± 0.563 | 0.027 |
| APTT PROLONGATION | 3.045 ± 1.217 | 2.248 ± 0.559 | 0.649 |
| FIBRINOGEN | 210.63 ± 16.702 | 218.19 ± 36.225 | 0.83 |
| FDP | 545 .45 ± 38.996 | 300 ± 68.313 | 0.0041 |

**TABLE-2. CORRELATION BETWEEN COAGULATION PROFILE AND BLEEDING IN NON APL AML PATIENTS(TOTAL NO. OF PATIENTS=38)**

| | **WITH BLEEDING (n=10) (MEAN ± SE)** | **WITHOUT BLEEDING (n=28) (MEAN ± SE)** | **p VALUE** |
|---|---|---|---|
| **PT PROLONGATION** | 5.75 ± 1.813 | 3.09 ± 0.276 | 0.027 |
| **APTT PROLONGATION** | 4.59 ± 1.463 | 2.54 ± 0.449 | 0.081 |
| **FIBRINOGEN** | 208.56 ± 30.627 | 248.51 ± 14.75 | 0.2 |
| **FDP** | 480 ± 53.33 | 250 ± 22.12 | 0.0001 |

**TABLE -3.CORRELATION BETWEEN DIFFERENT HEMATOLOGICAL PARAMETERS WITH CLINICAL BLEEDING IN APL PATIENTS.**

| | WITH BLEEDING (n=11) (MEAN ± SE) | WITHOUT BLEEDING (n=7) (MEAN ± SE) | p VALUE |
|---|---|---|---|
| PERIPHERAL BLAST CELL (PERCENTAGE) | 67.63 ± 4.76 | 78.33 ± 1.66 | 0.128 |
| TLC/$mm^3$ | 21650 ± 11432 | 14830 ± 4139.5 | 0.675 |
| TPC/$mm^3$ | 35727.27 ± 15054 | 70166.66 ± 4950.8 | 0.016 |
| DIC SCORE | 5.72 ± 0.5 | 2.5 ± 0.71 | 0.002 |

**TABLE-4. CORRELATION BETWEEN DIFFERENT HEMATOLOGICAL PARAMETERS WITH CLINICAL BLEEDING IN NON APL AML**

| | | | |
|---|---|---|---|
| PERIPHERAL BLAST CELL (PERCENTAGE) | 64.8 ± 5.91 | 58.82 ± 3.92 | 0.428 |
| TLC/$mm^3$ | 85850 ± 24673 | 29898.21 ± 4179.8 | 0.001 |
| TPC/$mm^3$ | 43000 ± 7015.9 | 71714.28 ± 10393 | 0.119 |
| DIC SCORE | 5 ± 0.714 | 1.96 ± 0.249 | 0.0001 |

et al[3] reported 32% and Nur S et al[7] reported 33.3% bleeding manifestations. There was significant correlation between PT prolongation and bleeding in both APL and Non APL AML group (p value - 0.027 in both the group). But APTT prolongation did not have any significant correlation (p value 0.649 in APL and 0.081 in Non APL AML). Most of the previous studies also show significant correlation between PT prolongation and bleeding but no significant correlation with APTT (Dally N et al[8],Weltermann A et al[9],C.Y.Chen et al[10]). There was no significant correlation between fibrinogen and bleeding in both APL and Non APL AML patients (p value 0.83 and 0.2 in APL and Non APL AML respectively). It is comparable with the studies done by Reddy VB et al [11]and Leinoe EB et al [12]who found no significant correlation between fibrinogen and DIC. Fibrinogen levels decline in patients with DIC due to ongoing consumption. But fibrinogen levels may be normal till severe DIC occur. FDP was significantly related to bleeding in both APL (p value-0.0041) and Non APL AML (p value-0.0001). Other studies done previously report similar findings (Cielinska S et al[13], Speiser W et al[14]). There was no significant correlation between blast cell percentage with bleeding in both the group of patients (p value-0.1287 and 0.4288 in APL and Non APL AML respectively). Studies by Hung C. et al[4] also did not find any correlation between leukemic cell count and DIC. There was no significant difference between the mean value of TLC in patients with bleeding and patients without bleeding in APL group (p value-0.6758). But in Non APL AML group total leucocyte count is significantly related to bleeding (p value-0.0013). Studies by Gerard J.et al[15]and Nowacki et al[16] in AML patients showed significant correlation between hyperleucocytosis and bleeding. Hyperleucocytosis causes leucostasis, invasion and disruption of microvasculature resulting in bleeding. Clinical bleeding manifestations are related to thrombocytopenia in APL group (p value-0.0166). The correlation between thrombocytopenia and bleeding manifestation is well established. Thrombocytopenia can be caused by decreased production by bone marrow or increased consumption in the process of DIC (Tatsumi U et al) [17].Bleeding may occur due to quantitative defect i.e thrombocytopenia as per study done by Eva B et al[18] or due to qualitative defect like decreased platelet activation as shown by Psaila B et al[19]. But in Non APL AML we did not find any correlation between total platelet count and clinical bleeding (p value-0.1197). In our study we found a significant correlation between DIC Score and clinical bleeding in both APL patients (p value-0.002) and Non APL AML patients (p value-0.0001). As per the studies by Bakhtiari K et al[20] ISTH (International society on thrombosis and hemostasis) DIC score has a sensitivity of 91% and specificity of 97% in diagnosing DIC. The ISTH DIC score proves useful and adequate as a marker of clinically significant DIC (Cauchie P et al) [21].

## CONCLUSION

Though bleeding is a major complication in APL patients, it also occurs in a significant number of patients in Non APL AML patients. DIC is the major cause of bleeding in both APL and Non APL AML group with hyperleucocytosis additionally contributing to the cause of bleeding in Non APL AML patients. PT prolongation and FDP are good indicators of DIC.

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*Original Article*

# EVALUATION OF RISK FACTORS AND PROGNOSTIC OUTCOME OF SPONTANEOUS INTRACEREBRAL HAEMORRHAGE

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## ABSTRACT

***Background And Objective:*** *Spontaenous Intracerebral Haemorrhage (SICH) has remained a serious disease despite recent improvements in management. This study was designed to (1) study various risk factors for SICH; (2) determine whether clinical/neuro-radiological parameters could predict the outcome of patients with SICH.* ***Materials & Methods:*** *Forty patients with CT scan evidence of SICH admitted to our hospital were randomly selected for this study conducted in-between October 2010 to September 2012. Data regarding different risk factors in detail was collected from all patients. Clinical parameters at the time of admission like level of consciousness, GCS score, and blood pressure, presence of gaze palsy, bilateral plantar extensor response, pupillary abnormalities, and ataxic respiration were assessed in all cases. CT Scan was analysed for parameters like site, volume of haematoma, presence of mid-line shift, hydrocephalus and intraventricular extension of haemorrhage. Follow up was done for 6 months period and outcome was assessed in terms of mortality.* ***Results:*** *Majority of patients were illiterate (68%). Hypertension (90%) was the major risk factor in our study. Majority of the hypertensives were on irregular treatment (55%). The other common risk factors were alcohol consumption (18%) and smoking (27%) and (5%) had family history of stroke. The overall mortality in our study group was 37%.There was a linear increase in mortality after the age of 50 years and the lethal outcome was significantly associated with age >80 years (100%), GCS score 3-4 (100%) ($p<0.05$), SBP > 180 mm Hg (52%) ($p<0.037$), DBP > 110 mmHg (53%) ($p<0.028$), MAP > 140 mmHg (64%) ($p<0.005$), presence of gaze palsy (70%) ($p<0.024$), bilateral extensor plantar response (58%) ($p<0.005$), pupillary abnormality (83%) ($p<0.01$), and ataxic respiration (100%) ($p<0.001$). Mortality was not significantly altered by the site of ICH.Patients with volume of haematoma > 30 $cm^3$ (75%) ($p<0.001$), presence of mid-line shift (61.5%) ($p<0.006$), intraventricular extension of haemorrhage (80%) ($p<0.001$) and hydrocephalus (100%) ($p<0.025$) in CT scan had significant poor outcome in our study.* ***Conclusion:*** *Incidence of SICH can be reduced by modification of risk factors like control of hypertension and abstinence from alcohol/smoking. The probability of lethal outcome can be calculated on admission in all patients with ICH by using clinical/neuro-radiological parameters that allow risk stratification of patients and appropriate care.* ***Key Words****: Spontaneous intracerebral haemorrhage (SICH); Glasgow coma scale Score (GCS); mean arterial pressure (MAP).*


## INTRODUCTION

Stroke is defined as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin.[1]

CVA is the third commonest cause of death in the west after heart disease and cancer. It ranks first among all neurological disease of adults, with more than 50 percent of all hospital admissions being stroke. Not only is the mortality associated with stroke, but also the morbidity puts a heavy emotional, psychological and financial burden both on the patient, as well as on the family and the state.[2] Spontaneous intracerebral haemorrhage account for approximately 10-15 percent

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of all stroke cases and is associated with the highest mortality rate (30-40%). Its clinical importance derives from its frequency, high morbidity and high mortality. It has still remained as a serious problem despite attempts at improving the outcome by medical and neuro-surgical treatment.[3]The causes of intracerebral haemorrhages are multiple. Hypertension is the most important risk factor for spontaneous intracerebral haemorrhage.[4] Other potential risk factors for spontaneous intracerebral haemorrhage includes excessive alcohol consumption, smoking, anticoagulant therapy, genetic factors, chronic amyloid angiopathy, bleeding from vascular abnormalities (arterio-venous malformations, aneurysms), drugs like cocaine/ amphetamine abuse, bleeding into the tumour and others. [5.6]Majority of the risk factors are modifiable. Hence identification of modifiable risk factors for ICH is important to decrease the incidence of spontaneous ICH at primary intervention level.Spontaneous ICH has still remained a serious disease despite attempts at improving outcome by medical and neuro-surgical treatment. There are many clinical/neuro-radiological parameters like Glasgow Coma Scale, severity of neurological deficit, site, size, volume of haemorrhage, presence of intraventricular extension, hydrocephalous and others that would predict the outcome of ICH.[8,9] Hence this study was performed to evaluate different risk factors and to determine whether clinical/neuro-radiological parameters would predict the outcome of ICH.

## MATERIAL & METHODS

Sixty patients with CT scan evidence of ICH admitted to V.S.S. Medical College and hospital, Burla were randomly selected for this study conducted in between September 2010 to September 2012.

The following cases were excluded from our study (1) Traumatic intracerebral haemorrhage (2) Primary subarachnoid haemorrhage (3) Haemorrhagic infarction (4) Tumour bleed (5) History of bleeding diathesis (6) Primary intraventricular haemorrhage (7) Prior history of stroke.

Initial workup of these patients included

- Hb%, TLC, DC, Total Platelet count, ESR, BT, CT, PT, aPTT, Urine-sugar, albumin, microscopy, FBS/2 hr. PGBS, Blood urea, Serum creatinine, Serum electrolytes ,Lipid profile , ECG, CT scan of brain, Chest X-Ray, M.R.I of brain, 2D Echocardiography, liver function tests, were done whenever needed.

Initially all patients were treated conservatively with anti-cerebral edema measures which comprised of Mannitol 1 gm/kg in three divided doses/day, followed by oral glycerol 30 ml three times a day. Those patients whose blood pressure was high were treated with antihypertensive agents appropriate to the degree of hypertension. Nutrition was maintained in all unconscious patients by nasogastric feeding and parenteral alimentation. Vigorous respiratory care and physiotherapy was instituted in all patients right from the time of admission. Patients were considered as hypertensives if they met the following criteria i.e. Presence of hypertension based on history, previous documentation/on medications, presence of hypertensive retinopathy or presence of left ventricular hypertrophy by ECG or echocardiography. Recent excess alcohol consumption was recorded prior to the onset of ictus. Blood pressure recorded at the time of admission was used for assessing prognosis. MAP was calculated by using the formula MAP = DBP + 1/3 pulse pressure. Detailed clinical examination for vital parameters and neurological deficit were done for all patients and Glasgow coma scale scoring was done at admission.

The following data were extracted by a radiologist from the patient's CT scan obtained at the time of admission. (i) Site of haematoma (ii) Volume of haematoma (iii) Presence of mid-line shift (iv) Presence of associated intraventricular haemorrhage (v) Presence of hydrocephalus

Volume of haematoma was calculated in the following manner. On the CT scan slice with the largest area of ICH, the longest diameter (A) of the haematoma was measured from the centimetre scale on the film. The largest possible diameter perpendicular to the longest diameter represented the second diameter (B).

The height of the haematoma was calculated by multiplying the number of slices involved by slice thickness, providing the third diameter (C). Each diameter was determined to half a centimetre. Haemorrhage within the ventricular system was not

measured. The three diameters were multiplied and then divided by two {(A x B x C)/2} to obtain the volume of ICH. Kothari and Co-authors have found that this formula (A x B x C)/2 correlated highly with volumes calculated by planimetric methods.

All cases were followed up for six months as out-patient or by communication through telephone/ letter/getting information by close relatives/patient himself. Prognostic factors were studied and outcome was assessed in terms of mortality.

**RESULT**

During the study period 60 cases of C.T. Scan proven spontaneous intracerebral haemorrhage cases were taken by simple random sampling and studied for presence of different risk factors and clinical/ radiological prognostic factors to assess outcome. Among 60 cases, 1(1.7%) patients was in the age group 31-40 years, 9(15%) in the age group of 41-50 years, 12(20%) in the age group of 51-60 years, 7(11.7%) patients were in the age group of 61-70 years, 8(13.4%) in the age group of 71-80 years , 1(1.7%) patients were in the age group >80 years . The youngest patient was 38 years old and the oldest patient was 84 years old. In our study 83.3% of the study group belonged to above 50 years age. Of the 60 cases studied, 38(63%) cases were males and 22 cases (37%) were females.

The most common risk factor we found in our study was hypertension i.e 54(90%). The other common risk factors found in our study were alcohol consumption 11(18%) and smoking 16(27%) patients. Family history of CVA was found in 5% cases. The other risk factors like anticoagulant therapy and drug abuse (cocaine, amphetamine) were not found (Table-1). Most of our patients were illiterates (68%). Only 32% are literates. Among the patients who had hypertension, 16 were newly detected hypertensives. 38 were known hypertensive of which 30(55%) patients were on irregular treatment/ had discontinued treatment. Only 8(15%) patients were on regular treatment. Majority (55%) of the hypertensives were on irregular treatment, which was responsible for fluctuations in blood pressure which could have been the cause for intracerebral haemorrhage. Mean serum cholesterol in our study group was 186.18 mg/dl. The mean serum cholesterol between different age groups varied from 181.14mg/dl to 188.65 mg/dl. The mean serum cholesterol in males was 184.16mg/dl and that in females was 189.21mg/dl. From the table it is evident that hypertension was a common and major risk factor for both sexes. Among males, 87% were hypertensives, 21% were alcoholic and 42% were smokers. Among females, 95% were hypertensives, 9% were alcoholic and none were smokers. Alcohol consumption and smoking were more common in males. In the age group of 31-40 years; hypertension was present in 100%, alcohol consumption in 0% and smoking in 0%. In the age group of 41-50 years, 81.8% were hypertensive, 18% were alcoholic and 36% were smokers. In the age group of 51-60 years, 80.9% were hypertensive, 9.5% were alcoholic and 38% were smokers. In the age group of 61-70 years, 100% were hypertensive, 23% were alcoholic and 23% were smokers. In the age group of 71-80

**Table 1: Distribution of spontaneous ICH patients with respect to risk factors**

| Risk factors | Number | Percentage |
|---|---|---|
| Hypertension | 54 | 90 |
| Alcohol consumption | 11 | 18 |
| Smoking | 16 | 27 |
| Anticoagulation therapy | 0 | 0 |
| Drug Abuse (Cocaine/Amphetamine) | 0 | 0 |
| History of cerebro vascular accident in first degree relatives | 3 | 5 |
| Others | 0 | 0 |

years, 100% were hypertensive, 30.7% were alcoholic, and 7.7 % were smokers. In the age group of >80 years, 100% were hypertensive and none were alcoholic and smokers. From the table it is evident that hypertension was a major risk factor in all the 3 age groups.

**ASSESSMENT OF FACTORS FOR PROGNOSTIC OUTCOME**

In our study among 60 patients, 22 patients died. The mortality was 37%.

The mortality in the age group of 31-40 years was 100%, 41-50 years was 0% ,51-60 years was 28.6%, 61-70 years was 54%,71-80 years was 54% and >80years was 100%. As the age increased, mortality increased. A statistically significant association was found between old age and mortality. Among 38 male patients, 15 patients (39%) died. Among 22 female patients, 7 patients died (32%). No significant association was observed between sex and mortality ($x^2$=0.35; CC=.042; P<.792) indicating that mortality pattern were same in both sexes.

to these data a significant association was observed indicating that higher the SBP, DBP and MAP, higher were the mortality rate (Table-2). MAP was a better indicator for prognosticating the mortality risk.

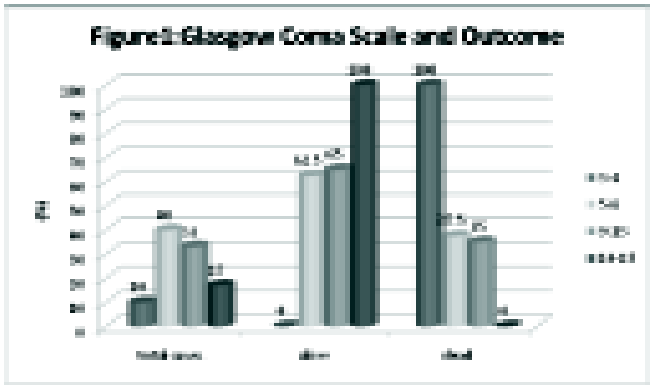
The mortality was 100% in patients who had GCS score 3-4, 37.5% in patients who had GCS score 5-8, and 35% in patients with GCS score 9-13(Fig:1). No mortality was found in those with GCS score 14-15. Thus, low GCS score was found to be a good indicator of poor prognosis. Ten patients had gaze palsy. The mortality was 70% among patients who had gaze palsy and 30% in patients who did not have gaze palsy. It was statistically significant. Patients with gaze palsy had a poorer prognosis in our study. Six patients had abnormal pupils at presentation and 5 of them died (83%). Presence of pupillary abnormality at presentation had bad prognosis. Ten patients had ataxic respiration and all of them died (100% mortality), which indicate that tentorial coning with respiratory centre involvement had grave prognosis. Twenty four patients had bilateral plantar extensor response with high mortality rate i.e.

**TABLE2: HYPERTENSION AND OUTCOME**

| Blood Pressure | Total Cases | Alive | | Dead | |
|---|---|---|---|---|---|
| | | No | % | No | % |
| Systolic BP in mmhg >180 | 25 | 12 | 48 | 13 | 52 |
| <180 | 35 | 25 | 72 | 10 | 28 |
| $X^2$=3.96; CC=.314; p<.037(S) | | | | | |
| Diastolic BP in mmhg >110 | 27 | 13 | 47 | 14 | 53 |
| <110 | 32 | 24 | 75 | 8 | 25 |
| $X^2$=4.2; CC=.328; p<.028(S) | | | | | |
| MAP in mmhg >140 | 25 | 9 | 36 | 16 | 64 |
| <140 | 35 | 26 | 74 | 9 | 28 |
| $X^2$=5.86; CC=.398; p<.005(S) | | | | | |

The mortality was more than two times (57.89%) among patients who had diastolic BP>110 mmHg compared to those who had diastolic BP<110 mmHg (23.80%). The mortality was more than three times (64.70%) among patients who had MAP>140 mmHg compared to those who had MAP<140 mmHg (21.73%).When contingency coefficient test was applied

58% which indicated presence of midline shift with a false localizing sign of compression of opposite cerebral peduncle and had bad prognosis. In our study the incidence of haematoma as per site was as follows: Basal Ganglia (57%), Thalamus (13%), Lobar (22%), Cerebellar (3%), and Pons (5%). The most common site was basal ganglia followed by lobar haemorrhages



and thalamus. The mortality was 32% in basal ganglia, 50% in thalamic haemorrhage, 23% in lobar haemorrhage, 50% in cerebellar haemorrhage, 100% in pontine haemorrhage. In our study pontine haemorrhage had the highest mortality (100%) followed by cerebellar, probably being in posterior fossa nearer to vital centres. Thirty-six patients had volume of haematoma <30 $cm^3$ and 24 patients had volume >30 $cm^3$. The mortality was 11% in patients who had haematoma volume <30$cm^3$ and 75% in patients in whom the volume of haematoma was >30$cm^3$. There was a statistically significant increase in mortality in patients who had volume of haematoma >30$cm^3$.Among 26 patients who had midline shift, 16 patients died (61.5%) indicating poor prognosis in patients who had midline shift which statistically significant. All four patient who had intraventricular extension of haemorrhage had poor outcome. 20 patients had intraventricular extension and among them 16 died (80%). It was statistically significant. Four patients who had hydrocephalous died (100% mortality). Presence of hydrocephalus had a statistically significant poor outcome in our study group.

## DISCUSSION

Among the 60 cases we studied, the incidence of intracerebral haemorrhage increased as the age advanced. More than 83.3% of ICH occurred in the age group above 50 years. It is comparable to other studies. In Qureshi et al., [6] 85% of the cases were of age more than 50 years. 63% of cases were males and 37% were females in our study. Though males outnumbered females, it is statistically insignificant.

The most common risk factor in our study was hypertension (70%). It was followed by smoking (27%) and alcohol consumption (18%). It is comparable with Qureshi et al.[6] Among hypertensives 55% were on irregular treatment and only 15% were taking regular treatment. Among hypertensives irregular treatment / non-compliance was a major problem found in our study which is comparable to the study done by Qureshi et al.[6] Thus most of the intracerebral haemorrhage can be prevented, if patients were educated about compliance of treatment. Among alcoholics, recent alcohol consumption prior to onset of ictus was seen in 11 patients (18%). Thus it is evident that consumption of alcohol increases the risk of ICH .It is similar to Juvela et al., [19] where he had found that recent alcohol consumption increases the risk of ICH. Alcoholism and smoking were more common in males which is similar to Qureshi et al. Hypertension was an important major risk factor in all the age groups and alcoholism was found more in younger age group compared to elderly which is again similar to Qureshi et al.[6] In our study mean serum cholesterol was 186.18 mg/dl. Konishi et al. in his study had found an association between low serum cholesterol (< 160 mg/dl) and ICH in Japan population. The difference between Konishi et al. and the present study is probably due to difference in race and food habits. The outcome in terms of mortality was analyzed with respect to following clinical/neuro-radiological parameters. As the age advances the mortality increases. In our study mortality was 28.6% between 51-60 years, 54% between 61-70 and 71-80 years and 100% in >80 years. In Qureshi et al. the mortality was 23% in the age group 30-49 years 40% in the age group 50-69 years and 62.85% in the age group >70 years.It is evident in our study that patients who had systolic BP > 180 mm Hg and diastolic BP > 110 mm Hg had mortality of 52% and 53% respectively. So the initial blood pressure plays a major role in the outcome. Both increase in systolic and diastolic blood pressure had poor prognostic outcome. The MAP > 140 mm Hg also had significant mortality of 52% in our study. Thus initial SBP, DBP and MAP can be considered as prognostic indicators of mortality. In our study also, similar to Daverat et al. the mortality was around 70% in patient who had gaze palsy, severe motor weakness and bilateral plantar extensor response. In our study, patients who had ataxic respiration, abnormal pupils and who were comatose had 100% mortality. So they can be considered as very poor

prognostic indicators. The GCS score is inversely proportional to the mortality. In our study the patients who had GCS score of 3-4 had mortality of 100% which is comparable with Qureshi et al. In our study 90% of patients whose GCS score <8 had poor outcome. In our study the basal ganglionic haematoma constituted 57% followed by lobar (22%), thalamic (13%), cerebellar (3%) and pontine (5%),. The outcome was not related to site of haematoma. The highest mortality was seen with pontine haematoma (100%) followed by cerebellar(50%), thalamic(50%), basal ganglia(32%), Lobar(23%). In our study, as the volume of haematoma increased, the mortality increased and was statistically significant. In our study, 75% of patients with volume of haematoma > 30 $cm^3$ had poor outcome Presence of midline shift was associated with 61.5% mortality. Its presence indicates poor prognosis and it is statistically significant. The presence of intraventricular extension of hemorrhage had (80%) mortality.The presence of hydrocephalus had (100%) mortality and is a significant poor prognostic indicator.

## CONCLUSION

Spontaneous intracerebral haemorrhage (SICH) is associated with high mortality and morbidity despite recent improvements in management. So efforts must be directed towards better understanding and modification of risk factors. The major risk factor in our study was hypertension. The other common risk factors were alcohol consumption and smoking. Thus, measures to ensure adequate control of hypertension/ compliance of treatment among hypertensives, abstinence from alcohol and smoking may reduce the incidence of SICH. Old age, low GCS score, high SBP, high DBP, high MAP, presence of gaze palsy, pupillary abnormality, bilateral extensor plantar response, ataxic respiration would indicate bad prognosis in SICH. In addition to diagnosis of ICH, CT Scan can also be used as an useful tool in assessing prognostic outcome of ICH, by using radiological parameters like larger volume of haematoma, presence of midline shift, intraventricular extension of haemorrhage and hydrocephalus which indicated bad prognosis.

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*Original Article*

# STUDY OF PREVALENCE OF IFG AND IGT IN NON DIABETIC SUBJECTS WITH CORONARY ARTERY DISEASE & EVALUATION OF OTHER RISK FACTORS FOR ATHEROSCLEROSIS

**N.R. Mohanty[*] , J. Nayak[**] , S.R. Panda[***], R.K. Dalai[****]**

**ABSTRACT**

*This study enrolled 60 cases of nondiabetic coronary artery disease patients and 25 age , sex and risk factor matched controls. Mean age in the control group was 47.88± 13.98yr. where as in the case it was 59± 9.32yr.The mean BMI & waist circumference was higher in the case group compared to control. Dyslipidemia was more prevalent in the case group. The mean carotid IMT was more & statitistically significant in the case group.IFG was found in 9(15%)cases &IGT was found in 13(22%) cases and both IFG &IGT was found in 3(5%) cases. In total abnormal glucose regulation was found in 42% cases. These findings stress the need for early screening & management of pre-diabetes preventing further progression to Diabetes.* ***Key words:*** *pre-diabetes, cardiovascularisk factors, intimal media thickness, abnormal glucose regulation.*

## INTRODUCTION

Coronary artery disease is the most common form of heart disease worldwide [1].The total no of coronary artery disease cases in India increase from 27 million in year 2000 to 35 million in 2005.[2]Some risk factors of coronary artery disease are modifiable like hypertension, Diabetes mellitus, smoking, obesity, hyperlipidemia & others are nonmodifiable like age,gender,family history & genetic. [3,7]Out of all the risk factors diabetes mellitus is one of the most important risk factor for coronary artery disease [3]. IFG & IGT are precursor to diabetes & intermediary step between normoglycemia & hyperglycemia. This metabolic state accompanies with major risk factors for atherovascular disease i:e. Metabolic syndrome, insulin resistance.[4].Currently worldwide 314 million people are having IFG & IGT and the projected figure is 500 million by year 2025 [4].In India the number of IGT is suspected to be nearly 36 million today and this is likely to increase to 56.2 million in 2025[4].Risk of coronary heart disease begins to increase at least 15 yrs before onset of hyperglycemia in a diabetic The risk of coronary heart disease is higher in IFG & IGT patients compared to normal population, some times Myocardial Infarction may be the initial presentation of IGT or overt Diabetes [4]. The development of chronic complications of diabetes,either micro or macrovascular, can begin earlier in the pre-diabetes phase as demonstrated by UKPDS and DPP, with increasing prevalence from IFG to IGT [7,8].The highest prevalence is observed in patients with both conditions[9]. Decreased level of HDL-cholesterol,increased level of LDL-cholesterol, triglycerides and hypertension, are present more frequently among prediabetic individual, increasing the cardiovascular risk[10].So this study is planned to assess the prevalence of IFG & IGT state in patients of non diabetic coronary artery disease, thereby permitting early initiation of appropriate preventable measures & to assess other cardiovascular risk factors (smoking, raised BMI, hypertension, hyperlipidemia, carotid atrery intimal media thickness) in those category of patients.

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## MATERIALS & METHODS

60 patients of non diabetic CAD patients & 25 subjects of control matched by age,gender,risk factors were taken for this study. Every patient was examined during OPD or during admission for a detailed medical history, clinical examination, routine blood chemistry.FBS, 2hr PGBS, lipid profile,ECG,2D echo, carotid Doppler study. Results were analyzed using Graph pad instat 3 &theses values were used as descriptive measures of normally distributed variables. Statistical significance of parameters between groups were evaluated using student's t test which was inferred at $p<0.05$.The strength of correlation between various lipid fractions, age,waist circumference, BMI, IMT were separately using pearson correlation analysis.

## OBSERVATIONS

In the present study 53(88.33%) were males & 7(11.66%) were females among cases and 22(88%) males & 3(12%) females in control group. Maximum number of cases were in age group of 55 to 64 years. Male to Female ratio in control was 7.3:1 & 7.5:1 in cases.

In the present study the mean age was calculated to 47.88±13.98 yr in controls and 59±9.32 in cases. At the same time Male to Female ratio was found to be 21:4 in controls and 53:7 in case group. Table – 1 indicates mean BMI was 21.67±3.67 in controls & 23.18±3.96 in cases. FBS and 2 hr PPBS have significant rise in cases in comparison to controls with p value of < 0.05. though all lipid parameters were more in cases than controls but statistically significant difference was found in cases of cholesterol & VLDL level .

The mean carotid IMT in control was 0.611±0.130 & 0.703±0.105 in case group and it was statistically significant.

IFG was found in 9(15%) of case group.IGT was found in 13(22%)of case group &Both IFG & IGT were found in 3(5%) of case group. Glucose regulation was normal in control group.

2hr PGBS level correlated positively with the variables like AGE, WC, S.TG in both control and case group. It was significant only in case of S.TG in the case group.

## DISCUSSION

The present study "study of prevalence of IFG and IGT in non diabetic subjects with coronary artery disease & evaluation of other risk factors for atherosclerosis" includes 60 cases of non diabetic coronary artery disease patients.

On comparing the different risk factors it was found that history of smoking, hypertension and alcohol intake were more in number of cases in comparision to controls. Along with this mean BMI in cases was 23.18±3.961 kg/m2 in comparison to 21.67±3.67 kg/m2 in controls. INDO HEART SURVEY[11] (2008) reported similar findings of increased BMI in different categories of impaired glucose regulation. The mean waist circumference of cases was more similar to the work done by David Faeh et al[12]

Among the biochemical parameters, FBS and 2 hr PPBS showed a significant rise among cases. Similarly Dyslipidemia was more prevalent in the case group as compared to control group. However it was statistically significant only in case of Total cholesterol and VLDL cholesterol (p value=0.002 & 0.003 respectively). INDO HEART SURVEY[11] (2008) revealed increased triglycerides in the Abnormal Glucose Regulation categories. Total cholesterol was marginally higher in the IGT group and though LDL was raised in both IFG & IGT group it was not significant. CHINA HEART SURVEY[13] showed increase in the lipid parameters in the Abnormal Glucose Regulation group compared to the control group.

The present study registered impaired fasting glucose in 9 (15%) cases, Impaired glucose tolerance in 13 (22%) cases & both in 3 (5%) cases. In total abnormal glucose regulation was found in 42% cases. INDO HEART SURVEY on latent abnormal glucose regulation in patients with coronary artery disease without diabetes across India included 350 patients in

**TABLE-1: DISTRIBUTION OF SELECTED CLINICAL& METABOLIC RISK FACTORS IN STUDY GROUPS**

| RISK FACTORS | CONTROL (n=25) | CASES (n=60) | UNPAIRED 't' TEST (P VALUE) |
|---|---|---|---|
| AGE( IN YEARS) | 47.88±13.98 | 59±9.32 | <0.0001 |
| MALE:FEMALE | 21:4 | 53:7 | |
| SMOKING | 5 | 28 | |
| ALCOHOL | 9 | 5 | |
| HYPERTENSION | 9 | 12 | |
| BMI (kg/m2) | 21.67±3.67 | 23.18±3.961 | 0.107 |
| WAIST CIRCUMFERENCE (in cms) | 81±8.69 | 82.71±8.40 | 0.848 |
| FBS (mg%) | 86.4±10.86 | 98.26 ±13.99 | *0.0003* |
| 2HR PGBS(mg%) | 124.6±18.46 | 135.73±18.53 | *0.014* |
| TOTAL CHOLESTROL(mg%) | 146.48±27.30 | 174±38.58 | *0.002* |
| TRIGLYCERIDE (mg%) | 125.44±39.4 | 126±40.14 | 0.915 |
| VLDL-C (mg%) | 26.1±9.6 | 34.64±9.54 | *0.003* |
| LDL-C (mg%) | 92.04±24.03 | 103±33.19 | 0.147 |
| HDL-C(mg%) | 43±7.08 | 42±8.18 | 0.507 |

**TABLE-2: COMPARISON OF MEAN CAROTID IMT IN STUDY GROUP**

| IMT (in mms) | Control (n=25) | Case (n=60) | Unpaired 't' test (P Value) |
|---|---|---|---|
| Carotid | 0.611±0.130 | 0.703±0.105 | 0.001 |

**TABLE-3: PREVALENCE OF IFG & IGT IN STUDY GROUPS**

| | CONTROL(n=25) | CASE(n=60) |
|---|---|---|
| IFG(mg%) | 0 | 9(15%) |
| IGT(mg%) | 0 | 13(22%) |
| IFG &IGT(mg%) | 0 | 3(5%) |

IFG was found in 9(15%) of case group.IGT was found in 13(22%)of case group &Both IFG & IGT were found in 3(5%) of case group. Glucose regulation was normal in control group.

**TABLE-4 : COMPARISON OF RISK FACTORS IN CASE GROUP WITH IMPAIRED GLUCOSE REGULATION**

| VARIABLES | IFG(n=9) | IGT(n=13) | IFG&IGT(n=3) | P VALUE |
|---|---|---|---|---|
| AGE(in yrs) | 58.11±10.12 | 59.45±9.03 | 60±12 | 0.937 |
| M:F | 9/0 | 12/1 | 2/1 | |
| SMOKING | 6 | 7 | 0 | |
| ALCOHOL | 2 | 0 | 0 | |
| HYPERTENSION | 1 | 5 | 2 | |
| BMI(kg/m2) | 24.54±3.63 | 23.26±4.45 | 23.15±3.01 | 0.751 |
| WC(in cm) | 82.41±8.4 | 84.36±7.86 | 85.66±6.02 | 0.936 |
| FBS( mg%) | 118.66±4.21 | 97.72±6.87 | 119.66±5.5 | <0.0001 |
| 2hr PGBS(mg%) | 133.44±8.01 | 162.45±9.41 | 157±12.12 | <0.0001 |
| TC(mg%) | 194.44±61.54 | 175.27±26.89 | 175±53.67 | 0.632 |
| TG(mg%) | 141.33±51.15 | 143.9±33.79 | 96±14 | 0.199 |
| LDL-C(mg%) | 109.44±54.67 | 99.81±28.7 | 116.33±41.62 | 0.790 |
| MEAN CAROTID IMT(mm) | 0.671±0.088 | 0.69±0.07 | 0.76±0.20 | 0.176 |

Waist circumference was highest in subjects with both IFG & IGT. Total cholesterol was highest in IFG group. Mean carotid IMT was highest in group having both IFG &IGT.

**TABLE-5:CORRELATION OF FBS WITH VARIABLES IN STUDY GROUPS**

| VARIABLES | CONTROL (n=25) | | CASE( n=60) | |
|---|---|---|---|---|
| | Correlation coefficient (r) | P value | Correlation coefficient (r) | P value |
| AGE (Yr) | 0.089 | 0.668 | 0.125 | 0.339 |
| WC(cm) | 0.176 | 0.398 | 0.098 | 0.454 |
| BMI(kg/m2) | 0.149 | 0.477 | 0.134 | 0.304 |
| S.TC (mg%) | -0.048 | 0.819 | 0.108 | 0.410 |
| S.TG (mg%) | 0.045 | 0.827 | 0.104 | 0.425 |
| LDL – C(mg%) | -0.146 | 0.483 | 0.032 | 0.805 |

FBS correlated positively with the variables like Age, WC, BMI & S.TG in both the control and case groups though it was not clinically.

**TABLE-6: CORRELATION 0F 2HR PGBS WITH VARIABLES IN STUDY GROUPS**

| VARIABLES | CONTROL (n=25) | | CASE (=60) | |
|---|---|---|---|---|
| | Correlation coefficient (r) | P value | Correlation coefficient (r) | P value |
| AGE (yr) | 0.257 | 0.214 | 0.062 | 0.635 |
| WC(cm) | 0.352 | 0.084 | 0.107 | 0.412 |
| BMI (kg/m2) | 0.356 | 0.080 | -0.021 | 0.870 |
| S.TC (mg%) | -0.041 | 0.845 | -0.063 | 0.631 |
| S.TG(mg%) | 0.012 | 0.952 | 0.253 | 0.05 |
| LDL-C( mg%) | -0.150 | 0.474 | 0.029 | 0.820 |

2hr PGBS level correlated positively with the variables like AGE, WC, S.TG in both control and case group. It was significant only in case of S.TG in the case group.

which 176 (50.28%) had impaired glucose regulation {IFG in 28 cases,IGT in148 cases and 75 cases had newly detected Diabetes}. CHINA HEART SURVEY of 773 acutely admitted coronary artery disease patients, found impaired glucose tolerance in 267 (34.5%) patients and Impaired fasting glucose in 35 (4.5%) patients. Various surveys in different parts of the world demonstrated an increase in cardiovascular risk and mortality rate among the population having abnormal glucose regulation & dislipidemia.[14,15,16,17]

According to table - 2, mean carotid IMT in study population was significantly higher in comparision to controls. This observation is in agreement with the study of David Faeh et al[13] & INSULIN RESISTANCE ATHEROSCLEROSIS STUDY (IRAS)[18]

In this study FBS & 2 hr PPBS showed positive correlation with the variables like age, waist circumference, BMI & Serum triglyceride level both in cases and controls. But only correlation of 2 hr PPBS with s. triglyceride level of cases were statistically significant.

## CONCLUSION

Abnormal glucose regulation is common in patients admitted to hospital with Coronary artery disease and is undiagnosed in the majority of these patients. Our data showed that IGT and to a lesser extent IFG were associated with impaired cardiovascular conditions. These findings provide further evidence for increased cardiovascular risk associated with Pre-diabetes. As Abnormal glucose regulation is a strong risk factor for cardiovascular events, earlier detection of it will allow clinicians to institute more rigorous control of patients with hyperglycaemia and therefore improve outcomes. In particular, early identification and treatment of individuals with Impaired glucose regulation will reduce the risks of progression to Abnormal glucose regulation and associated complications.

With the rising prevalence and mortality due to Coronary artery disease in the Indian population, it is vital that secondary preventive measures be modified and glucometabolic abnormalities beyond diabetes should be looked for in each Coronary artery disease patient. OGTT is effective and simple test to identify glucose abnormality and should be recommended as routine screening test for detecting latent glucose abnormalities in the Indian population.

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*Original Article*

# LIPID PROFILE IN SYSTEMIC LUPUS ERYTHEMATOSUS - A CASE CONTROL STUDY

**S. Dakua*, M.R. Behera**, J.K Panda***, P.K. Padhi******


## ABSTRACT

***Background:*** *Dyslipidaemia is an independent risk factor for ischaemic heart disease. Patients with systemic lupus erythematosus (SLE) have accelerated atherosclerosis; however, there are limited studies of the lipid profile in patients with SLE in India.* ***Objective:*** *To assess the abnormality of lipid profile in patients with SLE.* ***Methods:*** *This observational study was conducted in the department of General Medicine SCB Medical College from the period of September 2011 to September 2012. 101 patients with SLE and 100 controls were studied.* ***Results:*** *The patients with SLE were having atherogenic dyslipidaemia. SLE patients had high serum cholesterol (p=<0.000l), high serum triglyceride (p=<0.000l) and low HDL (p=<0.000l) as compared to control.* ***Conclusions:*** *We found that abnormal lipid profiles are very common in patients with SLE, though the patients are very young. There was significant increase in serum cholesterol, triglyceride and VLDL while decrease in HDL in SLE patients than controls. (p<0.05).* ***Keywords****: Systemic lupus erythematosus, dyslipdemia, premature atherosclerosis.*


## INTRODUCTION

The description of late stage mortality and morbidity in systemic lupus erythematosus (SLE) in the past decade has focussed attention on accelerated atherosclerosis in SLE. The exact mechanism of this accelerated atherosclerosis remains unclear. However, disease activity with its immunologic events, the presence of anticardiolipin antibodies and hyperlipidaemia contribute to development of atherosclerosis[1]. Traditional risk factors for coronary artery disease were very common in the Hopkins Lupus Cohort study, despite the fact that average age of the patients was only 38.3 years[2] Hyperlipidaemia in SLE may be causally related to or influence pathogenic process of lupus[3]. Hyperlipidaemia is one of the three leading risk factors for death in patients with SLE[4], but Hopkin's Lupus Cohort Study showed that preventive practices for coronary artery disease are focussed on control of hypertension and not against obesity, hypercholesterolemia, and smoking. Therefore, early diagnosis, treatment and prevention of dyslipidaemia are important aspects of treatment in patients with SLE.

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## AIMS AND OBJECTIVES

To assess and compare the lipid profile in patients of SLE and Controls.

## MATERIALS AND METHODS

All consecutive adult patients who fulfilled American College of Rheumatology Revised Classification Criteria for SLE (1997), and admitted to the P.G. Dept. of Medicine, SCB Medical College, Cuttack between Sept. 2011 to Sept. 2012 were included in the study. Normal age and sex matched individuals were enrolled as control.

