# C O N T E N T S

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# C O N T E N T S

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# Indian Association of Clinical Medicine

**Founder-President: MC Gupta** (Agra)

## GOVERNING BODY

# Overdoing is Bad

### BM Hegde*

Modern Western medicine, with all its hi-tech, is slightly off balance like the tower of Pisa. I have been shouting from the house top that it is being overused, misused, and abused. My colleagues were angry. Now, the cat is out of the bag! 2,500 odd American doctors were recently interviewed. More than half of them admitted that about half of the investigations, and an equal percentage of interventions, are useless and unnecessary. I am happy that the truth has come out. If that were so in the USA, with so many regulations, think of the hapless Indian patients, where money alone runs the show.

The US study did show that even coronary stents are overused by 50 per cent. This is obvious, looking at the huge money involved in this sickness care. Even overdiagnosis is not unusual. 26 per cent of diagnoses are not warranted. The American medical system is the most expensive, at nearly two trillion dollars a year, and is not accessible for half of the lower income group there. It would be a great boon to rationalise it, in view of this. (*Is US Medicine the best in the world?* Barbara Starfield. *JAMA* 2000; 284: 483).

It is not surprising that a Professor of Medicine at Yale, Mary Tinnetti, recently wrote the following about the American system in her article, *The end of disease era* (*Amer J Med* 2004; 116: 179). "The time has come to abandon disease as the focus of medical care. The changed spectrum of health, the complex interplay of biological and nonbiological factors, the aging population, and the inter-individual variability in health priorities render medical care that is centered on the diagnosis and treatment of individual diseases, at best, out of date and, at worst, harmful. A primary focus on disease may inadvertently lead to undertreatment, overtreatment, or mistreatment. The numerous strategies that have evolved to address the limitations of the disease model, although laudable, are offered only to a select subset of persons and often, further fragment care. Clinical decision making for all patients should be predicated on the attainment of individual goals and the identification and treatment of all modifiable biological and nonbiological factors, rather than solely on the diagnosis, treatment, or prevention of individual diseases. Anticipated arguments against a more integrated and individualised approach range from concerns about medicalisation of life problems to "this is nothing new" and "resources would be better spent determining the underlying biological mechanisms." The perception that the disease model is "truth" rather than a previously useful model will be a barrier as well. Notwithstanding these barriers, medical care must evolve to meet the health care needs of patients in the 21st century.

Recently NICE found out that most of the newer expensive anti-cancer drugs have not even been found useful in patients, but they are used anyway. If one were to dispassionately audit our system we will soon realise that our target is not our patient, but our rice bowl!

One of the paradoxes of modern medicine is that, despite the great triumphs and successes, from 1980 onwards there has been an enormous surge in the popularity of alternate therapies, previouly of interest to a small minority. One of the reasons may be that the alternate medicine doctors spend a lot more time with their patients to increase their placebo effect, which has now been considered more effective than drugs but our overdoing could have contributed to the success of alternate systems through less expensive

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

systems. Discovery of more powerful drugs has led to doctors overusing them with the fond hope that their grievous side-effects might be forgotten *in lieu* of their benefits! This faith has led to adverse drug reactions being one of the leading causes of death and disability. Since most alternate systems are based on non-materialist fundamentals, most of the hard core materialists think they are fake. The WHO, in 2003, published a review of 293 controlled studies of acupuncture to show that acupuncture does work in a variety of conditions, but hardcore critics are still doubtful.

# Correlation of High Serum Ferritin with Acute Myocardial Infarction in Different Age Groups of Patients

NK Sharma*, PS Goga**, SR Meena***, R Chandel****, S Chittora****, R Sagar*****, Kapil Jaiswal**, Harish HB**

## Abstract

*Background: Elevated body iron stores have been implicated as a risk factor for acute myocardial infarction (AMI).*

*Objectives: To study the association of serum ferritin with AMI and to assess the relationship of serum ferritin with the established conventional risk factors for AMI.*

*Methods: A cross sectional, case-control study of 75 cases of AMI and 75 controls without coronary heart disease (CHD) between the ages 30 - 70 years. Serum ferritin levels were estimated using ELISA and other risk factors were assessed by history and biochemical analyses.*

*Results: Mean serum ferritin (263.674 ± 89.029 µg/l) was significantly higher in cases than controls (98.833 ± 62.682 µg/l). Amongst the patients of AMI, significantly higher level of serum ferritin was found in diabetics (340.63 ± 90.78 µg/l) than non-diabetics (225.19 ± 58.30 µg/l), male elderly (> 60 years of age) smokers (304.20 ± 88.60 µg/l) compared to non smoker (206.37 ± 48.88 µg/l), elderly male with high (> 150 mg/dl) LDL cholesterol (323.48 ± 86.73 µg/l) compared to patients with normal (< 150 mg/dl) LDL cholesterol (249.33 ± 66.12 µg/l). Similarly, young patients of AMI (< 50 years of age) with high (> 160 mg/dl) triglyceride had significantly higher serum ferritin (324.06 ± 160.68 µg/l) compared to patients having normal (< 160 mg/dl) triglyceride level (242.46 ± 70.78 ug/l). Also, male patients of AMI with high (> 40 mg/dl) VLDL cholesterol had significantly higher serum ferritin (326.49 ± 77.95 µg/l) compared to male patients with normal (< 40 mg/dl) VLDL cholesterol (257.18 ± 85.46 µg/l).*

*Conclusion: High serum ferritin level (> 200 µg/l) may provide a cost effective tool for predicting a impending AMI, especially in diabetic patients, elderly male smokers, elderly males with high LDL cholesterol, younger patients with high triglyceride and male patients of AMI with high VLDL cholesterol level.*

*Key words: Acute myocardial infarction (AMI), conventional risk factors, serum ferritin.*

## Introduction

AMI is one of the most common causes of morbidity and mortality in the industrialised world, and is becoming increasingly common in India as well. The mortality rate in AMI is approximately 30% within first month, of which 50% are attributed to sudden cardiac death, and affects people in their most productive period of life[1].

The WHO Region for South-East Asia has set a target of reducing premature mortality from cardiovascular disease and other non-communicable diseases (NCDs) by 25% by 2025 and has developed a regional action plan to achieve this target[2].

Atherosclerosis is the primary cause of heart disease and stroke. Deaths arising as a complication of atherosclerosis claim the lives of millions of people each year in the Western world, and are also rapidly rising in developing countries[3,4].

Iron is a transition metal that can catalyze toxic redox reactions and, it has been suggested to be involved in many harmful biological processes in the human body[5,6]. Free radicals (FR), especially the hydroxyl radical (-OH), are extremely reactive and initiate tissue damage and lipid peroxidation[7]. Consequently, when excess iron is consumed and transferrin becomes saturated, free iron can be released. The production of FR by free iron has been found in some studies to cause oxidative damage to the coronary arteries, and possibly oxidize LDL, resulting in even more coronary damage[8].

The association of high iron stores and coronary heart disease was first suggested by Sullivan in 1981[9]. Subsequently, results of various studies showed statistically significant association of high serum ferritin and AMI[10-12]. Supporting evidence comes from *in vitro* lipid peroxidation and lipoprotein modification studies[13], cholesterol fed iron overloaded animal models[14] and from analysis of the

*Professor and Unit Head, **Post-graduate Resident, ***Senior Professor and Head, ****Assistant Professor, ****Clinical Tutor and MO, Department of Medicine, Government Medical College, Kota - 322 001, Rajasthan.
Corresponding Author: Dr Prem Singh Goga, Badkapura, Hindaun City, Koravli, Rajasthan - 322 230,
E-mail: dr.premgoga@gmail.com

composition of human atherosclerotic lesions[15]. Since serum ferritin concentrations are directly proportional to intracellular ferritin concentrations, it is considered to be the best clinical measure of the body iron stores[16] and the most feasible to use in epidemiologic studies[17]. However, some authors did not find any significant association of high serum ferritin and AMI[18,19].

The main objective of our study was to study the relationship of serum ferritin with ST elevated AMI in univariate analysis, and to assess the relationship of serum ferritin with classical coronary risk factors like diabetes mellitus, smoking, alcohol intake, body mass index, lipid profile, and hypertension.

## Materials and method

This was a cross sectional case-control study of 75 cases of AMI admitted in the medicine emergency/general wards from January 2016 to December 2016 in Govt. Medical College and Hospital, Kota, Rajasthan. 75 people without CHD were chosen as the control group. Individuals varied from 30 - 70 years and different age groups were made accordingly, viz., 30 - 40 years, 40 - 50 years, 50 - 60 years, and 60 - 70 years of age.

### Inclusion criteria

The diagnosis of AMI was based on any two of the following criteria:

- Typical history of severe chest pain radiating to the neck or arms for < 12 hours duration

- ECG changes of ST elevation > 2 mm in two or more chest leads, or > 1 mm in two or more limb leads

- Rise in serum cardiac enzymes concentration (troponin T or I), more than twice the upper limit of normal

- Presumably, new onset left bundle-branch block

### Exclusion criteria

- Haemochromatosis

- Liver disease

- Iron therapy

- Past history of AMI or CHD

- Aceruloplasminaemia

- Anaemia – haemolytic anaemia, sideroblastic anaemia, iron deficiency anaemia

- Hereditary hyperferritinaemias

**Controls:** Age and sex-matched controls were selected for each case, irrespective of presence of risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking and alcohol intake) from subjects attending the outpatient department of the hospital for minor ailments or routine medical check-ups, subjects accompanying patients or amongst office working staff from various departments of this institution without having CHD or any evidence of CHD (assessed by symptoms, clinical examination and normal electrocardiogram).

All the subjects were assessed by clinical examination, ECG, serum creatine kinase-MB (CK-MB). Height and weight were recorded. Body mass index (BMI) was calculated by the formula, weight in kg/height$^2$ in meter. Body mass index > 25 kg/m$^2$ was considered as a risk factor for AMI. Cases and controls were investigated for conventional risk factors (BMI, blood sugar and lipid profile). History of smoking and alcohol consumption was noted in details. Estimation of lipids was done by enzymatic method using autoanalyser, while glucose oxidase and peroxidase (GOD-POD) method was used for measurement of blood sugar. Serum ferritin was measured in all the subjects by enzyme-linked immunosorbent assay (ELISA) test.

### Statistical evaluation

Data for both groups was expressed as mean ± SD. Student's t-test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups (Inter-group analysis) on metric parameters. Chi-square test was used to find the significance of study parameters on categorical scale between two groups. The p value ≤ 0.05 was considered significant.

### Results

A total of 75 cases and an equal number of controls were studied. Both the groups were age and sex matched. The mean age was 54.79 ± 11.15 years in patients with AMI and 52.77 ± 11.18 years in control subjects. Mean haemoglobin in cases (12.94 g%) and controls (12.77 g%) was statistically matched; this was important because serum ferritin level varies directly with haemoglobin. The mean value of serum ferritin (µg/l) in controls and cases were found to be 98.833 ± 62.682 µg/l and 263.674 ± 89.029 µg/l respectively (p < 0.05). High serum ferritin levels (> 200 µg/l) were significantly associated with AMI ($\chi^2$ = 37.167, OR = 9.25, 95% CI = 4.34 - 19.73, p < 0.05). Correspondingly, more patients with AMI (68%) compared to control subjects (18.66%) had concentrations above the cut-off of 200 µg/l (Table I). The mean value of controls and cases for cholesterol (mg/dl) 86.73 ± 22.59 and 186.16 ± 46.49, LDL cholesterol (mg/dl) 88.40 ± 34.75 and 117.29 ± 39.56, VLDL cholesterol (mg/dl) 27.84 ± 09.68 and 33.96 ± 15.25, triglycerides (mg/dl) 138.66 ± 48.77 and 166.90 ±

75.83, HDL cholesterol (mg/dl) 44.86 ± 06.61 and 38.68 ± 06.15, respectively (Table II). There was no significant difference in mean serum ferritin level between males and females.