Persons suffering from diabetes mellitus or hypertension, Persons having 1st degree relative suffering from diabetes mellitus or hypertension, Persons having family history of family hyperchrolesteroemia, and Persons suffering from infection were excluded from this study.

### Evaluation

Investigations to support diagnosis of SLE were performed by ANA (Hep-2), anti-ds-DNA antibody, C3 and C4. Associated biochemical, hematological tests were done and urine was evaluated. Fasting lipid profile was measured for both patients of SLE and Controls.

## OBSERVATION

A total of 101 patients with SLE and 100 age and sex matched controls were included in the present study. The age of the patients ranged from 15 to 47 years with a mean of 27.17 (± 8.4) years. Maximum number of patients belonged to age group of 16-40 years (93.08%). The age of control group ranged from 16 to 46 years with a mean of 27.64 (± 8.6) years. Females constituted 96% and 89% of case and control population respectively.

The mean cholesterol in SLE patient was 179.6±43.38 and in controls was 154.8±21.16 which was statistically significant (p=<0.0001). The mean triglyceride in SLE was 174.1±60.54 and in control was 132.2±25.54 which was statistically significant (p=<0.0001). The mean HDL in SLE was 40.82±7.27 which was lower compared to control (47.12±5.72) which was statistically significant (p=<0.0001). The mean LDL in SLE was 111.0±38.55 and in control was 81.61±23.88 which was statistically significant (<0.0001). The mean VLDL in SLE was 28.74±5.02 and in control was 26.12±4.65 which was statistically significant (p=0.0001) (Table-1).

Among SLE patients, the lipid values of patients on steroid were compared with those not on steroid. The mean cholesterol level in patients taking steroid was 183.9±40.59 and those not on steroid was 177±45.25 with p value 0.22. The mean triglyceride level in those taking steroid was 177.8±60.85 and those not on steroid was 172.8±60.0 with p value 0.79. The mean HDL level in those patients taking steroid was 41.03±7.13 and in patients not taking steroid was 40.70±7.42 with a p value 0.62. The mean LDL level in those steroid was 113.8±37.69 and in patients not taking steroid was 107.7±15.59 with p value 0.29. The mean VLDL level among SLE patients taking steroid was 29.11±5.2 and patients not taking steroid was 28.52±5.0 with p value 0.57 (Table-2).

## DISCUSSION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that predominately affects premenopausal females, with a peak age of onset between 20-30 years. The condition can manifest with a broad spectrum clinical signs and symptoms, ranging from relatively minor symptoms such as arthralgia to life-threatening organ involvement. SLE confers a massive CVD risk, which is far greater than described in other autoimmune diseases. The dyslipidaemia seen in conjunction with SLE is more typical of that described in the general population in relation to CVD, with elevations in TG, LDL and TC and a parallel fall in HDL levels. Mean fasting serum cholesterol, triglyceride and LDL levels were significantly higher in SLE patients when compared to control group (p<0.000l) but HDL was significantly low than controls (p<0.000l). The mean serum VLDL was also significantly higher in SLE patients (p=0.0002) (Table-I). This pattern of dyslipidemia was also observed by Borba F et al(2006)[5], S Kakati et al(2003)[6]. But in the study of Sabia JM et al(2008)[7] triglyceride was slightly increased in the patients group and total cholesterol and LDL-C levels were significantly reduced patients compared to controls (P <0.001). The reason attributed to was intake of statins by SLE patients. SLE is a classic model of chronic immune complex-mediated inflammatory disease. The possible role of inflammation in modulating LPL enzyme is emphasized by the recent description of a significant down-regulation of LPL activity induced by TNα, IL-l and IFN-gamma (Semb et al. 1987[8]). It is well known that the acute phase response promotes an altered hepatic synthesis of a wide array of proteins involved in lipoprotein metabolism, in coagulation and in the complement system (Gabay et al. 1999[9]). Therefore, it seems reasonable to accept that inflammatory conditions of the disease itself would induce specific alterations in the lipid profile. An enhanced production of these cytokines is characteristic of SLE, particularly during active disease (Spronk et al. 1992[10]), and it supports their role in lupus dyslipoproteinemia. It was recently described that levels of circulating TNF are raised in SLE and it correlates with active disease and triglyceride levels (Svenungsson et al. 2003[11,12]). The recent description of high frequency of antibodies to lipoprotein lipase (anti-LPL) in SLE is another explanation for higher lipid levels since these autoantibodies modulate LPL activity in SLE (Reichlin et al. 2002[13]; de Carvalho et al. 2004[14]) and is possibly a cause for autoimmune hyperlipidemia (Beaumont et al. 15). Borba F et al (2006)[5] al coined a term ([lupus pattern" of dyslipoproteinemia for elevated levels of very low density lipoprotein cholesterol (VLDL) and triglycerides (TG), and lower high-density lipoprotein cholesterol (HDL) levels. Table-2 highlights lipid profile in patients on steroid. It is evident that though the lipid profile was high among SLE patients taking steroid it was not statistically significant when compared to naive patients. This observation has also been made by Chung CP et al (2007)[16], who found no significant alteration in lipid profile with use of steroid. Steroids form the main stay

**TABLE-1**

**COMPARISION OF LIPID PROFILE BETWEEN SLE PATIENTS AND CONTROL**

| **Lipid Profile** (mg/dl) | **SLE** Mean±SD (Ranges) | **Control** Mean±SD (Ranges) | **P Value** |
|---|---|---|---|
| Cholesterol | 179.6±43.48 (97-296) | 154.8±21.16(121-206) | <0.0001 |
| Triglyceride | 174.1±60.54(89-310) | 132.2±25.54 (87-198) | <0.0001 |
| HDL | 40.82±7.27(25-62) | 47.12±5.72(38-59) | <0.0001 |
| LDL | 110.0±38.55(40-213) | 81.61-23.88 (34-137) | <0.0001 |
| VLDL | 28.74±5.02(20-42) | 26.07±4.65 (15-40) | 0.0001 |

**TABLE-2**

**RELATIONSHIP BETWEEN LIPID PROFILE AND USE OF STEROID IN SLE**

| **Lipid Profile** (mg/dl) | **USE OF STEROID** | | **P Value** |
|---|---|---|---|
| | Not on Steroid therapy Mean±SD (Ranges) | On Steroid Therapy Mean±SD (Ranges) | |
| Cholesterol | 177±45.25 (97-296) | 183.9±40.59(110-282) | 0.22 |
| Triglyceride | 172.8±60.0 (89-310) | 177.8±60.85(97-299) | 0.79 |
| HDL | 40.70±7.42 (28-62) | 41.03±7.13 (25-56) | 0.62 |
| LDL | 107.7±19.59 (43-213) | 113.8±37.69 (40-200) | 0.29 |
| VLDL | 28.52±5.0 (20-42) | 29.11±5.2 (20-40) | 0.57 |

of treatment in SLE and it alters lipid values significantly. Chronic corticosteroids use in SLE is associated with increased total plasma cholesterol and its fractions (LDL and HDL) levels, and also TG (Bruce et al. 1999[17]), which is presumed to be mediated by increased plasma insulin levels, increased lipid production by the liver and impaired lipid catabolism (Sholter et al. 2000[18]). This effect could be identified after a short period of 1-2 months of this therapy (llowite et al. 1988[19]) and is also dose related since daily low prednisone dose does not significantly alter the lipid profile (Petri et al. 1994[20]). In fact, Petri et al showed that for each 10 mg increase in prednisone, there is a 7.5 mg/dl corresponding increase in serum cholesterol (Petri et al. 1994[20]). Our finding of lack of significant difference in lipid profile between patients on steroid therapy visa-vis naive patients could be explained by the fact that these patients were on hydroxychloroquine therapy (6.5 mg/kg/day) which has been observed to lower lipid levels possibly by negating insulin resistance effect induced by steroid.

## CONCLUSION

There is paucity of published data about SLE from India. We found that abnormal lipid profiles are very common in patients with SLE, though the patients are very young. There was significant increase in serum cholesterol, triglyceride and VLDL while decrease in HDL in SLE patients than the controls. SLE produces autoantibodies which form complexes with either the enzymes like lipoprotein lipase or with the apolipoprotein and slows down their catabolism, which may produce varieties of dyslipidaemia. Regular use of statins could be an important adjunct therapy and this needs to be objectively proved by randomised control study.

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## BEST PAPERS OF 2013

The following original article and case report are selected as best papers of 2013 by the following refrees and are to be awarded on 9th November, 33rd APICON Odisha Branch, 2013 at Burla.

Refrees : Prof. R.N. Sahoo (Cuttack), Prof. M. Satpathy (Cuttack), Prof. Sarat Mohanty (Berhampur)

**Original Article**

*Title :* Aetiology of acute viral hepatitis (AVH) with particular emphasis on magnitude of hepatitis a virus (HAV) infection and its clinical course in adults.

Authors : U.C. Patra, M. Nayak, C.R. Sarangee, A Devi

**Case Report :**

*Title :* Coloboma-microopthalmous syndrome associated with sensorineural hearing loss, hematuria, cleft lip and cleft palate complicated with severe vivax malaria – a case report.

Authors : M.K. Mohapatra, P.C.Karua, P.K.Bariha, M.R.Patel, A.K.Behera

*Original Article*

# STUDY OF CARDIAC DYSFUNCTION IN PATIENTS OF CHRONIC KIDNEY DISEASE

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**ABSTRACT**

***Aim :*** *The present study was undertaken to assess the prevalence of systolic and diastolic dysfunction, to determine the prevalence of left ventricular hypertrophy (LVH) from left ventricular mass index (LVMI), to correlate the degree of cardiac dysfunction with severity of chronic kidney disease (CKD) by echocardiography in patients of CKD on conservative management.* ***Material & method:*** *75 CKD patients were included in the study and were divided into three groups - Group A: Age and sex matched healthy controls (n=20). Group B: Patients with mild to moderate CKD (n=45) (S. Creatinine =1.5-6.0 mg/dl). Group C: Patients with advanced CKD (n=30) (S. Creatinine > 6.0 mg/dl).* ***Results:*** *The prevalence of left ventricular hypertrophy (LVH) along with systolic dysfunction in severe CKD group was 10.0% (p<0.2653), higher than mild/moderate CKD group which was 2.2% (p<1.0). The prevalence of LVH along with diastolic dysfunction in severe CKD group was 76.7% (p<0.0001), which was significantly higher than mild/moderate CKD group which was 44.4% (p<0.0001). In mild to moderate CKD group 51.1% (p<0.0001) patients were found to have LVH, while in severe CKD group 76.7% (p<0.0001) of patients had LVH. In mild to moderate CKD group 48.9% patients had concentric LVH, while in severe CKD group 73.3% had concentric LV hypertrophy. In diabetic CKD patients LV dysfunction was predominantly diastolic irrespective of the degree of LV hypertrophy.* ***Conclusion:*** *Systolic dysfunction was well preserved in majority cases of CKD as found from the Ejection Fraction and Fractional Shortening parameter whereas diastolic dysfunction was more commonly found in CKD patients.* ***Key words:*** *chronic kidney disease, left ventricular hypertrophy, left ventricular mass index systolic dysfunction, diastolic dysfunction.*

## INTRODUCTION

Chronic kidney disease (CKD) is a state of irreversible impairment of renal function. It is a worldwide public health problem, with adverse outcomes of kidney failure, cardiovascular disease and premature death.[1] Cardiovascular disease is the leading cause of morbidity and mortality in patients at every stage of chronic kidney disease. Between 30-45% of patients reaching ESRD already have advanced cardiovascular complications.[2]

It is now well recognised that chronic kidney disease (CKD), when present in patients with HF, independently predicts poor outcomes.[3,4] JNC-7 report has recognised CKD as an independent cardiovascular risk state.[3, 5] Cardiac disease is the major cause of death in dialysis population accounting for 40% of deaths in international registries.[6, 7]

In the cardiovascular system, left ventricular hypertrophy (LVH) is the most frequent finding but the prevalence of left ventricular systolic and diastolic dysfunction is less clear.[6,8] Cardiac disease frequently predates the start of dialysis and LVH is common in moderate to severe chronic renal failure. Echocardiography should be performed early in the course of CKD and may be valuable in the monitoring

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of therapy of these patients.[6, 9] Cardiac disease is frequently noted in individuals around the time of commencement of dialysis, but there is little information on the prevalence and natural history of cardiac function in the patients with milder degrees of chronic renal failure. Furthermore, early detection and management of cardiac dysfunction will improve outcome in patients of CKD.

## MATERIALS & METHODS

The study was undertaken at S.C.B. Medical College, Cuttack, Odisha during the period from September 2011 to September 2012. All patients of Chronic Kidney Disease admitted to Postgraduate Department of Medicine and satisfying the following criteria were included in the study. Criteria for diagnosis of Chronic Kidney Disease was as given by- National kidney foundation: K/DOQI clinical practice guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. [1]

CKD is defined as the presence, for at least 3 months, of evidence of kidney damage with an abnormal GFR or alternatively, by a GFR < 60 ml/min /1.73m$^2$ BSA.[1]

Kidney damage is evidenced by- proteinuria >300mg/day[9] or pathological abnormality found in histopathological study [9] or renal imaging study (USG) showing bilateral contracted kidneys < 9cm with thinned parenchyma and reduced corticomedullary differentiation.

Patients with CKD with the following diseases were excluded from the study - coronary artery disease, valvular heart disease, congenital heart disease, cardiomyopathies, patients on haemodialysis, patients on treatment with erythropoietin, h/o of alcohol intake and smoking.

75 CKD patients were included in the study. The study population was divided into three groups - Group A: Age and sex matched healthy controls (n=20), Group B: Patients with mild to moderate CKD (n=45) (S. Creatinine =1.5-6.0 mg/dl), Group C: Patients with advanced CKD (n=30) (S. Creatinine > 6.0 mg/dl).

## RESULTS

In group-B, maximum 22 cases (48.9%) were in the age group of 56-75 years and in group-C, maximum 14 cases (46.7%) were in the age group of 36-55 years. In group-A, mean age was 43.9 $\pm$ 17.4 years. In group-B, mean age was 57.7 $\pm$ 14.6 years. In group-C, mean age was 53.5 + 13.2 years.

In group-B, out of 45 no. of patients Male were 28 cases (62.2%) and female were 17 cases (37.8%) with a Male:Female ratio of 1.6:1. In group-C, out of 30 patients, male were 23 cases (76.7%) and female were 7 cases (23.3%) with a Male:Female ratio of 3.3:1. Out of total 75 cases Male were 51 cases (68%) and Female were 24 cases (32%) with the Male:Female ratio of 2.1:1, showing male preponderance. Highest incidence of male CKD patients was in the age group of 56-75 years as compared to female CKD patients in the age group of 36-55 years.In group-B, 15 cases (33%) were found to be diabetic. In group-C, 7 cases (23.3%) were found to be diabetic. Overall in the study group 22 cases (29.3%) were diabetic and 53 cases (61.7%) were non-diabetic.

Both systolic and diastolic blood pressures were elevated in Group-B and Group-C patients with degree of elevation maximum in Group-C. Blood pressure was within normal range in the control population.

BMI and Hb values were significantly lower in Group-B and Group-C patients compared to normal controls, being lowest in Group-C. Blood urea and serum creatinine values showed increasing levels as severity of CKD patients increased. Patients in Group-C showed hyperkalemia. Lipid profile abnormalities were noted in all CKD patients with maximum abnormality found in patients having severe CKD (Group-C).

Ejection Fraction (EF) was significantly lower in CKD patients (p value <0.05) compared to controls, but was within normal range.

Mean left ventricular mass index was increased in CKD patients compared to controls which was statistically significant.

Among the CKD patients in Group-B 23 cases (51.1%) had LVH, out of which 22 cases (48.9%) had concentric LVH and 1 case had eccentric LVH. In Group-C CKD cases 23 cases (76.7%) had LVH, out of which 22 cases (73.3%) had concentric LVH and 1 case had eccentric LVH. (p value A:B = < 0.0001, A:C = < 0.0001). Among CKD cases of Group-B 16 males (57.1%) had LVH and 7 females (41.2%) had LVH whereas in Group-C 17 males (73.9%) had LVH and 6 females (85.7%) had LVH. (Fig.1)

Ejection Fraction was lower in all CKD patients which was statistically significant (A vs.B= <0.05, A vs. C= <0.05, B vs. C= >0.05) as compared to controls, but was within normal range. No difference was observed among cases and controls in Fractional Shortening level.

In the CKD patients, 1 case (2.2%) (p<1.0) had systolic dysfunction whereas 20 cases (44.44%) had diastolic dysfunction in Group-B and in Group-C 3 case (10.0%) (p<0.2653) had systolic dysfunction whereas 23 cases (76.7%) had diastolic dysfunction. Diastolic dysfunction was the predominant abnormality noted in CKD patients.

Diastolic dysfunction was noted in 33 (73.33%) cases of Group-B, out of which 22 (44.44%) (p<0.0001) cases had concentric LVH. In Group-C diastolic dysfunction was found in 26 (86.67%) cases, out of which 23 (76.67%) (p<0.0001) cases had concentric LVH.

In Group-B 38 (84.4%) cases had HTN and 23 (51.1%) (p<0.0001) cases had LVH. In Group-C 29 (96.7%) cases had HTN and 23 (76.7%) (p<0.0001) cases had LVH.

Both systolic and diastolic blood pressures were elevated in CKD cases. There was no significant difference between diabetic and nondiabetic cases. In Group-B out of 30 nondiabetic CKD cases, 25 (83.3%) cases had HTN and out of 15, diabetic CKD cases 13(86.7%) cases had HTN. In Group-C out of 23 nondiabetic CKD cases 22 (95.6%) cases had HTN and out of 7, diabetic CKD cases all 7(100.0%) cases had HTN. Among cases with diastolic dysfunction in Group-B, 20 (66.7%) were nondiabetic and 13 (86.7%) were diabetic whereas in Group-C, 26 (86.7%) were nondiabetic and 7 (100.0%) were diabetic.

## DISCUSSION

All the cases of CKD were in a wide age group range of 16 to 80 years. As per the 2nd annual report, CKD REGISTRY OF INDIA, INDIAN SOCIETY OF NEPHROLOGY, 2007 overall mean age for a CKD patient is 48.3 + 16.6 years. [(10)] In our study mean age of all CKD cases was 57.7±14.6yrs in group B and 53.5 ± 13.2 years in group C. In a similar study by P Dangri the mean age of the CKD cases was 37.9 ± 8.2 years in group B and 36.9 ± 9.7 years in group C. [(11)]

In total 51 cases (68%) were males and 24 cases (32%) were females. Males predominated with a M:F ratio of 2.1:1. As per the 2nd annual report, CKD REGISTRY OF INDIA, INDIAN SOCIETY OF NEPHROLOGY, 2007 among CKD patients 68.9% were males & 31.1% were females. [(10)] Males preponderance was probably due to higher incidence of Diabetes Mellitus and Hypertension in them. [(10)] The study done by Dangri et al in 2003 also showed Male (17) to Female (13) ratio of 1.3:1.The mean age in male CKD cases was 59.0 ± 16.9 yrs and in female CKD cases was 55.5 ± 9.7 yrs in group-B. The mean age in male CKD cases was 54.8 ± 11.1 yrs and in female CKD cases was 41.4 ± 8.4 yrs in group-C.

As per the 2nd annual report, CKD REGISTRY OF INDIA, INDIAN SOCIETY OF NEPHROLOGY, 2007 30.3% CKD patients were due to diabetic nephropathy. [(10)] Overall in the study group 22 cases (29.3%) had diabetes mellitus. Hence our finding were consistent with that of CKD Registry of INDIA.

Premature cardiovascular disease is a significant cause of morbidity and mortality among patients with CKD. Systolic functions are usually well preserved in hypertensive and even diabetic patients with uraemia. [(6)] In the present study, the mean ejection fraction in patients with mild/moderate CKD and several

**Table-1 BIOCHEMICAL PARAMETERS IN THREE GROUPS**

| | Group-A (n=20) | Group-B (n=45) | Group-C (n=30) |
|---|---|---|---|
| BMI | 24.3 ± 3.4 | 20.1 ± 3.2 | 19.8 ± 3.5 |
| HAEMOGLOBIN | 12.9 ± 0.6 | 9.5 ± 1.7 | 7.4 ± 2.5 |
| B. UREA | 28.4 ± 10.5 | 72.3 ± 31.1 | 181.3 ± 75.1 |
| S. CREATININE | 0.7 ± 0.1 | 2.9 ± 1.1 | 9.6 ± 3.3 |
| S. SODIUM | 138.1 ± 6.0 | 131.1 ± 11.8 | 129.8 ± 9.8 |
| S. POTASSIUM | 4.1 ± 0.5 | 4.0 ± 1.2 | 5.1 ± 1.2 |
| T. CHOLESTEROL | 152.4 ± 19.0 | 180.6 ± 41.9 | 225.0 ± 29.1 |
| TRIGLYCERIDE | 84.1 ± 24.5 | 169.9 ± 51.1 | 199.3 ± 32.3 |
| HDL | 49.3 ± 7.8 | 42.5 ± 7.9 | 41.5 ± 6.3 |
| LDL | 84.1 ± 26.9 | 106.8 ± 29.9 | 135.7 ± 30.8 |
| VLDL | 25.1 ± 6.7 | 22.0 ± 9.9 | 34.3 ± 12.7 |

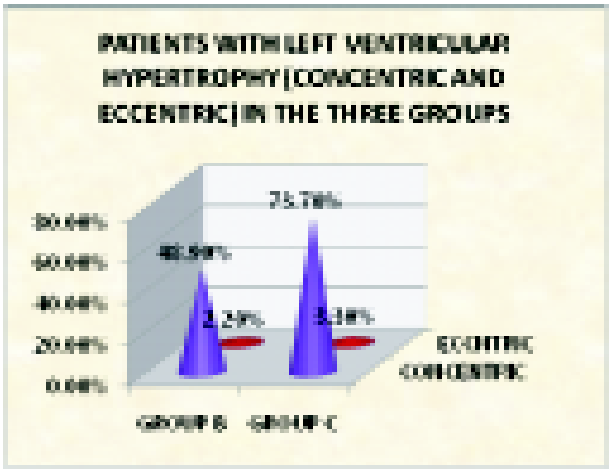
**Table-2 ECHOCARDIOGRAPHIC PARAMETERS IN THREE GROUPS**

**Table-3 MEAN LEFT VENTRICULAR MASS INDEX AND ITS SEX-WISE DISTRIBUTION IN THREE GROUPS**

**Table-4 LEFT VENTRICULAR SYSTOLIC FUNCTIONS INDICES (EJECTION FRACTION AND FRACTIONAL SHORTENING) IN THE THREE GROUPS.**

| | Group-A (n=20) | Group-B (n=45) | Group-C (n=30) |
|---|---|---|---|
| **EF** ( MEAN±SD) | 67.0 ± 6.1 | 62.2 ± 7.2 | 61.6 ± 8.3 |
| EF<50% | nil | 1(2.2%) | 3(10.0%) |
| **FS** ( MEAN+SD) | 33.9 ± 3.4 | 32.7 ± 5.3 | 33.2 ± 6.2 |
| FS<25% | nil | 1(2.2%) | 3(10.0%) |

**Fig.1**




CKD groups showed a downward trend but neither of the CKD groups had mean LVEF < 50%. These findings are similar to the findings of Raj et al (1997).[12] These previous studies, Dangri et al (2003), [11] Ayus et al (1981),[13] suggest that LVEF is well maintained in patients with CKD which was also observed in the present study. Among patients in the mild/moderate CKD group, only 1 (2.2%) patient had LVEF < 50%, while 3 (10%) patients in severe CKD group had LVEF < 50% which was not significantly different from controls, as well as mild/moderate CKD population.

In our study, there was no significant difference

in the mean fractional shortening among the three groups, however, 1 case (2.2%) in mild/moderate CKD group and 3 cases (10.0%) patients in severe CKD group had fractional shortening ≤ 25%. In our present study we found mean FS in the controls 33.9 ± 3.4%, in group B CKD patients 32.7 ± 5.3%, and in group C CKD patients 33.2 ± 6.2. Dangri et al,[11] Raj et al ,[12] Harnett et al (1995), [14] Colan et al (1987) [15] studies also show that fractional shortening as a function of left ventricular systolic function is well maintained in CKD patients.

In the present study, the number of patients with LVH and systolic dysfunction (ejection fraction < 50%) was 1 (2.2%) in mild/moderate CKD group and 3 (10%) in severe CKD group. Thus, in the present study, systolic function was well preserved in patients with mild/moderate and severe CKD which is in concordance with the previous studies done by P Dangri et al (2003), Greaves et al (1994), Harnett et al (1995), Colan et al (1987), and Raj et al (1997).

Left ventricular diastolic dysfunction is an important cause of cardiac morbidity in ESRD patients. Diastolic dysfunction appears to be the initial left ventricular dysfunction and might even precede left ventricular hypertrophy. London et al (1993) reported a significant reduction in E/A ratio in haemodialysis patients as compared to controls. [16] The prevalence of diastolic dysfunction in the present study was found to be 73.33% (33 patients) in mild/moderate CKD group and 86.67% (26 patients) in severe CKD group.

In the present study the number of patients having both LVH and as well diastolic dysfunction was 20 (44.44%) in mild/moderate group, whereas it was 23 (76.67%) in severe CKD group. Thus, in comparison to systolic function, diastolic function was deranged in more number of patients suggesting that diastolic dysfunction is first to appear in patients with chronic renal failure. Among the various factors that contribute to diastolic and systolic dysfunction, uncontrolled hypertension and anaemia, which are usually present in CKD, play a significant role. In the present study, 89.3% had hypertension and anaemia was present in all the patients, suggesting that these factors might also have contributed towards development of diastolic and systolic dysfunction.

LVH is the single strongest independent predictor of adverse cardiovascular events. [17] In our study, we found that LVMI showed a progressive rise with increase in severity of renal failure. This finding is consistent with the study done by Greaves et al. [9] In the present study, we found LVMI 88.0 + 22.3 in controls, 117.5 + 38.8 in group B CKD patients and 140.0 + 38.1 in group C CKD patients, which was significantly higher. In the present study, we found that 23 (51.1%) patients in mild/moderate CKD group and 23 (76.7%) patients in severe CKD group had LVH. These results conform to prevalence of LVH in patients with ESRD from 40% to 80% in various studies. Raj et al [12] had also demonstrated that the prevalence of LVH increases with progressive decline in renal function. In the present study concentric LVH was found in 48.9% cases with mild/moderate CKD and 73.3% in severe CKD group, while eccentric hypertrophy was seen in only 2.2% of patients in mild/ moderate CKD group and 3.3% in severe CKD group, suggesting that concentric LVH is far more common than eccentric LVH in CKD population (Fig.I). A study by Huting et al had suggested eccentric hypertrophy to be a predominant form of LVH in CKD patients. [18] A study by London et al suggested that LV hypertrophy in ESRD combines features of concentric as well as eccentric hypertrophy. [19]

In the present study, in mild/moderate CKD group, 57.1% males had LVH and in severe CKD group 73.9% of males had LVH. On the other hand, 41.2% females in mild/ moderate CKD group and 85.7% females in severe CKD group had LVH, suggesting that prevalence of LV hypertrophy was more in females. In the study by P Dangri, in mild/moderate CKD group, 23% males had LVH and in severe CKD group 94% of males had LVH. On the other hand, 61% females in mild/ moderate CKD group and all females (100%) in severe CKD group had LVH. [11] Deveroux et al had found that when sex specific

criteria are used to find the prevalence of LVH in hypertensive male and female populations, a higher proportion of female patients exhibited LVH.[20] In the present study, higher prevalence of LVH in females as compared to males especially in mild/moderate CKD group may be because of sex specific criteria taken for LVH. High prevalence of anaemia and hypertension in patients with CKD may also partly account for increased prevalence of LVH in patients with CKD.

There was no statistically significant difference between the various echocardiographic parameters among diabetic and nondiabetic CKD cases. In diabetic CKD patients LV dysfunction was predominantly diastolic irrespective of the degree of LV hypertrophy.

## CONCLUSION

In conclusion, systolic dysfunction was well preserved in majority cases of CKD as found from the Ejection Fraction and Fractional Shortening parameter whereas diastolic dysfunction was more commonly found in CKD patients. In diabetic CKD patients LV dysfunction was predominantly diastolic irrespective of the degree of LV hypertrophy. Echocardiography should be performed early during course of CKD to detect LV dysfunction and take necessary measures to prevent or delay further progression to reduce cardiovascular morbidity and mortality. Anemia and hypertension, being major contributors of LVH, should also be treated adequately to prevent cardiovascular events.

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*Original Article*

# TO EVALUATE THE LEVEL OF PLASMA CHOLINESTERASE IN ORGANOPHOSPHOROUS POISONING

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## ABSTRACT

***Objective:*** *To compare the outcome of continuous and intermittent infusion of cholinesterase reactivator and to evaluate the prognostic value of plasma cholinsterase level in organophosphorous poisoning.* ***Method:*** *This observational study was carried out by a pre designed protocol. All the diagnosed case of organophosphorous poisoning above 15 yrs of age who have not previously received cholinesterase reactivator were studied during the period November 2010 to October 2012 in the indoor of medicine department of VSS MCH Burla, Odisha. Out of 45 patients every 3rd case was given continuous infusion of pralidoxime . & other were given intermittent infusion upto 72 hr. Cholinesterase estimation was done at the outset at 24hr, at 48 hr, at 72hrs. After 72hrs, according to the clinical profile & the plasma cholinesterase level dose of pralidoxime (PAM) & further duration of treatment were determined.* ***Result:*** *Death rate among continuous infusion group was 6.6% and among intermittent infusion group was 16.6%. The rise in mean cholinesterse level after 72hr of admission was. 5067 U/L in continuous infusion group & 3303 U/L among intermittent infusion group. Complication rate were almost similar in both the group. The mean cholinesterase level at the time of initial presentation was 609.5 U/L among death group against 1356.12 U/L among survival group.* ***Conclusion:*** *Although the complication rate among both the continuous & intermittent infusion group were almost similar, the final outcome in the form of death was significantly lower and the mean choliesterase rise was significantly higher among the continuous infusion group. Mean cholinesterase level at the time of initial presentation was significantly lower in death group.* ***Key Word:*** *Organophosphorous poisoning, plasma cholinesterase, pralidoxime, continuous infusion, intermittent infusion.*


## INTRODUCTION

Organophosphorous(OP) compounds are commonly used as agricultural insecticides. Acute organophosphorous poisoning is a significant global health problem, with hundreds of death each year of which most such deaths are in developing world.[1,2,3]

Organophosphorous compounds inhibit acetylcholinesterase and butyrylcholinesterase[4,5] enzymes resulting in over stimulation at cholinergic synapses. Management of severe poisoning is difficult and is complicated due to the paucity of clinical trial evidence to guide treatment, with no clear evidence of benefit from any therapy other than oxygen, atropine, and diazepam.[6]

In treatment of OP poisoning atropine remains the mainstay of therapy worldwide,. Atropine is a competitive antagonist of acetylcholine at the muscarinic post synaptic membrane and in the CNS. It will block the muscarinic manifestations of OP poisoning.

Oximes which help to regenerate acetylcholinestrase at muscarinic, nicotinic and CNS sites are widely used.[7,8,9,10] The beneficial effects of Oximes has been much debated due to absence of adequate studies and results.[11] Intermittent bolus dose

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of oxime is the usual recommendation have variable outcome. Continuous infusion of oxime has also been tried in severe cases. Both intermittent & continuous infusion of oximes have variable outcomes. People require oxime infusion ranging from 1-2 week. The variable pattern of administration of cholinesterase reactivator is based on clinical judgement. There is no quantitative guideline for this.

So to decide whether the assessment of plasma cholinesterase at the outset and at different times during treatment will help to recommend continuous or intermittent infusion, and the duration of treatment. It will also assess the exact dose required in an individual case and it may help in determining the outcome of these cases.

## MATERIAL AND METHODS

An observational study of 45 patients of organophosphorous poisoning admitted to the Department of Medicine, V.S.S. Medical college, Burla was carried out between November 2010 to October 2012 . All patients above 15 yrs of age of both sexes showing clear evidence of consumption of organophosphorous compounds were included. Patients who received oxime before blood was drawn for study were excluded. All the patients were given a 2gm loading dose of pralidoxime over 30 min. Then the patients were divided into two groups. Group A (continuous): Every 3rd patient were given continuous infusion of pralidoxime 6gm over 24 hrs upto 72hrs. Group B(intermittent): Rest of the patients were given intermittent infusion of pralidoxime 2gm 8 hrly upto 72hrs. Plasma cholinesterase estimation was done at the outset, at 24 hr, at 48hr, and at 72hrs besides other routine investigation.

After 72hrs, according to the clinical profile and plasma cholinesterase level, further dose and duration of pralidoxime were determined. At the end of the study both the groups were compared in relation to rise in cholinesterase level, hospital stay, development of complications and mortality using standard statistical methods.

## RESULTS

Out of 45 patients 28 (62.2%) were males and 17 (37.8%) were female. 44.5% were within the age group of 21-30 yrs followed by 35.5% in between 31-40 yrs age groups and 17.8 % between 16-20 yrs of age. Chlorpyriphos was the commonest organophosphorous (OP) compound responsible for poisoning i.e 40% followed by chlorpyriphos+ cypermethrine (26.7%), phorate (17.8%) malathion, dimethoate, methyl parathione (Table 1).

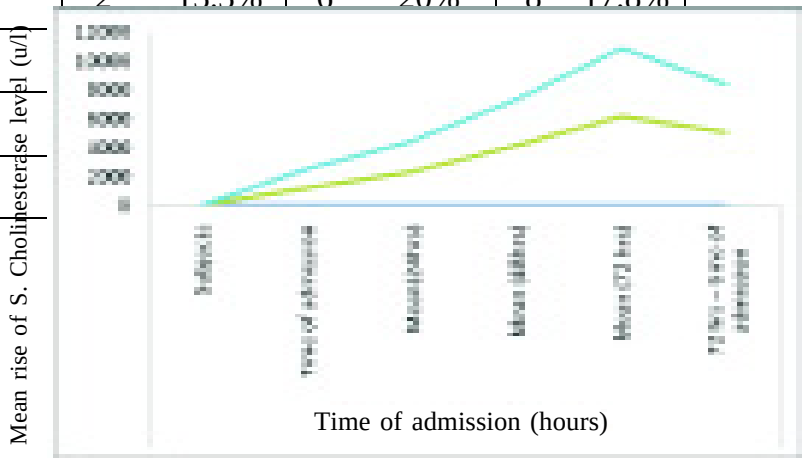
Based on symptoms salivation was the most prominent symptoms i.e. 51.1 % followed by tachypnoea that was 48.9%, vomiting in 35.6% cases, altered sensorium in 8.9% , pain abdomen in 6.7 % and diarrohea in 6.7%. Among the signs constricted pupil was the major finding (55.6%) followed by moist mouth (53.3%), tachycardia (44.4%) and chest crepitation (37.8%). During hospital stay, out of 45 patients 8(17.8%) patients developed urinary tract infection (UTI), 6 (13.3%) patients developed bed sores, 5 (11.1 0/0) patients developed aspiration pneumonia, 3 (6.7%) patients developed intermediate syndrome and 1(2.2%) patient developed acute respiratory distress syndrome (Table 2). Mean cholinesterase (CHE) values at the time of admission were almost similar in both group A and group B. The baseline CHE value for both group A and group B were nearly same. It was 1203 u/l in group A and 1283 u/l in group B. As the days progressed the CHE values also gradually increased but the rate of rise in CHE values was much more faster in group A who received continuous infusion of pralidoxime (Figure 1). In comparison between the CHE values between 72hr and at the time of admission, in group A it was 1203 u/l at the time of admission which increased up to 6203 u/l at 72 hrs but in group B it increased from 1283 u/l to 4280 u/l from day of admission to 72 hrs. The p value for CHE rise from the time of admission to 72 hrs was 0.02. Mean level of the serum cholinesterase at the time of admission in patients who died was 609 u/l and in patients who survived was 1356 u/l which is very much significant with a P value of 0.04. Patients who received continuous infusion of

**Table - I**
**Distribution of study subjects by types of organophosphorous compounds consumed**

| OP compound | Group A( 15) | | Group B( 30) | | Total ( 45) | |
|---|---|---|---|---|---|---|
| Chlorpyriphos ( CP) | 6 | 40% | 12 | 40% | 18 | 40% |
| Chlorpyriphos + cypermethrin (CP + CM) | 4 | 26.6% | 8 | 26.70/0 | 12 | 26.7% |
| Phorate ( PH) | 2 | 13.3% | 6 | 20% | 8 | 17.8% |
| Dimethoate (DM) | | | | | | |
| Malathione(MA) | | | | | | |
| Methyl parathion (MP) | | | | | | |

**Table - II**
**Complication during hospital stay**

| Complication | Group A (15) | Group B( 30) | Total (45) |
|---|---|---|---|
| Intermediate syndrome | 1 (6.7%) | 2 (6.7%) | 3 (6.70/0) |
| Aspiration pneumonia | 2 (13.30/0) | 3 (100/0) | 5 (11.1%) |
| Bed sore | 2 (13.3%) | 4(13.3%) | 6(13.30/0) |
| UTI | 3( 20%) | 5(16.7%) | 8( 17.8%) |
| ARDS | 0 | 1(3.3%) | 1 (2.2%) |
| ArrhYthmia | 0 | 0 | 0 |
| ARF | 0 | 0 | 0 |




**(FIGURE – 1)**

pralidoxime had lower death rate i.e.6.7% as compared to 16.7% death rate in patients who received intermittent infusion ( 2.2%).

## DISCUSSION

Out of 45 cases 62.2% cases were males and 37.80/0 were female which was in contrast to previous study by Das S.N. et al in Odisha and Balani et al that reported female preponderance. 44.5% were within age group 21-30 yrs followed by 35.5% in between 31-40 yrs age groups. The young age group presentation is probably due to the fact that they can't handle stressful situation and take drastic steps like ending life. The suicide in young is due to failure in studies, marriage, jobs. Chlorpyriphos was the commonest organophosphorous(OP) compound responsible for poisoning i.e 40% followed by chlorpyriphos+ cypermethrine (26.7%). Sailesh et al in 1994, Samuel Jhonson in 1995, Shiv Kumar in 2006, Alimar Vikram in 2005 from India have reported methyl parathion and monQcrotophos as the commonest OP poisoining. Chlorpyriphos is widely used in agricultural field in Odisha,it is cheap and easily available in the household and commonly marketed in the name of Agarophos. In various parts of the world the type of OP compound poisoning depend upon the availability of the compound in the locality. Most of the poisoining cases were suicidal in nature. As it is a cheaper agent and easily available it is widely used as a suicidal agent. Salivation was the most prominent symptoms i.e. 51.1 % followed by tachypnoea that was 48.9%, Such observations were more or less universal in most series of Namba et al 1984, Agarwal S.B. 1993, Sungur et al 2001. Among the signs constricted pupil was the major finding (55.60/0) followed by moist mouth (53.3%), tachycardia (44.4%). The signs are predominantly of cholinergic crisis like Wadia et al. Though bradycardia was expected due to cholinergic effect, it was not found. Rather tachycardia was seen due to previous atropinisation at peripheral hospitals. There was significant rise of plasma CRE level among continuous infusion group as compared to intermittent infusion group with a p value of 0.02. Individual plasma cholinesterase level at the time of admission of the patients who died were 300 u/l, 480 u/l, 587 u/l, 600 u/l, 790 u/l, 900 u/l. So the patients presenting with a cholinesterase level of less than 900 u/l should be given enough attention.

## CONCLUSION

Organophosphorous compounds are one of the most common agents used for suicidal poisoning. Out of several type of OP poison chlorpyriphos was seen in maximum cases possibly due to more wide spread use in agriculture. The most important determinant of death in Organophosphorous poisoning is the severity which can be assessed clinically as well as measurement of plasma cholinesterase level. Those who had initial cholinesterase level less than 900 had a certain chance of death. So while treating enough attention must be given to these patients. Continuous infusion of pralidoxime proved to be better than intermittent infusion even if the total dose is" same. So severe cases of organophosphorous poisoning should be treated by continuous infusion.