**Table I: Association of AMI with high serum ferritin.**

| Serum ferritin | Cases (%) (n = 75) | Controls (%) (n = 75) | Total (%) (n = 150) | p-value |
|---|---|---|---|---|
| ≥ 200 µg/l | 51 (68%) | 14 (18.66%) | 65 (43.33%) | $\chi^2 = 37.167$ OR = 9.258, 95% CI = 4.34-19.73 p < 0.05* |
| < 200 µg/l | 24 (32%) | 61 (81.33%) | 85 (56.66%) | |

*Statistically significant; CI: confidence interval; OR: odds ratio.

**Table II: Characteristics of cases and control groups.**

| Parameters | Cases (n = 75) mean ± SD | Control (n = 75) mean ± SD | p-value (by t test) |
|---|---|---|---|
| Haemoglobin (g%) | 12.94 ± 0.87 | 12.77 ± 0.69 | 0.187 |
| Mean age (years) | 54.79 ± 11.15 | 52.77 ± 11.18 | 0.187 |
| Ferritin (µg/l) | 263.674 ± 89.029 | 98.833 ± 62.682 | 0.001 |
| Cholesterol (mg/dl) | 186.16 ± 46.49 | 86.73 ± 22.59 | 0.0001 |
| HDL cholesterol (mg/dl) | 38.68 ± 06.15 | 44.86 ± 06.61 | 0.0001 |
| LDL cholesterol (mg/dl) | 117.29 ± 39.56 | 88.40 ± 34.75 | 0.0001 |
| Triglycerides (mg/dl) | 166.90 ± 75.83 | 138.66 ± 48.77 | 0.0001 |
| VLDL cholesterol (mg/dl) | 33.96 ± 15.25 | 27.84 ± 09.68 | 0.0001 |

The mean serum ferritin level in each of the age groups in the cases (i.e., 30 - 40 years, 40 - 50 years, etc.) was significantly higher, compared to their respective controls. As the age increases, mean value of the serum ferritin also increases, but it was not statistically significant. While in the case of females in the 61 - 70 years age group, mean serum ferritin (298.32 ± 78.94 µg/l) was significantly

higher compared to cases in the 30 - 40 years of age group (173.96 ± 21.06 µg/l) (t = 2.611, p = 0.028).

In univariate analysis, classical risk factors like DM, hypertension, BMI > 25 kg/m², HDL cholesterol < 35, LDL cholesterol > 150 mg/dl and smoking were found to be significantly associated with AMI (Table III).

We also assessed the relationship of serum ferritin with other CHD risk factors. Mean serum ferritin level was significantly high in patients of AMI with diabetes mellitus (340.63 ± 90.78 µg/l) compared to patients of AMI without diabetes mellitus (225.19 ± 58.30 µg/l) (Fig. 1). Male smoker patients > 60 years of age had (304.20 ± 88.60 µg/l) statistically higher serum ferritin level compared to non-smokers of similar age group (206.37 ± 48.88 µg/l) (Fig. 2).
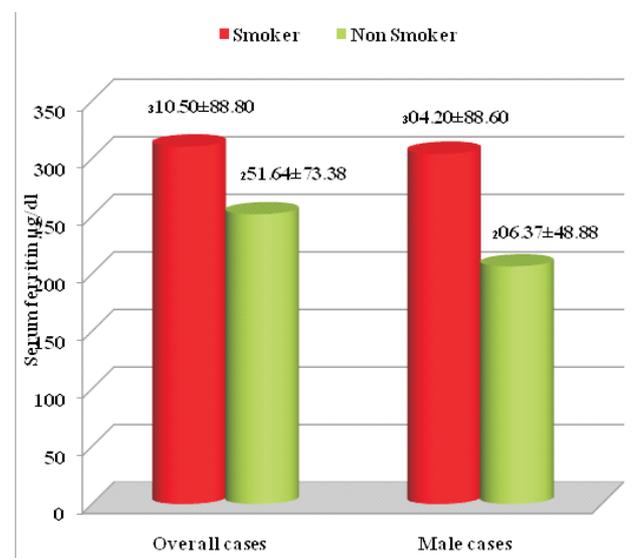


*Fig. 2: Comparison of mean serum ferritin (µg/L) between smokers and non smokers 61 - 70 years of age group among cases.*
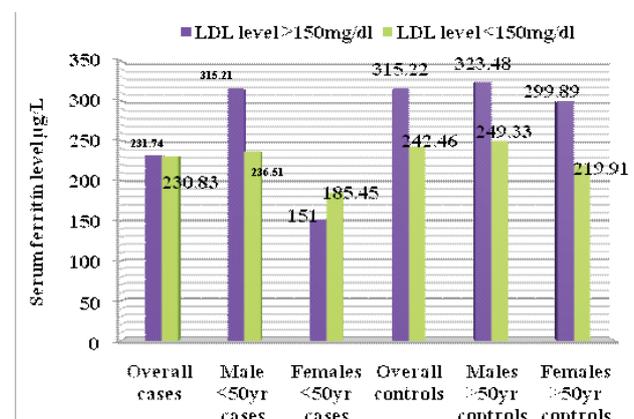


*Fig. 3: Comparison of mean serum ferritin (µg/l) in relation to serum LDL cholesterol level in cases.*



*Fig. 1: Comparison of mean serum ferritin (µg/l) between diabetic and non diabetic cases and controls.*