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*Original Article*

# A STUDY OF CARDIOVASCULAR CHANGES IN NEWLY DETECTED HYPOTHYROID PATIENTS OF SOUTHERN ODISHA

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## ABSTRACT

***Introduction :*** *Hypothyroidism has significant cardiovascular manifestations. Overt and subclinical hypothyroidism both are associated with cardiovascular dysfunction and with an increased risk of cardiovascular disease.* ***Aim*** *: Present study was carried out with an objective to study all the cardiovascular changes associated in newly detected hypothyroidism, to know the cardiovascular involvement in sub-clinical hypothyroidism.* ***Material & Methods :*** *Based on the symptoms, clinical examination and hormonal assay, newly detected hypothyroid patients were subjected to detailed cardiovascular examination, electrocardiograph, echocardiography and Tread mill test. Patients were investigated, before the thyroid hormone replacement therapy.* ***Results :*** *Hypothyroidism was newly diagnosed more in females and maximum in agegroup 17-47 years (69.9%) of age group. Out of 60 patients, 63.3% had symptoms less than 3 months duration. Cardiovascular symptoms was present in 12 (20%) of patients. Bradycardia was observed in 7% of the patients. Stage 1 hypertension was noticed in 13.3% (diastolic blood pressure). Low voltage complexes in electrocardiogram was present in 40% study group. Pericardial effusion was present in 26.7% patients. Tread mill test was positive for inducible ischaemia in two patients. Diastolic dysfunction was noticed in 26.6% study group. Altered lipid profile was present in 16.7% (S. cholesterol) and 53.4% (S.Triglycerides).* ***Conclusion:*** *Hypothyroidism is common in females, maximum between 17-47 years agegroup. Majority of the patients did not have any cardiovascular changes. Observed cardiovascular changes were ECG abnormalities, pericardial effusion and diastolic blood pressure and diastolic dysfunction. Systematic study was done to know the early effects of hypothyroidism on cardiovascular system.The identification of patients with hypothyroidism is an important individual and public health issue. Hence, early detection and initiation of hormone replacement therapy can minimize associated cardiovascular changes.* ***Key words :*** *Hypothyroid state, Subclinical hypothyroidsm, cardiovascular.*


## INTRODUCTION

The most common functional disorder of the thyroid gland is hypothyroidism.[1] It is a clinical state, due to the decreased secretion of thyroid hormones or more rarely, from their impaired activity at tissue level.[8]

It is the most common pathological hormone deficiency. Pathology of the thyroid gland (Primary hypothyroidism) accounts for over 99.5% of cases of thyroid gland failure and < 0.5% result from disorder of the pituitary gland or hypothalamus (central hypothyroidism).[8] Overt hypothyroidism refers to cases in which the serum thyrotropin (TSH) concentration is elevated and serum T4 (free thyroxine) is below the reference range, while subclinical hypothyroidism is defined as an elevated serum TSH value, associated with a serum free T4 within the reference range.[2]

Thyroid hormones have a profound effect on a number of metabolic processes in virtually all tissues

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and hence virtually every tissues in the body is affected to a greater or lesser extent by thyroid hormone deficiency, the heart being particularly sensitive to its effect.[11]

The clinical features dependent on patients age, rate at which hypothyroidism develops.[7] As thyroid hormones are universal determinants of organ function, there may be a multiplicity of symptoms.[5]

The cardiovascular risk in hypothyroid patients is related to an increased risk of functional cardiovascular abnormalities.[3] The pattern of cardiovascular abnormalities is similar in subclinical and overt hypothyroidism, suggesting that a lesser degree of thyroid hormone deficiency may also affect the cardiovascular system.[10]

Echocardiography changes in hypothyroidism includes sinus bradycardia, prolongation of PR interval, low voltage complex, alteration of ST segments and flattened or inverted T waves, RBBB, LBBB and rarely complete heart block.[9]

ECHO changes in hypothyroidism include pericardial effusion, wall motion abnormalities, diastolic dysfunction and systolic dysfunction.[4]

It is important to detect clinical or subclinical thyroid diseases in time for the effective treatment and for prevention of the cardiovascular damages before manifestation of cardiovascular system and effective.

The Rotterdam study in post menopausal women and a prospective study in Japan have shown increased prevalence of atherosclerosis and IHD in subclinical hypothyroid patients.[8]

But Whickham study has failed to find any correlation between subclinical hypothyroidism and cardiovascular morbidity and mortality.

This dissertation is undertaken to study the cardio vascular changes in newly detected hypothyroid patients attending MKCG Medical College And Hospital, Berhampur, Odisha during the study period from August 2010 to August 2012.

## OBJECTIVE

1. To study all the cardiovascular changes associated with newly detected Hypothyroidism.

2. To know the cardiovascular involvement in sub-clinical hypothyroidism

## MATERIALS & METHODS

The present study was a cross sectional study involving sixty newly detected hypothyroid patients selected on basis of simple random sampling method diagnosed by clinical evaluation and confirmed by thyroid hormone assay by chemiluminescence immuno assay ( CLIA ) method. reference ranges [TSH (0.34 – 4.25)microIU/ml ,total T4 ( 5.4 – 11.7) microgm/ dl,fT4 ( 0.7 – 1.24) ng/dl,total T3( 77-135 )ng/dl,fT3 (2.4 – 4.2) pg/ml ].Patients with TSH >10 microIU / ml and low fT4 were considered overt hypothyroids, and TSH ranging (4.2- 10)microIU/ml and normal fT4 were considered subclinical hypothyroids.Study extended over a period of 2 years.

Secondary hypothyroidism cases, hypothyroid patients who are already on treatment, Patients on antiepileptics, OC pills, amiodarone, gluco corticoids, NSAIDs and patients with other diseases like HTN, diabetes, pernicious anemia, collagen disorders, primary cardiac and other endocrine disorders and pregnant ladies were excluded from study.

## INVESTIGATIONS

The following investigations were done to diagnose hypothyroidism (Newly detected) and with associated cardiac profile : Complete blood count, FBS/ 2 hr PGBS, Serum FT3, FT4, TSH, Lipid profile, FNAC of thyroid gland (if indicated), Chest X-ray, ECG, 2D Echocardiogram, Tread Mill test.

- Analysis of data was made on basis of parameters like mean deviation,standard error,the t-test and the proportion test.P value of <0.05 was considered statistically significant.

**OBSERVATION**

Out of 60 patients 46 (76.7%) were females with mean age of 37.5±14.0 years and 14(23.3%) were males with mean age of 47.4± 17.4 years. Out of all, maximum(33.3% )were in the age group of 27-37yrs. Out of total 12 subclinical hypothyroid patients 4 were elderly females which constituted 34% of the subclinical group.

**TABLE-I : CARDIOVASCULAR SYMPTOMS IN STUDY GROUP**

| Sl no | Symptoms | Male | Female | % |
|---|---|---|---|---|
| 1 | Chest pain | 2 | 0 | 3.3 |
| 2 | Breathlessness | 0 | 2 | 3.3 |
| 3 | Effort intolerance | 4 | 2 | 10 |
| 4 | Palpitations | 0 | 2 | 3.3 |

Cardiovascular symptoms was seen only in 12 patients (20%) which includes effort intolerance in 6 (10%), chest pain, breathlessness and palpitation in 2 patients each (3.3%) (Table-1). In this study 4 (7%) out of 60 patients had bradycardia.

**TABLE-2 : PREVALENCE OF SYSTOLIC HYPERTENSION (JNC 7 CRITERIA)**

| Sl no | | M | F | Total | % |
|---|---|---|---|---|---|
| 1 | Normal (<120) | 8 | 16 | 24 | 40 |
| 2 | Prehypertension (120-139) | 6 | 28 | 34 | 56.7 |
| 3 | Hypertension stage 1(140-159) | 0 | 2 | 2 | 3.3 |
| 4 | Hypertension stage 2(>160) | 0 | 0 | 0 | 0 |
| | Total | 14 | 46 | 60 | 100 |

Pre-hypertension (systolic) was present in 6 males and 28 females which constituted 56.7% of total population.Only 3.3% had stage1 systolic hypertension. (Table-2)

**TABLE-3 : PREVALENCE OF DIASTOLIC HYPERTENSION(JNC 7 CRITERIA)**

| Sl no | | M | F | Total | % |
|---|---|---|---|---|---|
| 1 | Normal (<80) | 8 | 16 | 24 | 40 |
| 2 | PreHypertension(80-89) | 4 | 24 | 28 | 46.7 |
| 3 | Hypertension Stage 1(90-99) | 2 | 6 | 8 | 13.3 |
| 4 | Hypertension stage 2(>100) | 0 | 0 | 0 | 0 |
| | Total | 14 | 46 | 60 | 100 |

Pre-hypertension (Diastolic) was present in 4 males and 24 females which constituted 46.7% of total population. Similarly stage 1 Diastolic hypertension was present in 13.3% of study group. (Table-3)

Lipid profile in this study revealed 16.7% of patients had high serum cholesterol, (Male 214.3±33.3 mg/dl, Female 199.1±28.6 mg/dl). 53.4% had high serum triglyceride (male 202.2±50.2, female 210.1±51.3 mg/dl) and 10% had high LDL levels (Male 113.8±26.7, Female 103.3±29.6 mg/dl). Mean HDL was (Male 53.7±6.1, Female 54.5±6.4 mg/dl). In subclinical group 6 out of 12 had raised triglyceride level that constituted 50% of all lipid abnormalities. Only 16.6% had raised LDL Cholesterol.

Only 4 of the 60 patients in the study group (7%) showed cardiomegaly in chest x-ray (PA) view.

**TABLE-4 : LOW VOLTAGE COMPLEXES IN ECG IN STUDY GROUP**

| Sex | Present | % |
|---|---|---|
| Male | 6 | 10 |
| Female | 18 | 30 |
| Total | 24 | 40 |

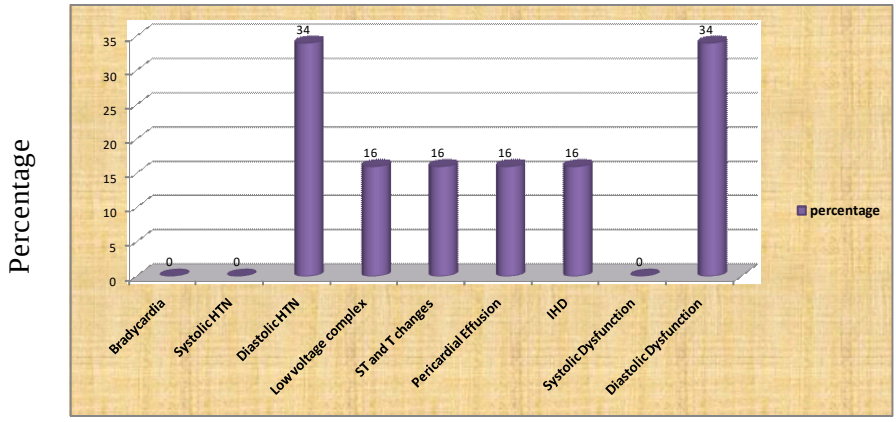
**TABLE-5 : ECHOCARDIGRAPHIC CHANGES IN STUDY POPULATION**

| Echo Findings | Number(n=60) | % |
|---|---|---|
| Pericardial Effusion | 16 | 26.6 |
| Systolic dysfunction | 4 | 6.6 |
| Diastolic dysfunction (mild) | 14 | 23.3 |
| Diastolic dysfunction (moderate) | 2 | 3.3 |
| Diastolic dysfunction (severe) | 0 | 0 |
| IVS Thickness | 4 | 6.6 |

In this study low voltage complexes in ECG were found in 24 (60%) of patients, out of which 6 (10%) were males, 18 (30%) were females. Similarly, 15% males had T-inversion in V3-V6 leads and RBBB was seen in 29% patients. (Table-4) 2 (3.3%) out of 60 patients showed positive test for inducible ischemia in tread mill study. All were males. None of the females were positive in this test.

2D Echo findings were normal in 33% cases. Diastolic dysfunction and pericardial effusion was found in 16 (26.6%) cases followed diastolic dysfunction in 16 (26.6%), systolic dysfunction in in 4 (6.6%) and increased inter IVS spectrum thickness 4 (6.6%) cases. Majority of the diastolic dysfunction being mild dysfunction. No cases found to have severe diastolic dysfunction. (Table-5)

**TABLE-6 : OVERALL CARDIOVASCULAR INVOLVEMENT IN SUBCLINICAL HYPOTHYROID GROUP (NO.12 CASES)**




## DISCUSSION

Majority of the patients were in the age group of 17-47 years (69.9%). Maximum incidence was in the third decade (33.3%). Mean age of the patients was 42.45 years with range from 17 to 70 years.

Male: Female ratio in the study was 1:3.2.

Comparing with other studies, Watanakunakorn et al in 1965 had got maximum prevalence in 6th decade i.e., 25%.

Streeten et al[14] in 1987 had noted mean age of prevalence was 49.8 with SD of 2.5. Similarly comparing sex distribution Vanhaelst L[15] in 1968 and William FC et al had noted a female to male ratio of 4:1 which is consistent with the present study finding i.e., 3.2:1

63.3% patients had symptoms less than 3 months duration. Mean duration of the symptoms before the patients reported was 3.5 months. About 26% of the cases had goitrous hypothyroidism, observed only in female patients. Six most common symptoms were general weakness and lethergy pain in muscles and joints. Facial puffiness, limbs swelling, skin changes hoarseness of voice and cold intolerance.

Cardiovascular symptoms-chest pain, effort intolerance and palpitation was present in less number of patients. Bradycardia was present in only 7% of the patients. This finding correlates with other study(wayne et al) As per JNC 7 criteria, stage-I systolic hypertension was present in 3.3% and stage I Diastolic hypertension in 13.3%. The incidence of hypertension in the present study correlates with the incidence reported by Saito I et al.[17]

- High serum cholesterol levels were present in 16.7%. Serum triglycerides high level was seen in 53.4%.

- In ECG changes, 40% low voltage complexes was present, followed by 'T'-wave changes (23.3%) and RBBB in 6.6%. This finding is consistent with other studies like by R. Varma[16] except conduction disturbances. M. H. Nikoo, M.D. SUMS 2002[12] also documented sinus tachycardia, QT prolongation and ventricular tachycardia which was not found in our study.

- 2D Echo findings were normal in 30% cases. Pericardial effusion was next common finding seen in 16 cases accounting to 26.7%. The study by R. Verma[16] in 1995 showed the prevalence of effusion to be 22.75%. Pericardial effusion is reported to occur in 30% to 80% of patients with hypothyroidism [Rawat B1 and Satyal A2, KUMJ (2003 VOLUME 2)]. Relatively low incidence of pericardial effusion may be due to selection of new hypothyroid cases. Diastolic dysfunction seen in 26.67%, majority of them being mild dysfunction. No cases found to have severe diastolic dysfunction. IVS thickness was found only in 4 cases. . In a study by R. Verma in 1995 it was seen that 27% of patients had diastolic dysfunction. Systolic dysfunction seen in 6.67% of patients. Forfar et al. (1982) and others have described low systolic function indices in hypothyroid patients. However small ridge ET al. (1987) have argued that this could be related to

relatively elderly patients included in the above studies. They found no such alteration in systolic function in their younger patients (aged 20-48 years). This was further supported by Fouron et al. (1982), Grossman et al. (1994) and Verma et al. (1995) who did not find any evidence of systolic dysfunction in hypothyroid patients. Rawat B1 and Satyal A2, KUMJ (2003 VOLUME 2) showed no systolic dysfunction. IVS thickness found in only in 4 cases in our study and above studies shows increased numbers in both subclinical and overt hypothyroidism. There is no evidence of LVPW thickness in our cases. Rawat B1 and Satyal A2 reported LVPW to occur. Bennet et al. (1983), Lee et al. (1990) and Bernstein et al. (1995) did not find similar incidences

TMT was positive for inducible ischaemia was present in 14.3% of the patients. The incidence of IHD in the present study correlates with the incidence reported by E. J. Wayne[5] and Watanakunakorn et al.

• In the subclinical hypothyroid group major manifestation was diastolic hypertension and diastolic dysfunction on echocardiography.Higher triglyceride level was the most common lipid abnormality.Ischemic heart disease was significantly associated with this group.

In the present study statistically significant association was found between degree of hypothyroidism and diastolic hypertension and low voltage complex in ECG. But no significant association was found between severity of hypothyroidism and prevalence of bradycardia, diastolic dysfunction and pericardial effusion.

## CONCLUSION

The hypothyroid patients present clinically with a myriad of symptoms and signs which are nonspecific. Hence a high index of suspicion is the key for the early diagnosis of hypothyroidism. Cardiovascular symptoms are less commonly associated with newly detected hypothyroidism. The occurrence of pericardial effusion in hypothyroidism is significantly related to the duration of the disease; hence the need for early diagnosis of hypothyroidism. X-ray chest is not a reliable tool of the diagnosis of pericardial effusion. Hence echocardiogram is the investigation of choice for the diagnosis of pericardial effusion. Altered lipid profile was found in the hypothyroid patients. Quite a significant number of patients were in pre-hypertension group. Various life style modifications can be advised preventing them going for stage I hypertension. The identification of hypothyroid patients is an important individual and public health issue. Early diagnosis and correction of hypothyroidism is necessary; so that early effects on cardiovascular system can be minimized.

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*Original Article*

# STUDY OF ELECTROLYTE ABNORMALITIES IN CHRONIC KIDNEY DISEASE

**S.K. Tete*, M. Murmu**, K.N. Padhiary*****


## ABSTRACT

***Background**: Many cases of chronic kidney disease of geographical area of Western Odisha which were with or without any risk factors often behave abnormally not showing typical features of CKD. **Aim and objectives**: Keeping this in view, clinical, biochemical & etiological evaluation of all cases of CKD of various stages were taken in this study to find out any different electrolytes abnormalities and the possible cause for atypical manifestations. **Materials and methods:** A total of 100 confirmed cases of CKD were evaluated by history, physical examination and suitable investigations. **Results**: Of total 100 cases 4(4%) in stage2, 14(14%) in stage3, 35(35%) in stage4, 47(47%) in stage 5 . The underlying risk factors (like HTN, DM, older age, family history, previous history of ARF, structural abnormality of urinary tract, recurrent UTI etc.) were found in 51 cases (51%) and the unexplained CKD was seen in 39 cases (39%) from total of 100 cases. 10 cases(10%) were associated with sickle cell disease. The atypical features detected in this study were 1) below 40yrs age group 24 cases(24%) out of which 5 were <25yrs, 2) 43 cases(43%) were having without edema despite highly raised creatinine (out of 43% of nonedematous CKD 30% were having unknown riskfactor (3) 50 cases(50%) were hypokalemic (significant association with unknown risk factor(4) 50% cases were having hyponatremic (significant association with unknown risk factor(5) 20 cases (20%) were hypocalcemic,(6) 34 cases (34%) with normal phosphate level despite in later stages of CKD. Association of calcium & phosphorous with unknown risk factor was insignificant. **Conclusions**: In western odisha we got several cases of CKD of unexplainable aetiology. Significant number of cases presented with atypical manifestations having no specific aetiology. The cause, may be due to RA system defect or may be genetic or environmental (dietary toxin, water). **Key words :** Chronic kidney disease, electrolytes, dyselectrolytemia.*


## INTRODUCTION

The world is currently facing a global epidemic of chronic kidney disease (CKD). As morbidity and mortality from infectious diseases declined, life expectancy has increased and chronic degenerative diseases become more prevalent, CKD is unique amongst the chronic non infectious illnesses. Risk factors include old age, hypertension, diabetes mellitus, family history, previous episode of acute kidney injury, autoimmune diseases, presence of protienuria, abnormal urinary sediments or structural abnormality of urinary tracts etc. Decrement in GFR leads to host of excretory, metabolic and endocrine functions abnormalities causing wide variety of clinical symptoms of fluid and electrolytes disturbances, endocrine-metabolic disturbances, haematological-immunologic abnormalities, cardiovascular and pulmonary disturbances and different others systemic abnormalities.

Electrolytes disturbances are one of the main features of chronic kidney disease which become prominent as the disease advances. Hyponatremia, hyperkalemia, hyperphosphatemia, hypocalcemia are the main electrolytes abnormalities observed [1]. In this institution of V.S.S medical college Burla, we encounter number of cases of CKD with abnormal electrolytes status. All types of abnormalities are noticed like

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hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hyperphosphatemia, hypophosphatemia, hypocalcemia etc. But these being unpublished data we want to conduct a study to see the spectrum of electrolytes abnormalities in our patients of CKD and try to find out if any specific contributing factor works.

## MATERIALS & METHODS

The Observational Study was conducted in Department of General Medicine, V.S.S Medical College Hospital, Burla. The patients of Chronic Kidney Disease who were admitted to Dept. of General Medicine, V.S.S MCH, Burla between november 2010 to october 2012 were taken in this study. Inclusion criteria for study was age >16yrs, serum creatinine >1.2 ml/dl, GFR < 90 ml/min per 1.73 $m^2$ (calculated by Cockcroft-Gault equation)[2] and renal ultrasonography showing features of CKD. The diagnosis of CKD was done by clinical history, physical examination and by laboratory evaluation. Clinical history was taken with giving special importance to important past illnesses, personal and family histories. Physical examination were done giving with particular importance to pallor, edema, blood pressure etc and features of electrolytes abnormalities. Laboratory investigations done were haemoglobin, urine routine microscopy, serum urea, serum creatinine, serum sodium & potassium, fasting blood sugar, ultrasonography of kidney, ureter & bladder.

All the diagnosed CKD patients who were included in this study were evaluated by Serum sodium, Serum potassium, Serum phosphorous, Serum calcium and other test as required. Analysis was done by applying standard statistical methods.

## OBSERVATION

Age distribution of 100 CKD patients is shown in Fig-1. Highest age of the patient was 86 yrs and lowest age the patients was 20 yrs. Mean age of distribution was 51yrs with a standard deviation of 13.98. Out of 100 cases 73 cases (73%) were male and 27 cases (27%) were female.

51% of CKD cases had known aetiology like HTN (25%), DM (19%), recurrent UTI (7%), h/o renal disease (5%), family history (5%) and rest of the cases 39% cases have undetermined aetiology. Out of 100, 10% cases of CKD found to have sickle cell disease [Fig-2].

Maximum no. of cases (82%) are in stage 4 & 5 with GFR <30 ml/min. In our study total 57% cases were edematous and rest were nonedematous. In stage 5, 26% cases were edematous and a significant number (21 %) were non-edematous. In stage 4, 21% were edematous and 14% non-edematous. In stage 3, 6% cases were both edematous and non- edematous. In stage 3, 3% cases were edematous.

Study shows 50% cases were found to be hyponatremic and 15% cases were hypernatremic. Most of the cases (50%) were found to be hypokalemic. Maxinum no. of cases (48%) are in hypocalcemia group, still 20% cases are in hypercalcemia range. Most of the cases (46%) have higher phosphorous level, also 20% in hypophosphatemia group.

Table1 shows the correlation coefficient of eGFR with different variables including the electrolytes. Negative Pearson's correlation coefficient value indicate the level of Age, SBP, DBP, potassium, phosphorus, Urea, Creatinine, eGFR , $K^+$, $PO_4^{-3}$ increases with the decline of GFR and positive Pearson's correlation coefficient value indicate the level of $Na^+$, $Ca^{+2}$ parameter decreases with the decline of GFR.

Table2 shows the comparison of different atypical electrolytes abnormalities with typical electrolytes abnormalities in CKD. Here mean age of hyponatremia is 49.4 (SD.±13.93) as compared to typical group with mean age of 52.6 (SD.±15.06) with male predominance in both group. When association of hyponatremia with risk factor (known & unknown) is compared, chi-square value found to be 11.005 (P value <0.001) which is significant. Thus showing a strong relationship between hyponatremia and unknown aetiology. Again mean age of hypokalemia is 48.5 (SD.±13.35) as compared to hyperkalemia with mean age of 53.69 (SD.±13.21) with most of the cases are male. When association of hypokalemia is compared with risk factor (known & unknown), chi-square value found to be 3.64 (P value <0.05) and thus association of hypokalemia with unknown aetiology found to be moderately significant. Mean age of both hypo-hyperphosphatemia found to be almost similar and when association with risk factor is compared, chi-square value found to be 12.66 (P value <0.001), indicating a strong relationship of hyperphosphatemia with known

aetiology. Mean age of hypercalcemia is 51.86 (SD.±14.78) as compared to hypocalcemia with mean age of 49.25 (SD.±13.27). Similarly when association with risk factor is compared, chi-square value found to be 17.7 (P value <0.05), showing a strong relationship of hypocalcemia with known aetiology.

Table3 shows the comparison of coexistence of SCD in two group with undetermined etiology**.** Out of total 10 cases 6 cases (60%) found to have atypical electrolytes abnormalities. In case of potassium level, 4 cases (8%) of hypokalemia out of 50 cases found to be associated with undetermined aetiology. So association of atypical potassium level with undetermined aetiology was insignificant as P value >0.05. Similarly association of atypical sodium level with undetermined aetiology was insignificant as P value >0.5.

## DISCUSSION

The current study was a cross sectional study done at V.S.S MCH, Burla between November 2010 to October 2012 to find out the different electrolytes disturbances found in different stages of CKD and find out it's aetiologies.

In our study the mean age of distribution was 51 years with a standard deviation of 13.98. Most of the patients belonged to 50 to 60 yrs. But still 24% of cases were below 40yrs age group, which are significant in number. SCD with CKD found to be in younger group of population. Also the unexpected abnormalities of hyponatremia and hypokalemia found to be more in younger age group as compared to the other expected abnormalities. According to Suhnggwon Kim et al 2009, mean age of CKD was 50.5±11.1 yr[3]. The prevalence increased remarkably with age. The prevalence in subjects aged 65 yr or older was much higher than the prevalence in subjects 35 to 44 yr of age. Advanced age is a well known risk factor for CKD (Imai E et al.2007, Zhang L et al.2008)[4].

51% of CKD cases have known aetiology like HTN (25%), DM (19%), recurrent UTI (7%), h/o renal disease (5%), family history (5%) and rest of the cases 39% cases have undetermined aetiology. Out of 100, 10% cases of CKD found to have sickle cell disease. This shows that in our study, significant proportion of cases were having unknown aetiology. Among usual risk factor hypertension and diabetes were common. SCD and CKD association were seen mostly among younger age group (10%) of population (i.e below 40 yrs) as prevalence of SCD is quiet common in our geographical area of western Odisha. Sklar AH et al (1990) showed that among SCD patients decreased in kidney functions has been reported in 5-30% [5]. Falk RJ et al 1992 also showed similar result [6]. In United States SCD accounts for < 1% of all new cases of end stage renal disease [7]. SCD can cause tubulointerstitial disease of salt losing nephropathy which affects the distal nephron which might be influencing the occurances of CKD in our study area. The other

**Figure 1**

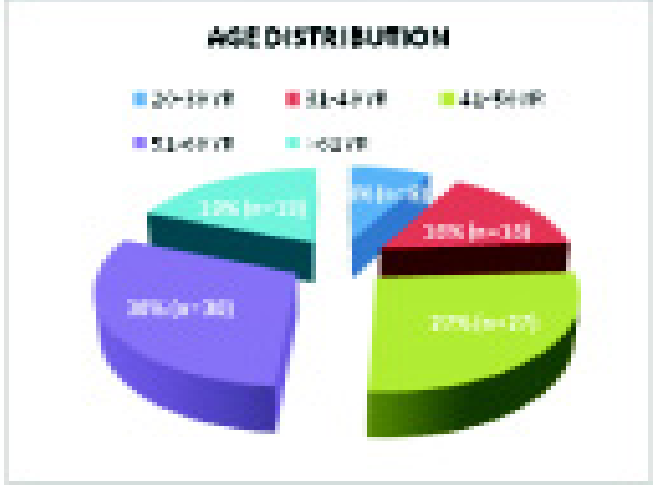


**Figure 2**

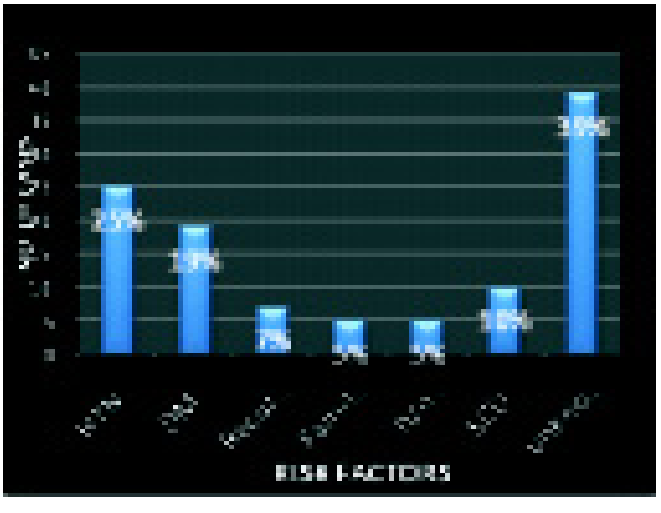

**TABLE 1: CORRELATION COEFFICIENT OF EGFR WITH DIFFERENT VARIABLES**

**TABLE 2 : COMPARISON OF ATYPICAL VRS TYPICAL ELECTROLYTE ABNORMALITIES IN CKD.**

| Electrolytes | | Age (yrs) Mean ± SD | Sex | Risk factor Association (%) | P value |
|---|---|---|---|---|---|
| $Na^+$ | Atypical (Hyponatremia) | 49.4±13.93 | M > F | Known- 22% Unknown-28% | <0.001 |
| | Typical | 52.6±15.06 | M > F | Known- 14% Unknown-19% | |
| $K^+$ | Atypical (Hypokalemia) | 48.5±13.35 | M > F | Known-15 % Unknown-35% | 0.05 |
| | Typical (Hyperkalemia) | 53.69±13.21 | M > F | Known-8% Unknown-6% | |
| $PO_4^{-3}$ | Atypical (Hypophosphatemia) | 49.42±12.96 | M > F | Known- 16% Unknown-9% | <0.001 |
| | Typical (Hyperphosphatemia) | 49.42±14.18 | M > F | Known-32% Unknown-20% | |
| $Ca^{+2}$ | Atypical (Hypocalcemia) | 51.86±14.78 | M > F | Known-55% Unknown-10% | <0.001 |
| | Typical (Hypercalcemia) | 49.25±13.27 | M > F | Known-13% Unknown-10% | |

**TABLE 3**

important finding is the identification of CKD of undetermined aetiology as the cause in as many as 39% of all CKD subjects. Patients in this category presented more frequently with advanced CKD, relatively short history, few symptoms until late in the disease, absent or mild hypertension and little or no proteinuria. Among these patient most of the cases were non-edematous inspite of being in late stage of CKD. These patients also have unexpected electrolytes abnormalities like hypokalemia, hyponatremia. Unique risk factors in this Indian population must be considered. These include dietary habits, use of indigenous medicines and possibility of industrial contamination. A significant proportion of population in this region consumes a variety of herbs and fruits. Whether any of these have an adverse impact on kidney function remains unknown. An association of CKD with herbal medicines has already been established in some parts of the world, as shown by Jha V (2010), Lai MN et al (2009)[8][9]. CKD of uncertain aetiology has also been reported from other parts of South Asia and amongst South Asians living in UK [10]. In Sri Lanka, male paddy farmers of poor socioeconomic status present with progressive non-proteinuric renal failure [11]. Suggested aetiologies include environmental toxins such as residual pesticides, fluoride, aluminum, cadmium and cyanobacteria in drinking water. Maternal malnutrition and resultant low birth weight in the offspring might predispose to CKD, possibly due to low nephron numbers. Some types of hereditary or acquired tubulointerstitial disease may be the risk factor which is required to be evaluated. But since most of the cases of undetermined aetiology in our area are in low socioeconomic status and mostly present in late stages, it is very difficult or a challenge in our counterpart to evaluate the exact cause.

In our study we found that 57% cases were edematous and rest were nonedematous. Out of 43% of nonedematous CKD 30% were having unknown risk factor. Despite in the last 2 stages of CKD, we encounter a no. of cases having hyponatremia but without edema, it means it may be due to tubular defect which leads to salt and water depletion in spite of rising urea and creatinine level.

51% of cases were found to be hyponatrmic and 16% were hypernatremic. In earlier stages of CKD, the level of sodium was not decreased below the clinical reference range. However, with the progression of CKD from stage III to stage V, hyponatremia occurred. Also the association of hyponatremia with unknown aetiology was assessed, the chi-square value (11.005) is significant (as $P < 0.001$). Yee J et al.1999 showed that hyponatremia usually occurs with GFR blow 10 ml/min [12].

However significant proportion (50%) of cases were found to be hypokalemic. Association of hypokalemia with unknown risk factor was moderately significant as chi-square value 3.64. A cohort study done at four US center for an average of 2.6 years by S. Korgaonkar et al (2010) suggests that patients who have CKD and low or even low-normal serum potassium are at a higher risk for dying than those with mild to moderate hyperkalemia[13]. Hypokalemia is not common in CKD, but in our study half of the cases are hypokalemic. Hypokalemia in CKD usually might be due to reduced dietary potassium intake, especially in association with excessive diuretic therapy or concurrent GI losses. Inappropriate prescription of diuretics might be responsible for it. Verification of the prescription and the drug should always be done to correlate this. Excessive carbohydrate rich meal in a malnourished patient can provoke hypokalemia due to stimulation of endogenous insulin. Especially in starvation hypokalemia can occur. Intestinal loss of $K^+$ due to diarrhoea is a globally important cause of hypokalemia in light of the worldwide prevalence of diarrhoeal disease especially in our part of country. Hypokalemia can also occur as a result of primary renal potassium wasting in association with other solute transport abnormalities. However after, whatever the evaluation were done which is possible by us, we did not get any such cause.

In our study, 46% showed increase phosphorous level but 20% showed decrease phosphorous level. Phosphorous level increases with decline of GFR. Hypocalcemia was found in 48% of cases and hypercalcemia in 20% of cases. Serum level of calcium was found to be decreased with the increase of stages of CKD. GFR hypercalcemia develops when the input of calcium to the circulation exceeds its removal by the kidney's filtration rate independent of the tubular calcium reabsorption rate. This readily occurs in patients with CKD [14]. Association of atypical manifestation of phosphorous and calcium with undetermined aetiology

is statistically insignificant. So may be the hormone involving the calcium and phosphorous metabolism is not involved in this atypical presentation. As atypical manifestation of sodium and potassium is significantly associated with undetermined aetiology, so the defect in the renin-angiotensin system may be involved in the atypical presentation.

## CONCLUSION

All cases of CKD do not behave identically. A group of patients have the tale-tell signs CKD and another group of patients have atypical manifestations like absent of edema, hyponatremia, hypokalemia, hypophosphatemia. We commonly encounter precipitating like hypertension, diabetes, h/o renal disease, recurrent UTI, family history and all others. However, cases with atypical manifestations found to have no specific aetiology. In atypical patients some interesting observation is made in relation to cause, with three possible site of defect, first one is renin-angiotensin system defect, second one is genetic, third one is environmental (particularly water intake in workplace). To know the cause, this aspect should be studied.

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*Original Article*

# ASSOCIATION OF LEVEL OF HBA1C WITH RISK OF CARDIOVASCULAR MORBIDITY AND MORTALITY IN PATIENTS WITH TYPE-2 DIABETES MELLITUS

**Sradhananda Mohapatra, Anisha Mohapatra**


## ABSTRACT

***Aim :*** *To assess the association of Level of HBA1C with risk of cardiovascular morbidity and mortality in patients with Type-2 diabetes mellitus.* ***Materials and Methods :*** *Total number of patients enrolled were 2240 (male= 1218, Female=1022). They were divided into 2 groups i.e. Group A & B. Group A (HbA1C level > 7) had 1770 patients and Group B (HbAIC level ≤ 7) had 470 patients.* ***Results :*** *Major cardiovascular events occurred in 107 patients in Group A and 27 in Group B. There is a significant relationship of overall increased morbidity and mortality in Group A and in Group B there was significantly less cardiovascular morbidity and mortality.*

***Keywords :*** *Type-2 Diabetes Mellitus, HbA1C, Cardiovascular risk.*

## INTRODUCTION

Diabetes mellitus affects nearly 1/10th of population of India and type 2DM is the main culprit. Diabetes is present at least 10 years before the actual diagnosis and by the time we diagnose diabetes nearly 50% of Beta -Cells are destroyed. China has the largest number of diabetes patients in the world (92.3 million) with India closing on at 63 millon, USA 24.1 million, Brazil 13.1 million and Russia 12.7 million.[1]

The reason for this explosive increase in the number of diabetic patients since the first national survey in 1971, where the prevalence was 2.3% is a matter of debate. This has been attributed to genetic pre-disposition in Indian patients, but logic says that it is not possible for genetic markers to have changed so much that in the last 40 years the prevalence could be 15 to 20% in urban areas , and about 7 to 10% in rural area.

The present criteria for diagnosis of diabetes are[2,3]:

1) Symptoms of diabetes with random blood sugar of 200mg/dl or more. 2) Fasting blood sugar of 126mg/dl or more. 3) 2hr post 75gm of glucose ingestion value of 200mg/dl or more. 4) HbA1c level of 6.5% or more.[3]

Recently much emphasis is given on the diagnosis of pre-diabetic state, so that action can be taken to delay the onset of diabetes by life style modification like Diet control, Weight reduction, graduated exercise, Cessation of smoking, Initiation of Metformin at low dose particularly in high risk individuals with strong family history of diabetes.

Pre-diabetes has been described as HbA1c level of 5.7% to 6.4% or fasting glucose level of 100mg % to 125mg%(Impaired fasting glucose), or 2hr post-prandial glucose level of 140mg% to 199mg% (Impaired glucose tolerance).

There has been conflicting opinion regarding tight control of diabetes to prevent cardio-vascular events of diabetes mellitus[4,5,6]. Since we come across a large number of patients of diabetes in our day to day practice, we undertook this study to correlate the level of HbA1c with risk of developing cardiovascular morbidity and mortality.

## BACKGROUND AND AIMS

As already mentioned there have been conflicting opinion regarding control of blood sugar level to normal or below normal level to prevent cardiovascular morbidity and mortality.

**ACCORD STUDY :** Was abandoned half way through because of higher incidence of mortality in the

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arm of tight control of blood sugar level particularly in the elderly. With this background in mind we wanted to undertake this study by estimating HbA1c level in adult patients who came to us for treatment. We tried to explore the relationship between HbA1c level and the risk of development of cardiovascular morbidity and mortality[7].

## MATERIALS AND METHODS

We recruited 4020 patients with Type 2 diabetes who were 40yrs of age or older and estimated their HbA1c level at 1st visit and at 4month interval thereafter using Bayer A1c now kit. This study was started on 1st Sept. 2010 to 31st August 2011. We followed up these cases for a further 20 months i.e. till 30th April 2013, and noted any cardiovascular events like unstable angina, acute myocardial infraction, patients undergoing CABG or patients who had nephropathy, stroke, CHF or patients who met death.

We excluded patients who had prior unstable angina, AMI in the past, Grade II or higher grade nephropathy, CHF, retinopathy from our study. We distributed rest of all other patients to two groups. In Group-A we had patients whose average HbA1c level was more than 7% and in Group-B we had patients whose average HbA1c level was 7% or less.

All adverse cardiovascular events were noted and survival was estimated by using Kaplan Meir method. Possibility of excess mortality in group A as compared with Group-B was 95% CI, using COX proportional hazard model.

We made adjustments for age, sex, prior cardio vascular disease and number of prior admissions for non-cardiovascular diseases. Each patient was followed up till occurrence of nephropathy, stroke, atherosclerosis, retinopathy and CHF or major cardiovascular events or death.

## RESULTS

At the end of our study that is on 30th April 2013 ,we had 2240 patients in all (1218 males and 1022 femals). In Group-A we had 1770 patients and in Group-B we had 470 patients. Major cardiovascular events occurred in 107 patients in Group-A and 27 in Group-B.

**ADJUCTED HAZARD RATIO AND CRUDE-p VALUE FOR BOTH GROUPS(GROUP-A & GROUP-B)**

**ALL PATIENTS N-2240**

| | **GR-A NO** | **GR-A ADJUCTED** | **GR-B NO** | **GR –B ADJUCTED** | **CRUDEp-** |
|---|---|---|---|---|---|
| | **HR(95%CI)** | | **HR ( 95%CI)** | | **VALUE** |
| **MORTALITYALL CASES** | | **37** | **1.28(1.18-1.40)** | | **07** |
| **1.13(0.95-1.33)** | **<0.03** | | | | |
| AMI | 22 | 2.96(.092-3.32) | 03 | 1.24(.90-1.61) | <0.001 |
| NEPHROPATHY | 08 | 2.22(1.40-2.90) | 01 | 1.96(1.26-2.22) | <0.002 |
| STROKE | 03 | 1.08(.88-1.25) | 01 | 1.06(.86-1.20) | <0.07 |
| CHF | 04 | 2.03(1.40-2.90) | 02 | 1.80(1.24-2.63) | <0.08 |
| **MORBIDITY ALL CASES** | **74** | | **1.56 (1.20 – 2.07)** | | **15 1.30** |
| **(1.16 – 1.86)** | **<0.09** | | | | |
| AMI | 11 | 2.86(.92-2.98) | 04 | 1.06(.96-1.28) | <0.002 |
| ATHEROSCLEROSIS | 17 | 1.78(1.28-2.46) | 03 | 1.26(1.14-1.67) | <0.003 |
| RETINOPATHY | 24 | 2.13(1.74-2.42) | 04 | 1.08(.96-1.32) | <0.003 |
| NEPHROPATHY | 14 | 2.03(1.40-2.93) | 03 | 1.13(.96-1.32) | <0.007 |
| CHF | 08 | 1.28(1.10-1.40) | 01 | 0.96(.90-1.12) | <0.004 |

## DISCUSSION

We found a significant relationship of overall increased morbidity and mortality in Gr-A(HbA1c Level more than 7%) and in Gr-B(HbA1c level 7% or Less) there was significantly less cardiovascular morbidity and mortality. This finding of ours was consistent with Framingham Heart Study[5]. Similarly microvascular complication like Nephropathy and Retinopathy were

also significantly higher in Gr-A as compared to Gr-B. There was also significant association between increased HbA1c level and increased carotid intima media thickness as in Gr-A.Co-morbid conditions like obesity, hypertension, dyslipidaemia, older age group and strong family history were noted and adjustment were done accordingly[10].

In cases of hypertension, dyslipidaemia and obesity we tried to correct these abnormalities with life-style modification and appropriate medications. It is noteworthy that patients who responded well to statin therapy had lower CV events and patients whose BP was controlled with 3 or less agents had lower risk of nephropathy and CV-morbidity[11]. It is important to note that inspite of our best efforts to counsel the patients we could not follow up a large number of patients who dropped out from the study as they were lost for follow up. Poor compliance of medication and regular follow up will lead to poor HbA1c control and will increase cardiovascular morbidity and mortality. This finding of ours was also supported by other groups[11,12].

Workers from various other groups have gone unto a further step by finding that lowering HbA1c level in Non-diabetics to below 6% increased overall morbidity which was reflected by ACCORD GROUP[8,9]. Hypoglycemia is a pressing problem when we try to bring down the glucose level to normal or less than normal level. Hypoglycemia has increased the incidence of cardiac-arrhythmia contributing sudden death.[13,14]

## CONCLUSION

Our study clearly depicts that a poor glucose control will have an adverse effect and will increase cardiovascular morbidity and mortality in diabetes patients. Hence HbA1c should be brought down to 7% by treatment with life style modification , OADs, and Insulin treatment. Importance should be given to the treatment of co-morbid condition like hypertension, dyslipidaemia and obesity which should be corrected to get an overall improvement. There is a word of caution :Too tight control of blood sugar leading to acute and chronic hypoglycemia will have adverse cardiac events and death. Hypoglycemia should be avoided in elderly where a HbA1c level of 8% is acceptable.