**Table III: Comparison of conventional risk factors for AMI in cases and controls (univariate analysis).**

| Risk factor | Cases (%) (n = 75) | Control (%) (n = 75) | Total (%) (n = 150) | p-value |
|---|---|---|---|---|
| Diabetes mellitus | | | | $\chi^2 = 11.227$ |
| Present | 25 (33.33) | 8 (10.66) | 33 | Odds ratio = 4.18 |
| Absent | 50 (66.66) | 67 (89.33) | 117 | CI = 1.74 - 10.05 p = 0.0008 (S) |
| Hypertension | | | | $\chi^2 = 6$ |
| Present | 21 (28) | 10 (13.33) | 31 | Odds ratio = 2.52 |
| Absent | 54 (76) | 65 (86.66) | 119 | CI = 1.20 - 6.73 P = 0.014 (S) |
| Smoking | | | | $\chi^2 = 5.50$ |
| Present | 35 (46.66) | 22 (29.33) | 57 | Odds ratio = 2.108 |
| Absent | 40 (53.33) | 53 (70.33) | 93 | CI=1.07-4.13 p = 0.029 (S) |
| BMI | | | | $\chi^2 = 4.761$ |
| > 25 kg/m$^2$ | 27 (36) | 16 (21.33) | 43 | Odds ratio = 2.07 |
| <25 kg/m$^2$ | 48 (64) | 59 (78.66) | 107 | CI = 1.003 - 4.288 p = 0.049 (S) |
| Alcoholic | | | | $\chi^2 = 3.749$ |
| Present | 29 (38.66) | 18 (24) | 47 | Odds ratio = 1.99 |
| Absent | 46 (61.33) | 57 (76) | 103 | CI = 0.986 - 4.039 p = 0.0528 (NS) |
| Serum cholesterol | | | | $\chi^2 = 3.36$ |
| > 200 mg/dl | 26 (34.66) | 15 (20) | 41 | Odds ratio = 2.12 |
| < 200 mg/dl | 49 (65.33) | 60 (80) | 109 | CI = 1.013 - 4.44 p = 0.066 (NS) |
| HDL cholesterol | | | | $\chi^2 = 7.142$ |
| < 35 mg/dl | 18 (24) | 6 (8) | 24 | Odds ratio = 3.631 |
| > 35 mg/dl | 57 (76) | 69 (92) | 126 | CI = 1.351 - 9.756 p = 0.0075 (S) |
| LDL cholesterol | | | | $\chi^2 = 5.310$ |
| > 150 mg/dl | 20 (26.66) | 8 (10.66) | 28 | Odds ratio = 3.045 |
| < 150 mg/dl | 55 (73.33) | 67 (89.33) | 122 | CI = 1.24 - 7.445 p = 0.0212 (S) |
| TG level | | | | $\chi^2 = 0.800$ |
| > 160 mg/dl | 25 (33.33) | 19 (25.33) | 44 | Odds ratio = 1.473 |
| < 160 mg/dl | 50 (66.66) | 56 (74.66) | 106 | CI = 0.726 - 2.991 p = 0.371 (NS) |
| VLDL cholesterol | | | | $\chi^2 = 2.600$ |
| > 40 mg/dl | 20 (26.66) | 11 (14.66) | 31 | Odds ratio = 1.97 |
| < 40 mg/dl | 55 (73.33) | 64 (85.33) | 119 | CI = 0.932 - 4.800 p = 0.106 (NS) |

*S = Significant, *NS = Non significant

Similarly, elderly male (> 50 years of age) patients having high (> 150 mg/dl) LDL cholesterol had (323.48 ± 86.73 µg/l) higher serum ferritin level compared to patients having normal (< 150 mg/dl) LDL cholesterol level (249.33 ± 66.12 µg/l) (Fig. 3). Also, younger patients (< 50 years of age) of both sexes having higher (> 160 mg/dl) triglyceride level had statistically higher serum ferritin level (324.06 ± 160.68 µg/l) compared to similar age group patients having normal (< 160 mg/dl) triglyceride level (242.46 ± 70.78 µg/l) (Fig. 4). This study also showed that, high (> 40 mg/dl) serum VLDL cholesterol in male patients of all age groups was associated with high serum ferritin level (326.49 ± 77.95 µg/l) compared to patients having normal (< 40 mg/dl) VLDL cholesterol level (257.18 ± 85.46) and thus, these patients may be at a higher risk of developing AMI (Fig. 5).

There was no statistically significant relationship of ferritin with hypertension, serum total cholesterol, HDL cholesterol, BMI and alcohol.

## Discussion

This study, including 150 (75 cases and 75 controls) subjects showed that elevated serum ferritin concentration was associated with increased risk of myocardial infarction.
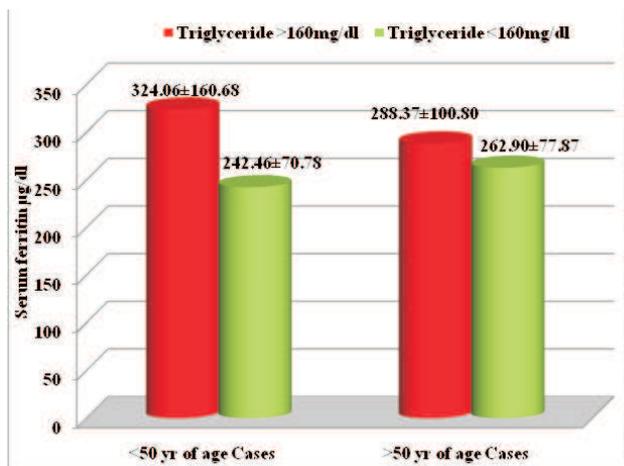
**Fig. 4: Comparison of mean serum ferritin (μg/l) in relation to triglyceride (TG) level, in cases.**
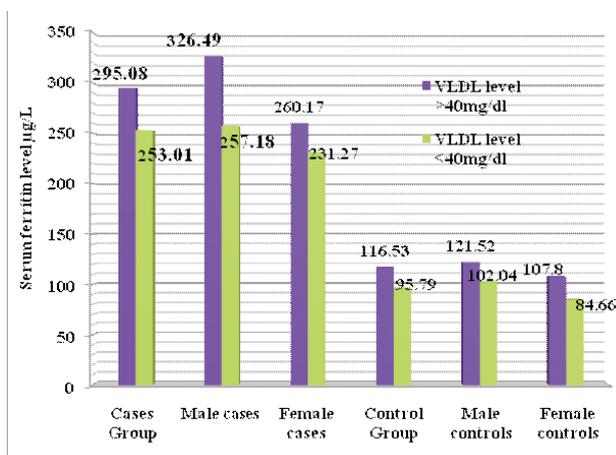


**Fig. 5: Comparison of mean serum ferritin (μg/l) in relation to serum VLDL cholesterol level in cases and controls.**

Epidemiological studies have found a positive relationship between body iron stores and CHD[17]. Subsequently, evidence of an association of elevated serum ferritin and increased risk of AMI came from various studies done by Salonen et al[9], Holay et al[10], Bharathi et al[11], and Rohit Ishran et al[12]. However, the results of some other studies did not show significant correlation between high ferritin and risk of AMI[18, 19].