## DISCLOSURE

Dr.S. Mohapatra has a research grant with Sonafi India Ltd. for Insulin studies and a teaching grant from Public Health Foundation of India. He is also in the speakers bureau for MSD, NOVARTIS AND JOHNSON AND JOHNSON for study on DPP-4 Inhibitors in Diabetes.

Dr.Anisha Mohapatra is a PG student with stipendary assistance from Govt. of Odisha and does not get any research assistance from any other source. At present she is involved with study on “Role of Vitamin D3 in Type 2 Diabetes mellitus”.

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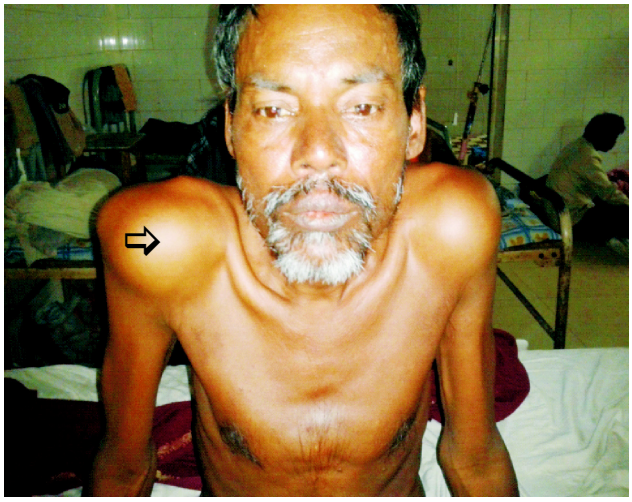
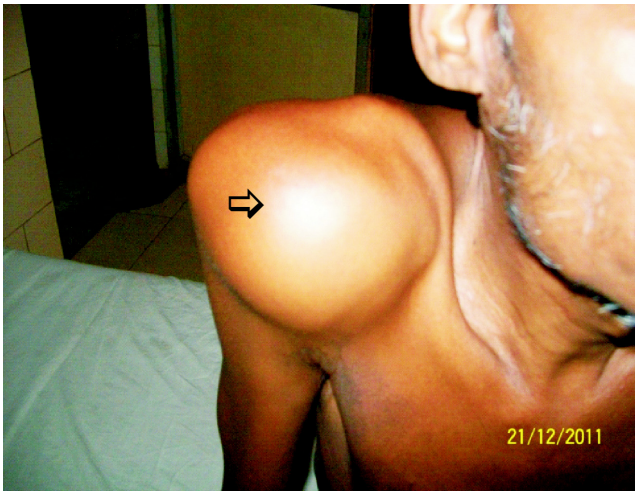
*Pictorial CME*

# AMYLOIDOSIS: "SHOULDER PAD" SIGN

**R.R. Sahoo*, S. Behera*, S. Sukriya*, A. Ratha**, Bidyut K Das*****






## DESCRIPTION

- A 60-year-old man presented with a two-year history of fatigue, weight loss, and shoulder enlargement. On physical examination, there was enlargement of the anterior shoulders.
- Abdominal fat biopsy was positive for congo red. Serum protein electrophoresis showed Monoclonal M spike.
- Amyloidosis is a disorder where insoluble protein fibers are deposited into tissues and organs leading to functional impairment.
- The "shoulder pad" sign is an enlargement of the anterior shoulder due to fluid in the joint and/or amyloid infiltration of the synovial membrane and surrounding structures. This type of soft tissue swelling can occur in up to 75% of amyloid cases.

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*Review Article*

# TUBERCULOSIS ASSOCIATED IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

**R Sen*, A K Sahu**, M R Behera*****

## INTRODUCTION

A paradoxical clinical worsening of a known condition or the appearance of a new condition after initiating antiretroviral therapy (ART) therapy in HIV-infected patients resulting from restored immunity to specific infectious or non-infectious antigens is defined as immune reconstitution inflammatory syndrome (IRIS)[1]. The Immune reconstitution is a widely recognized phenomenon that is seen in HIV infected patients receiving Highly active Antiretroviral therapy (HAART) which is characterized by

a) Suppression of viral replication .

b) Increase in the CD4 T Cell count & partial recovery of T Cell specific immune responses.

IRIS typically occurs during the initial months of ART and is associated with a wide spectrum of pathogens, most commonly mycobacteria, herpes-viruses, and deep fungal infections such as cryptococcal meningitis[1-2]. Tuberculosis (TB) is the most common opportunistic infection among human immunodeficiency virus (HIV) infected patients in our country. Patients with HIV-associated TB have advanced HIV disease and are at increased risk of death and new opportunistic infections. Highly active antiretroviral therapy (HAART) markedly decreases HIV-related morbidity and mortality in these patients. While the immune restoration following HAART reduces the risk of disease progression, it may also result in exacerbation of certain clinical manifestations . IRIS results from rapid restoration of pathogen-specific immune responses. It manifests as either a deterioration of previously diagnosed infection (paradoxical reaction) or an appearance of previously undiagnosed sub-clinical infection (unmasking reaction).

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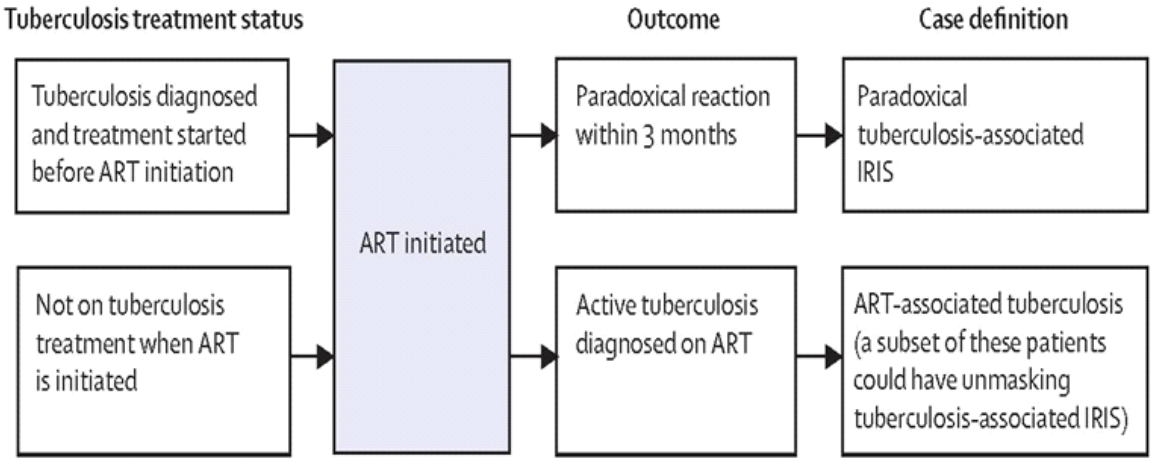
## TB IRIS

A considerable proportion of patients with HIV-associated TB but on HAART develop IRIS reactions. However, the diagnosis of TB-IRIS in resource-limited settings remains difficult to establish. Recently, a consensus case-definition for TB-associated IRIS has been proposed. This includes paradoxical TB-associated IRIS and antiretroviral treatment (ART) associated TB with provisional case-definition of unmasking TB-associated IRIS.

IRIS has been reported in 10 to 32 per cent of patients starting ART. The variation in reported frequency reflect differences in case definitions, and more importantly, differences in study populations with differing risk profiles and underlying burden of opportunistic infections. In a series from southern India TB-IRIS was reported in 7.6 per cent of patients. A study at AIIMS, New Delhi in 2011 by Sharma et al[3] reported incidence rates of 7.5 per cent for paradoxical TB-IRIS and 3 per cent for ART-associated TB in a retrospective study using consensus case-definitions. In a prospective study at the same institute, using stringent case-definitions criteria , paradoxical TB-IRIS was seen in 4 per cent of patients and ART-associated TB in 7.5 per cent of patients.

## CATEGORIES OF TUBERCULOSIS-ASSOCIATED IRIS.

Tuberculosis-associated IRIS can present as one of two main syndromes: (1) **a paradoxical reaction** after the start of ART in patients receiving tuberculosis




treatment (hence termed paradoxical tuberculosis-associated IRIS), or (2) a new presentation of tuberculosis that is "unmasked" in the weeks following initiation of ART with an exaggerated inflammatory clinical presentation or complicated by a paradoxical reaction (hence termed unmasking tuberculosis-associated IRIS).

## PARADOXICAL TUBERCULOSIS-ASSOCIATED IRIS

In paradoxical tuberculosis-associated IRIS, patients have been diagnosed with active tuberculosis before initiation of ART, and have typically been responding to anti-tuberculosis treatment. Following initiation of ART, IRIS presents as the development of recurrent, new, or worsening symptoms or signs of tuberculosis, such as fever, return of cough, or lymph node enlargement, or recurrent, new, or deteriorating radiological manifestations . These symptoms typically occur within the first few weeks and up to 3 months after ART is initiated, restarted, or changed because of treatment failure. Reports of the frequency of paradoxical tuberculosis-associated IRIS using a variety of existing case definitions range from 8% to 43%.[4-5] Risk factors for the disease include more advanced HIV disease with lower CD4 cell count, disseminated and extrapulmonary tuberculosis, a shorter delay between the start of tuberculosis treatment and initiation of ART, and a more vigorous immunological and virological response to ART. Most cases of paradoxical tuberculosis-associated IRIS are self-limiting.. Rates of morbidity and mortality attributable to paradoxical tuberculosis-associated IRIS may be higher in resource-limited settings where diagnostic and treatment options are restricted. Neurological tuberculosis-associated IRIS in particular can be associated with poor outcome.

## ART-ASSOCIATED TUBERCULOSIS AND UNMASKING TUBERCULOSIS-ASSOCIATED IRIS

Compared with paradoxical tuberculosis-associated IRIS, there is much less clarity surrounding the second major category of tuberculosis-associated-IRIS. High rates of tuberculosis have been diagnosed during ART, especially in the initial months of treatment in ART programmes[5]. Diagnoses of active tuberculosis before ART initiation might be missed because of the inherent insensitivity of tuberculosis diagnostics in patients with advanced immunodeficiency and only confirmed later during ART. Other patients might have active subclinical disease at the time of ART initiation and presentation of symptomatic disease might result from ART-induced restoration of an immune response against *Mycobacterium tuberculosis* antigens that causes inflammation. Some patients with a missed tuberculosis diagnosis or active subclinical tuberculosis at the time of ART initiation may later present with exuberant inflammatory clinical features that are consistent with a diagnosis of unmasking tuberculosis-associated IRIS .

## CASE DEFINITIONS

With the rationale described above, case definitions have been developed for "paradoxical tuberculosis-associated IRIS", "ART-associated tuberculosis", and "unmasking tuberculosis-associated-IRIS" These case definitions have been designed for use in resource-limited settings and are consensus case definitions that need validation in clinical practice.

### *Case definition for paradoxical tuberculosis-associated IRIS*[6]

There are three components to this case definition:

*(A) Antecedent requirements*

Both of the two following requirements must be met:

· Diagnosis of tuberculosis: the tuberculosis diagnosis was made before starting ART and this should fulfil WHO criteria for diagnosis of smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis, or extrapulmonary tuberculosis.

· Initial response to tuberculosis treatment: the patient's condition should have stabilised or improved on appropriate tuberculosis treatment before ART initiation—eg, cessation of night sweats, fevers, cough, weight loss. (Note: this does not apply to patients starting ART within 2 weeks of starting tuberculosis treatment since insufficient time may have elapsed for a clinical response to be reported)

*(B) Clinical criteria*

The onset of tuberculosis-associated IRIS manifestations should be within 3 months of ART initiation, reinitiation, or regimen change because of treatment failure.

Of the following, at least one major criterion or two minor clinical criteria are required:

*Major criteria*

· New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement—eg, tuberculous arthritis

· New or worsening radiological features of tuberculosis (found by chest radiography, abdominal ultrasonography, CT, or MRI)

· New or worsening CNS tuberculosis (meningitis or focal neurological deficit—eg, caused by tuberculoma)

· New or worsening serositis (pleural effusion, ascites, or pericardial effusion)

*Minor criteria*

· New or worsening constitutional symptoms such as fever, night sweats, or weight loss

· New or worsening respiratory symptoms such as cough, dyspnoea, or stridor

· New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

*(C) Alternative explanations for clinical deterioration must be excluded if possible*

· Failure of tuberculosis treatment because of tuberculosis drug resistance

· Poor adherence to tuberculosis treatment

· Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis has not been microbiologically confirmed)

· Drug toxicity or reaction.

### *Case definition for ART-associated tuberculosis and provisional case definition for unmasking tuberculosis-associated IRIS*[6]

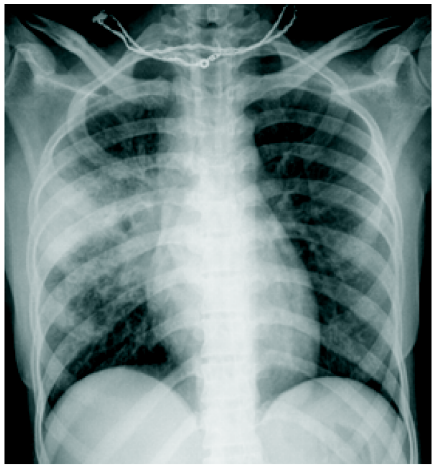
**ART-associated tuberculosis**

ART-associated tuberculosis (all cases of tuberculosis that are diagnosed during ART) should be defined as follows:

· Patient is not receiving treatment for tuberculosis when ART is initiated

· Active tuberculosis is diagnosed after initiation of ART

· The diagnosis of tuberculosis should fulfil WHO criteria for smear-positive pulmonary tuberculosis,



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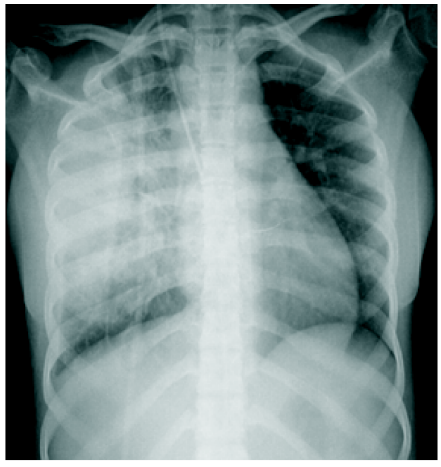
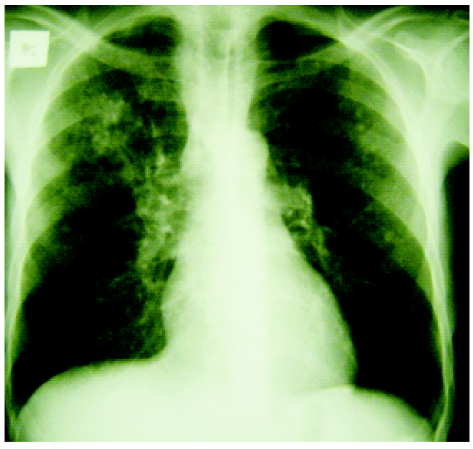


Pic. 1a Paradoxical TB IRIS Pic. 1b

(Picture-1a pulmonar infiltrates before treatment) (Picture-1b increased pulmonar infiltrates after treatment)



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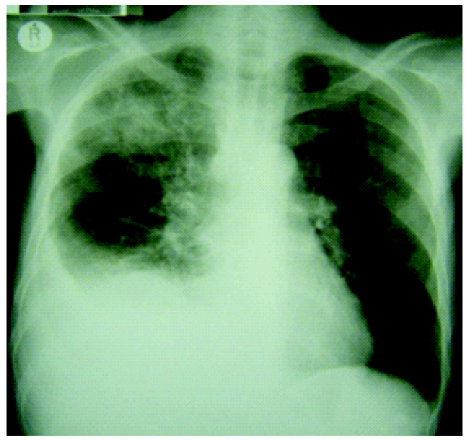
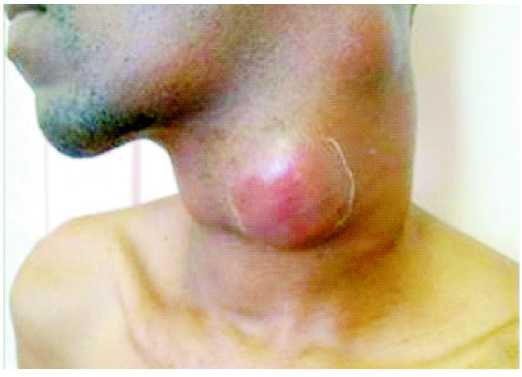
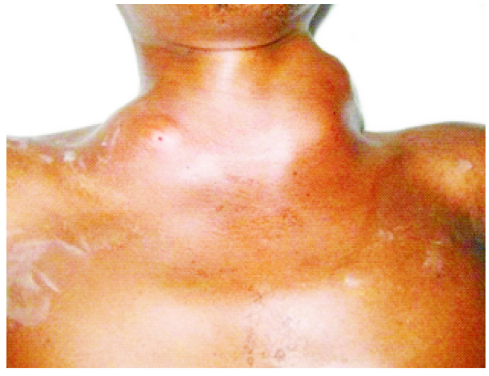


Pic. 2a Paradoxical TB IRIS Pic. 2b

(Picture-2a showing right upper lobe tubercular infiltration before treatment) (Picture-2b appearance of right pleural effusion after treatment)





Pic. 3a Pic. 3b

(Picture-3a & 3b showing Tuberculous lymphadenitis in TB IRIS

smear-negative pulmonary tuberculosis, or extrapulmonary tuberculosis.

**Unmasking tuberculosis-associated IRIS (provisional)**

The following could suggest a diagnosis of unmasking tuberculosis-associated IRIS:

· Patient is not receiving treatment for tuberculosis when ART is initiated and then presents with active tuberculosis within 3 months of starting ART

AND one of the following criteria must be met:

· Heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation. Examples include tuberculosis lymphadenitis or tuberculosis abscesses with prominent acute inflammatory features, presentation with pulmonary tuberculosis that is complicated by respiratory failure due to adult respiratory distress syndrome, and those who present with a marked systemic inflammatory syndrome related to tuberculosis.

· Once established on tuberculosis treatment, a clinical course that is complicated by a paradoxical reaction.

The use of standardised case definitions in different populations will help to provide greater insight into the incidence, clinical manifestations, risk factors, and impact of tuberculosis-associated IRIS, ultimately leading to better prevention and management strategies for this condition.

**Clinical features**

The commonest clinical manifestations of TB-IRIS are fever, lymphadenopathy and worsening respiratory symptoms[7-8]. Pulmonary disorders, such as new pulmonary infiltrates, mediastinal lymphadenopathy, and pleural effusions are also common.

Extrapulmonary presentations are also possible, including disseminated tuberculosis with associated acute renal failure , systemic inflammatory responses (SIRS) , and intracranial tuberculomas . Pulmonary TB-IRIS can be diagnosed by transient worsening of chest radiographs, especially if old radiographs are available for comparison. Other symptoms are nonspecific, and include persistent fever, weight loss, and worsening respiratory symptoms. Abdominal TB-IRIS can present with nonspecific abdominal pain and obstructive jaundice. (Pic.1a, 1b, 2a, 2b, 3a, 3b)

**MANAGEMENT OF TB-IRIS**

Most cases of TB-IRIS have a self-limited course and will resolve with continuing treatment with little or no change in overall management[9]. Use of non-steroidal anti-inflammatory agents may provide adequate relief of symptoms in mild cases, though the effectiveness of this approach remains unproven. Patients should continue anti-tuberculous therapy without change unless there is a reason to suspect the current regimen is inadequate (for example if MDR-TB is suspected, or drug-drug interactions could result in suboptimal serum anti-TB drug levels).

In nearly all cases, the patient with TB-IRIS should remain on antiretroviral therapy. Certain circumstances, however, may require temporary interruption of antiretroviral therapy, such as when life-threatening complications of IRIS develop (e.g. increasing intracranial pressure in the setting of TB meningitis, or an expanding abscess that compromises the patient's airway).

Although criteria for initiating corticosteroids remain poorly defined, administering prednisone for TB-IRIS cases when patients have persistent fever, abscesses, meningitis, or dyspnea is recommended[9]. The dosing and duration of corticosteroids should be tailored to individual patient circumstances. Patients with moderate to severe TB-IRIS should receive prednisone dosed at 1.5 mg/kg/day for 2 weeks, followed by a taper of 0.75 mg/kg/day over 2 additional weeks. Some patients, particularly those with very high mycobacterial loads or severe clinical deterioration, may require prolonged courses of corticosteroids.

**CONCLUSION**

Though IRIS occurs only in a small fraction of

patients undergoing HAART, it should be kept in mind in all patients who undergo clinical deterioration after starting ART inspite of there being laboratory evidence of increasing CD 4 cell counts. The use of standardised case definitions will help to provide greater insight into the incidence, clinical manifestations, risk factors, and impact of tuberculosis-associated IRIS, ultimately leading to better prevention and management strategies for this condition.

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*Review Article*

# ASSESSMENT OF MALNUTRITION IN THE GERIATRIC OUTDOOR

***P.K. Rathor **S. Moharana ***R. Sen, *P. Jena, ****D.N. Moharana**

## INTRODUCTION

The progressive ageing of the Indian population has resulted in increased prevalence of functional deterioration and also in the increased risk of hospitalization in the elderly. This has necessitated the development of a special evaluation system, the Comprehensive Geriatric Assessment(CGA), which would help in assessing the clinical, psychological, functional and socioeconomic changes associated with ageing and it is now considered essential in the practice and research in geriatrics.

### Comprehensive Geriatric Assessment: Aims, domains and process

The CGA is a multi-dimensional process[1] covering 4 broad assessment domains : medical status, functional status, psychological function and socioeconomic status. The assessment requires amultidisciplinary team involving a physician supported by a nurse, social worker, physiotherapist and psychologist.

The main aim of the CGA is the diagnosis of treatable conditions, including medical diagnoses and also psychological or social problems,so as to establish a rational therapeutic planand to ensure the appropriate use of services.

### Structure of the CGA process

In the CGA, the initial evaluation generates a list of problems, which serves as a platform for developing a plan of care in the team. Repeated evaluations are then performed to study the impact of the interventions and to assess the progress of medical, social and functional problems.[2-3] For being universally acceptable, the CGA has to be systematic, reproducible, objective and comparable.

### Malnutrition is a common geriatric problem requiring regular screening

Almost upto 80% of the hospitalized patients in the geriatric age group may be at risk of or are already suffering from malnutrition. In the community, the prevalence of malnutrition in the elderly ranges from 2% to 6%. However this situation frequently remains unrecognized and untreated in clinical practice.

Malnutrition has a detrimental role on the physical and cognitive function in the elderly and leads to increased vulnerability to incident disability and results in reduced quality of life. These changes may be reflected through changes in muscle mass (sarcopenia) and muscle quality,[5,6,7] bone alteration and cognitive dysfunction. Malnutrition may also lead to higher risk of complications and longer duration of hospital stay as well as higher risk of institutionalization and death.

Malnutrition, because of its high prevalence in the elderly, its multifactorial etiology and its high impact on negative outcomes,needs to be systematically screened.

### Nutritional issues in geriatric population

With increasing age there occurs nutritional problems like alterations in taste and smell, dysphagia which leads to increased risk of silent aspiration and pneumonia and a number of other functional changes in the GI tract.[8] GI changes that might occur include: impaired oesophageal peristalsis, decreased transpyloric flows and delayed gastric emptying, atrophic gastritis resulting in reduced absorption of different nutrients, increased colon transit times, constipation, diverticula etc.[9-10] The secretion of hormones (eg. Cholecystokinin,

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ghrelin, and leptin) neurotransmitters andcytokines may also be altered.

Some specific disorders like dysphagia,due to their high prevalence in the geriatric population, may require specific screening using specific tools. Other relevant factors that need to be identified include dementia, depression and decreased visual acuity, poor dentition etc. Commonly used medications like laxatives, digoxin etc which adversely affect appetite also need to be considered.

Some tools used in nutritional screening incorporate a number of factors which are directly associated with nutritional status – like mobility, cognition and co-morbidity. As malnutrition and dysphagia affects various facets in nutritional diseases,comprehensive and integrated strategies should be in place in different healthcare settings to detect, prevent and treat malnutrition.

**Screening is the first step in the treatment of malnutrition**

Assessment of nutritional status includes screening, diagnosis and monitoring of treatment. A standardized assessment helps in communicating relevant information between healthcare professionals and care settings.

Nutritional screening tools allow the identification of individuals at risk of malnutrition or those who are frankly malnourished thereby allowing further extensive assessment of their condition followed up by necessary nutritional interventions.[11]

As malnutrition is endemic in the elderly population, all institutionalized patients need to be screened at admission and periodically thereafter. For community dwelling elderly persons, a yearly routine examination is appropriate. Screening tools are also necessary in follow up for assessing the impact of the interventions. The screening tool assesses the current condition (eg. Body mass index, stability [weight loss], likelihood of progression [food intake]) and any comorbidity that could affect nutritional status.[12-13]

If frank malnutrition or actual risk of malnutrition is detected in the screening tools, nutritional assessment and physical examination needs to be performed quickly to quantify the severity of malnutrition, identify the underlying causes, guide nutritional intervention.

A detailed medical history, with focus on medical, psychological and social aspects needs to be taken. Mental and functional status of the patients need to be evaluated and medicines, presently being consumed by the patients need to be enumerated. Dietary assessment includes information about the patient's dietary habits and information about the food consumed by the patient in the previous few days.

In general physical examination,

I. General appearance
II. Condition of skin, hair and mucus
III. Detailed examination of oral cavity (ie. Presence or absence of teeth, oral hygiene etc)
IV. Anthropometric measurements such as weight status (recent percentage weight loss)
V. BMI
VI. Mid arm circumference need to be assessed.

**Laboratory tests that are useful include:-**

Haemogram, Total protein, Albumin, Prealbumin, Cholesterol, Transferrin.

**Tools used in identification of elderly at risk of malnutrition**

Mini Nutritional Assessment(MNA) and MNA (Short Form)

The MNA is being widely used in clinical practice.It was specifically developed by geriatricians in1994 to include nutritional screening as a part of CGA.

The MNA which can be performed in 10-15 mins, is considered to be the best screening and assessment tool for older people. It shows good prognostic value, and is useful for follow up.[8]

The MNA includes 18 items grouped in four fields.

Anthropometrics

I. BMI
II. Weight loss
III. Arm and chest circumference

General Assessment

I. Lifestyle
II. Medication
III. Mobility
IV. Presence of depression
V. Dementia

Dietary Assessment
I. Number of meals
II. Food and fluid intake
III. Autonomy to eat
Subjective assessment
Self perception of health and nutrition
The total score ranges from 0 to 30.[8 - 13]
>24 ——-> well nourished
17-23.5 ——> at risk of malnutrition
< 17 —-> malnourished

**MINI NUTRITIONAL ASSESSMENT** [8, 13]

**Part - I Anthropometric Assesment**

Instructions: Complete this questionnaire by writing the number of points scored in the boxes at the right of the questions. Add the numbers in the boxes and compare the total assessment to the Malnutrition Indicator Score.

| | | |
|---|---|---|
| 1. | Body Mass Index(weight in Kg)/(height in m) =<br>BMI < 19 = 0 points<br>BMI 19 to < 21 = 1 point<br>BMI 21 to < 23 = 2 points<br>BMI > 23 = 3 points | Points |
| 2. | Measure of Mid –arm circumference (MAC) in cm.<br>a. MAC < 21 cm. = 0.0 points<br>b. MAC 21 < 22 cm. = 0.5 points<br>c. MAC >22 cm. = 1.0 points | |
| 3. | Measure of Calf circumference (CC) in cm.<br>a. CC < 31 cm = 0 points<br>b. CC > 31 cm =1 point | |
| 4. | Have you had a weight loss during the last 3 months<br>weight loss greater than3kg(6.6 lbs.)= 0 points<br>Does not know = 1 point<br>weight loss between 1 and 3 kg.<br>(2.2 lbs. and 6.6 kg.) = 2 points<br>C. No weight loss = 3 points | |

Total points for this section I = _____
Add points for Section II General Assessment = _____
Section III Self Assessment = _____

**Part II. General Assesment**

Instructions: Complete this questionnaire by writing the number of points scored in the boxes at the right of the questions. Add the numbers in the boxes and compare the total assessment to the Malnutrition Indicator Score.

**PART III. Self Assessment**

Section I Anthropometric Assessment Points = _____
Section II General Assessment Points = _____
Section III Self Assessment Points = _____

**MINI NUTRITIONAL ASSESSMENT**
**PART-IV Dietary Assessment**

| | | |
|---|---|---|
| 1. | How many meals do you eat daily?<br>1 full meal daily = 0 points<br>2 full meals daily = 1 point<br>3 full meals daily = 2 points | **MALNUTRITION INDICATOR SCORE**<br>> 24 points = Well nourished _____<br>17 to 23.5 points = at risk for malnutrition_____<br>< 17 points = malnourished _____ ***Consult nutritionist |
| | | |
| 2. | Selected consumption markers for protein intake<br>At least one serving of dairy products (milk, cheese, yogurt) per day?<br>**Yes**____ **No**____<br>Two or more servings of legumes or eggs per week?<br>**Yes**____ **No**____<br>Meat, Fish, or Poultry every day?<br>**Yes**____ **No**____<br>If 0 or 1 Yes responses = 0.0 points<br>If 2 Yes responses = 0.5 points<br>c. If 3 yes responses = 1.0 points | Total points for Section IV Dietary Assessment = _____<br>**Add to**<br>Section I Anthropometric Assessment Points = _____<br>Section II General Assessment Points = _____<br>Section III Self Assessment Points = _____ |
| 3. | Do you consume 2 or more servings of fruits or vegetables per day?<br>No = 0 points<br>Yes = 1 point | **ASSESSMENT TOTAL POINTS (Maximum 30 points)) TOTAL = _____** |
| 4. | Has your food intake declined over the past three months due to loss of appetite, digestive problems, chewing or swallowing problems?<br>severe loss of appetite = 0 points<br>moderate loss of appetite = 1 point<br>no loss of appetite = 2 points | |
| 5. | How much fluid (water, juice, tea, milk …)do you consume daily?<br>(1 cup = 8 ounces)<br>less than 3 cups = 0.0 points<br>3 to 5 cups = 0.5 points<br>More than 5 cups = 1.0 points | |
| 6. | Ability to feed self<br>a. requires assistance with meals/feeding = 0 points<br>b. able to feed self, but has some difficulty = 1 point<br>c. able to feed self independently (no problems) = 2 points | |

In 2001, the MNA-SF was developed by Rubenstein and colleagues by incorporating 6 items from the full MNA and it demonstrated high specificity and correlation with full MNA.The maximum score of revised MNA-SF is 14; with a score of

>12 indicating good nutritional status

8 -12 indicating risk of malnutrition

< 7 indicating malnutrition[15]

**Complete the screen by filling in the boxes with the appropriate numbers. Total the numbers for the final screening score.**

**IF BMI IS NOT AVAILABLE, REPLACE QUESTION F1 WITH QUESTION F2.**
**DO NOT ANSWER QUESTION F2 IF QUESTION F1 IS ALREADY COMPLETED.**

**Nutritional Risk Screening(NRS 2002)**

This was developed for adult hospitalized patients.[16] It is atwo step process : a positive answer to any one of the following questions (about weight loss, BMI, oral intake, acute disease) leads to the second step which includes measures for nutritional status and disease severity. One additional point is to be added when the patient is 70 years or older. A final score of > 3 implies necessity of nutritional intervention while for scores of < 3 weekly screening is recommended.

**Malnutrition Universal Screening Tool(MUST)**

This was developed to detect both under nutrition and obesity in adults of different ages.[17] MUST includes measures of weight status (BMI and recent percentage weight loss) and the presence of acute disease resulting in no food intake food than 5 days. This method classifies patients into low risk (score of 0), medium risk (score of 1) and high risk of malnutrition(score of >2)

**Identification of dysphagia by screening**

Dysphagia is an important and common cause of malnutrition in the elderly with the presence being as high as 60% in some settings. Many neurological conditions (stroke,Parkinson's disease, dementia) or oropharyngealdiseases(eg. Head and neck cancer) present with dysphagia. Dysphagia ultimately results indehydration and malnutrition which can be prevented by early diagnosis and early treatment.

The Eating Assessment Tool (EAT-10) helps in the subjective assessment of dysphagia.[19] The patient rates his/her perceived level of difficulty on a scale of 0-4(0= no problem and 4=severe problem) and the whole test can be completed within 2 minutes. A score of more than 3 indicates presence of dysphagia. For such patients more sophisticated tests like the Volume – Viscosity Swallow Test(V-VST) is required.[20,21]

The V-VST is essential for the early diagnosis of oropharyngeal dysphagia.The patient is given boluses of increasing viscosities and volumes, with the test helping to select the most efficient volume and viscosity of bolus for each patient to ingest fluids.

If the EAT-10 score is 3 or higher or the V-VST is positive, the patient ought to be assessed by a speech swallow therapist and a nutritionist.Procedures like video fluoroscopy or endoscopy may be indicated. Nutritional assessment, food adaptation and adequate follow up care are needed.

**CONCLUSION**

Comprehensive geriatric assessment which explores medical, functional, psychological and socio economic status continues to be an evolving concept in geriatric practice.It is not routinely used, mostly because of time constraints in routine clinical practice. In this scenario, screening tools,generic or specific, single or multidimentional, are often useful.Further studies need to focus on the validity and reproducibility of the commonly used screening methods.

Malnutrition, being a common geriatric syndrome and arisk factor for several negative outcomes,needs extensive investigation. Among the screening tools, the MNA and the MNA-SF are being extensively used in clinical practice.this nutritional screening tool studies the different factors that might be related to reduced oral intake and malnutrition. Early diagnosis of malnutrition is essential in planning and implementing necessary interventions. In some cases dysphagia is a cause of malnutrtition and in such cases routine screening for dysphagia should be performed as a first step before proceeding for other investigations. The EAT-10 score is arapid, easy to use tool in this regard.

In general, the use of screening tools as a first step should be encouraged as it helps to focus on specific aspects that merit more detailed investigations.

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*Current Concept*

# MANAGEMENT OF HYPERGLYCEMIA IN ICU

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## INTRODUCTION

Hyperglycemia refers to rise in blood glucose level >100mg/dl which is an invariable feature in DM. Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. Epidemiology alone would make diabetes a common problem in the intensive care unit (ICU), but poorly controlled diabetes also predisposes to cardiovascular, renal, and infectious complications that often require intensive surgical and medical care. In addition, diabetes frequently occurs in severely ill ICU patients who have no prior history of the disease.

Whatever the primary problem, diabetes amplifies the challenges of intensive care. Often, diabetes itself is the primary problem, as in ketoacidosis and hyperosmolar coma. Whether diabetes is the primary or secondary disorder in an ICU patient, the effects of insulin deficiency and stress on metabolic homeostasis are the same.

### Diagnosis of Diabetes in the Intensive Care Unit

All acutely ill patients should have their blood glucose level measured at entry into the ICU and at regular intervals throughout their stay there. Any elevated glucose concentration should prompt closer scrutiny. Seriously ill patients with hyperglycemia may have a preexisting diagnosis of diabetes, but the majority will not. In one study of 1,200 subjects treated in a medical ICU, 70% of individuals at some time experienced a plasma glucose concentration more than 215 mg per dL, and only about 17% of these patients had a prior history of diabetes[1] . Newly discovered hyperglycemia may be seen in individuals who were unaware of preexisting diabetes, in cases of new-onset type 1 diabetes, or in patients who develop diabetes in response to their primary illness. Diabetes diagnosed in the ICU may or may not persist after the patient recovers. Hyperglycemic ICU patients should be evaluated for persistence of impaired glucose tolerance after recovery.

### Why Control hyperglycemia in the Intensive Care Unit?

Hyperglycemia in the Intensive Care Unit Predicts Adverse Outcome. It is intuitively plausible to assume that glucose concentration should always be in the normal range, and studies show that hyperglycemia in the ICU is associated with adverse outcome. Even mild hyperglycemia (plasma glucose concentration more than 110 mg per dL) has been shown to predict increased in-hospital mortality and the risk of congestive heart failure in patients with acute myocardial infarction[2]. Hyperglycemic patients also have an increased risk of wound infection as well as overall mortality following cardiac surgery. Hyperglycemia is also associated with poor outcome in patients with stroke. Even patients in whom diabetes is diagnosed

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for the first time during an ICU admission reportedly have an 18-fold increase in their risk of in-hospital mortality.

**How Does Hyperglycemia Adversely Affect Outcome?**

Hyperglycemia predisposes to disturbances in sodium, potassium, and phosphate concentrations. Because uncontrolled diabetes also provokes an osmotic diuresis, symptomatic hyponatremia can result. Hypokalemia predisposes to arrhythmia, and hypophosphatemia may interfere with platelet function and white cell motility. Control of glycemia prevents these problems and the need for compensatory correction. The susceptibility of patients with diabetes to infection is well recognized. Uncontrolled glycemia appears to impair innate immunity (cytokine responses), granulocyte function (chemotaxis, phagocytosis, and killing), and, possibly, lymphocyte function and antibody formation. Some microorganisms become more virulent in a high-glucose environment. Endothelial function may also be impaired by hyperglycemia. In general, better regulation of diabetes leads to improvement in these parameters.

**What Is the Evidence That Control of Blood Glucose Concentration Alters Clinical Outcome in Intensive Care Unit Patients?**

Recognizing that hyperglycemia is bad is not the same as saying that control of hyperglycemia in the ICU is beneficial. Attempting to normalize blood glucose concentration in the ICU is not without risk. The available evidence does not yet establish that intensive management of diabetes is unequivocally beneficial.

The best evidence for benefit attributable to intensive management derives from studies performed in a surgical ICU setting. Intensive insulin treatment reportedly improves myocardial performance and results in faster recovery after coronary artery bypass grafting . Continuous intravenous insulin infusion also reduces the risk of sternal wound infection in diabetic patients after cardiac surgical procedures . The studies reporting benefit, however, did not seek to normalize plasma glucose concentration. A more recent prospective study of surgical ICU patients by Van den Berghe et al. reported that intensive insulin therapy with a target plasma glucose concentration less than 110 mg per dL reduced in-hospital mortality by 34%, septicemia by 46%, acute renal failure by 41%, and critical-illness polyneuropathy by 44%[3] This study in particular, together with the results of retrospective studies, has generated widespread enthusiasm for the concept that intensive glycemic control is important in critically ill patients.

A question raised after release of the results of the study by Van den Berghe et al. was whether intensive management would show similar benefit in the medical ICU. In the mid-1990s a randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction had revealed a beneficial effect on mortality. In that study the mean glucose concentration in the intensively treated group was 173 ± 59 mg per dL. Another study reported a reduction in mortality in a small medical-surgical ICU after implementation of an intensive diabetes management protocol, but the study was not a randomized trial. Surprisingly, however, a subsequent report from the Van den Berghe et al. reported that intensive insulin therapy of patients in a medical ICU, while improving several indices of morbidity, did not reduce in-hospital mortality. Disturbingly, hypoglycemia (less than 40 mg per dL) occurred in 18% of subjects in the intensively treated group versus 3% of those in the conventionally treated group, and hypoglycemia was identified as an independent risk factor for death[4]. The data concerning hypoglycemia were particularly surprising as this problem had not been encountered in several other studies designed to evaluate the safety and practicality of implementing intensive insulin protocols in ICU settings .

This lack of a robust evidence-based and consistent dataset led to the implementation of two multicenter randomized controlled trials of blood glucose management in heterogeneous ICU populations. The

GLUControl trial & NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation). The GLUControl trial[5] is randomized 3,000 medical and surgical ICU patients in several centers in Europe to two regimens of insulin therapy targeted to achieve a plasma glucose concentration of either 80 to 110 mg per dL or 140 to 180 mg per dL. The NICE-SUGAR[6] (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) trial randomised 5,000 medical and surgical ICU patients at multiple centers in Australia, New Zealand, and Canada to intensive or conventional glycemic control . According to GLUControl trial incidence of severe hypoglycemia (BG<40 mg/dL) was significantly more frequent in patients assigned to tighter control group. Risk of death was not increased by hypoglycemia. No difference in mortality 17% vs. 15% and the conclusion of the authors was that there are no apparent benefits of tight glucose control. According to NICE-SUGAR trial 829 patients(27.5%) died in the intensive control group and 751(24.9%) in the conventional-control group which is a difference of 2.6%. Severe hypoglycemia(<40mg/dL) was recorded in 6.8% of patients in the intensive control group, vs. 0.5% in the conventional group. No difference between the two groups in median length of ICU or hospital stay & no difference between number of days of mechanical ventilation, positive blood cultures, or RBC transfusions.

These startling findings of these two large RCTs has raised doubts on the intensive insulin therapy regimen as advocated earlier with a plasma glucose goal of 80-140 mg/dl.Based on the NICE-SUGAR trial findings the American Association of Clinical Endocrinologists (AACE) released a newsletter dated 26th March 2009 in which they have stated that "*The Endocrine Society believes that we have entered an era of more nuanced and patient-appropriate recommendations as a result of these recent large, well-done outpatient and inpatient studies. We believe physicians should individually tailor their approach to glycemic control in their ICU patients, perhaps targeting glucose values between 144-180 mg/dl, until we better understand the reasons for these somewhat counterintuitive findings."*

Also the recent 2011 ADA guidelines echoes the same with plasma glucose goal of 140-180 mg/dl in critically ill patients. More stringent goals, such as 110-140 mg/dl may be appropriate for selected patients, if achievable without significant hypoglycemia .

**Goals**

It is recommended first that all critically ill or surgical patients with a plasma glucose concentration more than 180 mg/dL be treated to lower that concentration. Second, after treatment has been instituted, plasma glucose concentration should be maintained as close to the normal range as is safely possible. Glucose concentrations less than 140 mg /dL are avoided because they pose the hazard of hypoglycemia .

**Treatment of Hyperglycemia in the Critically Ill**

All ICU patients with plasma glucose concentrations persistently above 180 mg/dL should be treated with a continuous intravenous infusion of regular insulin. This applies to all patients, without regard to previous history of diabetes or previous treatment modalities. Patients known to have type 1 diabetes are absolutely insulin-dependent, and they must be treated with exogenous insulin at all times. Oral hypoglycemic agents should not be used in the ICU for many reasons. Their absorption, metabolism, and excretion cannot be predicted in the critically ill patient. Sulfonylureas can cause severe hypoglycemia and metformin in particular should be discontinued in critically ill patients because it can cause lactic acidosis in the setting of renal failure.

Recommendations for the institution and management of patients with ketoacidosis or hyperosmolar syndrome are given immediately after this section. For patients whose primary ICU diagnosis is not diabetic coma and whose initial plasma glucose concentration is less than 600 mg per dL, the recommend the treatment regimen is following.

| | | | | | |
|---|---|---|---|---|---|
| 217-252 | =217<br><br>218-236 | <br><br>Same or inc | | Current insulin dose (u/hr)+2u/hr<br>Plus optional 1-2u stat dose<br>Current insulin dose (u/hr)+1u/hr<br>Plus optional 1-2u stat dose | 1 hr |
| | 237-252 | Dec of =18 | | | |
| | 253-289 | Dec of<br>19-71 | | Current insulin dose (u/hr)<br>Plus optional 1-2u stat dose | 2 hr |
| | 290-324 | Dec of=72 | | Current insulin dose (u/hr)<br>×(current BSL÷previous BSL)<br>Or maintain current insulin dose | 1 hr |
| | >324 | | | | |
| >252 | <217<br><br><br>217-252 | | | Current insulin dose (u/hr)<br>×2(current BSL÷previous BSL)<br>Plus optional 1-2u stat dose<br>Current insulin dose (u/hr)+2u/hr<br>Plus optional 1-2u stat dose | 1 hr |
| | >252 | inc | | Current insulin dose (u/hr)<br>×2(current BSL÷previous BSL)<br>Plus optional 1-2u stat dose | |
| | | Same or dec of=36 | | Current insulin dose (u/hr)+2u/hr<br>Plus optional 1-2u stat dose | |
| | | Dec of<br>37-71 | | Current insulin dose | 2 hr |
| | | Dec of =72 | | Current insulin dose (u/hr)<br>×(current BSL÷previous BSL)<br>Or maintain current insulin dose | 1 hr |

| **NICE-SUGAR STUDY INITIAL INSULIN INFUSION PROTOCOL** | | |
|---|---|---|
| **First BGL in ICU (mg/dl)** | **Action to be taken** | **Next BGL check** |
| <45 | **NO INSULIN**<br>Ensure background nutrition or glucose infusion<br>Give bolus 20ml 50% glucose, recheck BGL | 30 & 60 mins |
| 45-62 | **NO INSULIN**<br>Ensure background nutrition or glucose infusion<br>Give bolus 10ml 50% glucose, recheck BGL | 30 & 60 mins |
| 63-81<br>82-180 | **NO INSULIN**<br>**NO INSULIN** | 1 hr<br>1 hr |
| 181-216 | 1 u/hr | 1 hr |
| 217-270 | 2 u/hr | 1 hr |
| 271-324 | 3 u/hr | 1 hr |
| >324 | 4 u/hr | 1 hr |

**Insulin Therapy**

The recommended insulin infusion algorithm that to a achieve a target blood glucose concentration of 140 -180 mg per dL is shown in the Figure . This protocol requires adjustment of the insulin infusion rate in response to both the absolute value and the rate of change of the plasma glucose concentration. Glucose concentration should be checked hourly until it is in the target range, and every 2 hours thereafter. During this initial period, adjustments to the insulin infusion rate will depend on the patient's sensitivity to insulin (see following discussion) and the observed response to therapy. These cannot be exactly predicted. Concurrent glucose infusions or parenteral or enteral feeding will affect the dose required.

It should be stressed that it is entirely appropriate to infuse insulin at low rates (e.g., 0.5 U per hour). A low rate of insulin infusion is often all that is needed to prevent ketoacidosis in a patient with type 1 diabetes. Only regular (crystalline) insulin is approved for intravenous infusion in the United States. There is no advantage to the use of rapid-acting semisynthetic insulin for this purpose, but it can be used when regular insulin is unavailable.

**Adjustment of the Insulin Infusion Rate**

The amount of insulin required by a given ICU patient will depend in large part on the degree of insulin resistance induced by the primary illness and its treatment and by the patient's body mass index. It will also depend on the type and amount of nutritional support being given. An escalating insulin infusion requirement is a sensitive indicator of increasing insulin resistance and requires careful reevaluation of the patient's overall metabolic status. Stressors that increase insulin resistance include sepsis, occult infections, heart disease, tissue ischemia, hypoxemia, and various medications. The most common offending medications are glucocorticoids and vasopressors.

In otherwise stable patients, instituting or increasing enteral or parenteral nutrition typically increases insulin requirements. Insulin-mediated glucose disposal is impaired in stressed patients with diabetes, and even extremely high insulin infusion rates cannot prevent hyperglycemia due to unmanageable carbohydrate loads. To control hyperglycemia in the ICU, a choice must sometimes be made between increasing insulin infusion rates and reducing carbohydrate feeding. Insulin infusion rates not be increased beyond 20 U per hour (480 U per day) without first decreasing any exogenous carbohydrate loads, especially in patients who are obese[6]. This suggestion is based on the fact that maximal insulin effects are achieved when only some of the available insulin receptors are occupied. High concentrations of insulin, such as those achieved during continuous intravenous infusions at high rates, desensitize target tissues at both the receptor and postreceptor levels, paradoxically enhancing insulin resistance.

Factors that increase insulin sensitivity in the ICU include improvement in any intercurrent illness, changes in medication, and reductions in enteral or parenteral feeding. Occasionally, hepatic failure, renal failure, or adrenal insufficiency leads to a decreased insulin requirement.For patients with type 1 diabetes, it is always inappropriate to stop insulin infusion because discontinuation of insulin can precipitate hyperglycemia and ketosis within hours. The proper response is to reduce the insulin infusion rate to 1 or even 0.5 U per hour and, if necessary, to give glucose in the form of 5% dextrose in water. It is also the same strategy for most other hyperglycemic ICU patients as well. Unless their primary disease state has improved dramatically, they frequently experience recurrent hyperglycemia. Patients with diabetes in the ICU should receive continuous intravenous insulin until they demonstrate clear improvement in overall clinical status and stability of glycemic control that extends over several blood glucose determinations.

**Transition to Other Forms of Therapy**

When the condition of an ICU patient with diabetes has improved to such an extent that continuous insulin infusion is no longer needed, subsequent therapy

will depend on the type of diabetes. Patients with secondary• drug-induced diabetes (e.g., catecholamine- or steroid-induced) may need no further treatment for glucose control after the offending drug is stopped. In contrast, all patients with type 1 and most with type 2 diabetes will continue to require insulin. For these patients, twice-daily subcutaneous injections of intermediate-acting insulin (neutral protamine hagedorn [NPH] insulin) should be started as the infusion is being discontinued.

It is not uncommon for glycemic control to deteriorate during the transition from intravenous insulin therapy to subcutaneous insulin therapy. It is essential that the intravenous infusion of regular insulin be continued for 2 to 3 hours after the first subcutaneous injection of NPH insulin is given. The initial dose of subcutaneous NPH insulin should be estimated from a review of the preceding intravenous insulin requirements. Presumably the individual ready to transition to subcutaneous therapy will have had reasonably stable insulin requirements. The recommendations are basing this dose on the average hourly insulin requirement during the 6 hours prior to discontinuation of the insulin drip using the following procedure:

Calculating the Starting NPH Insulin Dose

- The average hourly insulin drip rate for the last 6 hours is ____units/hr.
- Multiply by 24 to give a daily usage rate: ____units/day.
- Multiply by 70% to estimate the first day's total NPH dose: ____units.
- Administer in divided doses twice daily. Dose adjustment may be necessary after first dose given. Review daily thereafter.

These guidelines, in use at the University of Massachusetts Medical Center, are not intended to supplant clinical judgment. A continuous source of glucose (total parenteral nutrition [TPN], intravenous [IV] dextrose, or enteral feeds) is recommended for all patients receiving an insulin infusion. As with all guidelines, it should be expected that individual patients might require modifications to the basic recommendations.

The use of twice-daily intermediate-acting NPH insulin is convenient during this transition from intravenous to subcutaneous therapy because it provides the opportunity to reassess the patient's clinical status and to adjust subsequent doses twice daily. When patients who are eating experience postprandial hyperglycemia, a rapid-acting insulin (e.g., lispro, aspart, or glulisine) can be added. It is suggested that patients not be transitioned to longer-acting insulins such as glargine or detemir until they have been transferred out of the ICU. Some stable patients with type 2 diabetes can be managed with oral hypoglycemic agents or diet alone, but again, that therapeutic decision is best made after discharge from the ICU on a regimen of subcutaneous injections of intermediate-acting NPH insulin.

## PITFALLS IN THE CARE OF THE CRITICALLY ILL PATIENT WITH DIABETES

### Sliding Scales

We cannot overstate the need to obtain frequent blood glucose specimens for evaluating glucose control. In an ICU, these should be used to guide adjustments of the rate of insulin infusion. There is no role for intermittent insulin boluses that are given only after hyperglycemia has occurred ; the use of sliding scales• should be actively discouraged. Patients with type I diabetes whose insulin is withheld until hyperglycemia occurs can quickly become ketoacidotic.

A patient who has begun taking insulin should continue to receive it daily until the need has unequivocally disappeared. A previously normoglycemic patient who develops diabetes in the course of a severe illness should be treated continuously with insulin until the stress of the illness has been reduced to the point at which an independent assessment of the need for insulin can be made.

### Sporadic Insulin Administration

Unfortunately, some patients are treated with regular insulin injections on an intermittent schedule,

whenever a very high blood glucose concentration is noticed. This disorganized approach to the management of diabetes leads to erratic glycemic control and potentially serious shifts in fluids and electrolytes. The best way to avoid these problems is to maintain ICU patients with diabetes on a continuous infusion of regular insulin.

**Hypoglycemia due to Sensitivity to Short-Acting Insulin**

Unusual sensitivity to insulin can be observed in two situations. The first is in some patients presenting with hyperosmolar hyperglycemic syndrome. When treated with short-acting insulin, their glucose concentration my decline very rapidly. The second situation occurs in patients with long-standing type 1 diabetes. They sometimes develop extreme sensitivity to the glucose-lowering effects of short-acting insulin. The reason is unclear, but this sensitivity frequently contributes to increased risk of hypoglycemia in these patients. This is principally a problem in outpatient management and should rarely complicate ICU diabetes management with insulin infusions. However, in the insulin-dependent patient with long-standing diabetes, the initial use of short-acting insulin should be approached with some caution. Hypoglycemia can result from the use of as little as 5 to 10 U given either subcutaneously or intravenously. When short-acting insulin is needed for patients who are suspected to be sensitive, the initial doses should be small (2 to 4 U) and the response monitored by bedside blood glucose determinations

## CONCLUSIONS

Key to successful care of the very ill patient with diabetes is careful monitoring of glycemia and fastidious treatment with a continuous infusion of insulin. All these patients have a defect in normal metabolic regulation, and only attentive treatment can compensate for the diabetes during the metabolic stress of critical illness or surgery. Careful monitoring of blood glucose followed by adjustment of insulin infusion rates minimizes swings to either hyperglycemia or hypoglycemia. Bedside blood glucose determinations make this intensive metabolic care possible not only in the ICU but also in the operating room, recovery room, emergency department, and procedure suite. The diabetic comas are often described as discrete entities, but they frequently present as overlapping disorders . Patients in DKA often have concurrent mild lactic acidosis and may also develop hyperosmolality. Initial treatment of all diabetic comas must always emphasize fluid and electrolytes. DKA and HHS also require insulin. Physicians must obtain the relevant history, perform a thorough physical examination, classify the disorder, and treat appropriately. With care, nearly all patients with DKA and most with HHS can survive.

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*Current Concept*

# SHOULD BETA BLOCKERS BE FAVORED AS FIRST LINE ANTIHYPERTENSIVE AGENTS ?

**D.R. Das***

**ABSTRACT**

*Beta blockers are heterogenous class of agents with diverse pharmacologic properties, The unfavorable data revealed in the recent meta-analysis is from studies involving the traditional beta blockers (propranalol, atenolol) which are non vasodilating. The vasodilating beta blockers (carvedilol, nebivolol, bisoprolol) reduce blood pressure through reduction of systemic vascular resistance rather than decreasing cardiac output as is seen with traditional beta blockers. Traditional beta blockers have adverse effects on metabolic and lipid parameters whereas vasodilating beta blockers have neutral or beneficial effects on metabolic and lipid parameters. Vasodilator beta blockers lower BP to a similar degree as other antihypertensive drugs. They also provide better central aortic pressure reduction than traditional beta blockers. It is unlikely that there will be a single first line drug for hypertensives as most patients will eventually require multiple drugs to control their blood pressure. The choice of treatment will be influenced by associated co-morbidities, underlying cardiovascular risk factors, age of the patient and potential adverse effects.* ***Keywords*** *: Beta blockers, Hypertension*

## INTRODUCTION

Beta blockers have been widely prescribed to treat hypertension over the years. While the benefits of these agents in reducing cardiovascular events in people with preexisting heart disease are clear[1], their clinical benefits in individuals with uncomplicated hypertension are less well-defined. Questions have been raised about beta blockers as first-line treatment options in hypertension[2]. Recent meta-analyses have questioned whether beta blockers are an appropriate therapy given outcomes data for other antihypertensive drug classes. Much of the unfavorable reports were from studies involving non vasodilating, traditional beta blockers such as atenolol. Vasodilatory beta blockers (carvedilol, nebivolol, bisoprolol) reduce blood pressure (BP) by reducing systemic vascular resistance while maintaining cardiac output rather than reducing cardiac output as is observed in atenolol, propanolol. Vasodilatation may also ameliorate adverse effects on metabolic and lipid parameters including an increased risk for new onset diabetes. In patients with hypertension and diabetes or coronary artery disease, vasodilating beta blockers cause effective BP control with neutral or beneficial effects on important parameters for the comorbid disease[3].

Although traditional beta blockers effectively lower brachial (arm) BP, recent clinical data suggests that they are less effective in reducing central aortic lpressure compared with other antihypertensive drugs[4]. Increased central aortic pressure has been associated side effects in particular fatigue and sexual dysfunction. However, vasodilator beta blockers have very few side effects comparable to placebo.

### Pseudo-antihypertensive Efficacy

Traditional beta blockers are not only less efficacious at reducing arm blood pressure but also have a lesser effect on important central aortic pressure when compared with RAAS blockers, diuretics and calcium antagonists. In the CAFÉ (Conduit Artery

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Functional End Point) study[5] for the same peripheral blood pressure, a 4.3 mmHg greater central aortic systolic pressure and 3.0 mmHg greater central aortic pulse pressure was noted with atenolol based treatment compared with the amlodopine-based treatment. The study results also strongly suggest that central aortic systolic blood pressure may be more predictive of cardiovascular events like myocardial infarction and stroke, than the brachial BP measurement. Considering this discrepancy between arm and central blood pressure the antihypertensive effect of beta-blockers can be best described as a 'pseudo antihypertensive' efficacy.

**Beta Blockers in Hypertension and Other Cardiovascular Indications**

Bangalore et al.[6] in their review critically analyzed the evidence supporting the use of beta blockers with hypertension and evaluated the evidence for its role in other indications. Given the increased risk of stroke, their "pseudo antihypertensive" efficacy (failure to lower critical aortic pressure), lack of effect on regression of target end organ effects like left ventricular hypertrophy and endothelial dysfunction, the risk benefit ratio for beta blockers is not desirable. However, beta blockers remain very efficacious agents for the treatment of heart failure, certain types of arrhythmias, hypertrophic obstructive cardiomyopathy and in patients with prior myocardial infarction.

Giles et al.[7] in their correspondence article, "beta blockers therapy in hypertension-A need to pause and reflect", have emphasized that most of the evidence summarized by Bangalore et al.[6] concerns studies of atenolol. However, the authors did not stress the point that less favorable clinical outcomes seen with atenolol versus other therapies might be due to an absence of 24 hours efficacy as atenolol was used 50mg once daily. In fact, the INVEST (International Verapamil-Trandolapril Study)[8] showed no difference in outcomes between a beta blockers and calcium antagonist, because in this trial atenolol was given twice daily. Similarly, data from UKPDS (United Kingdom Prospective Study)[9] also showed atenolol given twice daily to have efficacy similar to an ACE-inhibitor in preventing cardiovascular complications in hypertensive diabetic patients.

**Drugs for First line Treatment in Hypertension**

National and International guidelines recognize five classes of drugs for the first-line treatment of hypertension- beta blockers, diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers. However, achieving a lower BP is more important than a choice of drugs used in the treatment. Many patients will need more than one drug to achieve the desired level. Beta blockers remain important and effective drugs but age and co-morbidities need to be considered when selecting a first line of drug. In younger patients, beta blockers should remain the first line anti-hypertensive drug. There are different types of beta blockers (Table 1).

**Joint National Committee (JNC)**

Beta blockers along with diuretics were regarded as the preferred first line treatment from 1984-1997 (JNC III to VI). The JNC VII recommends beta blockers as first line treatment for 'compelling' indications on an equal basis with calcium antagonists, RAAS blockers[2].

**European society for hypertension/European society of cardiology**

European society for hypertension/European society of cardiology (ESH/ESC) guidelines published in 2008 maintain beta blockers as first line therapy for hypertension. They also recommend beta blockers as suitable drugs for initiation and maintenance of blood pressure treatment. Furthermore, ESH/ESC and the American College of Clinical Endocrinologists recognize the difference between vasodilatory beta blockers and traditional beta blockers in patients with metabolic risk factors. Beta blockers, particularly vasodilating beta blockers, will continue to play a critical role in treatment of hypertension hence it will be a mistake to dismiss the entire class[7].

Khan and McAlister[10] in their meta-analyses of beta blockers as first line therapy for hypertension, confirm that they should not be used in older patients (age >60 years) if they do not have another indication for those agents such as heart failure, post myocardial infarction (MI) or symptomatic coronary artery disease. They recommend use of beta blockers as first line

**Classes of beta blockers**

| Action | Adrenergic Selectivity | Examples |
|---|---|---|
| Non-selective | beta 1 and beta 2 | Propranolol, Sotalol* |
| Selective | beta 1 > beta 2 | atenolol<br>Metoprolol Succinate<br>Metoprolol Tartarate (sustained release), bisoprolol |
| Non-selective and vasodilating | beta 1, beta 2 and alpha 1 | Labetalol, carvedilol |
| Non-selective and vasodilating (nitric oxide pathway) | beta 1 and beta 2 | nebivolol |
| **used primarily as a class III antiarrhythmic drug* | | |

therapy in younger patients without contraindications or prior intolerance to thiazide diuretics. In younger patients, beta blockers are associated with a significant reduction in cardiovascular morbidity and mortality.

Khan and McAlister organized their meta-analysis according to different age groups. The primary outcome was composite of stroke, MI and death. They identified 32 randomized controlled trials that evaluated the efficacy of beta blockers as first line therapy for hypertension in preventing major cardiovascular outcomes. Trials on older (> 60years) patients were separated from those younger (mean age <60 years) patients. On analysis they found in placebo controlled trials, beta blockers reduced major cardiovascular events in younger patients by 14% but not in older patients. In active comparative trials, beta blockers showed efficacy similar to that of other antihypertensive drugs in younger patients. Hence they recommend that beta blockers should be used as first line drug of choice in younger patients but not in elderly.

**Vasodilatory Beta Blockers**

The peripheral vasodilation reduces cardiac after load and preload and reverses adverse arterial remodeling (stiffness)[11].

**Carvedilol**

Carvedilol is a vasodilating third generation beta blocker without the negative hemodynamic and metabolic effects of traditional beta blockers, which can be used as cardioprotective agent. Compared with traditional beta blockers, carvedilol maintains cardiac output, has a reduced prolonged effect on heart rate and lowers BP by decreasing vascular resistance. It also has favored effects on metabolic and lipid metabolism suggesting that it could be considered for treatment of hypertensive patients with metabolic syndrome or diabetes mellitus[12].

**Nebivolol**

Nebivolol reduces systemic vascular resistance through stimulation of nitric oxide release[13]. It is safe and well tolerated. In an open 6 week trial in 6,356 cases of mild hypertension (DBP-90-115 mmHg), and mean SBP of 162 mmHg, nebivolol (5-10 mg daily) significantly reduced mean SBP and DBP from baseline (-24 and -13 mmHg respectively, P<0.001 for both)[3]. In a meta-analysis of 12 randomized clinical trials in hypertension, achievement of BP target reduction with nebivolol was higher than that of ACE inhibitors and similar to that of other beta blockers,CCBs and Iosartan[14]. Nebivolol is an alternative to other beta blockers used in heart failure but has less robust evidence of survival benefit. It is contraindicated in patients with hepatic impairment and should be avoided

in severe renal failure. Stopping nebivolol abruptly can worsen heart failure or precipitate angina, MI or ventricular arrhythmias in patients with ischemic heart disease.

**Bisoprolol**

It is a selective type B1 adrenergic receptor blocker and is beneficial in the treatment of hypertension, ischemic heart disease, congestive heart failure, preventive treatment before and primary treatment after heart attack, decreasing the chance of recurrence[15].

*Mechanism of action* : It is cardioprotective because it selectively blocks catecholamine (adrenalin) stimulation of beta 1 adrenergic receptors which are mainly found in heart muscle cells and heart conduction tissue but also found in juxta-glomerular cells in the kidney.

Bisoprolol decreases the adrenergic stimulation of heart muscle and pace maker cells[16]. Beta blockers can precipitate bronchial asthma. However, bisporolol, metoprolol, nebivolol have less effect on the beta 2 (bronchial) receptors and therefore relatively cardio selective. They have lesser effect on airways resistance but are not free of this side effect. Bisoprolol is used to treat cardiovascular diseases such as hypertension, coronary artery disease, arrhythmias and treatment of MI after the acute event. Bisoprolol should be started with low doses as it reduces also the muscular power of the heart[17]. Bisoprolol has a higher degree of beta 1 selectivity compared to other beta 1 selective beta blockers however nebivolol is 3.5 times more beta-selective[18].

**Labetalol**

Labetalol is a nonselective beta blocker with alpha receptor-blocking activity and minimal intrinsic sympathomimetic activity. Therefore, it has been useful in hypertensive emergenies. Because of its safety, it is mainly used in hypertension during pregnancy. Labetalol is generally well tolerated in these clinical studies. On the basis of data from small clinical trials, labetalol is equally effective in lowering SBP and more effective in lowering 24-hours DBP compared to a CCB or ACE inhibitors[18].

**Beta Blockers in Hypertension with Associated Co-morbidities**

Beta blockers are used in patients of hypertension associated with diabetes mellitus, coronary artery disease and heart failure or in patients who have had MI[19]. In these particular conditions, the effects of beta blockers on the myocardium itself may provide benefits beyond lowering BP[20].

**Diabetes Mellitus**

With traditional beta blockers, there is risk of new onset diabetes mellitus (DM). A meta analysis by Bangalore *et al.*[21] of 12 trials involving 94,492 hypertensive patients reported a 44% increased new onset DM risk with pooled data of atenolol and propranolol compared with placebo. However, vasodilatory beta blockers (carvedilol and nebivolol) have shown neutral or beneficial effects on metabolic parameters in patients with diabetes and hypertension[22,23]. Additionally, carvedilol and nebivolol had no adverse effect on glycosylated hemoglobin.

However, the GEMINI (Glycemic effects in Diabetes Mellitus Carvedilol-Metroprolol comparison in hypertensives) trial[24], treatment of diabetics with metoprolol resulted in the increase in HbA1c, whereas treatment with carvedilol did not increase and carvedilol improved insulin resistance. Similarly nebivolol improved insulin resistance, proving the fact that not all beta blockers have same effect. In another GEMINI trial[25], patients on metroprolol had significant weight gain but patients on carvedilol did not, stressing the point that all beta blockers are not the same.

**Coronary artery disease**

American Heart Association (AHA) recommends a BP of <130/80 mmHg for patients associated with coronary artery disease. Treatment of coronary artery disease is recommended because beta blockers not only reduce BP but also decrease myocardial oxygen demand[25]. Because of amelioration of rest and hyperemic coronary blood flow, vasodilatory beta blockers are a better option than traditional beta blockers in patients with high coronary risk.

**Post myocardial infarction**

AHA guidelines recommend beta blockers in hemodynamically hypertensive patients after MI[19]. Among the vasodilatory beta blockers, only carvedilol is indicated for patients with post MI left ventricular dysfunction[26].

**Effects on left ventricular hypertrophy (LVH) regression**

Left ventricular hypertrophy is strong predictor of cardiovascular mortality and morbidity and its regression lowers the risk, independent of blood pressure lowering effect[27]. In a meta-analysis of 104 studies comparing the various anti-hypertension treatments on LVH regression, beta blockers caused the least LVH regression compared with RAAS blockers, calcium antagonists and diuretics. Beta blockers unlike RAAS blockers, do not decrease collagen content in the myocardium and hence are not that effective in LVH regression[28].

**Heart failure**

Beta blockers specifically bisoprolol, metoprolol succinate and carvedilol improve systolic heart failure by inhibiting the negative stress associated with sympathetic nervous system activation. Fonarow et al.[29] have shown that risk for mortality and rehospitalization are significantly lower in patients with LVF who continue beta blockers after discharge compared to patients not continuing beta blockers treatment.

**Chronic heart failure**

Many studies have shown a substantial reduction in the mortality rate (-30%) and morbidity with beta blockers as well as improvement in symptoms and the patient's well being[30]. Particularly, bisprolol, metoprolol and nebivolol have shown good results. Multiple meta-analysis have echoed this observation, showing mortality benefit in the overall cohort[31].

## CONCLUSION

There are intrinsic differences among members of beta blockers. Actually, vasodilatory beta blockers lower BP to a similar degree as other antihypertensive drugs. They also provide better control on aortic pressure reduction than traditional beta blockers and have favorable or neutral metabolic effects. As per recent recommendations, most patients will require multiple drugs to achieve BP goals. In patients with co-morbidities, combination therapy will be essential to achieve lower goals. Hence while addressing the question of beta blockers' effectiveness, the answer lies not in crude generalizations but in assessing individual patients and specific beta blocking agents[3].

It is unlikely that there will be a single first line drug for hypertensives as most patients will eventually need multiple drugs to control their blood pressure. Treatment has to be individualized for all patients. The choice of treatment should not only be influenced by underlying cardiovascular risk factors, co-morbidities but also by the age of patients and potential adverse effects. The appropriateness of using newer beta blockers as first line agents or add-on in specific situations can not be over-estimated.

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*Case Report*

# KIKUCHI'S DISEASE - A RARE BUT OFTEN MISSED ENTITY: 3 CASE REPORTS

**Sunita Sethy *, R. Sen*, P.K. Samal*, M. Layek*, Bidyut K Das****

**ABSTRACT**

*Kikuchi's disease is an idiopathic, generally self-limiting cause for lymphadenitis that can be clinically and histologically mistaken for lymphoma, tuberculosis or systemic lupus erythematosus. Differentiating this condition from common disorders associated with lymphadenopathy is extremely important from the clinician's point of view. We report 3 cases of kikuchi' disease.****Keywords:*** *Kikuchi's disease, lymphadenitis, autoimmune disorder*

## INTRODUCTION

Kikuchi-Fujimoto disease (KFD) or histiocytic, necrotizing lymphadenitis is an uncommon, idiopathic, generally self-limited cause of lymphadenitis.[1,2,3,4] Kikuchi first described the disease in 1972 in Japan. Fujimoto and colleagues independently described Kikuchi's disease in the same year. The cause of Kikuchi-Fujimoto disease is unknown. Viral or post viral etiology has been proposed.[5,6] There are also been reports of a possible link between KFD and systemic lupus erythematosus (SLE).[7,8,9] Kikuchi-Fujimoto disease is an extremely rare disease in the Western population but is more commonly seen in Japanese and Asian populations. It is more common in females and in people under 30 years of age compared to other age group.[7,8] We present 3 cases of Kikuchi's disease, one diagnosed earlier as case of Tubercular lymphadenitis and subsequently confirmed as Kikuchi's diesase by lymph node biopsy.The second patient had autoimmune thyroiditis and a third was patient of SLE who developed Kikuchi's disease while on follow up.

Case – 1A 18-year-old female presented with multiple neck swellings and fever of 1 month duration associated with recurrent episodes of vomiting. There was no weight loss,haematemesis or haemoptysis. There was no previous history of tuberculosis. She did not have history of any significant medical problems.

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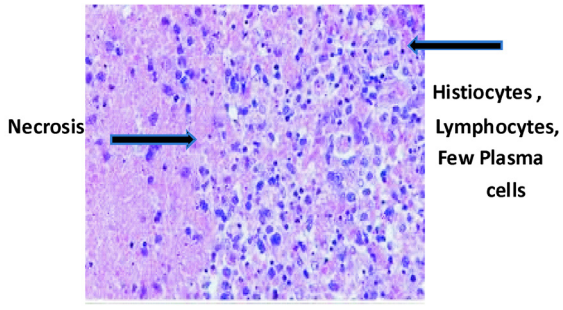
Prior to admission, patient was being treated at a private hospital for tubercular lymphadenitis based on fine needle aspiration cytology (FNAC) of the right posterior cervical node showed features suggestive of nonspecific reactive lymphadenitis . USG of the neck had revealed lymphadenopathy involving right cervical groups, few showing necrosis and calcification- The patient was started on ATT, CAT–1 However, she developed severe gastritic intolererance to ATT ,and the medication was discontinued after 10 days.She was at refered to SCB for further management.

Clinical examination revealed bilateral , mobile and non tender-cervical lymphadenopathy , which measured about 2x3cms in size each on the right cervical region.There were 2-3 lymph nodes in left posterior cervical (2x2cm) and right submandibular (1x1cm) region. The blood pressure was 128/86 mm Hg and the pulse rate was 88/min. She was afebrile. Systemic examination revealed no abnormality. Hemoglobin-11g%, DC-N64L34E2M0, TLC-6400. ESR was 18mm/1st hr.FBS was-110 mg/dl Sr.urea-28mg/dl, creatinine-1.1mg/dl, sodium-134 mg/dl and potassium-3.4 mg/dl.Urine RE & ME-normal. Mantoux with 5 TU showed an induration of 4 mm. Ultrasound abdomen and chest radiograph reports were normal.

In view of continued fever and persistent lymphadenopathy, a lymph node biopsy was carried out and the histological features revealed necrotising lymphadenitis suggestive of Kikuchi's disease(fig-1)

**FIG.1 H&E SECTION OF LYMPHNODE IN KIKUCHI (LOW POWER)**




The patient was treated symptomatically with NSAIDS and recovered over a period of 2 weeks.

Case -2

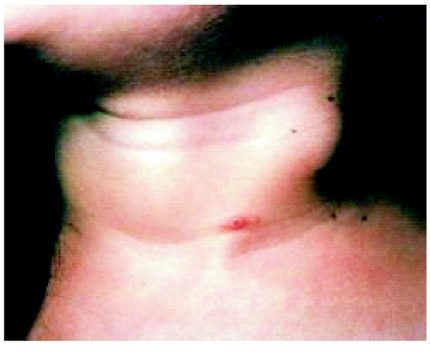
A 29 year old woman presented with multiple neck swellings, fever, malaise of two month duration.

There was no previous history of tuberculosis She had recently been diagnosed as case of hypothyroidism and was on Levothyroxine once daily

Clinical examination revealed bilateral ,mobile, firm and tender cervical lymphadenopathy, largest node being left posterior cervical about(3x4cm),other nodes were left posterior cervical(2x2cm) and right posterior cervical(2x1cm).(Fig 2). There were tender bilateral small inguinal lymph nodes(1.5x 1.5cms). There was no matting of lymph nodes or discharging sinus.

Her blood pressure was 122/82mm Hg, pulse rate was 120/min and she was febrile. Her cardiovascular, respiratory and neurological examinations were normal. There was no hepato-splenomegaly

**FIG.2. PICTURE SHOWING CERVICAL LYMPHADENOPATHY**



Routine investigation showed a Hb- of 12g/dl, TLC-7200, DC-N58L36E4M2, Peripheral smear was within normal limits. ESR was 48 mm in 1$^{st}$hr.Randomblood glucose-116 mg/dl, Sr.urea-26 mg/dl,Sr. creatinine-0.8mg/dl, Sr.Na-132 mg /dl,Sr.K-3.4 mg/dl. liver function tests were normal. Blood and urine culture were negative. Mantoux test with 5 TU showed induration of 4mm.USG of abdomen and Chest x ray were normal. Serum ANA(EIA)-was 4.59(Positive), but other markers of lupus like dsDNA, C3, C4 were normal.) Sputum for AFB was negative.

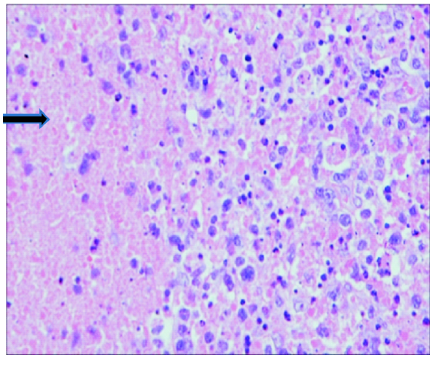
USG of neck revealed features suggestive of chronic thyroiditis, and presence of bilateral multiple cervical lymphadenopathy.

Serum T3-118ng/dl, T4-9.50microgms/dl, TSH-19.79micro U/ml, Anti-TPO Ab-636.50.

FNAC of right cervical lymphnode showed features of granulomatous lymphadenitis, but lymphnode biopsy histopathological picture revealed areas of karyorrhectic nuclear debris, phagocytic macrophages with engulfed nuclear material, lymphocytes and immunoblasts.many histiocytic cells having reniform nuclei with paucity of neutrophils in the necrotic areas suggestive of necrotizing lymphadenitis-Kikuchi's disease. Patient had evidence of autoimmune thyroiditis and was in hypothyroid state for which levothyroxine dose was increased. She continued to have persistently high fever and tender lymphadenitis which did not respond to NSAIDs. She was started on prednsisolone 0.5 mg/kg/BW which was tapered over period of 6 months.She remained on maintainance dose of thyroxine. There has been no relapse for the last last 1 year.

**FIG.3 : H&E SECTION OF LYMPHNODE IN KIKUCHI DISEASE IN LOW POWER**

Coagulative necrosis surrounded by karyorrhectic debris, histiocytes and plasmacytoid lymphocytes



Case-3

A 31 year old female presented with complains of fever with chills and rigor for one and half months associated with morning rise of temperature and multiple swellings in the axillary region for the same duration. The patient was a known case of SLE for 3 years and was on maintenance dose of prednisolone 7.5 mg/day, and hydroxychloroquine(400mg/day).

There was no previous history of tuberculosis.

Clinical examination revealed pallor, bilateral enlargement of anterior group of axillary lymph nodes,largest being left anterior axillary (3x4cm)in size,tender, firm and mobile The other node being right anterior axillary(2x1cm)with similar features.

Her blood pressure was 124/84 mm of Hg, pulse rate-88/min. She was febrile. Routine haematological examination revealed Hb-9.6mg/dl,TLC-5800,DC-N66L32E0and ESR was-50. Fasting blood glucose-98mg/dl,Sr.urea 38 mg/dl,Sr,creatinine-1.2mg/dl,Sr.Na-136 mg/dl,Sr.K-3.5 mg/dl, liver function test was normal. Widal negative, ICT for malaria was negative. Blood and urine cultures were negative. All viral markers(HIV, HEPATITIS, CMV,EBV) were negative.CRP was 106.5mg/dl. Gamma Quantiferon assay was negative Chest X Ray PA view revealed haziness over b/l lung fields. USG-of abdomen showed evidence of mild splenomegaly. Mantoux test with 5 TU units was <5mm. FNAC of the enlarged lymph nodes showed non-specific lymphadenitis. Patient was empirically treated with ATT , Category I, keeping in view a background history of SLE, immune suppressed, long history of fever with axillary lymphadenopathy. After receiving ATT for 1 day the patient developed generalized rashes headache and vomiting Which necessitated withdrawal of ATT. She was treated symptomatically with anti histamine and she recovered

Fever did not subside and the the dose of steroid was reduced in view of normal C3 and C4 level indicating stable lupus activity. A lymph node biopsy was carried out and histological features showed features of necrotizing lymphadenitis suggestive of Kikuchi's disease The dose of steroid was hiked to 0.5 mg/kg which was tapered over 6 months to stable dose of 7.5 mg/day to control SLE. There has been no relapse in the last 2 years.

## DISCUSSION

Kikuchi's disease is a rare, benign condition of unknown etiology, which mostly afflicts young women and presents with tender cervical lymphadenopathy. This is often accompanied by fever and features of upper respiratory tract infection.[12] All our cases were young women and had the characteristic features associated with Kikuchi's disease. Cervical lymphadenopathy is present in 56% to 98% of cases, more commonly consisting of tender lymph nodes involving the posterior cervical triangle (88.5%), generally unilateral (88.5%). The size of lymph node ranges from 0.5 to 4 cm (93.4%), and occasionally, lymph nodes are larger than 6 cm[22]. Painful lymphadenopathy is seen in up to 59% of patients. Less common symptoms include arthralgia, skin rashes, weakness and night sweats. Some patients may also have hepatosplenomegaly.[12,13] The exact etiology of Kikuchi's disease is not known. Viral agents such as Epstein Barr virus (EBV), Human immunodeficiency virus (HIV), Herpes simplex virus, Dengue virus, Human T lymphotrophic virus 1 (HTLV1) , Parvovirus B19, Parainfluenza,Yersina enterocolitica and Toxoplasma have been suggested as possible etiological agents, but none have been confirmed so far[2,16] Interestingly, there are several reports suggesting an association between Kikuchi's disease and other autoimmune disorders like systemic lupus erythematosus (SLE), and autoimmune thyroiditis.[6,7,8,9,15] Two of our patients had a background of autoimmunity-one SLE and the other autoimmune thyroiditis. In view of the rarity of the disorder the associations could be. anecdotal.

The pathogenesis of Kikuchi's disease has not been clearly elucidated, however, the clinical presentation, course and histological changes suggest an immune response of T cells and histiocytes to an infectious agent. It is supposed that the primary event may be the activation of T lymphocytes and histiocytes. Proliferating CD 8 T cells enter the cycle of apoptosis, which may form the areas of necrosis in lymph nodes and then the cellular debris are removed by histiocytes.[11,19,26]

Routine laboratory investigations usually does not aid in the diagnosis except for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)

which might be elevated in some patients and many patients have a low white blood count.[17,18,19] Fine-needle aspiration cytology (FNAC) only has a limited role in establishing the diagnosis of Kikuchi's disease. Diagnosis is based on histopathological findings of a lymph node biopsy. Morphologically, it is characterized by irregular paracortical areas of coagulative necrosis with abundant karyorrhectic debris, which can distort the nodal architecture, and large number of different types of histiocytes at the margin of the necrotic areas. The karyorrhectic foci are formed by different cellular types, predominantly histiocytes and plasmacytoid monocytes but also immunoblasts and small and large lymphocytes. Neutrophils are characteristically absent and plasma cells are either absent or scarce.[19,20] The immunophenotype of Kikuchi's disease is primarily composed of mature CD8-positive and CD4-positive T lymphocytes. The histiocytes express histiocyte-associated antigens such as lysozyme, myeloperoxidase (MPO) and CD68 which can be detected by immunohistochemistry.[22,23]

Clinically Kikuchi's disease may mimic systemic lupus erythematosus (SLE) lymphoma (especially T-cell non- Hodgkins lymphoma) and tuberculosis as all these diseases can present with lymphadenopathy and fever. Careful histopathologic examination will thus help us to distinguish KFD from other diseases. Histological feature which helps in the differentiation of KFD from the lymphadenopathy of systemic lupus erythematosus is almost total absence of plasma cells in the involved nodal tissue.[11] Features that distinguish KFD from malignant lymphoma include incomplete architectural effacement with patent sinuses, presence of numerous reactive histiocytes, relatively low mitotic rates, absence of Reed-Sternberg cells.[11]

No specific treatment is available for Kikuchi's disease. Treatment is generally supportive. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used to alleviate lymph node tenderness and fever. The use of corticosteroids has been recommended in severe form of disease.[24] The disease usually runs a benign course and the condition is self-limiting course and usually resolves in several weeks to months. The disease has a recurrence rate of 3% to 4%. All our patients responded to either NSAID or steroid therapy and two of them are in remission for over a year.

## CONCLUSION

Although the incidence of Kikuchi-Fujimoto disease is rare, this disorder must be considered as a differential diagnosis when a young female patient presents with fever and cervical lymphadenopathy. Clinically Kikuchi's disease may mimic tuberculosis or lymphoma. Therefore, a careful histopathological examination of lymphnode biopsy is mandatory before arriving at the diagnosis. Early recognition of the disease is of crucial importance in minimizing potentially harmful and unnessary treatment.