High ferritin was found to be a strong indicator of presence of carotid artery atherosclerosis (assessed sonographically). Iron induced lipid peroxidation, involved in the early steps of the human atherogenesis, is the proposed underlying pathogenic mechanism[20].

The mean serum ferritin level in female cases of 61 - 70 years of age group was significantly higher, compared to 30 - 40 years (n = 3) of age group. Because of limited data, larger case-control studies would be required to confirm

these facts.

The mean serum ferritin level in all diabetic cases irrespective of sex or age, was higher compared to cases without diabetes and this difference was statistically significant (p < 0.0001), but there was no significant difference in controls (Fig. 1). These findings were similar to other studies done by Haidari et al[21], Holay et al[10], and Bharathi et al[11]. Also, in elderly (> 60 years of age) male cases, the mean serum ferritin level was significantly higher in smokers compared to non-smoker cases of AMI (Fig. 2). Similar to other studies done by Bharathi et al[11], serum ferritin was significantly higher in all smoker cases compared to non-smoker cases. However, larger case-control studies would be required to confirm these facts.

In this study, mean serum ferritin level in patients of AMI in the presence of dyslipidaemia, elderly male (> 50 years of age) patients with high (> 150 mg/dl) LDL cholesterol compared to patients with normal (< 150 mg/dl) LDL cholesterol, younger (< 50 years of age) patients of AMI with high (> 160 mg/dl) triglyceride compared to patients with normal (< 160 mg/dl) triglyceride and all male patients of AMI with high (> 40 mg/dl) VLDL cholesterol compared to patients with normal (< 40 mg/dl) VLDL cholesterol had significantly high serum ferritin level (p < 0.05).

The elevated serum ferritin concentrations were associated with increased risk of AMI; also ferritin may adversely affect risk of AMI in the presence of other risk factors.

## Conclusion

According to this study, serum ferritin may provide an important, simple, and cost-effective tool for predicting an impending AMI especially in diabetic patients, elderly male smokers, elderly males with high LDL cholesterol, younger patients with high triglyceride and males with high VLDL cholesterol level.

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*"You cannot wait for inspiration.*
*You have to go after it with a club."*

– JACK LONDON.

# ORIGINAL ARTICLE

# To Study Ankle-Brachial Index and its Relation with the NIHSS (National Institute of Health Stroke Scale) Score for Prediction of Severity in Patients of Acute Ischaemic Stroke

Deepti Sharma*, Mukesh Verma**, SR Meena***, Pallavi Vij**, Arpit Agarwal*****

## Abstract

Background: Ankle-brachial index (ABI), which is closely related to atherosclerosis of the lower extremities, is widely used as a marker for Peripheral ortery disease (PAD). ABI may also reflect the severity of systemic atherosclerosis. Abnormal ABI in acute ischaemic stroke patients is an indirect indicator of generalised atherosclerosis and initial stroke severity is a strong predictor of long-term outcome in stroke patients. The present study was undertaken to ascess whether a low ABI was associated with a severe presentation in acute ischaemic stroke patients.

Aims and objectives: To correlate the ABI of patients of acute ischaemic stroke, with NIHSS, score to predict severity of stroke.

Material and method: 100 patients of acute ischaemic stroke, fulfilling the inclusion criteria were compared with age-sex matched control subjects. ABI was assessed in all study subjects and was corrrelated with the NIHSS score among patients of acute ischaemic stroke.

Results: Mean age of patients was $61.0 \pm 13.36$ years, with male predominance, male: female ratio 1.5 : 1. Ankle-brachial index was abnormal (< 0.9) in 46% patients. Low ABI was associated with older age, higher BMI ($p < 0.001$), higher WHR ($p < 0.05$) and hypertension ($p < 0.001$). Mean NIHSS score at the time of admission was $13.35 \pm 6.10$ and at the time of discharge was 10.51. There was a linear decrease in ABI with increasing NIHSS score, and higher NIHSS score was associated with low ABI and greater number of stroke risk factors ($p < 0.001$).

Conclusion: Patients with low ABI values presented with more severe ischaemic stroke. Measurement of the ABI identifies subjects at increased risk for ischaemic stroke.

Key words: Ankle brachial index, peripheral artery disease, waist hip ratio, body mass index.

## Introduction

Stroke or cerebrovascular accident, is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Strokes are broadly categorised as ischaemic or haemorrhagic[1].

Stroke is the second leading cause of death worldwide, causing 6.2 million deaths in 2011, and third most common cause of disability-adjusted life years in the world. The age standardised incidence of stroke has reduced by 12% in high-income countries whereas in India, it has increased by 12%[2]. Stroke is a major disabling health problem in developing countries like India.The annual incidence rate and case fatality rate of stroke in India is higher than in the western countries[3].

The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. Major causes of ischaemic stroke are cerebral embolism, atherosclerotic thrombotic disease of the

cerebral or extra-cerebral vessels, and nearly 30% of strokes remain unexplained, despite extensive evaluation, that is cryptogenic[4].

Atherosclerosis is a disease of large and medium sized muscular arteries and is characterised by endothelial dysfunction, vascular inflammation and the build-up of lipid, cholesterol, calcium and cellular debris within the intima of the vessel wall. Atherosclerosis is the underlying disease process leading to ischaemic heart disease (IHD), cerebrovascular accidents and peripheral vascular disease[5].

A number of factors that may be classified as modifiable and non-modifiable increase the risk for ischaemic stroke[6]. Non-modifiable risk factors for stroke include older age, male gender, ethnicity, family history, and prior history of stroke. Modifiable risk factors may be subdivided into lifestyle and behavioural risk factors and non-lifestyle factors. Modifiable lifestyle factors include lack of physical activity, cigarette consumption (risk of stroke is two or three times

*Senior Professor and Unit Head, **3rd Year Resident, ***Senior Professor and Head of Department, ****2nd Year Resident, Department of Medicine, Government Medical College and Associate Group of Hospital, Kota - 320 001, Rajasthan. Corresponding Author: Dr Deepti Sharma, 1-T-1, opp. Govt. Dispensary, Vijyan Nagar, Kota, Rajasthan - 324 005, Tel: 09414182588, E-mail: drdeeptisharmakota@gmail.com.

greater than in non-smokers), alcohol abuse, and illicit drug use[6].