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*Case Report*

# HODGKIN'S LYMPHOMA FOLLOWING TREATMENT WITH IMMUNOSUPPRESSANTS FOR APLASTIC ANEMIA - A CASE REPORT

**P. Sahu*, N. Mohanty**, S.S. Acharya***, S.S. Kurien**, D. Mishra****

**ABSTRACT**

*Pharmacological immunosuppression is one of the most important risk factors for hematological malignancies . This report presents a rare case study of Hodgkin's lymphoma (lymphocyte rich type) following treatment with anti-thymocyte globulin(ATG) and Cyclosporine for Aplastic anemia in a 27 year old male.* ***Keywords :*** *Hodgkin's Lymphoma, Immunosuppressants, Aplastic Anemia.*

## INTRODUCTION

Acquired aplastic anemia is a rare hematopoeitic disorder of the stem cells. It can be treated successfully with immunosuppressants and or bone marrow transplantation. Long term survivors of acquired aplastic anemia are at high risk of developing malignancies, specially haematological malignacies like NHL, Adult T cell lymphoma /leukemia ,acute myeloid leukemia. Here we report a case of Hodgkin's disease (lymphocyte rich variety) following treatment with cyclosporine which is very rare.

## CASE REPORT

A 27 year male (Picture-1) presented with fever, generalised weakness and dyspnoea on exertion for one month. Fever was low grade with no diurnal variation, not associated with cough or dysuria. On examination there were no significant findings except pallor. Routine investigations revealed Hb-2.4gm%, TLC-4300/$mm^3$ with differential count of $N_{44}E_2L_{54}$, TPC -2.9Lakh/$mm^3$ , peripheral smear was suggestive of microcytic hypochromic anaemia .His ESR was 80 mm/1$^{st}$ hr .His renal function test was within normal range and liver function tests revealed SGOT/SGPT 195/112 IU/L respectively. In view of low Hb level unresponsive to conventional treatment his Hb electrophoresis was done which was normal AA band.Bone marrow aspiration study showed decreased cellularity, relative increase of fat cells and reduced myeloid cell cellularity; suggestive of hypoplastic marrow with megaloblastoid erythropoiesis.In consultance with haematologist he was started on treatment protocol for hypoplastic anaemia i.e antithymocyte globulin (40mg/kg body wt ×4 days ) and cyclosporine 200mg twice daily. Along with it he received two units blood transfusion. The haemogram was repeated on 7$^{th}$ day after initiation of therapy which revealed Hb 8gm% TLC 7800/$mm^3$ TPC 3.1 lakh / $mm^3$.The patient was doing well and all his baseline parameters improved significantly, the elevated liver enzymes returned to normal values .He was then discharged with the advice to continue cyclosporine 100mg twice daily with iron supplementation and broad spectrum antibiotics.

Nine months later, he presented with complains of abdominal discomfort and swelling of both feet for 3 days. On examination found to have pallor ,pitting pedal oedema, nonsignificant lymphadenopathy in the posterior triangle with palpable liver 5cm below right costal margin along the mid clavicular line, with evidence of free fluid in abdomen. Ultrasonography of abdomen revealed hepatomegaly, splenomegaly and ascitis. Cyclosporine was stopped and furosemide tablets were started and asked to come for review after 2 weeks. On review, the patient had significant lymphadenopathy and there was pedal edema. The lymph nodes in the posterior triangle were enlarged varying in size from 1cm to 1.5 cm, firm in consistency, nonmatted, nontender, with no local rise of temperature. Abdomen examination revealed tense ascitis (Picture-2) and

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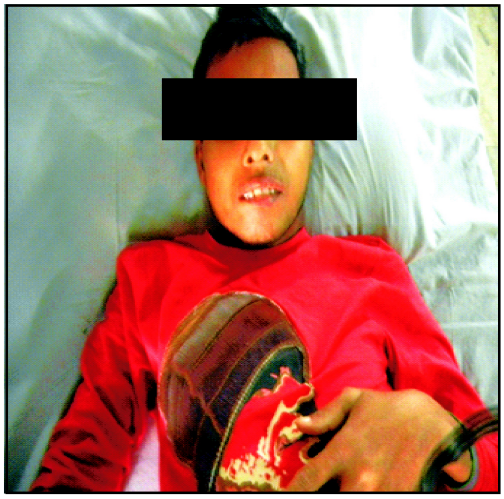


Picture-1 : Photograph of the patient

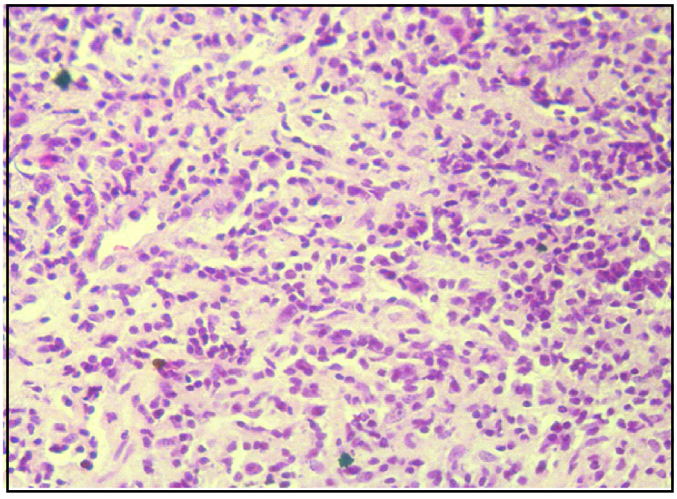
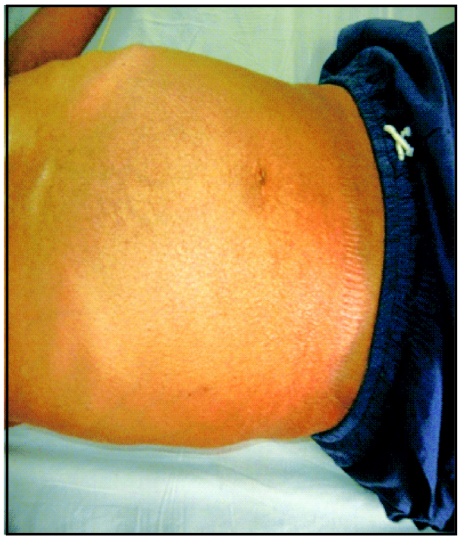


Figure-1 showing polymorphous population of cells with diffuse pattern with complete loss of lymph node architecture



Picture-2 : Photograph of his abdomen showing ascitis

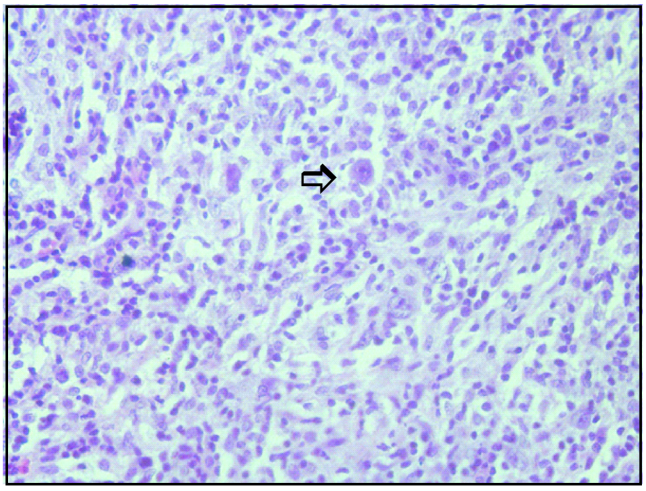


Figure.2 Histopathology of lymphnodes showing mononuclear RS cells (white arrow)

other system examination had no obvious abnormality. His routine haemogram was Hb-9.6gm/dl, TLC-11200/cmm, differential count was Neutrophil 82%, Eosinophil 2%, Monocyte 4%, Lymphocyte 12%, TPC-2.6 lakh/$mm^3$, his renal function test & liver function test were within normal range, ascitic fluid was white in colour and analysis showed, cell count of 680 nucleated cells/$mm^3$mostly lymphocytes (90%) without any malignant cells, protein 1.8gm/dl,sugar 128mg/dl, cholesterol 94.6mg/dl, trigiyceride 282mg/dl suggestive of chylous ascitis. There was rapid accumulation of ascitic fluid causing respiratory embarrassment forwhich repeated paracentesis was carried out.

Ultrasonography of abdomen revealed para-aortic lymphadenopathy with hepatosplenomegaly and ascitis. Chest X-ray was normal. The lymph nodes were subjected to FNAC study which were suggestive of reactive hyperplasia. As there was rapid accumulation of ascitic fluid even after repeated paracentesis causing respiratory embarrassment and FNAC reports were inconclusive it was decided to go

for alymph node excision biopsy and histopathology study. Histopathology reports showed complete loss of lymph node architecture, with diffuse pattern, with polymorphous population of cells comprised of mononuclear and binuclear RS cells, popcorn cells, mature lymphocytes, occasional polymorphs and plasma cells -with these above mentioned findings a diagnosis of Classical Hodgkin's Lymphoma (Lymphocyte Rich Type) was made. (photographs of the slides attached). Hence a diagnosis of Ann Arbor Stage iii Hodgkin's lymphoma was made and put on chemotherapy (CHOP regimen). With chemotherapy patient improved significantly with disappearance of lymph nodes and ascites.

## DISCUSSION

Immuno-suppressive therapy and bone marrow transplantation now yield long term survival rates of >60 % in aplastic anemia[1]. This long term survival of patients with these therapy have led to the various complications like haematological malignancies[2,3,4] like MDS, AML, Non Hodgkin's lymphoma, adult T cell lymphoma/leukemia. As much of studies on long term complications following immunosuppression in aplastic anemia are unavailable,datas collected from studies relating to long term complications following immunosuppression in organ transplantation have been taken into consideration.

The most common type of malignant neoplasm among patients with organ transplantation with immunosuppressants is Non Hodgkin's lymphoma[5]. It has an estimated annual incidence of 1.4% -3.6% in the above group. The majority are B cell type, 15% are of T cell type. It is seen that Lymphoma developed in patients on cyclosporine for 10-12 months. Relative risk increases along with the age of the patient, multiple courses of the immunosuppressants. In a study on long term complications in aplastic anemia, a case of Non Hodgkin's lymphoma has been reported with immunosuppressant without marrow transplantation[5].

In available literatures we did not come across any case of Hodgkin's lymphoma reported either with ATG or with Cyclosporine. In our case after nine months of immunosuppressive therapy patient developed lymphoma (this excludes possibility of association of lymphoma with aplastic anemia itself)[6].

Our young patient who received one course of ATG and maintenance dose of cyclosporine for the treatment of aquired aplastic anaemia, after which he developed Hodgkin's lymphoma responded well to the stoppage of cyclosporine and two cycles of CHOP regimen. The cause of development of Hodgkin's Lymphoma in this patient is whether due to ATG or Cyclosporine is yet to be determined.

## CONCLUSION

Hence all patients receiving treatment for acquired aplastic anemia with immunosuppressive therapy should be followed up for complications like Hodgkin's disease. Timely stoppage of immunosuppressive therapy and necessary further treatment will benefit these patients. Hence similar cases should be reported to enable further analysis of risk factors.

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*Case Report*

# AN UNUSUAL CASE OF JUVENILE HYPOTHYROIDISM WITH NEPHROCALCINOSIS AND LARGE PERICARDIAL EFFUSION.

**S.K Mohapatra*, D.K. Patel**, B.K. Kullu***, S. Sasidharan#, N. K. Patel#, L.K. Sahoo#**


## ABSTRACT

*Juvenile Hypothyroidism ,despite being a common disease prevalence studies from India are inadequate. Congenital Hypothyroidism is reported 1in 2640 neonates from a study conducted in Mumba.The association of congenital hypothyroidism and nephrocalcinosis is extremely rare with only few cases reported world wide[1]. Pericardial effusion is also an uncommon manifestation of Juvenile Hypothyroidism. We hereby report a case of Juvenile Hypothyroidism with Nephrocalcinosis and a large pericardial effusion with impending pericardial tamponade.* ***Keyword:*** *Juvenile Hypothyroidism, Nephrocalcinosis, Pericardial Effusion.*


## INTRODUCTION

Global studies of school-aged children report that Juvenile Hypothyroidism occurs in approximately 0.3% .Acquired hypothyroidism is most commonly a result of chronic lymphocytic thyroiditis. Deceleration of growth is usually the first clinical manifestation. Goitre may be a presenting feature and myxedematous changes of skin, constipation, cold intolerance, lethargy develop insidiously. Surprisingly school work and grades usually donot suffer, even in severely hypothyroid children. Osseous maturation is delayed and adolescents typically have delayed puberty. Additional features include nerve entrapment, bradycardia, weight gain,ataxia, abnormal laboratory studies (hyponatremia, macrocytic anemia, hypercholesterolemia, hyperprolactinemia). Pericardial effusion is an extremely rare finding in Juvenile hypothyroidism[1,8].

Association of nephrocalcinosis with congenital hypothyroidism has rarely been reported[2,3,4,5] and association of nephrocalcinosis with acquired juvenile hypothyroidism is probably, even more rare. A large pericardial effusion has also been rarely reported in congenital hypothyroidism as well as in acquired hypothyroidism in peadiatric age group and young adults

## CASE REPORT

A 16 year old female,9TH class student,from Bargarh district of Odisha presented to the medicine ward with progressively increasing breathlessness for 1 month, with no history of fever or cough. She had normal growth till the age of 5 years after which her parents noticed retardation of growth. She is the second child of her parents and her antenatal,natal and post natal history were uneventful.She attained growth and developmental milestones normally till the age of five.She

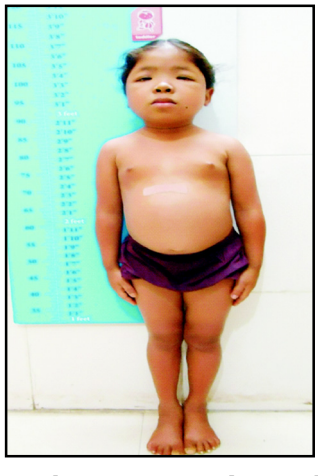

Fig.1 showing stunted growth

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has poor appetite from early childhood and she takes non vegetarian diet.She has not attained menarche.She has average scholastic performance.There is family history of tuberculosis as her father had been treated for pulmonary tuberculosis 15 years back.

On examination the patient appeared severely stunted for her age with absent secondary sexual characters.Her height was 106cm(below 3rd percentile) and body weight-16kg(below third percentile),arm span-104 cm,upper segment to lower segment ratio of 1.038.There was hypertelorism,puffy eyelids,flat nasal bridge, swollen protruded lips,loss of lateral 1/3 of eye brows and coarse dry skin.(Fig.1) She had normal intelligence for her age.The abdomen was protruberant. On cardiovascular examination there was low volume pulse,elevated jugular venous presssure, second left intercostal space was dull on percussion and heart sounds were muffled.

She was clinically diagnosed to be a case of Juvenile Hypothyroidism with pericardial effusion. Routine investigation revealed haemoglobin 9.8g%, Total leukocyte count-7200/mm3, Differential count- N55 L41 E4, ESR-19mm/hour, Blood Urea-34mg%,serum creatinine-0.8mg%, serum sodium-138meq/l,serum potassium-4.3meq/l. Urine routine examination revealed no abnormality. Serum total cholesterol was-226 mg/dl,HDL- 44 mg/dl and LDL-154mg/dl.Mantoux test read 10mm at 72hours.Thyroid function tests revealed : T3 <0.26ng/ml (normal- 0.8 – 2.1 ng/ml),T4 <0.46mcg% (normal – 4-12 mcg%), TSH >60.00miu/ml (normal 0.5-5.0 miu/ml).

Anti microsomal antibody(AMA) was found to be <5iu/ml (negative if <34iu/ml),serum calcium-8.83mg/dl(8.88-10.6) and serum intact PTH 24.43 pg/ml (15- 65). Chest x-ray PA view at admission showed gross cardiomegaly (Fig.2).

Electrocardiogram showed low voltages in every leads.On echocardiography she was found to have a large pericardial effusion (Posterior - 25.8mm,anterior – 13mm, inferior – 18.5mm,lateral – 39.7mm,apical 12mm) (Fig.3) and 950ml of straw coloured fluid was aspirated by pericardiocentesis .The fluid analysis revealed total leucocyte count of 900/mm3,mostly lymphocytes, total protein of 8.0gm% and ADA activity of 10.9 u/l.No organisms were found on gram stain and AFB staining.Ultrasonogram of abdomen and pelvis showed bilateral nephrocalcinosis with mild hydronephrosis and normal sized ovary with multiple follicles. (Fig.4)

X-ray skull lateral view showed incomplete closure of anterior fontanelle, prominent pituitary fossa and delayed dentition with unerupted permanent teeth. (Fig.5) X-ray of long bones showed absence of appearance of ossification centre for lesser trochanter of femur, (Fig.6) X-ray of right wrists absence of fusion

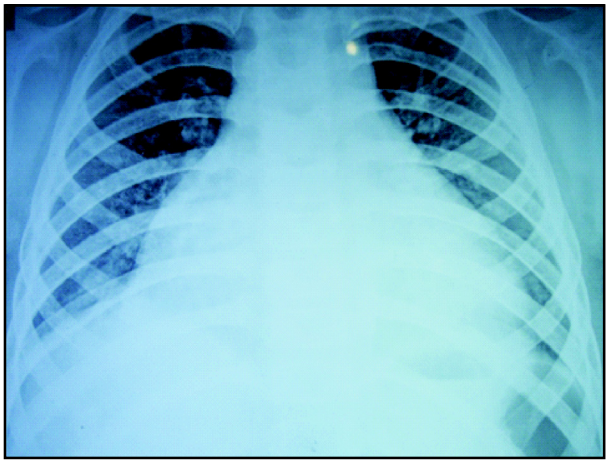

Fig : 2.Chest x-ray at admission showing large pericardial effusion

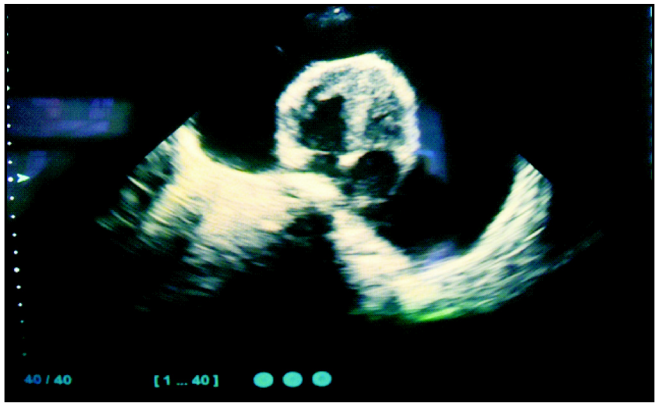


Fig:3,echocardiogram showing large pericardial effusion.

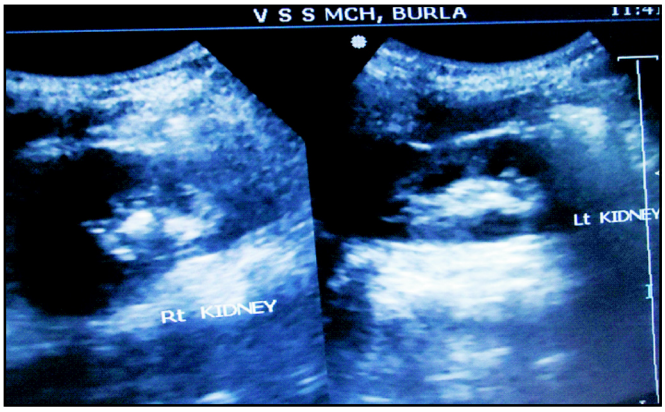


Fig:4, Ultrasonogram of abdomen and pelvis showing bilateral nephrocalcinosis with mild hydronephrosis.

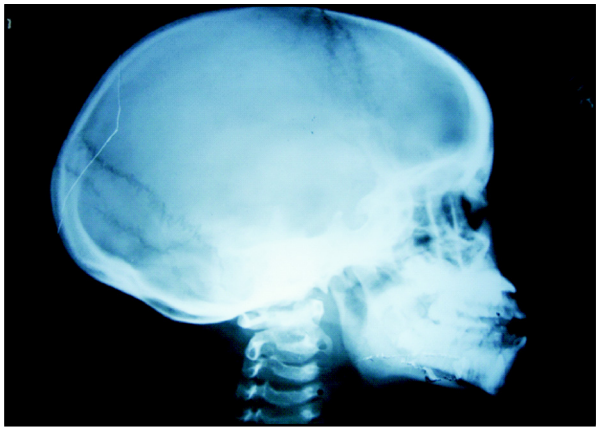

Fig :5, x-ray skull lateral view showing incomplete closure of anterior fontanelle,prominent pituitary fossa and delayed dentition with unerupted permanent teeth .

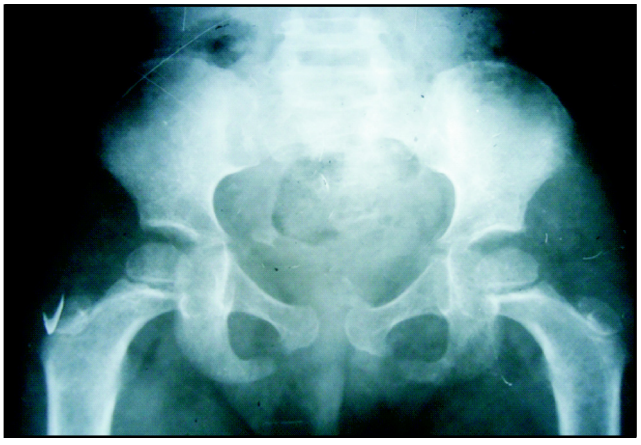

Fig : 6, x-ray showing absence of appearance of ossification centre for lesser trochanter of femur.

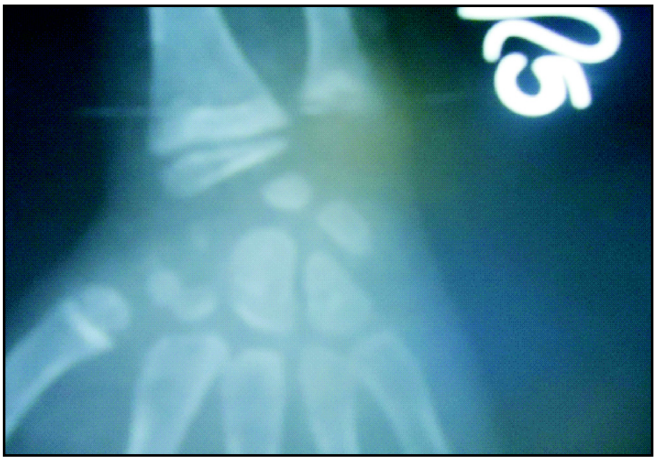

Fig : 7, x-ray right wrist showing absence of fusion of lower epiphysis of first metacarpal and absence of appearance of distal epiphysis of ulna.

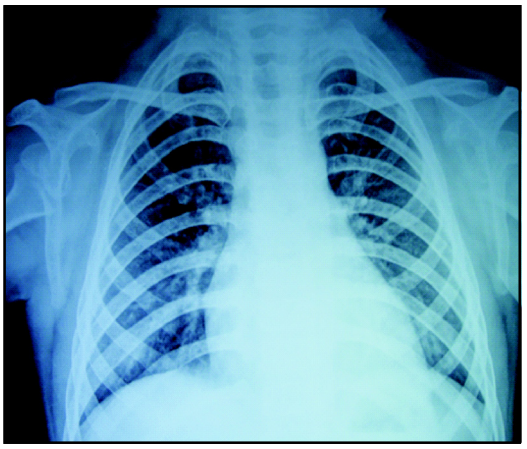

Fig : 8,chest x-ray showing resolution of pericardial effusion at 2 months follow up.

of lower epiphysis of first metacarpal bone and absence of appearance of distal epiphysis of ulna ,suggestive of an approximate bone age of 5 years. (Fig.7)

**MANAGEMENT**

The patient was diagnosed to be a case of Juvenile Hypothyroidism with Nephrocalcinosis and Pericardial effusion.In view of her delayed skeletal and sexual maturation with normal intelligence and thyroid function tests,the case was diagnosed to be Juvenile Hypothyroidism.Pericardial effusion was diagnosed clinically and confirmed by echocardiography. Nephrocalcinosis was diagnosed by ultrasonography with a normal serum calcium and serum parathormone levels.

The patient was started on 50microgram thyroxine daily and the dose was gradually increased to 75microgram daily over 4weeks.Dietary advice and iron supplements were provided.In view of the high endemicity of tuberculosis in the area,history of pulmonary tuberculosis in father and positive mantoux test, the patient was also treated,empiricaly for tubercular pericardial effusion with short course steroids and anti tubercular drugs.After discharge the patient was reviewed every month.Her general condition improved and resolution of pericardial effusion (Fig.8) and normalization of thyroid function was evident by 2months and her height increased by 3cms after 4 months of treatment.

## DISCUSSION

Juvenile hypothyroidism is most commonly a result of chronic lymphocytic thyroiditis. Prevalence studies from India are inadequate .In a population based study from cochin the prevalence of hypothyroidism was found to be 3.9% in adults[3]. Studies in school-aged children in developed countries report that hypothyroidism occurs in approximately 0.3% of children[9]. In a study from Mumbai, it was found that congenital hypothyroidism occurs in 1 out of 2640 neonates compared to the worldwide average value of 1 in 3800 neonates[3]. In a population based study from Cochin the prevalence of hypothyroidism was found to be 3.9%[3].

Deceleration of growth is usually the first clinical manifestation of Juvenile Hypothyroidism.Goitre may be a presenting feature and myxedematous changes of skin, constipation, cold intolerance, lethargy develop insidiously. Surprisingly school work and grades usually donot suffer,even in severely hypothyroid children.Osseous maturation is delayed and adolescents typically have delayed puberty.Additional features include nerve entrapment,bradycardia,weight gain,ataxia,abnormal laboratory studies (hyponatremia, macrocytic anemia, hypercholesterolemia, hyperprolactinemia). Pericardial effusion is an extremely rare finding in Juvenile Hypothyroidism[8].

The association of congenital hypothyroidism with nephrocalcinosis has been reported previously[4,5,6]. Newman[6] in 1973 reviewed the entity and found that 23 cases were reported in world literature. The mechanism of nephrocalcinosis postulated was that intact mitochondria can accumulate calcium against concentration gradient as an active process using oxidative phosphorylation in proximal or distal renal tubular cells. This mechanism is altered in hypothyroidism, leading to high intracytoplasmic calcium concentrations predisposing to nephrocalcinosis[1]. Studies have shown that supplementation of thyroxine increases serum calcium and 1,25-dihydroxyvitamin D levels. Serum parathormone levels have also been reported to be elevated in adult hypothyroid patients on treatment with thyroxine.This further predisposes to nephrolithiasis.In our case,nephrocalcinosis was present with normal serum parathormone and serum calcium values. After extensive review of literature we couldnot find any case reports of Juvenile Hypothyroidism associated with nephrocalcinosis.The pathophysiology of nephrocalcinosis in juvenile hypothyroidism could be the same as postulated for congenital hypothyroidism.

## CONCLUSION

We are reporting this case because of the unusual presentation of a large pericardial effusion and the rare association of nephrocalcinosis along with other typical features of Juvenile Hypothyroidism.

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*Case Report*

# POLYANGITIS WITH EOSINOPHILIC GRANULOMATOSIS (CHURG-STRAUSS SYNDROME) - AN UNCOMMON VASCULITIS : A CASE REPORT

**Madhukara HM*, Balaji M*, Rohit Kumar*, Saroj K Sahu*, Sarit S Pattnaik*, A V Reddy*, Bidyut K Das****

**ABSTRACT**

*Churg-Strauss Syndrome (CSS) is an autoimmune, mediumand small vessel,vasculitis in persons with history of airway allergic hypersensitivity. ChurgStrauss syndrome is a systemic disorder characterized by asthma, transient pulmonary infiltrates, hypereosinophilia, and systemic eosinophilic vasculitis and may involve multiple organ systems.We report a rare case of CSS who presented with neurological manifestations and renal failure.* ***Keywords:*** *Hypereosinophillia, asthma, vasculitis.*

## INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), is a multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral blood eosinophilia[1]. It was first described in 1951 by Churg and Strauss. Onset typically occurs in patients aged from 15 to 70 yrs. The syndrome is characterized by three distinct and progressive phases[1]. The initial prodromal phase of asthma and allergic rhinitis, which may precede systemic disease by 3 to 7 years. The second phase is heralded by fever, weight loss, peripheral eosinophilia, and eosinophilic infiltration of the lungs, upper respiratory tract, and gut. The thirdphase is manifested by systemic vasculitis, leading to cardiac failure, myocardial infarction, cutaneous disease, peripheral neuropathy, hypertension, renal diseases, and arthralgias[1]. In India few cases having cutaneous [9], pulmonary[10] and even renal[11] manifestations have been reported earlier. We report a case of CSS with neurological, pulmonary & renal manifestations

## CASE HISTORY

A 45 year old male presented with the complaints ofabdominal pain 3 ½ months, low backache for 3 months radiating to calf along with tingling sensation of lower limbs and recurrent history of cold 2 1/2m. Pain in the lower abdomen was colicky in natureassociated with loss of appetite butnot associated with loose stools. Calf pain was present throughout the day aggravated during night hours and associated with tingling sensation over posterior aspect of both lower limbs. There was no history of lower limb claudication.

He had past history of recurrent attacks of cold and running nose for 4-5 years for which he was being treated locally whose details were not available. While being evaluated , he developed loose motion for 3 days which subsided after antibiotic therapy.

On examination, patient had pallor, pulse- 94/ min, BP=112/76 mm Hg, all peripheral pulses were well felt. General examination was otherwise unremarkable. Examination of the respiratory system revealed bilateral vesicular breath sounds with prolonged expiration, diffuse rhonchi and crepitations. Examination of CNS showed diminished touch sensation over L4 and L5 dermatomes on the left side and over L4 dermatome on the right side. Reflexes were normal. Other systems did not reveal any abnormality.

Investigation revealed Hb=8.5gms/dl, TLC=18,020/cmm, DLC, N=27%, E=57%, L 13% M3%, PLT-4.6 l. Urine, normal S, Urea 54mg/dl, S creatinine-1.7mg/dl. LFT S.bilirubin 0.9mg/dl, AST 65, ALT 33, ALP 421, FBS -78mg/dl.

Chest X–ray showed hazy middle & lower zones.(Pic.1) HRCT thorax-patchy mosaic perfusion

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with ground glass opacities bilateral middle zones.(Fig.2 & Fig.3) USG Abdomen-Bilateral isoechoeic kidney and X-ray LS spine was normal.

NCV study ofb/l lower limb showed motor neuronal, axonal peroneal neuropathy.

P-ANCA waspositive and anti MPO - 94RU(normal is 0-20), anti-PR3 44 (normal is 0-20) (significantly elevated).

Patient was diagnosed to be a case of CSS based on ACR criteria.He was started on 1mg/kg/d of prednisone orally. After 10 days of steroid therapy there was dramatic reversal of symptoms. Eosinophil count came down to 4% and but his S. creatininepersisted at 2mg/dl. We planned to start cyclophosphamide therapy after 4 weeks steroid and was discharged two weeks after admission with no respiratory distress and good general health.

**DISCUSSION**

CSS is a rare systemic vasculitis (2.5 cases/ 100 000 adults/year) occurring usually in people with history of asthma and is associated with blood and tissue eosinophilia [6]. The most commonly involved organ is the lung followed by the skin, however, can affect any organ system of the body[1].

Our patient gave history of recurrent upper and lower respiratory tract infection for 4-5 years although there was no definite history of asthma. Subsequently, he developed neurological manifestations in the form peripheral neuropathy which was established by NCV studies. HRCT thorax revealed lung involvement and USG abdomen and renal function test revealed renal involvement. High eosinophil counts were detected incidentally.

In India, one case each of CSS with cutaneous vasculitis, pulmonary-eosinophilic pleural effusion & renal-glomerulonephritis have been reported[9,10,11]. However there are no reports indicating neurological involvement from India.

The symptoms and signs in CSS are variable and may follow a sequential involvement of different systems[1]. They are characterised by:

1. Prodromal phase: Characterized by atopic disease, allergic rhinitis and asthma. Occurs in 2nd and 3rd decades.

2. Eosinophilic phase: Peripheral blood eosinophilia and eosinophilic infiltration of many organs and commonly lung.

3.Vasculitic phase: life-threatening sequelae and heralded by constitutional symptoms. Skin involvement is common in the form of tender subcutaneous nodules, palpable purpura and hemorrhagic lesions.

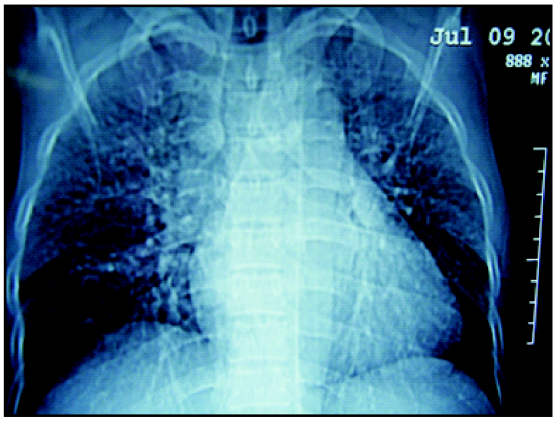
Pulmonary manifestations include lung infiltrates,pleural effusion rarely pulmonary haemorrhage.Neurological manifestations in the form of mononeuritis multiplex or polyneuropathy rarely cranial nerve involvement.GI involvement in the form pain abdomen,diarhhea and bleeding.Renal involvement is less common and usually in the form of glomerulonephritis.Cardiac involvement in the form of infarction and arrythmias is responsible for 50% of deaths[5].

The differential diagnosis of eosinophilia includes,

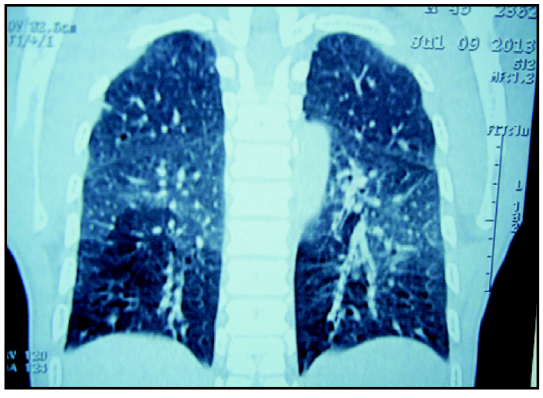
1. Acute eosinophilic pneumonia(Loefflers syndrome)
2. Chronic eosinophilic pneumonia.
3. Idiopathic hypereosinophilic syndrome.
4. Tropical pulmonary eosinophilia
5. Fungal infections like ABPA, bronchocentricgranulomatosis

In acute and chronic eosinophilic pneumonia, only pulmonary involvement is seen. While in idiopathic hypereosinophilic syndrome, there wont be any evidences of vasculitis and there is persistent eosinophilia for more than 6 months.In ABPA , there is only pulmonary involvement confirmed by demonstration of fungal hyphae in BAL.

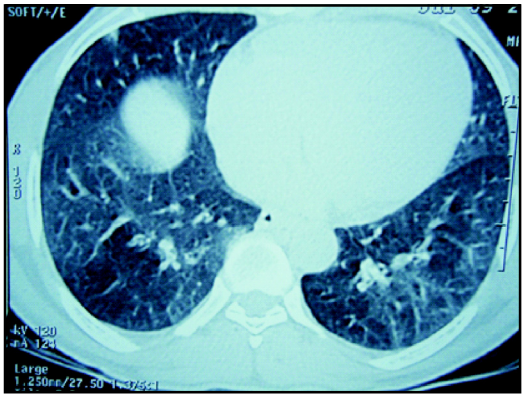
The American College of Rheumatology (ACR) has proposed six criteria for diagnosis of CSS [2]. These criteria are (1) asthma (wheezing, expiratory rhonchi), (2) eosinophilia of more than 10% in peripheral blood, (3) paranasal sinusitis, (4) pulmonary infiltrates (may be transient), (5) histological proof of vasculitis with extravascular eosinophils, and (6) mononeuritis multiplex or polyneuropathy. It has been reported that the existence of four or more of these six criteria yields a sensitivity of 85% and a specificity of 99.7%[2].Our patient had 4 of above 6 criteria and therefore diagnosed as



Pic.1 Chest X-ray showing hazy lung fields.



Pic.2 HRCT thorax showing bilateral ground glass opacities and mosaic perfusion in middle and lower zones respectively.



Pic.3 Showing ground glass opacities in bilateral lung field.

CSS. p-ANCA is not included as a diagnostic feature in ACR criteria.

Presence of p-ANCA in a systemic vasculitiswho have a prior history of asthma along with tissue and blood eosinophilia makes a strong case for the diagnosis of CSS[3]. Although classified as p- ANCA associated vasculitis it is positive in only 40%-60%.However, our patient had a significantly high levels of anti MPO adding to the strength of the diagnosis.

A biopsy of the involved tissue can further help in the diagnostic process. Histological findings such as a)eosinophilic infiltration of tissueb)extensive areas of necrosis;c)eosinophilic/giant cell vasculitis; andd)interstitial/perivascular necrotizing granuloma have been described [6].

Our patient responded well to steroid therapy although serum creatinine levels remained high after 2 weeks of therapy. We presume that the duration of treatment

Was too short for reversal of renal dysfunction. However, a course of cyclophosphamide along with steroid was planned after 1 month of steroid therapy. But the patient did not report back.

Treatment regimen is based on FFS (five factor score) highlighting organ involvement.

FFS includes following five factors:[4]

1. Cardiac involvement
2. Gastrointestinal (GI) disease (bleeding, perforation, pancreatitis)
3. Renal insufficiency (Creatinine> 1.6 mg/dl)
4. Proteinuria (> 1gm/day)
5. Central nervous system (CNS) involvement (mononeuritis, polyneuropathy)

FFS is scored 0-2 (0=no factor, 1=1 factor, 2=>1 factor present).In addition, immunosuppressants such as cyclophosphamide is required in patients with

1. FFS2
2. FFS1 with cardiac or CNS involvement
3. FFS0 with ANCA positivity (risk of renal complications in future).

Our patient had a score of 2, therefore, cyclophosphamide was considered along with the primary therapy of CSS which is systemic glucocorticoids[7].The duration of treatment is prolonged with induction of remission (steroids alone or in combination with cyclophosphamide) followed by

maintenance treatment sometimes lasting for 12–18 months or longer (azathioprine being the preferred agent with steroids).Prognosis with treatment has a survival rate of 70% at 5 years[8]. Of the five factors, cardiac and GI involvement appears to have the worst prognosis. Our patient had no cardiac or GI manifestation[9].

## CONCLUSION

CSS (Churg–Strauss Syndrome) is a rare vasculitic syndrome and should be suspected in a patient of asthma and eosinophilia if they develop renal, neurological, GI or cardiac manifestations. Diagnosis is mainly clinical and primary therapy is steroid along with immunosuppressant like cyclophosphamide.

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*Case Report*

# DICHLOROVOS INDUCED DELAYED POLYNEUROPATHY WITH BILATERAL FOOT DROP : AN UNUSUAL PRESENTATION OF ORGANOPHOSPHOROUS POISONING

**P.K. Mohanty*, L.K. Dash**, M. R. Mohapatra***, R.K. Singh*****

**ABSTRACT**

*Organophosphorous poisoning usually presents with an acute cholinergic crisis with or without intermediate syndrome. Rarely a delayed onset polyneuropathy may follow. We report a case of Dichlorovos (an organophosphate) poisoning who developed predominantly lower limb weakness with bilateral foot drop and distal paraesthesia, 3 weeks after onset poisoning. The electrophysiological study showed no generation of potential in common peroneal and posterior tibial nerves of both sides.* ***Keywords :*** *Organophosphorous, Dichlorovos, polyneuropathy, foot drop.*

## INTRODUCTION

Organophosphorous (OP) compounds are the most common cause of intentional poisoning in India[1], although unintentional outbreaks occur at times[2,3,7]. In a recent study over two months period in our institute with a total of 70 cases of intentional poisoning, the organophosphorous compounds alone or in combination with pyrethroids contributed to 65% of cases of poisoning.

Dichlorovos or 2,2 dichlorovinyl dimethyl phosphate is a highly volatile organophosphate that can get absorbed through all routes of exposure like other organophosphates. Poisoning with the organophosphates give rise to acute cholinergic crisis by inhibition of acetylcholinesterases[4]. However they may present with intermediate syndrome[5], OP induced delayed poly-neuropathy(OPIDP)[2,3] and chronic organophosphorous induced neurotoxicity(COPIND)[6]. Although we have treated a lot of cases of organophosphorous poisoning, the incidence of organophosphorous induced delayed neuropathy was observed by us for the first time in a case of Dichlorovos poisoning. The present case is reported in view of its rarity as a cause of polyneuropathy.

## CASE REPORT

A 26 year old farmer presented to medicine OPD with weakness of both lower limbs and difficulty in walking for 20 days and tingling, numbness and pain in both feet and weakness in both hands for 15 days. Initially he was unable to walk but the symptoms were improving slowly at the time of presentation. There was no urinary retention or incontinence.

Earlier, he was hospitalized for 14 days in our institute for Dichlorovos poisoning with aspiration pneumonia. He was then treated with Atropine, Pralidoxime, Piperacillin-Tazobactam, Amikacin and Metronidazole, and his condition improved. At the time of discharge he was not having any neurological symptoms or signs. About a week after his discharge he had developed the present symptoms.

On examination his pulse was 84/min, regular and blood pressure 110/70 mm of Hg. There was no fever. Nervous system examination revealed wasting of calf muscles and hypotonia in both lower limbs. The power was grade 4 in muscles around the shoulder and

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elbow, grade 3 around wrist and there was weakness of small muscles of both hands. Power in muscles around hip and knee was grade 4. Power in dorsiflexors of ankles was grade 0 and planter flexors grade 1, on both sides. Deep reflexes were depressed in upper limbs. In lower limbs, knee reflex was depressed and ankle jerks were absent. Plantar reflex could not be elicited. Patient had bilateral foot drop with high stepping gait(fig.1.a and 1.b). Sensory examination revealed impairment of vibration sensation below both malleoli. Touch, pain and temperature sensations were preserved. Coordination was normal in upper limbs. There was no cranial nerve involve ment

On investigation he had a fasting plasma glucose of 95 mg/dl, serum sodium of 138 mmol/l, potassium of 4.8mmol/l, serum urea 46mg/dl and serum creatinine1.0 mg/dl. Hematological parameters were normal. Nerve conduction study revealed no action potential generation in both side common peroneal and posterior tibial nerves. Compound muscle action potential (CMAP) was decreased and distal motor latencies increased in both median nerves. The findings were consistent with predominantly motor polyneuropathy (table 1).

CMAP-COMPOUND MUSCLE ACTION POTENTIAL, DML-DISTAL MOTOR LATENCY, MNCV-MOTOR NERVE CONDUCTION VELOCITY, mV-MILIVOLTS, ms-MILISECONDS, m/s-METRE SECOND, n.-NERVE, µV-MICROVOLTS.

Considering the temporal profile of presentation, the physical findings and nerve conduction studies, a diagnosis of organophosphorous induced delayed polyneuropathy was made. Patient was treated symptomatically with amitryptiline and pregabalin for pain and paraesthesia. He was discharged 4 days later, after evaluation and observation, as his neurological features were not detoriorating.

**DISCUSSION**

Poly-neuropathies are important causes of morbidity and mortality in young persons. The common causes include the Gullian –Barre syndrome and toxic neuropathies due to substances like arsenic, lead, mercury, organophosphates and drugs like cisplatin and vincristine[7]

Organophosphorous compounds can give rise to a delayed polyneuropathy known as Organophosphorous Induced Delayed Polyneuropathy (OPIDP) in exposed animals and humans. This typically presents 1-3 weeks after onset of acute cholinergic crises with cramping mucle pain followed by weakness of lower limbs and foot drop. Later upper limb weakness may develop. There is distal paresthesia in form of tingling and numbness although objective sensory loss is rare[8]

Morgan JP et al studied the cases of Jamaica ginger (Jake) paralysis and followed them for a period of 47 years. In 1930 thousands of Americans were poisoned by illicit Jamaican ginger adulterated with tri-ortho-cresylphosphate(TOCP), an organophosphate. The earliest of reports were peripheral neuritis but later an upper motor neuron lesion supervened involving various cells groups and tracts of spinal cord[2] . Toxic polyneuropathy following gingili oil consumption contaminated by tri-cresyl phosphate in 20 young adolescent girls were reported by Senanayake N et al from Sri Lanka [3] .

First outbreak of toxic polyneuritis in India occurred in Bombay due to Triortho-cresylphosphate poisoning reported by *Vora D D et al.(1962)* followed by reports from west Bengal in 1962 and 1992 respectively by *Chaudhari RM* and *Chakraborty A et al*[7]. OPDIP was found to be associated other organophosphates as well.

In the present case, the patient came with weakness in both lower limbs with bilateral foot drop, depressed tendon reflexes, distal paraesthesia(tingling, numbness and pain) ,high stepping gait and minimal impairment if vibratory sense, 3weeks after onset of poisoning. The case did not have cranial nerve involvement nor symptoms and signs of pyramidal tract involvement. Angelo Moretto and Marcello Lotti noted

**1.a** **1.b**

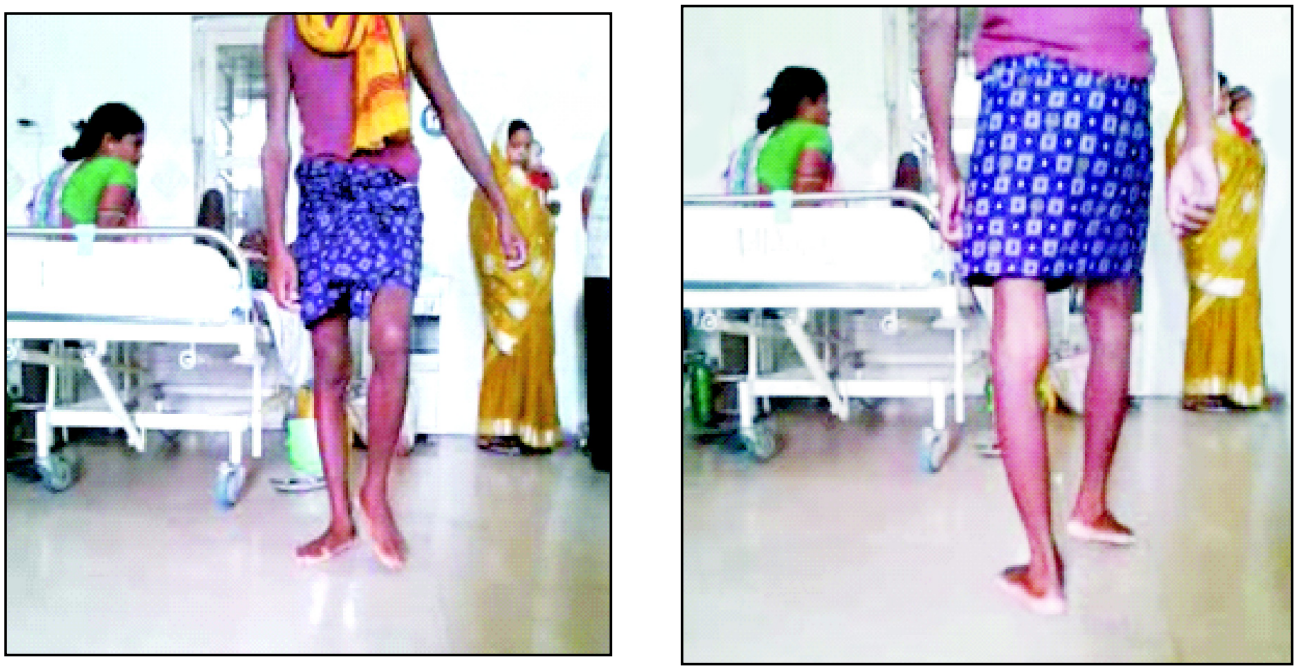

**Fig 1.a and b- showing left and right foot drop respectively**

**Table-1. (A) MOTOR NERVE CONDUCTION STUDY**

| **CMAP** | Normal values (mV) | Observed values (mV) |
|---|---|---|
| Rt. Median n. | >4.4 | 0.55 |
| Lt. median n. | >4.4 | 3.49 |
| Common peroneal n. | >2 | No potential |
| Posterior tibial n. | >3 | No potential |
| | | |
| **DML** | Normal values(ms) | Observed values(ms) |
| Rt. Median n. | <4.2 | 5.33 |
| Lt. Median n. | <4.2 | 5.21 |
| Common peroneal n. | <5.8 | No potential |
| Posterior tibial n. | <6.5 | No potential |
| | | |
| **MNCV** | Normal values(m/s) | Observed values(m/s) |
| Rt.Median n. | >49 | 50.10 |
| Lt.median n. | >49 | 43.56 |
| Common peroneal n. | >42 | No potential |
| Posterior tibial n. | >41 | No potential |

**(B) SENSORY NERVE ACTION POTENTIAL (SNAP)**

| SNAP | Normal values(μV) | Observed values (μv) |
|---|---|---|
| Rt.Median n. | >20 | 11.72 |
| Lt. median n. | >20 | 29.68 |
| Sural n. | >6 | No potential |

similar features in three cases of poisoning due to chlorpyrifos, methamidophos and a combnation of isofenophos and phoxim[9]. Vaconcellos LR et al reported a case of Dichlorovos poisoning with similar features after 2 week[10] . Wadia RS et al reported neurotoxicity after poisoning with Dichlorovos[11] .

Electro-physiological study revealed predominantly distal motor involvement of peripheral nerves with mild sensory involvement suggestive motor axonopathy similar to observations of Maretto A et al[9].

The exact mechanism of this delayed polyneuropathy induced by organophosphates is not known. However, one of the mechanisms is inhibition of Neuropathy Target Esterase, a protein localized in the endoplasmic reticulum in neurons. Pioneering work has been done by Johnson M K in elucidating various facets of this underlying mechanism. He found that phosphorylation and subsequent "aging" of neuropathy target esterase (NTE) in neurons of central and peripheral nervous system was responsible for the axonal degeneration. It was suggested that only a critical level of inhibition (70 to 80%) followed by ageing can result in neurotoxicity.Ageing occurs following removal of a –R(alkylgroup) of OP from the phosphoryl enzyme complex[8]. NTE is the 6$^{th}$ member of a 9-protein family called Patatin- like-phospholipase domain containing proteins, PNPLA1-9. Some of the organophophates and other substances which inhibit NTE but failed to produce aging may protect the person from neurotoxic effects[12].

A second mechanism studied is imbalance in calcium homeostasis. The organophosphates may induce activation of calcium activated neutral proteases and increases in calcium/calmodulin dependent protein kinases. These events lead to aberrant phosphorylation of cytoskeletal proteins(alpha and beta –tubulin, microtubule associated protein -2, neurofilament triplet proteins and myelin basic protein) and protein digestion in terminal axon,that can proceed similarly to Wallerian type degeneration.Experimental studies demonstrated alleviation of OP induced neurotoxicity by restoring calcium balance[13] .

The recent developments have ushered in a number of experimental studies to intervene the above mechanisms. Progress has been made but translation into clinically available agent to prevent or treat the OPIDN is yet to materialize.

## CONCLUSION

Acute or chronic exposure to organophosphorous compounds could be responsible for predominantly motor polyneuropathy. This aspect must be investigated in young patients presenting with cases like the one we report.

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## ARTICLE SUBMISSION

Articles preferably original articles and case reports are invited from the esteemed physicians of the state for the next issue of OPJ. Articles are to be submitted in the JAPI format. (Manuscript submission Page No.152). For details please contact the undersigned.


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*Case Report*

# EVAN'S SYNDROME - A CASE REPORT

**R.R. Sahoo*, B. Nayak*, S. Sukriya*,P.R. Barik*, J.K. Panda**, S.P. Mohanty**, P.K. Padhi*****

**ABSTRACT**

*Evan's syndrome is a rare disease charecterised by the simultaneous or sequential development of autoimmune hemolytic anemia(AIHA) and immune thrombocytopenia(ITP) and/or immune neutropenia. It is diagnosed in only 0.8-3.7% of all patients with either ITP or AIHA at onset[1]. We herein describe the case of a 22 year old female who presented with unexplained anemia, jaundice and investigations confirmed the condition as Evan's syndrome.* ***Keywords****: Evan's syndrome(ES), autoimmune thrombocytopenia(ITP), autoimmune hemolytic anemia(AIHA).*

## INTRODUCTION

ES, first described in 1951 by Robert Evans, is an autoimmune disorder characterised by the combination of autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), and sometimes associated with immune neutropenia, in the absence of known underlying causes[2,3]. Thus, by denition a true Evans syndrome is a diagnosis of exclusion and other secondary causes needs to be excluded namely, systemic lupus erythematosus[4], lymphoproliferative disorders[5,6], or primary immunodeficiencies[7]. In childhood, ES may be associated with autoimmune lymphoproliferative syndrome(ALPS) due to mutations in the Fas apoptic pathway.

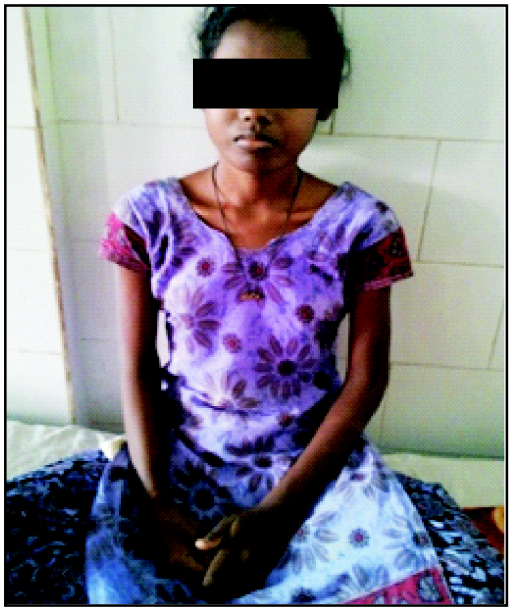
In Evan's syndrome patients may present with AIHA or ITP separately or concomitantly. Neutropenia occurs in up to 55% of patients at presentation, Pancytopenia was reported in 14% in a case study involving 42 patients in 1997(8). Clinical presentation includes the usual features of hemolytic anemia: pallor, lethargy, jaundice, heart failure in severe cases; and thrombocytopenia: petechiae, bruising, mucocutaneous bleeding. Examination may reveal lymphadenopathy, hepatomegaly and/or splenomegaly[9,10,11]. The lymphadenopathy and organomegaly may be chronic or intermittent and in some cases may only be apparent during episodes of acute exacerbation[10,11]. AIHA is dened by a hemoglobin (Hb) level of 11 g/dL or less at diagnosis with features of hemolysis (low haptoglobin level and/or elevated LDH and/or bilirubin levels) and a positive direct antiglobulin test (DAT) or when the DAT is negative, after the exclusion of other causes of acquired or hereditary hemolytic anemia[12]. ITP is dened according to exclusion criteria for ITP[12]. Immune neutropenia is dened by a neutrophil count below 1.5 x 109 /L on 2 separate occasions at least a week apart, without any other obvious cause and without any exposure to a myelotoxic drug[12]. Exclusion criteria were the following: presence of numerous fragmented red cells (> 5%) on the blood smear with a negative DAT, suggesting a thrombotic thrombocytopenic purpura; a diagnosis of chronic cold agglutinin disease, any other cause of hereditary or acquired hemolytic anemia; drug-induced hemolytic anemia and/or thrombocytopenia. Beyond the DAT, the presence of other autoantibodies (eg, antinuclear or antiphospholipid antibodies) is not a criteria for exclusion.

**Case Report -** A 22 years old female presented to Medicine outpatient department, SCB Medical College,

*Postgraduate Student, **Associate Professor, ***Professor, Department of Medicine, SCB Medical College, Cuttack.

Cuttack with generalized weakness for 6 months, yellowish discolouration of sclera for 5 months with history of blood transfusion (8 units over last 6 months). (Pic.1) There was no history of fever, bleeding manifestations, hematemesis/melaena, swelling of abdomen, irregular menses. On examination there was severe pallor, icterus, mild hepatosplenomegaly with no lymphadenopathy. Other systems revealed no abnormality.

She received blood transfusion, platelet concentrate and was put on Prednisone(2 mg/ kg wt). After a week there was no response and her Hb levels remained low. Soluble methylprednisone in a dose of 30mg/kg daily for 3 doses was given as bolus dose. Her Hb level increased from 4.5 g% to 8 g% and platelet counts increase after 1 week. She was discharged with prednisone(1 mg/ kg wt).



Picture-1 showing photograph of the patient

**Investigations** - Hb- 4.5 gm%, TLC- 6000 cells/ cumm, Reticulocyte count- 18% and TPC-40000 cells/ cumm. Her peripheral smear showed microcytic hypochromic anemia with polychromasia. Her serum iron- 39 micro gm /dl (Normal- 41 - 141 micro gm/dl), serum ferritin 14 microgm/dl (N- 10-150 microgm/dl) and serum iron binding capacity was mildly high (440 microgm/ dl N= 251 - 406 micro gm/dl). Bone marrow aspiration study revealed erythroid hyperplasia. LFT- S.Total BR – 3.1mg/dl, Direct – 0.8mg/dl, SGOT – 38IU/L, SGPT – 21IU/L, ALP–210IU/L. BT, CT, PT and APTT were within normal range. HBsAg, HIV, ANA, dSDNA, APLA (antiphospholipid antibody panel) were normal. Serum lactate dehydrogenase LDH was elevated (1693 U/l, N= 115-224/l). Hemoglobin electrophoresis was normal. Coomb's DAT (Direct anti globulin test) was positive. X-ray chest was normal and USG confirmed hepatosplenomegaly. Thyroid functions were normal.

## DISCUSSION

Evan's Syndrome can be classified as primary (Idiopathic) or secondary. In adults, an underlying cause can be expected in about 70% cases[13]. There are case reports of Evan's Syndrome secondary to SLE, evolving lupus, primary antiphospholipid syndrome, Sjogren's syndrome, common variable immuno deficiency, IgA deficiency, B and T cell non Hodgkins malignant lymphomas and chronic lymphocytic leukaemia[14]. There was no evidence of other secondary causes from clinical examination and investigations in our case. In a major study by Michael et al[12] of sixty eight patients of Evan's Syndrome, the main characteristics were: female:male ratio of 3:2, mean age at onset-55±33 yrs, mean Hb level(g/dl) at onset and/ or mean lowest level during follow up- was 7.6±1.9/6.3±1.2, mean(median and range) platelet level(109/l) at ITP onset and/mean lowest level during follow up 31(median 12.5:2 to 100)/18±1.5, DAT pattern: IgG-43%, IgG+C3d-53% and negative in 4%.

The management of Evan's Syndrome is challenging. Blood and platelets transfusion is the treatment given to alleviate symptoms. The first line of treatment is prednisolone, but relapses are frequent after weaning of steroids[15]. Our case did not respond to prednisone, in a dose of 2 mg/kg/day. She responded to pulse methylprednisone (1gm/dose) 3 doses. Other treatment options are IVIG, immunosuppressants, danazol and even splenectomy. Rituximab ,a chimeric monoclonal antibody against CD20 has been well

tolerated by patients of refractory Evan's Syndrome[16]. In extreme refractory conditions a small number of patients have been treated by stem cell transplantation[17]. Our patient responded to methylprednisone bolus followed by 1mg/kg of oral prednisone. Relapses are common and needs regular monitoring to prevent deterioration of the condition.

## CONCLUSION

ES is a chronic state of profound dysregulation of immune system and can be primary and secondary. The distinction between primary and secondary ES is important as it will influence the management of the disease. Most patients respond well to high dose steroid. Combination therapy of steroids and rituximab should be instituted in refractory cases

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*Case Report*

# RECURRENT QUADRIPARESIS IN GITELMAN'S SYNDROME

**Sujit K. Tripathy[*], S.K. Mishra[*], S. Behera[**], Saroj K. Tripathy[***]**

**ABSTRACT**

*We report here an unusual case of Gitelman's syndrome in a 42 yr male, who presented as recurrent hypokalemic periodic palsy and recovered only after magnesium along with potassium supplement.* ***Key Words:*** *autosomal recessive, renal tubulopathy, Trousseu's sign.*

## INTRODUCTION

Gitelman's Syndrome is an autosomal recessive salt-losing renal tubulopathy that is characterised by hypokalemia, hypochloremic metabolic alkalosis, secondary hyperaldosteronism, hypomagnesemia and hypocalciuria without hypertension[1]. The prevelance is estimated to be 25 per million, making it one of the most frequent inherited renal tubular disorders[2]. It is due to mutation in the gene SLC12A3 located in chromosome 16q13 that codes for thiazide sensitive Na-Cl co-transporter (NCCT) in the distal convoluted tubule[3]. Patients usually present in late childhood and adolescent with fatigue, weakness, carpopedal spasm, cramps, and tetany.

## CASE REPORT

A 42 yr male presented with sudden onset weakness in both lower limbs that progressed rapidly to involve upper limbs within a few hours, making him unable to move on the bed. He had no complain of difficulty in breathing or retention of urine. There was no history of any antecedent respiratory tract infection, fever, diarrhoea, vomiting or any drug intake. The patient had experienced similar muscle- weakness one year back from which he recovered after treatment. He gave history of tiredness, fatigue and muscle cramp off and on.

On general examination, he was of average body built, with normal pulse rate, blood pressure and respiratory rate. He had Carpopedal spasm and Trousseu's sign.

Neurological examination revealed normal higher functions and cranial nerves. Examination of motor system revealed normal bulk of muscles, hypotonia and power in upper limb was 2/5 that in lower limb was 1/5 on both sides. Deep tendon reflexes were diminished. Bilateral plantar reflex was flexor. Bladder and Bowel function were intact. There was no sensory deficit. Rest of the systems were normal.

His haemoglobin, TLC, DC, FBS were normal. He had S. urea 33mg/dl, creatinine 1.4mg/dl, S. sodium 138mmol/ lt. , potassium 2.4mmol/lt., S. chloride 90 meq./lt. (N 101-109), S. ionised calcium 0.82mmol/lt. (N1.15-1.33), S. Magnesium 0.9mg/dl( N1.6-2.3).His serum thyroid and parathyroid hormone levels were normal. ABG was suggestive of metabolic alkalosis - PH 7.563 (N7.35-7.45), HCO3-36.8 (N22-30) mmol/l, PCO2 34(N32-45) mmHg. His 24 hr Urinary potassium was 82mmol/d (N<45 mmol/d), calcium 0.2 mmol/d (<1 mmol/d), chloride 156 mmol/lt, urinary PH was 6.

ECG revealed decrease amplitude of T waves and prominent U waves especially in chest leads. Nerve conduction velocity was normal.

Considering hypokalemia, hypomagnesemia, hypochloremic alkalosis in a normotensive person with high urinary potasium and low urinary calcium excretion, a diagnosis of Gitelman's Syndrome was made. The patient was treated with spironolactone, along with potassium and magnesium supplements and liberal salt intake leading to improvement of quadriparesis, maintaining serum potassium level between 3.5-4.5 mmol /lt.

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## DISCUSSION

In Gitelman's Syndrome impaired sodium and chloride reabsorption in either the thick ascending loop or the distal convoluted tubule cause hypovolumia which activates the renin-angiotensin-aldosterone system (RAAS). The consequent hyper-aldosteronism, together with increased distal flow and sodium delivery, stimulates increased sodium reabsorption in the collecting tubule via the epithelial sodium channel(ENaC). This promotes increased potassium and hydrogen ion secretion, causing hypokalemia and metabolic alkalosis. It remains unclear how this defect leads to severe magnesium wasting[3]. It has been shown that passive $Ca^{2+}$ reabsorption in the proximal tubule and reduced abundance of the epithelial $Mg^{2+}$ channel TRPM6, located in the DCT explains thiazide-induced hypocalciuria and hypomagnesemia, respectively[4]. Since thiazides are known to inhibit NCCT, and in view of the phenotypic resemblance between GS and chronic thiazide-treatment, it is very likely that similar mechanisms are involved in the pathogenesis of respectively hypocalciuria and hypomagnesemia seen in Gitelman's Syndrome[4].

Hypokalemia and hypochloremic metabolic alkalosis without hypertension more often may be due to excessive vomiting or diuretic abuse than to Bartter's or Gitelman's Syndrome. But very low urinary chloride level differentiate excessive vomiting from Bartter's or Gitelman's Syndromes. Diuretic abuse can be diagnosed by history and screening the urine for offending agents.

Gitelman's Syndrome can be distinguished from most forms of Bartter's Syndrome by the presence of severe hypomagnesemia and hypocalciuria.

Gitelman's Syndrome require lifelong therapy with potassium and magnesium supplements and liberal salt intake. High doses of spironolactone or amiloride used to treat the hypokalemia, metabolic alkalosis and magnesium wasting. However magnesium repletion is essential to correct the hypokalemia and to control muscle weakness, tetany and metabolic alkalosis[3].

In general, the long term prognosis of Gitelman's Syndrome is excellent. However, the severity of fatigue may seriously hamper some patient's daily activities.Cardiac workup is recommended to screen for risk factors of cardiac arrhythmias[5]. Progression to renal insufficiency is extremely rare[2].

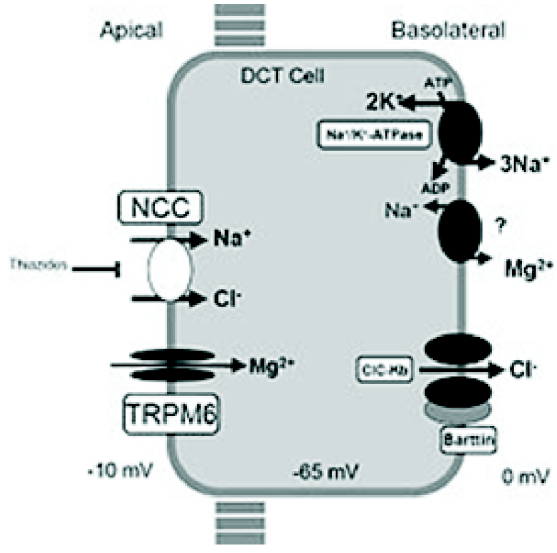


**Fig. 1**

A model of transport mechanisms in the distal convoluted tubule. Sodium-chloride (NaCl) enters the cell via the apical thiazide-sensitive NCC and leaves the cell through the basolateral Cl- channel (ClC-Kb), and the Na+/K+-ATPase. Indicated also are the recently identified magnesium channel TRPM6 in the apical membrane, and a putative Na/Mg exchanger in the basolateral membrane. These transport mechanisms play a role in familial hypokalemia-hypomagnesemia or Gitelman's syndrome.

## CONCLUSION

Every cases of recurrent hypokalemic quadriparesis or paraparesis should be evaluated to exclude Gitelman's Syndrome.

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*Case Report*

# WILSON'S DISEASE PRESENTING AS PURE HEPATIC FORM IN AN ADOLESCENT

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**ABSTRACT**

*A case of Wilson's disease, a rare autosomal recessive disorder of copper metabolism is reported here. The patient, a 16 year old boy presented with swelling of abdomen and legs, yellowish discoloration of eyes and urine, low grade fever and bleeding from nose . He had jaundice, ascites, other signs of liver cell failure, splenomegaly. Slit lamp examination of eyes revealed bilateral Kayser-Fleischer ring with normal visual acuity. Investigations revealed low serum albumin (2.0 gram/dl), increased serum bilirubin and normal liver enzymes.Ultrasonography of abdomen revealed cirrhotic changes of liver, splenomegaly and ascites. Serum ceruloplasmin level was 7.5 mg/dl. 24 hours urinary copper excretion was 226.30 microgram per Litre. Liver biopsy revealed cirrhotic changes. He was advised to take copper chelating agent (penicillamine) in a dose of 1 gram/day and oral zinc in a dose of 150mg/day.* ***Keyword :*** *Wilson's disease, KF ring, cirrhosis of liver.*

## INTRODUCTION

Wilson's disease or hepatolenticular degeneration is an autosomal recessive hereditary disease, that localizes to ATP7B gene on chromosome 13 characterized by a deficiency of ceruloplasmin, the serum transport protein for copper. The most pronounced involvement is in the liver, brain, with typical involvement of the lenticular nucleus. Various hepatic forms like acute hepatitis, chronic hepatitis, cirrhosis of liver and acute fulminant hepatic failure can occur in early childhood[1]. Neurological manifestations appear in the second decade and early symptoms are in coordination, tremor, dysarthria, dystonia, rigidity and difficulty with fine motor tasks[2]. Neuroimaging studies and gross pathology can show diffuse or focal atrophy. Typical sites of cerebral involvement are deep grey matter and central white matter. Grey matter nuclei involvement is more common, usually bilateral symmetric in the putamen, caudate, thalamus, globus pallidus, dentate nucleus, pons and mesencephalon.

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## CASE REPORT

A 16 year old boy (fig.1) born out of consanguineous marriage presented with swelling of abdomen followed by legs, yellowish discoloration of eyes and urine, low grade fever since past 1 month and bleeding from nose since past 2days. There was no history of similar illness or jaundice or drug intake in the past. No positive family history. Only sibling, an elder sister is healthy. Physical examination revealed pallor, icterus, pedal edema, gyneacomastia, KF ring in both eyes (confirmed by slit lamp examination)(fig 2), ascites with dilated veins in the epigastrium & Rt hypochondrium splenomegaly 4cm below the Lt costal margin, liver was not enlarged. Examination of respiratory system revealed evidence of right sided pleural effusion. He had normal neurological examination. A clinical diagnosis of Wilson's disease was confirmed by investigations - S.bilirubin-8.9mg/dl (total), 2.8mg/dl (indirect), SGOT 29IU/L, SGPT-37 IU/l, S.Albumin-2 gm/dl, A:G ratio-0.3, INR-2.6, HBsAg & Anti HCV were negative, Ultrasonography findings of abdomen showed shrunken liver, coarse hepatic echo structure, gross ascites, dilated portal vein (15mm)

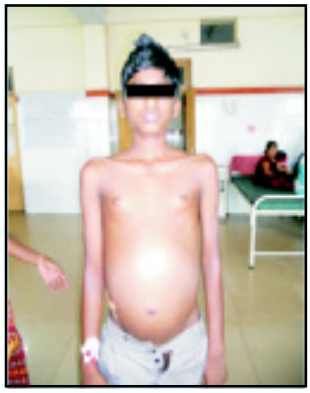

**Figure 1 showing Gynaecomastia and asicites**

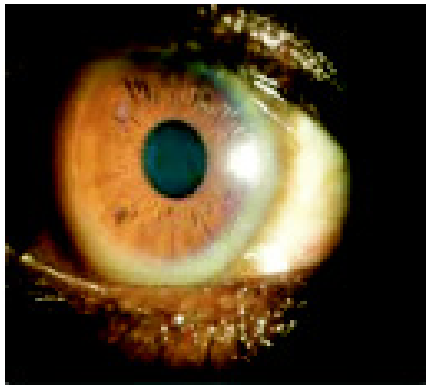

**Figure 2 : KF Ring**

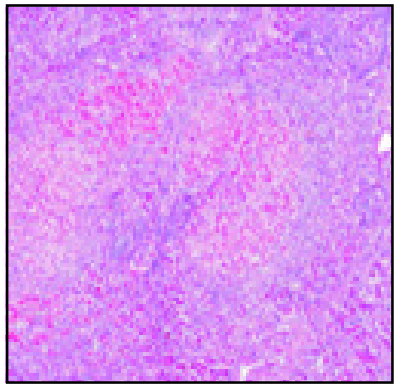

**Figure 3 : Liver Biopsy showing evidence of cirrhosis of liver**

splenomegaly consistent with cirrhosis of liver with portal hypertention. Serum ceruloplasmin <7.5mg/dl, 24 hour urinary copper excretion -226.30 microgram per Liter. Liver biopsy showed evidence of cirrhosis (Fig.3). Genetic analysis was not done. Screening of sibling was not done as she was residing elsewhere.

## DISCUSSION

Clinical presentation of WD is between 5 to 50 years. It is possible that the disease manifests at a younger age in Indian children. The average intake of copper in India ranges from 5.7-7.1 mg/day and is higher than the reported 0.34-1.1 mg/day in Western countries. The practice of cooking food in copper/copper alloy pots might be contributory[3]. However, early childhood WD usually presents with chronic liver disease or hemolytic anemia and neurological manifestations are rare before the age of ten years[4]. Chronic active hepatitis, culminating in cirrhosis is the most common hepatic presentation, but some patients present with fulminant liver failure. Typical neurological signs include tremor, rigidity, drooling, speech changes, incoordination, tremor, difficulty with fine motor tasks, and gait difficulties. Psychiatric manifestations include compulsive behavior, aggression, and depression, impulsive behavior, and phobias. Our patient presented for the first time with decompensated cirrhosis.KF rings are found in 90% of symptomatic patients, invariably in those with neurological form of the disease but however it may be absent in 40-60% of those with hepatic disease[3]. In our patient we found KF ring in hepatic form of the disease. Diagnosis is based on clinical evaluation along with biochemical and neuroimaging confirmation. Biochemical studies reveal a low serum ceruloplasmin level (<20 mg/ dl) and increased urinary copper excretion (more than >100 microgram copper per 24 hours). Hepatic copper estimation, of more than 250 g/g of dry tissue (Normal 15-55 g/g) is the most definitive method of diagnosis[5,6]. The disease is treated with lifelong use of chelating agents such as D-penicillamine or trientine hydrochloride, drugs that help remove copper from tissue. Use of zinc for maintenance therapy and for treatment of asymptomatic siblings has been advised[1,4].

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*Case Report*

# PONCET'S DISEASE: A RARE PRESENTATION IN TUBERCULOSIS

**Rohit Kumar*, Madhukara HM*, Balaji M*, Saroj K Sahoo*,**
**Ashoka Rath**, Bidyut K Das*****

**ABSTRACT**

*Reactive arthritis in tuberculosis is known as Poncet's disease. It is a rare form of arthritis observed in patients with active tuberculosis. Since clinicians are mostly unaware of this entity it is likely to be underdiagnosed. One such case is reported here in a 32 years old female patient.*
***Key words:*** *Reactive arthritis, Poncet's disease, Tuberculosis,*

## INTRODUCTION

Poncet's disease or tuberculous reactive arthritis is the occurrence of polyarthritis/oligoarthritis in patients with active tuberculosis[1]. It was first reported by Antonin Ponset,a French surgeon in 1897[2]. Septic tuberculous arthritis is usually monoarticular, involving direct invasion of tubercular organism leading to destruction of the joint. Musculoskeletal manifestations are the most common extrapulmonary tuberculosis accounting for 10-19% of cases[3] Poncet's disease is a form of reactive arthritis in a background of active tuberculosis, involving mostly large joints like knees, ankles, wrists and elbows without direct bacteriologic involvement of joints. It is believed to be an immunological reaction to tubercular protein sensitizing CD4 T cells[4]. The phenomenon of molecular mimicry between mycobacterial antigens and host collagen tissue is another pathogenetic mechanism implicated[5]. This is an unusual and rare condition. Considering the incidence of TB in our country, the number of reported cases of Poncet's disease are few. Many clinicians are unaware of this presentation in tuberculosis, hence this entity is likely to be underdiagnosed. We present here a case of Poncet's disease associated with pulmonary tuberculosis.

## Case Report

A 32 years old female patient presented to our department on 23.9.2013 with complaints of low grade fever for the last 3 months associated with pain in the ankles, elbows and wrist joints for the last 1 month. Fever was low grade and there was evening rise. There was no cough or expectoration. Joint pain was symmetrical and it was associated with red tender nodules on the shin of both legs that came in crops. She also complained of weight loss and fatigue.

There was no involvement of the small joints or low backache. There was no history of uveitis, photosensitivity or malar rash, oral ulcers, dysnoea, diarrhoea, burning micturition, skin tightening,Raynauds or proximal muscle weakness.

On examination, there was pallor, a temperature of 100F, pulse rate 102/min and BP of 110/70mm of Hg. There was no lymphadenopathy. There were two to three erythematous tender nodules on both the shins suggestive of erythema nodosum. Examination of the Musculo Skeletal System (MSK) revealed bilateral tender ankle joints with restriction of movement. There was no effusion. Systemic examination was within normal limits. A provisional diagnosis of sarcoidosis was entertained and the case was investigated.

Investigations revealed Hb -10.3 gm%,TLC-11,200/cu.mm, DC: N-78%,L-20%, ESR of 116 mm Hg per 1st hour. Mantoux test with 5 TU was > 10mm. Renal function, LFT and urine microscopic examination were within normal limits. Chest X-ray revealed

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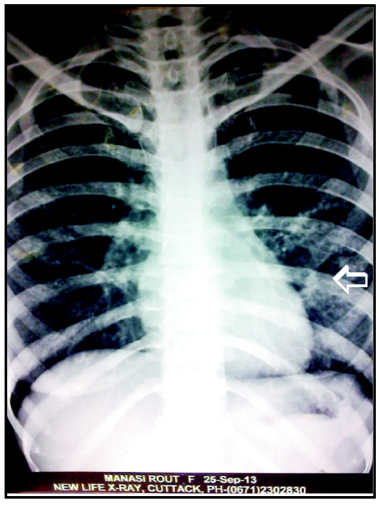
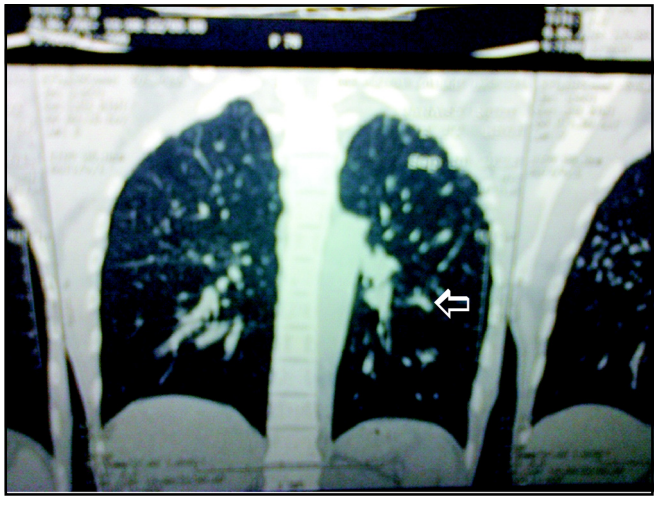



Picture-1 : X-ray chest PA view showing infiltrative lesions in the left middle and lower zones



Picture-2 : HRCT of the Lungs showing 'Tree in Bud appearance'

infiltrative shadows bilaterally(left>right) in mid zones and lower zones. (Pic.1) HRCT of thorax revealed multiple Tree in Bud appearance suggestive of tuberculosis.(Pic.2) Sputum for AFB could not be done since the patient had no expectoration.

The patient was put on anti-tubercular therapy Category I. She became afebrile, joint pain was reduced in intensity and the tender nodules resolved completely.

**DISCUSSION**

Musculoskeletal presentation in tuberculosis is characterised by either direct involvement of the bacteria affecting the bones and joints or as a result of immunological reaction to some components of tuberculous bacillus. The former has been widely recognised and is treated early while the latter escapes the attention and remains under-diagnosed. This case had pulmonary tuberculosis with reactive arthritis and erythema nodosum. The case remained undiagnosed for three months since arthritis was a dominant feature and its relevance to tuberculosis was unrecognised.The prevalence of Poncet's disease appears to be low as reported in literature[9]. A recent publication reports 57 cases worldwide based on literature review till 2012[14]. The issue that needs to be addressed is how aware we are about Poncet's.

It has been defined as tuberculous reactive arthritis (Poncet's disease) and shares the characteristic features of classical reactive arthritis associated with spondyloarthritis group of disorders. Poncet's disease more often affects young patients and is slightly more common in females. Our index case was a young female. The onset is not as acute as in regular enteric or genitourinary reactive arthritis[6]. It presents as asymmetrical oligo or polyarthritis of large or small joints or both.The spine and sacroiliac joints are not involved. The ankles and knees are commonly affected. It has been observed that Poncet's disease mainly occurs in patients with extrapulmonary TB[6,7], the most common site being the lymph nodes[7]. It is always associated with active tuberculosis elsewhere. However, recent data suggest that extrapulmonary TB might be present in only half of the cases[9] Primary tuberculosis of the joint is widely known as tubercular septic arthritis, in which mycobacterium tuberculosis can be isolated from the joint and histology of the synovial tissue may reveal granulomatous changes associated with classical tubercular infection.

Poncet's disease is a sterile arthritis which is presumed to be caused by an immunological reaction, mediated by CD4 T cells to tubercular antigen[3,8]. A possible role of mycobacterial heat shock protein

65(HSP) has also been investigated. Since the structure of mycobacterial and human HSP are 50% homologous, molecular mimicry may be involved in the causation of arthritis[6]. The disease occurs in a small proportion of patients with tuberculosis, therefore, a genetic predisposition linked to HLA has also been proposed. However, the precise pathogenetic mechanism is still uncertain.

Erythema nodosum(EN) is an important clue to suspect Poncet's. A study revealed that EN is observed in 6% of cases[9]. These are tender, erythematous nodules on the anterior aspect of legs that are more easily palpated than visualised and represent septal panniculitis[7]. Our patient had tender nodules but they were not subjected to biopsy. EN are found in association with various conditions. Tuberculosis was formerly the most important cause[10]. But the prevalence of tuberculosis among patients with EN has decreased markedly[11]. Differential diagnosis of erythema nodosum includes other Infections namely,Beta haemolytic Streptococcus, histoplasmosis, coccidiomycosis,Yersinia enterocolitis, systemic diseases like sarcoidosis, IBD, dermatomyositis, and drugs like penicillin,sulphonamide and OC pills[7].

An interesting feature in this case was the"Tree In Bud" appearance on HRCT of lungs. It refers to a pattern seen on CT of lungs in which centrilobular bronchial dilatation and filling by mucus,pus or fluid,demarcates the normally invisible branching course of the peripheral airways and resembles a budding tree[12]. It was first described in a case of endobronchial spread of mycobacterium tuberculosis[13]. It is now recognised as a CT manifestation of various disorder such as Infection (bacterial, fungal, viral, parasitic), congenital disorders (Cysticfibrosis, Kartagener syndrome), idiopathic disorders (obliterative bronchiolitis, panbronchiolitis), connective tissue disease(sjogren's syndrome) and peripheral pulmonary vascular disease[12].

The diagnosis of Poncet's depends on a high index of suspicion and exclusion of common causes of asymmetrical oligoarthritis associated with fever. This was done based on a detailed clinical examination and appropriate investigation possible in our setup. On the basis of certain important findings the diagnosis of Poncet's Disease was entertained and excellent response to anti tubercular therapy provided supportive evidence. The presence of erythema nodosum as well as tree in bud appearance on HRCT chest that led to the diagnosis of Poncet's disease was an unique combination that has been reported rarely.

## CONCLUSION

In conclusion, the differential diagnosis of patients presenting with oligo/polyarthritis with fever should always include Poncet's disease, especially in regions of high prevalence of tuberculosis. Correct identification of this rare complication of TB may avoid delay in initiation of appropriate treatment.