Peripheral arterial disease (PAD) refers to atherosclerosis and thromboembolic processes that affect the aorta, its visceral arterial branches and arteries of lower extremities[6]. Traditional risk factors for PAD are similar to those that lead to atherosclerosis in the carotid, coronary and other vascular beds.

Patients with symptomatic lesions in one vascular territory have additional atherosclerotic lesions, which are often asymptomatic, in other vascular regions. Likewise, patients with atherosclerosis in multiple vascular regions also have worse prognosis than patients with atherosclerosis in just one vascular territory. Thus, in patients with known coronary artery disease, the additional presence of PAD worsens prognosis considerably[7].

Ankle-brachial index, which is closely related to atherosclerosis of the lower extremities, is widely used as a marker for PAD[8]. ABI is not only a marker of lower limb PAD, but may also reflect the severity of systemic atherosclerosis.

Large, population-based, prospective, observational studies suggest that PAD, coronary artery disease (CAD) and cerebrovascular disease (CVD) not only share vascular risk factors, but also have a clear correlation with each other in the progression of atherosclerosis[9-11]. Evidence that adults, with peripheral vascular disease in the lower extremities, are at the higher risk for cardiovascular disease and stroke is clearly established[12].

Measurement of ABI is easy inexpensive and has a high sensitivity and specificity for PAD. However, PAD is often under-diagnosed and the risk is under-estimated by clinicians. Measuring the ABI is a useful tool in this respect, helping physicians, both, in large scale population studies as well as during consultation. The ABI can also be used as a tool to monitor the efficacy of therapeutic interventions and for prognostic purposes. Prognostic information in patients with PAD may provide the basis for optimal management strategies. Since ischaemic stroke is highly prevalent among patients with PAD. ABI can predict the severity of stroke in these patients.

Initial stroke severity is a strong predictor of long-term outcome in stroke patients. When considering poor outcomes in patients with PAD, the severity of stroke may be different between patients with and without PAD. The present study was done to determine the association of ABI using high resolution B-Mode Ultrasonography colour Doppler with NIHSS (National institutes of health stroke scale) score, for prediction of severity in patients of acute ischaemic stroke.

## Aim of the study

To correlate the ankle brachial systolic index of patients suffering from acute ischaemic stroke with NIHSS score to predict severity of stroke.

## Materials and method

The study was conducted in patients with acute ischaemic stroke admitted in various wards of M.B.S. Hospital, Kota in 2016, after obtaining informed consent. The study population consisted of 100 acute ischaemic stroke cases and 100 age-sex matched control subjects. The diagnosis of acute stroke was made on the basis of following criteria: (1) Temporal profile of clinical syndrome; (2) Clinical examination; (3) CT scan of brain or MRI of brain. Systemic investigations were performed in every patient, including 12-lead electrocardiography, chest X-ray and standard blood tests. ABI examination was part of the standard evaluation. Severity of stroke was determined with the National Institute of Health Stroke Scale (NIHSS) in all patients at the time of admission, after 24 hours of admission and at the time of discharge.

### Patient selection

Cases of acute ischaemic stroke (CT scan/MRI brain proved) admitted within 7 days after the onset of ischaemic stroke were selected for the study. Patients admitted beyond 7 days, haemorrhagic stroke, venous sinus thrombosis, infection, malignancy, any amputation of upper or lower extremities and patient not willing to participate were excluded from the study.

### ABI measurement

Measurement of ABI was done by a trained radiologist, using a B-MODE Doppler ultrasonic instrument with 8- MHZ vascular probe (Hewlett Packard 2000 high-resolution ultrasound unit). Systolic blood pressure readings were taken in the right and left brachial arteries, right and left dorsalis pedis arteries, and right and left posterior tibial arteries. The ABI at rest was measured after the participants had been resting in the supine position for at least 10 minutes. The ABI in the right and left leg will be calculated by dividing the right and the left ankle pressure by the brachial pressure. The higher of the 2 brachial blood pressure readings was used in case of a discrepancy. Again, the higher of the dorsalis pedis and posterior tibial artery pressures was used in case of discrepancy in systolic blood pressure readings between the 2 arteries. In the absence of blood flow in the dorsalis pedis artery, pressure in posterior tibial artery was measured.

### Risk factors

Hypertension was defined as a systolic BP $\geq$ 140 mmHg or

diastolic BP $\geq$ 90 mmHg, at least twice, during a resting state or as a history of use of antihypertensive medications[16]. Diabetes mellitus was defined as fasting blood glucose $\geq$ 126 mg/dl or a history of use of insulin or oral hypoglycaemic agents[17]. Hyperlipidaemia was defined as serum total cholesterol $\geq$ 200 mg/dl, LDL cholesterol $\geq$ 130 mg/dl or a history of use of lipid-lowering drugs after diagnosis of hyperlipidaemia[18]. Patients were considered as current smokers if they had smoked cigarettes within the previous month.

### Statistical analyses

Statistical methods used were unpaired student's t-test and determination of correlation coefficient (r value) between ankle brachial index and other variables by using Graph pad Instat version 3.10. A value of $p > 0.05$ is considered as not significant and $p < 0.05$ as significant. Using the database, descriptive analyses were performed. Statistical significance between groups was calculated using cross-tabulation and the $\chi^2$ test, means were compared using student's t test or ANOVA.

### Results

A total 100 patients of acute ischaemic stroke were included in study and compared with 100 age-sex matched control subjects. The study included 60% males and 40% females. Males outnumbered females, by 1.5 : 1. The cases ranged from 22 - 88 years of age with mean age of $61.0 \pm 13.36$ years. Maximum number of cases were in age group of 61 - 70 years, i.e., 30% cases. Out of 100 patients of study group, 46% were found to have abnormal ABI ($< 0.9$) and 54% had normal ABI ($> 0.9$). The BMI in the study group was $> 25$ kg/m$^2$ in 33% of acute ischaemic stroke patients and 67% had BMI $< 25$ kg/m$^2$. In the study group, mean waist hip ratio was 0.934 in male acute ischaemic stroke patients, and 0.925 in female acute ischaemic stroke patients.

Hypertension was the most common risk factor of ischaemic stroke, seen in 52% cases, followed by smoking in 48%, diabetes mellitus in 24%, hyperlipidaemia in 22%, and prior ischaemic heart disease in 12% cases.

Out of 100 patients of the study group, 84% patients had at least one risk factor and 16% subjects had no risk factors. There was a negative correlation of ABI with the number of risk factors; greater the number of risk factors, lower was the ABI.

In our study, there was higher prevalence of hypertension, higher BMI, and waist to hip ratio in patients with low ABI and a linear decrease in ABI was noticed, with increasing number of risk factors ($p < 0.05$).

The mean NIHSS score at the time of admission was $13.35 \pm 6.10$, (range was from 2 to 26). Out of 100 patients of acute ischaemic stroke, 15% were in NIHSS group 21 - 42 (severe stroke), 21% were in NIHSS group 16 - 21 (moderate-to-severe stroke) and 58% were in NIHSS group 5 - 15 (minor-to-moderate stroke) at the time of admission. A strongly negative, and statistically significant correlation was found between ABI and NIHSS score at the time of admission ($p < 0.001$).

The mean NIHSS score at time of discharge was 10.51 (range was from 1 to 24). Out of 100 patients of acute ischaemic stroke, 6% were in NIHSS group 21 - 42 (very severe stroke), 9% were in NIHSS group 16 - 21 (moderate-to-severe stroke) and 74% were in NIHSS group 5 - 15 (minor-to-moderate stroke) at the time of discharge. A strongly negative, and statistically significant correlation was found between ABI and NIHSS score at the time of discharge ($p < 0.001$).

A linear decrease in ABI was seen with increasing NIHSS score, and higher NIHSS score was associated with low ABI and greater number of the risk factors ($p < 0.05$).

Only 28.26% (13 out of 46) subjects of acute ischaemic stroke with ABI $< 0.9$ migrated to lower NIHSS score group at time of discharge; on the other hand 49.29% (25 out of 54) subjects of acute ischaemic stroke with ABI $> 0.9$ migrated to lower NIHSS score group at time of discharge. Subjects with ABI $< 0.9$ had higher or same NIHSS score group at time of discharge.

In our study, low ABI was noticed in acute ischaemic stroke patients, with or without conventional risk factors. It was concluded that low ABI is strong and independent marker of severe acute ischaemic stroke. Low ABI reflects the combined effect of many risk factors over time, and once atherosclerosis has developed, ABI would be expected to be a better predictor than one risk factor alone. It was concluded that there was no single risk factor responsible for low ABI but other risk factors could be present simultaneously.

### Discussion (Table I - XI) (Fig. 1 - 7)

100 acute ischaemic stroke patients and 100 age and sex-matched control subjects were included in our study. Although the control subjects were free from acute ischaemic stroke, some of them had risk factors for ischaemic stroke and, it can be expected that they represented a stage in the progression to ischaemic stroke. ABI is important in view of its relationship to cerebral atherosclerosis. The view, that measurement of ABI may be used as an indicator of atherosclerosis, is supported by association of ABI with ischaemic stroke risk factors and atherosclerosis in other arteries.

Tables I, II, III: In the present study out of 100 cases, males were 60% and females were 40%. Males outnumbered females by 1.5: 1. Purroy *et al* in their study had found male: female ratio of 1.9: 1. Coll *et al* in their study had found male: female ratio as 1.7: 1. This higher incidence among males was due to variability of ischaemic stroke risk factors, selection of subjects and pre-existing PAD.

**Table I: Distribution of patients according to age and sex in acute ischaemic stroke patients.**

| | Acute ischaemic stroke patients | | |
|---|---|---|---|
| Age (yrs) | Male | Female | Male + female = Total number |
| < 40 | 7 | 1 | 7 + 1 = 8 |
| 41 - 50 | 11 | 5 | 11 + 5 = 16 |
| 51 - 60 | 18 | 7 | 18 + 7 = 25 |
| 61 - 70 | 13 | 17 | 13 + 17 = 30 |
| > 70 | 11 | 10 | 11 + 10 = 21 |
| Total | 60 | 40 | 60 + 40 = 100 |

**Table II: Age and ABI distribution of subjects.**

| | Controls | | | Stroke patients | | |
|---|---|---|---|---|---|---|
| Age (yrs) | No. | ABI < 0.9 | Mean ABI | No. | ABI < 0.9 | Mean ABI |
| < 40 | 6 | 1 (16.6%) | 1.12 | 8 | 4 (50%) | 0.939 |
| 41 - 50 | 16 | 1 (6.2%) | 1.09 | 16 | 9 (56.2%) | 0.921 |
| 51 - 60 | 26 | 2 (7.6%) | 1.07 | 25 | 11 (44%) | 0.917 |
| 61 - 70 | 28 | 2 (7.14%) | 1.06 | 30 | 14 (46.6%) | 0.889 |
| > 70 | 24 | 1 (4.16%) | 1.08 | 21 | 8 (38%) | 0.874 |
| Total | 100 | 7 (7%) | 1.04 ± 0.11 | 100 | 46 (46%) | 0.90 ± 0.12 |

*Linear decrease in mean ABI with increasing age was seen in acute ischaemic stroke patients but not in controls. Statistical comparison of mean ABI in control and acute ischaemic stroke patients showed significant difference ($p < 0.05$).*

**Table III: Mean ABI in control and acute ischaemic stroke patients.**

| | Controls | Stroke patients |
|---|---|---|
| Total no | 100 | 100 |
| ABI < 0.9 | 7 (7%) | 46 (46%) |
| Mean ABI | 1.04 ± 0.11 | 0.90 ± 0.12 |