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*Case Report*

# PANCREATIC PSEUDOCYST DUE TO ACUTE ORGANOPHOSPHATE POISONING

**N. Mohapatra*,P. Jena**, P.K. Rathore**, D.N. Moharana***, Rohit Kumar****, S. Panda****, M. Layek****, S. Swain******

**ABSTRACT**

*Acute pancreatitis is one of the complications associated with acute organophosphate(OP) poisoning, but this association has not been widely recognized. We report here a case of an 18 year old female who developed vomiting, abdominal pain and tenderness during treatment for acute OP poisoning. Serum amylase and lipase levels were high and abdominal ultrasonography(USG) and computed tomography(CT) revealed pancreatitis and a pancreatic pseudocyst of size 7.6 cm x 4.3 cm. She was managed conservatively and discharged after improvement . During follow up after three weeks the pseudocyst size had regressed to 4 cm x 2.3 cm.* ***Keywords :*** *Organophosphate poisioning, Acute pancreatitis, Pancreatic Psueocyst.*

## INTRODUCTION

Organophosphate compounds are widely used as agricultural chemicals and due to their widespread availability, suicidal poisoning by these compounds is very common. These agents are potent inhibitors of acetylcholinesterase enzyme, resulting in an increase in acetylcholine activity which is responsible for the symptoms seen in acute OP poisoning, such as abdominal pain , diarrhoea, hypersialorrhoea, vomiting and miosis. Acute pancreatitis has been reported as a complication of OP poisoning in a number of case studies[1-5], though this association is still not widely recognized. In adults the frequency of acute pancreatitis related to OP poisoning is 12.7%[6]. There are few case reports of pancreatic pseudocyst developing as a complication of OP induced acute pancreatitis[7-9]. Therefore we present here a rare case who developed a pancreatic pseudocyst due to acute OP poisoning.

## CASE REPORT

A female patient aged about 18 years was admitted in the Emergency Department of our hospital with a history of OP(Chlorpyrifos) poisoning 6 hours earlier in a suicidal attempt. She had received atropine and gastric lavage had been done at a peripheral hospital before being referred to our hospital. On examination she was conscious but irritable and tachypneic, pulse-120/min, BP-120/80mmHg. There was no pallor, jaundice or cyanosis. Chest examination revealed bilateral crepitations and abdomen was soft and nontender. Pupils were moderately dilated and planters were flexor. Treament with atropine and pralidoxime were started. Investigations revealed haemoglobin-12 gm/dl, total leucocyte count-14,600/cumm, differential count-polymorphs 78%, lymphocyte 16% and eosinophil 6%, random blood glucose-96 mg/dl, LFT and RFT were normal. Serum cholinesterase was 220 U/L.

On the 7th day of treatment the patient complained of pain abdomen radiating to the back, and had repeated bouts of vomiting. On examination, jaundice was detected. There was tenderness and rigidity over upper abdomen without organomegaly or evidence of free fluid in the abdomen. Hence acute pancreatitis was suspected . Laboratory investigations were: LFT- T.Bil.-3.7 mg/dl, D.Bil.- 2.5 mg/dl, ALT-142 IU/L, AST- 112 IU/L, ALP- 176 IU/L, random blood glucose- 168 mg/dl, blood urea- 14 mg/dl, serum

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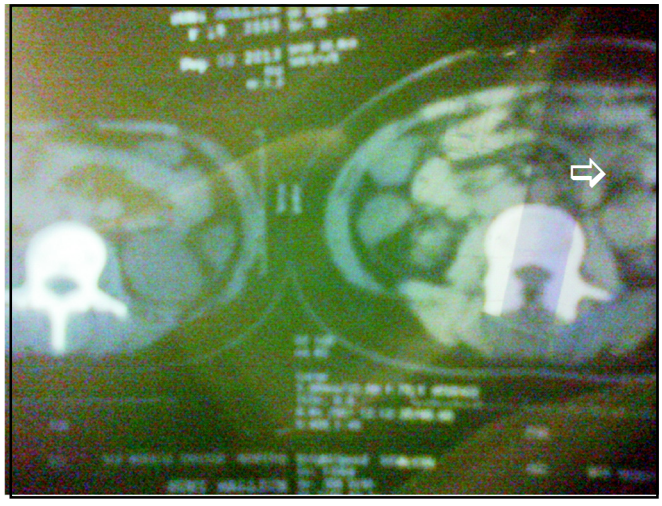
creatinine- 0.8 mg/dl, calcium(ionized)- 0.98mg/dl, amylase-212 U/L, lipase- 844 U/L, total protein-6.2 mg/dl, albumin- 3.4 mg/dl, prothrombin time- 18.8 sec., serum cholinesterase- 2010 U/L. Abdominal USG showed oedema of the body and tail regions of the pancreas with heterogenous hypoechoic collections in lesser sac and anterior to tail of pancreas. There was no evidence of cholelithiasis. CT abdomen done 2 days later revealed a pancreatic pseudocyst of size 7.6 cm x 4.3 cm in the lesser sac, anterior to the tail of pancreas.(Pic.1) Conservative management with intravenous fluids and total parenteral nutrition, proton pump inhibitors, antiemetics, analgesics, antibiotics was done. She improved symptomatically over the next 6 days and her laboratory parameters also normalised. She was then discharged from the hospital with advice to follow up in the OPD. 3 weeks later her abdominal ultrasound showed the size of the cyst to have reduced to 4 cm x 2.3 cm.



Pic.1 CT Abdomen showing Pancreatic Pseudocyst in a case of OP Poisoning.

## DISCUSSION

Dressel TD et al. described the first case report of acute pancreatitis and pancreatic pseudocyst as a complication of acute OP in 1979[10].The course of acute pancreatitis following OP poisoning is generally subclinical[11]. Lankisch et al. reported two cases of painless acute haemorrhagic pancreatitis subsequent to OP intoxication[5]. Organophosphates cause excessive cholinergic stimulation of the pancreatic acinar cells and the Oddi's muscle. This results in increase of pancreatic exocrine secretion and ampullary spasm, leading to pancreatic ductular hypertention, interstitial oedema and enzyme elevation. This hyperstimulation is thought to be the mechanism of acute pancreatitis in OP poisoning[10-12].

A pancreatic pseudocyst develops within a period of 1 to 4 weeks following the onset of acute pancreatitis as a result of pancreatic enzymes, debris, fluid, tissues and blood collection. The common symptom is abdominal pain that may or may not radiate to the back. Pseudocysts that are > 5 cm in diameter may persist for > 6weeks after their formation[13]. Most of the pancreatic pseudocysts resolve spontaneously , but those which do not resolve may lead to serious complications such as pain due to expansion of leision, rupture, haemorrhage and abscess[13]. UC Singh et al. recently reported a case of huge pancreatic pseudocyst after 10 days of OP poisoning who needed surgical intervention[7]. In our patient of OP poisoning acute pancreatitis was initially subclinical. Seven days later, due to the abdominal pain and tenderness acute pancreatitis was suspected and was confirmed by laboratory tests and abdominal USG. CT abdomen done on the 9th day revealed a pancreatic pseudocyst of size 7.2 cmx 4.3 cm. Jaundice and transient rise in liver enzymes could be due to pancreatitis. Possible etiological factors for acute pancreatitis (alcohol, diabetes, biliary diseases, trauma, drugs) were excluded. Hence we diagnosed this case of pancreatic pseudocyst as a complicaton of organophosphate induced pancreatitis. Conservative management was done and the patient improved. Three weeks later the size of the pseudocyst had regressed to 4 cm x 2.3 cm.

## CONCLUSION

Acute pancreatitis and its complications should be kept in mind while managing patients of acute organophosphate poisoning. Patients should be closely monitored, and those with ongoing or recurrent abdominal discomfort should be evaluated further for

pancreatic damage, so that early diagnosis and appropriate treatment can greatly reduce the morbidity and mortality.

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*Case Report*

# CUTANEOUS ANTHRAX - A CASE SERIES

**S. Mishra*, D.R. Tripathy*, R. Sathpathy*, N.R. Mohanty**, N. Mohapatra***, CBK Mohanty*****

**ABSTRACT**

*Anthrax is a zoonotic disease caused by Bacillus anthracis.Cutaneous form of the disease is the most common clinical form.In this article we report 19 cases of cutaneous anthrax admitted to our hospital on the same day from the same locality.They were administered oral antibiotics with a presumptive diagnosis of cutaneous anthrax,routine investigations were done and aspirated pus was sent for microbiological evaluation.Patients recovered completely with treatment without any complications and were discharged.* ***Keywords :*** *Anthrax, Cutaneous Anthrax.*

## INTRODUCTION

Anthrax*(Greek:Black)* is a disease of domestic hervivores caused by the bacterium *Bacillus anthracis* (large 1x3-10μm,gram positive rods) which lives in topsoil and is ingested by animals while grazing[1-4]. Infection in humans is rare and it presents as a localised cutaneous lesion,gastrointestinal infection or as overwhelming pneumonia and disseminated disease.Among them cutaneous form is most common and represents 90% of all human cases.It is a particular problem in tropical environments in Africa, Asia, South and Central America, and the Caribbean in locations where veterinary services are lacking and traditions and economic conditions lead to butchering and use of meat, hide, and wool from animals that die suddenly[5-8].Human to human transmission is rare.

## CASE REPORT

19 cases (12 males and 7 females, from the same location) were admitted to our hospital with complaints of skin lesions and history of fever. Their history suggested of handling of carcasses. All patients had irregular edged necrotic vesciculobullous lesions on an erythematous and edematous base on their forearm and hand, developed within one week following the contact. Out of all cases four cases had gross cellulitis of the hand. (Pic.1&2) There were no systemic findings and all had stable vitals. They were diagnosed as cases of cutaneous anthrax and started with ciprofloxacin and doxycycline. Routine laboratory findings were within normal limits. On the following day pus was aspirated from the skin lesions and sent for gram staining and culture.5 out of 19 cases revealed typical bamboocane shaped gram positive. 2 cases revealed gram positive cocci in pairs and few pus cells. Rest cases revealed only pus cells.

All the cases were treated successfully with oral antibiotics and topical wound care.

## CASE DISCUSSION

Cutaneous anthrax occurs mainly on the exposed parts of the body, usually the hands, fingers, arms, face, or neck[1-3,9-16]. In greater than 90% of cases, there is a single lesion. After an incubation period of 1 to 7 days (usually 2 or 3 days), local pruritus is the initial symptom, followed within a day by a papule a few millimeters in diameter. Usually, on the second day one or more vesicles appear on the papule or in a ring around it. After enlargement or coalescence of the vesicles during the subsequent 1 to 3 days, the papule ruptures, forming a round 0.5- to 3-cm ulcer that dries to become a depressed, brown eschar that turns black, thick, and adherent to the underlying tissue during the

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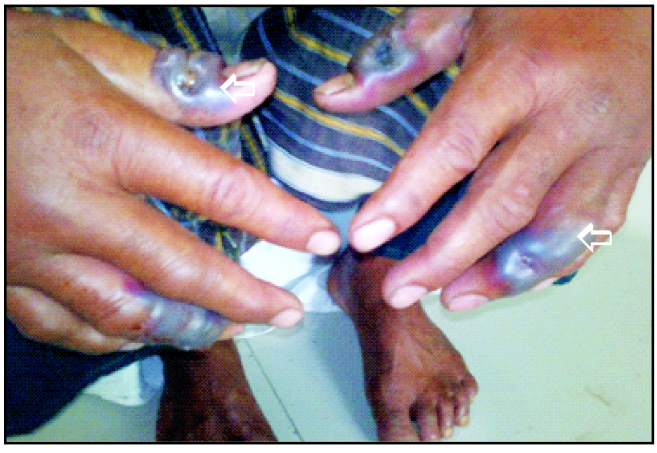

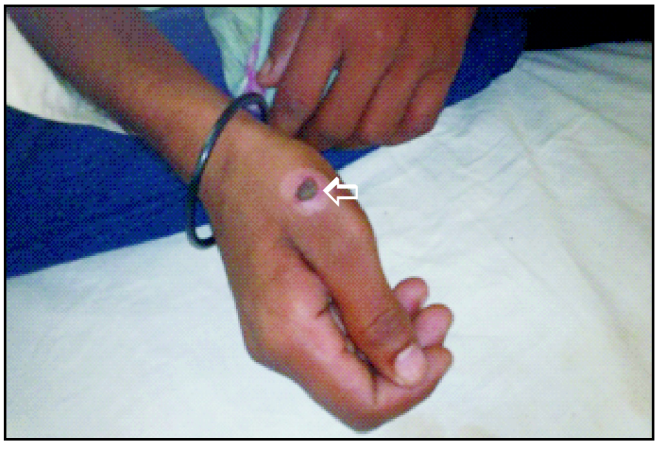

Pic.1 & 2 Showing irregular edged necrotic vesiculobullous lesions with brownish black eachar suggestive of cutaneous anthrax.

next few days. It is painless unless it is superinfected. Regional adenopathy, fever, malaise, nausea and vomiting may be present. The infection is self limited(slowly over 2-6 weeks),but hematogenous spread with sepsis or meningitis may occur.

## CONCLUSION

In areas where anthrax is endemic,it is very important to educate people under risk to take necessary preventive measures while handling carcasses. We should also consider anthrax in the differential diagnosis of cases presenting with typical ulcers and had contact with animals or their products. Early initiation of appropriate treatment is of crucial importance as it would decrease related morbidity and mortality.[16]

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*Case Report*

# MULTIPLE MYELOMA WITH RARE PRESENTATIONS

**S. Sahu*, R. Mohanty**, N. Mohapatra**, P.K. Thatoi***, M.K. Parida*, S.N. Jena***

**ABSTRACT**

*We report 2cases of Multiple myeloma with atypical presentations.A 60 year old female presented with fever, altered sensorium and had gross deformity of extremities. She had pallor, bilateral diffuse coarse crepitation and rhonchi. Laboratory investigation revealed anemia, very high ESR, raised blood urea and creatinine, high Calcium (ionised). Automated capillary zone serum protein electrophoresis revealed monoclonal "M" band present at beta2 region. X-ray of skull and pelvis showed diffuse osteopenia. Another 50 year male diagnosed as a case of multiple myeloma was found to have pulmonary tuberculosis, which is a very rare association.* ***Keywords :*** *Multiple myeloma, Monoclonal gammopathy, Plasmacytoma.*

## INTRODUCTION

Multiple myeloma is a clonal B-cell malignancy characterised by proliferation of plasma cells that accumulate mainly within bone marrow and secrete monoclonal immunoglobulin (Ig) or Ig light chain (syn. paraprotein, M-protein). It may be associated with lytic bony lesions,diffuse osteoporosis or pathological fracture. Normal Ig production is impaired (immuneparesis; hypogammaglobulinemia) Uncommon cases are 'non-secretory' with no detectable serum or urine paraprotein.[1]

## CASE REPORT : 1

A 60 year female presented with chief complaints of fever for 15 days, altered sensorium for 10days. There was no history of cough, headache, convulsion or vomiting. She was not a known case of diabetes mellitus or hypertension. On examination she was stuporous, febrile(102), pulse-120/min, BP-110/60mmHg, respiratory rate-30/min. There was moderate pallor.She had gross flexion deformity of her extremities.(Picture-1 and 2) Examination of chest revealed diffuse coarse crepitation and rhonchi. CVS and GI system were within normal limits. CNS examination revealed, she was stuporous with GCS-5/15,no meningeal signs, both pupils were of normal size and normally reacting to light, bilateral plantar extensor and no focal neurological deficit. Laboratory investigation revealed: Hb-6gm%, ESR-145mm/1$^{st}$ hr, TLC-5600/cumm, DC:Neutrophil 60%, Lymphocyte 34%, Eosinophil 5%, Monocyte 1%, TPC-1.7 lacs/cumm, peripheral smear comment:reduced red cell mass with microcytic hypochromic cells,few teardrop and pencil shaped cells, no normoblasts,WBC series showing no atypical cells. MP-ICT: negative Blood urea-68mg/dl, creatinine -2.3 mg/dl, $Na^+$ -146meq/L,$K^+$ -5.4meq/L, $Ca^{2+}$ -8.6mmol/L, phosphate- 2.5 mg/dl . LFT:Bilirubin (T)- 0.7mg / dl, (D) 0.2mg /dl, AST-31IU/L, ALT-20IU/L,ALP-298 IU/L, Protein-5.7mg /dl Albumin-3.5mg/dl. Widal test was negative. Urine RE and ME:RBC-1-2/hpf,pus- 4-6/hpf, epi-3-5/hpf. Chest X-ray PA view was normal. CT scan of brain was normal. Automated capillary zone serum protein electrophoresis was done which revealed monoclonal "M" band present at beta2 region. X-ray of skull and pelvis showed diffuse osteopenia. X-ray of arms shows diffuse osteopenia of humerous bone. (Picture-3)

## CASE REPORT : 2

A 50 year male from Cuttack was admitted to Medicine Ward, SCB Medical College, Cuttack with chief complaints of intermittent fever, pain abdomen, non productive cough, loss of appetite, loss of weight

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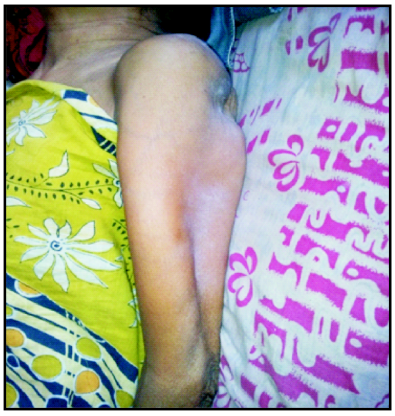
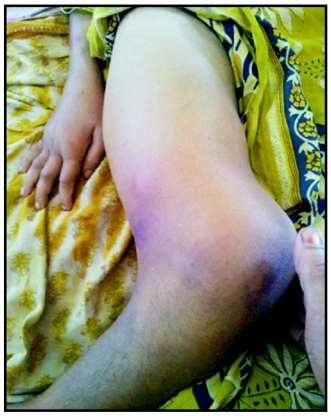
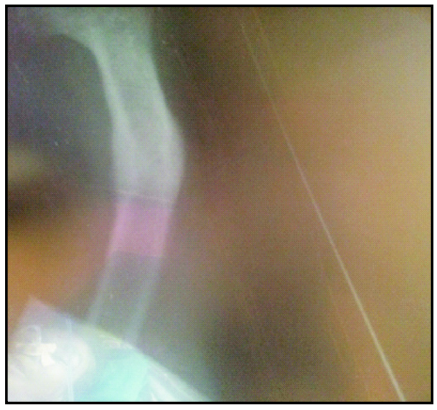


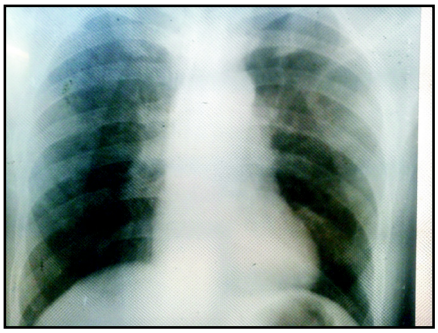
Pic.1 showing deformity of arm.



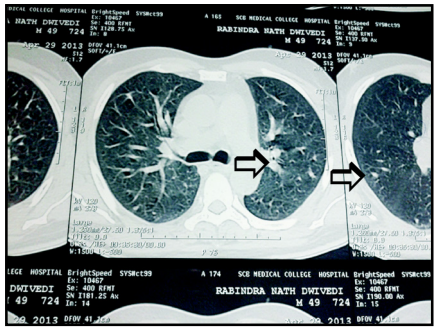
Pic.2 showing deformity of lower limb



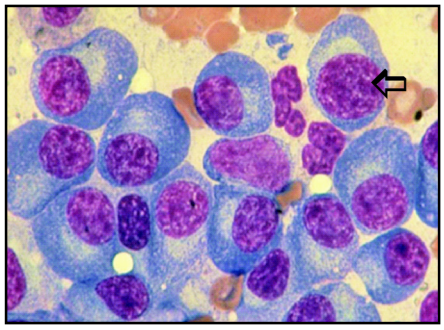
Pic.3 X-ray showing diffuse osteopenia and sclerosis of margins of humerous



Pic.4 normal chest x-ray PA view



Pic.5 CT thorax showing nodules in lung parenchyma



Pic.6 Bone marrow study showing plasma cells.

and breathlessness for 8 months. There was no history of chest pain, hemoptysis, jaundice. He was neither a smoker nor an alcoholic.

He had a history of bronchial asthma since childhood. Physical examination revealed average body build with average nutritional status and weight of 60 kg. He was febrile (temp- $101^0$F), pulse- 120/min regular, BP-110/80mm of Hg, respiratory rate-30/min.There was moderate Pallor, no icterus, clubbing, cyanosis, lymphadenopathy, pedal edema or thyromegaly and JVP was not raised. Examination of respiratory system revealed bilateral vesicular breath sounds and diffuse rhonchi. CVS and GI examination revealed no abnormality. On CNS examination there was no focal neurological deficit. Investigation revealed Hb-5.6gm%, ESR160mm/1$^{st}$hour, TLC5650/cu.mm, DC:Neutrophil 65.0%, Lymphocyte 20%, Monocyte 10%, E 4% B 1%, TPC-3.09 lacs/cu.mm. Reticulocyte count-3.77%. Blood urea-32.6mg/dl Creatinine-0.8mg/dl,$Na^+$-131meq/L,$K^+$-3.9meq/L. Urine RE and ME revealed pus cells-3-4/HPF, epithelial cells-3-4/HPF, culture-no growth. LFT:S. Bilirubin (T)-0.4mg/dl, (D)-0.2mg/dl, AST-37IU/L, ALT-26IU/L, ALP- 994 IU/L .$T_3$ 0.61 ng/ml, T46.57 ug/dl, TSH-2.5 micro iu/ml.

USG of abdomen and pelvis was normal. 2D-Echocardiogram was normal. Chest x-ray PA view was normal. (Picture-4) HRCT of thorax revealed few nodules in bilateral lung parenchyma suggestive of Tuberculosis. (Picture-5) Automated capillary zone serum protein. Electrophoresis revealed presence of monoclonal “M”spike. Bone marrow aspiration revealed plasma cells 10%. Urinary free light chain assay revealed kappa chain-488.97mg/L(N-0.78-13.48) and lambda chain—375.33mg/L (N-2.22-5.9). Patient was treated with anti tubercular drugs and became afebrile after 8days of starting treatment. Later on chemotherapy was given.

## DISCUSSION

Multiple myeloma accounts for 1% of all malignancies and 10% all haematological malignancies,[2] Incidence being 4/100000/annum.[2] Median Age-66yr,<3% in age<40yr. M:F ratio1.5. Multiple myeloma arises from a post germinal centre B-cell in lymphnode or spleen that has undergone antigen selection, somatic hypermutation of V region and switch recombination of IgH genes. Myeloma cells activate stroma,triggering paracrine and autocrine secretion of cytokines and growth factors including IL-6, Insulin Like growth factor-1 (IGF-1), Vascular Endothelial Growth factor (VEGF), TNF-α, Basic fibroblast growth factor (BFGF), Macrophase inhibitory factor-1α(MIP1α), Stem Cell Factor (SCF), Hepatocyte growth factor (HGF) and IL-1α. IL-6 is the major growth factor.[3] Bone lesion in multiple myeloma is due to osteoclast(OC) activation and osteoblast(OB) inhibition causing characteristic 'punched-out'lytic lesions and hypercalcemia asso.with normal ALP.OC proliferation and activation is triggered by OC-activating Factors(OAFs), formed by myeloma cells and stroma including MIP-1á , RANK-ligand, VEGF, TNF-α, IL1α, Parathyroid Related Hormone Protein, HGF, IL6. Production of RANK- ligand antagonist, osteoprotegerin is downregulated. Osteoblast Inhibition and decreased bone formation is due to dysregulation of Runx2/cbfal, wntandIL-3 and suppression by dickhoff-1(DKK-1). BM infiltration by neoplastic clone causes anaemia,immuneparesis of normal Ig production predisposes to infection. hypogammaglobulinemia has been classically associated with infection by encapsulated bacteria, such as Streptococcus pneumoniae and Haemophilus influenzae. Though extra-pulmonary tuberculosis like spinal TB has been reported in myeloma patients specially on bortezomib therapy,[4,5] pulmonary tuberculosis has not been reported. Physico-chemical properties of paraprotein determine wheather amyloid deposition,renal damage or hyperviscocity (IgA>IgG) occur. Most patients present with bone pain(75%) or pathological fracture; kyphosis and loss of height may occur due to vertebral Compression fracture.Weakness and fatigue (>50%), recurrent infection (10%), thirst, polyuria, nocturia or edema due to renal failure (H"10%) are also common. Acute hypercalcemia, symptomatic hyperviscosity (mental slowing, visual upset, purpura, hemorrhage), neuropathy, spinal cord compression, amyloidosis, coagulopathy are less frequent. â2-microglobulin is the most powerful prognostic factor and is used with serum CRP,a surrogate measure for IL-6. Combination of Lenalidomide,Bortezomib and Dexamethasone achieves nearly 100% response rate.Median survival of a patient with myeloma is 7to8yrs,with subset of younger patients surviving>10yrs.Major causes of death are progressive myeloma,sepsis,renal failure or therapy related myelodysplasia.

## CONCLUSION

Multiple myeloma should be suspected in a patient above 50years with bone pain,anaemia, lethargy, recurrent infection,renal impairment, hypercalcemia, neuropathy or in whom high ESR is detected. Atypical features are rare at presentation but should be kept in mind and if suspicious,specific investigations should be done to establish the diagnosis and initiate treatment

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*Case Report*

# CEREBELLAR INFARCTION IN A YOUNG FEMALE FOLLOWING VASCULOTOXIC SNAKE BITE

**R. Sathpathy*, D.R. Tripathy*, S. Mishra*, N.R. Mohanty**, P. Patro***, N. Dhal***, CBK Mohanty******

**ABSTRACT**

*Neurological deficits can occur following snake bite. It is usually due to intracerebral haemorrhage or subarachnoid bleed as a result of depletion of clotting factors. A healthy 16 years old female developed altered sensorium within 3 hours of snake bite. CT Brain revealed left cerebellar infarction with mass effect. Clotting time and bleeding time were normal. The possible mechanism for infarction in this patient is discussed.* ***Key words :*** *Cerebrovascular Accident, Cerebellar Infarction, Snakebite, Young stroke.*

## INTRODUCTION

In India more than 20,00,000 snake bites are reported annually, of which 35,000 to 50,000 people die.[1] Russell's viper, *Vipera russelli siamensis,* is the leading cause of fatal snake bite in India.[2] The clinical characteristics include local cellulitis, renal failure, and hemorrhagic manifestations including pituitary and intracranial hemorrhage. In this report we present an unusual complication, cerebellar infarction following Russell's viper bite.

## CASE REPORT

A 18 years old female was bitten by viper as told by the accompanying persons at 5 PM on 3 August 2013 while she was working in her backyard. She developed vomiting followed by sudden onset altered sensorium within 3 hours with bleeding from the bite site. she was treated with 5 vials of antisnake venom in local hospital and referred to our hospital. At the time of admission, patient was stuporous (Pic.1) with right hemiplegia, pupils were equal in size and normally reacting to light on both sides, fundoscopy was normal. Patient had hypotonia of all 4 limbs, plantars were extensor. Bitemark was seen over dorsum of the left foot with local cellulitis. Other systems were normal. Haemoglobin, ESR, blood Sugar, Urea and Serum Creatinine were normal with neutrophilic leucocytosis, clotting time was 7 minutes 50 seconds. Bleeding time was 7 minutes. Prothrombin time was 13.3 seconds. Activated partial thromboplastin time was 25.5 seconds and platelet count was 2,00,000 cells/cumm. Electrocardiogram was normal. CT Brain taken after 72 hours of the bite revealed left cerebellar infarction with mass effect.(Pic.2) Patient was treated with antibiotics and 30 vials of polyvalent ASV, mannitol, clopidogrel and atorvastatin. Patient was discharged on request after 10 days in a stupourous state.

## DISCUSSION

Cerebral complications, particularly ischemic complications, after snake bite are rare.[2] Very few cases of cerebral infarction resulting from a viper bite have been reported. In a study of 309 patients with snake bite, Mosquera, *et al*. reported cerebrovascular complications in 8 patients (2.6%), 7 hemorrhagic strokes and ischemic stroke in 1 patients.[6] Bashir and Jinkins reported a patient in whom envenomation with Russell's viper resulted in hemiplegia and aphasia, consistent with a middle cerebral artery infarction.[3] Murthy, *et al.* reported a case of cerebral infarction and diffuse encephalopathy following a viper bite. Viper snake venom is a complex toxin with rich components dominantly affecting hemostatic mechanisms. In large

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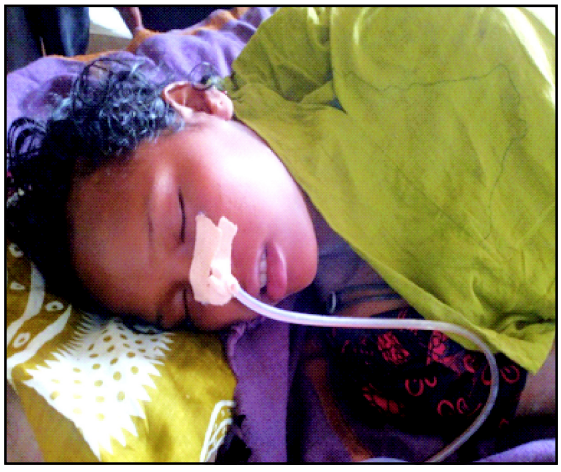
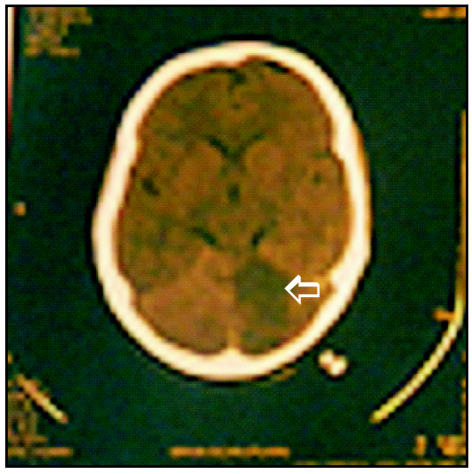


Picture-1 : Stuporous patient following vasculotoxic snakebite.



Picture-2 : Arrow showing hypodense lesion in left cerebellum following vasculotoxic snakebite.

doses, it can cause massive intravascular coagulation leading to small and even large vessel occlusions resulting in cerebral infarction. Toxic vasculitis caused by certain viperine species may result in thrombosis. Bashir and Jinkins suggested direct action of the venom on vascular endothelial cells.[3] Hemorrhagins, the complement mediated, toxic components of Viperidae snake venom may result in severe vascular spasm, endothelial damage, and increased vascular permeability,[4] all of which may contribute to vascular occlusion.Hypercoagulation due to procoagulants in the venom,[5] such as arginine, esterase, and hydrolase and hyperviscosity caused by hypovolemia and cerebral infarction may be totally unrelated and may be the manifestation of an inherent deficiency of protein C, protein S, and antithrombin III. Our patient was young and had no vascular risk factor. We feel in our patient the cerebral infarction was the result of toxic vasculitis or toxin induced vascular spasm and endothelial damage.Better outcomes have been reported with immediate ASV treatment. In the study by Thomas *et al.*, of the 33 patients with envenomation by *Bothrops lanceolatus* who had not received ASV or received ASV after 8 hours of envenomation, 14% developed thrombotic complications and 4 of the 14 patients who had not received ASV died. Of the 70 patients who received ASV within 6 hours of envenomation, none thrombotic complications.[7] Our patient, despite treatment with ASV within 1 hour of envenomation developed delayed cerebral infarction on the second day. Our case also operfusion secondary to hypotension may also contribute to vessel occlusion.

## CONCLUSION

Our case illustrates that one should work up for possible cerebral infarction in a victim of viper envenomation and focal neurological deficits.

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*Case Report*

# UNUSUAL CAUSE OF HEMOPTYSIS - HYDATID DISEASE OF LUNG

**B. Nayak*, A. Dash*, S.N. Jena*, J.K Panda**, P.K. Padhi*****

**ABSTRACT**

*Hydatid disease of lung, commonly caused by Echinococcus granulosus remains asymptomatic for a long time. Cough with expectoration is the presenting feature. Radiographic and related imaging studies are important in detecting this disease.* ***Key words*** *: hydatid cyst,lung,hemoptysis.*

## INTRODUCTION

Hydatid disease is caused by larvae of tape worm Echinococcus granulosus and E.multilocularis. Dog is the definitive host and humans are intermediate host. After humans ingest the eggs, embryos escape from eggs and are carried to various organs, most commonly liver and lungs. The liver is involved in two-thirds of E.granulosus and lungs in about 10-30% of cases[1].

Hydatid disease is endemic in India where highest prevalence is reported in Andhra Pradesh and Tamilnadu[2].

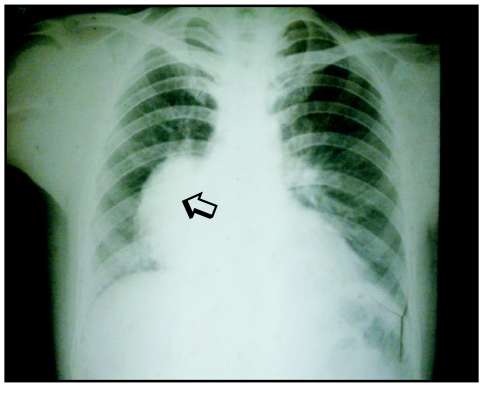
We present a case of isolated pulmonary hydatid cyst in adult and difficulties faced in diagnosis.

***CASE HISTORY:*** A male patient aged 35yrs admitted to Department Medicine of SCB MCH, Cuttack in April 2012 with chief complaints of cough with minimal expectoration for 4 days and developed haemptysis 2 days after hospitalisation. Clinically patient was alert conscious, tachypnoec (26/min), tachycardia(100/min). Respiratory system examination revealed central mediastinum, B/L vesicular breath sound with few crackles over Rt infra-axillary andinfra scapular region. Review of other system revealed no abnormality. Routine blood examination revealed Hb-11gm%, TLC-7400/cmm, neutrophil-77%, lymphocyte-21%, eosinophil-2%, ESR-25mm/ 1st hr.

Chest radiograph showed dense homogenous opacity with no air bronchogram in right mid and lower zone with obliteration of right border of cardiac silhoutte. (Picture-1) USG Thorax showed cystic space occupying lesion in right paracardiac region. 2D Echocardiogram revealed no abnormality.

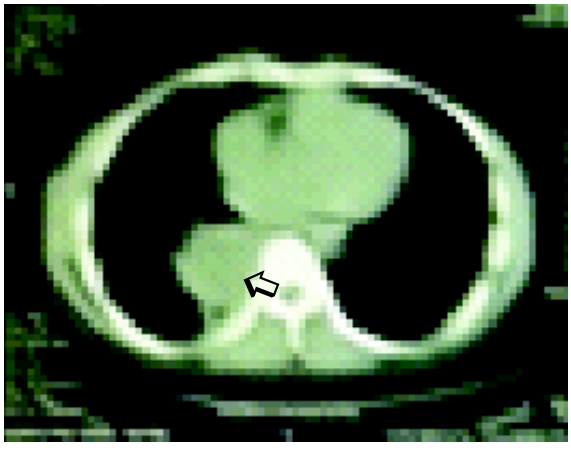
CT thorax showed well delineated thick walled cystic lesion of approx. 4.5x5.0 cm size seen in right lower lobe with adjacent passive atelectatic changes. (Picture-2).

***DISCUSSION***- Humans are in the rather undignified position of being an accidental intermediate host, whose ultimate destiny is normally to live in the intestine of the dog. Hemoptysis is an unusual presenting features of hydatid cyst of lung. Hemoptysis in adult is most often caused by tuberculosis, bronchitis, bronchiectasis, trauma or bronchogenic carcinoma.[3] Mechanism of hemoptysis in hydatid cyst of lungs may be due to pressure erosion of a bronchus or obstructive effect with bronchial infection.[4] CT and radiography are the diagnostic method of choice in evaluating Echinococcal



Picture-1 : (Chest X-ray PA view showing homogenous opacity in right mid and lower zone)

*PG Student, **Asso. Prof, ***Prof. PG Dept Of Medicine SCB Medical College, Cuttack, Odisha.



***Picture-2*** : (CT Thorax showing thick walled cystic lesion in right lower lobe)

cyst. MRI, CT and ultrasound reveal well-defined cyst with thick or thin walls.

Incidence of hydatid cyst affecting various organs/tissue. (Table-1)[5]

**Table-1 : Incidence of hydatid cyst affecting various organs/tissue.[5]**

| Organs / tissues | Incidence |
|---|---|
| Liver | 60% |
| Lung | 30% |
| Kidney | 2.5% |
| Heart | 2.5% |
| Spleen | Less than 2% |
| Brain | |
| Bone | |
| Orbit | Only few cases reported |
| Ur inary bladder | |
| Spinal extradural space | |
| Breast | |
| Submandibular gland | |

## CONCLUSION

Hydatid cyst of lung can be diagnosed with high index of suspicion in patient having past medical history of contact with pet animal.

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## Association of Physicians of India, Rourkela
## APICON 2012

### Balance Sheet as on 30.06.2013

| Liabilities | Amount (Rs.) | Assets | Amount (Rs.) |
|---|---|---|---|
| **Reserve & Surplus** | | **Current Assets** | |
| Profit & Loss A/c. | 152,440.00 | Bank A/c. | 151,635.00 |
| | | Cash in hand | 805.00 |
| | Rs. **152,440.00** | | Rs. **152,440.00** |

### Income and Expenditure A/c. of APICON 2012 Conference for the period 01.08.12 to 30.06.13

| Particulars | Amount | Particulars | Amount |
|---|---|---|---|
| To API Orissa Branch | 50,000.00 | By Advertisement in souvenir | 672,400.00 |
| To Bank Charges | 400.00 | By Registration Fee | 103,800.00 |
| To Accounting Charges | 2,400.00 | | |
| To Fooding Expenses | 307,850.00 | | |
| To Delegate Accomodation | 45,000.00 | | |
| To Mementos | 19,089.00 | | |
| To Orchestra & Music Expenses | 43,000.00 | | |
| To Photography | 400.00 | | |
| To Postage & Courier | 36,000.00 | | |
| To Printing & Stationery | 95,265.00 | | |
| To Vehicle Expenses | 6,302.00 | | |
| To Travelling & Conveyance | 16,035.00 | | |
| To Audit Fees | 1,000.00 | | |
| To Meeting Expenses | 1,019.00 | | |
| To Net Profit | 152,440.00 | | |
| | Rs. **776,200.00** | | Rs. **776,200.00** |

G. C. BANKA & CO. MAIN ROAD ROURKELA CHARTERED ACCOUNTANTS

APICON ODISHA 2012 Org. Secretary

APICON ODISHA 2012 Treasurer

APICON ODISHA 2012 Chairman Org. Comm.

| | A | B | C | D | E | F | |
|---|---|---|---|---|---|---|---|
| 1 | **API odisha State Branch** **Profit & Loss Account Period of Nov 12 to Oct 13** | | | | | | |
| 2 | **Date** | **Particulars** | **Amount** | | **Date** | **Particulars** | **Amo** |
| 3 | 11-Nov-12 | APICON Rourkela | 33900.00 | | | Opening Balance | |
| 4 | 7-Feb-13 | News Bullitine | 12720.00 | | 14-Feb-13 | Advt in OPJ | |
| 5 | 24-Feb-13 | 1st GB Meeting | 28289.00 | | 27-Mar-13 | Membership Collection | |
| 6 | 25-Apr-13 | Seed Money & loan for APICON 2013 | 70000.00 | | 21-May-13 | From Fixed Deposit | |
| 7 | 12-May-13 | 1st CME | 95093.00 | | 6-Jun-13 | APICON 2012 (Rourkela) | |
| 8 | 21-Jul-13 | 2nd GB Meeting | 41765.00 | | 14-Aug-13 | Advt in OPJ | |
| 9 | Nov12 to Oct13 | Office expenses | 40170.00 | | 21-Oct-13 | APICON 2012 (Rourkela) | |
| 10 | Nov12 to Oct13 | Rennovation work | 124550.00 | | Nov12 to Oct 13 | Bank Interest | |
| 11 | 19-Feb-13 | New Furnitures(Central table and chairs) | 94000.00 | | | | |
| 12 | Nov12 to Oct13 | Bank Charges | 202.00 | | | | |
| 13 | | **540689.00** | | | | | |
| 14 | | Cash at Bank | ***23097.00*** | | | | |
| 15 | | | **563786.00** | | | | |
| 16 | | | | | | | |
| 17 | | | **Fixed Diposit Account No** | | | **Matuarity Date** | |
| 18 | | | 30168562477 | | | 14 Nov 13 182922 | |
| 19 | | | 30168571061 | | | 14 Nov 13 163985 | |
| 20 | | | 30169636723 | | | 14 Nov 13 256395 | |
| 21 | | | 30169638551 | | | 14 Nov 13 152604 | |
| 22 | | | 32181004318 | | | 8 feb 15 263132 | |
| 23 | | | ***Total Available Balance in FD*** | | | ***1019038*** | |

# JOURNAL OF THE ASSOCIATION OF PHYSICIANS OF INDIA ORISSA STATE BRANCH

## Manuscript submission : Check List for Contributors

1. Letter of submission.
2. Copyright statement signed by all the authors.
3. Three copies of manuscript with copies of illustrations attached to each.
4. Title page.

   Title of manuscript.

   Full name(s) and affiliations of author(s); institution(s) and city(ies) from which work originated.

   Name, Address, Telephone, Fax numbers and e-mail address of corresponding author.

   Number of pages, number of figures and number of tables.
5. Structured abstract (objectives, methods, results, conclusion) along with title, and key words.
6. Article proper (double spaced on A/4 size paper).
7. Acknowledgements (separate sheet).
8. References (double spaced, separate sheets, Vancouver style).
9. Maximum number of references for Original articles - 20, Short articles-10,

   Case reports-6, Documentation-3, Correspondence-3.
10. Each table on separate sheet.
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12. Photographs in envelope appropriately marked.
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14. Covering letter signed by all authors confirming that they have read and approved the contents and also confirming that the manuscript is not submitted or published elsewhere.
15. Statement regarding Ethics Committee Approval and informed consent from subjects.*
16. Floppy diskettes are Compulsory Now*

* This is new addition to the check list, contributors to note.

- Hon Editor.