*Mean ABI in control group was 1.04 ± 0.11 whereas in the acute ischaemic stroke group was 0.90 ± 0.12. ABI < 0.9 was present in 7% subjects in control group and among 46% subjects in acute ischaemic stroke group. The difference in these values was statistically highly significant ($p < 0.0001$).*

All the cases in this study were in the age group of 22 to 88 years. Maximum number of cases were in age group of 61 - 70 years, i.e., 30% cases. Mean age in control group was 61.5 ± 12.36 years, and in acute ischaemic stroke group was 61.0 ± 13.36 years. 76% (76 out of 100) subjects of the acute ischaemic stroke group and 78% (78 out of 100) subjects in control group were more than 50 years of age. There was a statistically significant correlation between low ABI and increasing age in acute ischaemic stroke group but not in control group. Weimar *et al* in their study in 2008 also showed similar results, having mean age of 63 years. In their study, observed prevalence of PAD was more in older persons and also showed a strong association of increasing age with abnormal ABI, especially in males. Results of our study are also comparable with that found by Purroy *et al*. They showed similar mean age group of 61.2 ± 11.5 years, and low ABI, associated with older age and hypertension[13].

Mean BMI in control and acute ischaemic stroke subjects group was 21.8 ± 2.39 and 24.1 ± 4.34 kg/m$^2$, respectively. In our study, no subjects in control group and 33% subjects in ischaemic stroke group were obese, rest were non-obese. The difference in these values was statistically significant ($p < 0.001$). There was a linear decrease in mean ABI, noticed with high BMI in acute ischaemic stroke subjects but not in the control group. Lee *et al*, in their study observed significant negative correlation between low ABI and higher BMI[14] ($p < 0.001$). Janin Gronewold *et al*, in their study noticed significant association of low ABI with higher BMI, in acute ischaemic stroke subjects.

In this study, 35.4% (33 out of 93) females in control group and 38% (35 out of 92) females in the acute ischaemic stroke group had a waist hip ratio > 0.85 while 100% (1 out of 1) males in control group and 55% (11 out of 20) males in the ischaemic stroke group had waist to hip ratio > 0.9. The mean WHR in control group was 0.89 ± 0.03, and in acute ischaemic stroke group it was 0.934 ± 0.07. On statistical comparison, significant difference was noted between two groups ($p < 0.05$). Mustafa Inanc Dogan *et al*, in their study noticed low ABI-associated with increasing waist-hip ratio. Janine Gronewold *et al*, in their study observed increased WHR-associated with low ABI[15].

In this study, 28% subjects in control group and 52% subjects in acute ischaemic stroke group were hypertensive. The mean ABI of hypertensive subjects in control and ischaemic stroke group was 1.044 ± 0.14 and 0.88 ± 0.13, respectively. ABI < 0.9 was present in 10.71% hypertensive control subjects and 65.38% hypertensive ischaemic stroke subjects, while 5.55% normotensive control subjects and 25% normotensive ischaemic stroke subjects had ABI < 0.9, respectively. The difference in these values was statistically significant ($p < 0.05$). Albert *et al*, in their study

showed ABI was lower in hypertensive than normotensive subjects in ischemic stroke patients[16]. Purroy *et al*, in their study showed 68% acute ischaemic stroke subjects with ABI < 0.9 were hypertensive[13].

**Table IV: Mean value, standard deviation of baseline characteristics of acute ischaemic stroke patients and controls.**

| Variables | Acute ischaemic stroke patients (n = 100) | Mean ABI | Controls (n = 100) | Mean ABI | Test value ($\chi^2$ test) | P value |
|---|---|---|---|---|---|---|
| Gender | | | | | | |
| Male | 60 | 0.912 ± 0.11 | 67 | 0.99 ± 0.12 | 0.777 | |
| Female | 40 | 0.894 ± 0.13 | 33 | 1.06 ± 0.11 | Df = 1 | 0.378 |
| Smoking | | | | | | |
| Yes | 48 | 0.903 ± 0.13 | 40 | 1.01 ± 0.11 | 0.994 | |
| No | 52 | 0.907 ± 0.10 | 60 | 1.06 ± 0.10 | Df=1 | 0.319 |
| DM | | | | | | |
| Yes | 24 | 0.88 ± 0.13 | 31 | 1.010 ± .012 | 0.903 | |
| No | 76 | 0.91 ± 0.11 | 69 | 1.057 ± 0.11 | Df = 1 | 0.342 |
| HTN | | | | | | |
| Yes | 52 | 0.87 ± 0.13 | 28 | 1.044 ± 0.1 | 24.832 | |
| No | 48 | 0.94 ± 0.10 | 72 | 1.042 ± 0.1 | Df = 1 | 0.001 |
| IHD | | | | | | |
| Yes | 12 | 0.87 ± 0.12 | 19 | 0.982 ± 0.10 | 1.374 | |
| No | 88 | 0.90 ± 0.11 | 81 | 1.057 ± 0.11 | Df = 1 | 0.241 |

*Statistically significant difference in ABI was found between hypertensive subjects of both control and acute ischaemic stroke groups.*

*Statistically, no significant difference was found between the mean ABI of control and acute ischaemic stroke patients in gender smoking, diabetes mellitus and ischaemic heart disease.*

| Variables | Acute ischaemic stroke patients (n = 100) Mean ± SD | Controls (n = 100) Mean ± SD | Test value t-test | P value |
|---|---|---|---|---|
| BMI | 24.1 ± 4.34 | 21.8 ± 2.39 | t = 4.64 | 0.0001 |
| WHR | 0.9 ± 0.07 | 0.89 ± 0.03 | t = 1.31 | 0.01 |
| TC | 172.3 ± 34.96 | 174.7 ± 11.57 | t = 0.652 | 0.515 |
| HDL | 42.4 ± 7.29 | 42.9 ± 1.49 | t = 0.672 | 0.505 |
| LDL | 101.6 ± 21.35 | 106.1 ± 20.61 | t = 1.516 | 0.131 |
| TG | 114.8 ± 59.84 | 116.8 ± 24.82 | t = 0.309 | 0.758 |

*Statistically significant difference was found between the mean BMI of control and acute ischaemic stroke patients.*

**Table V: ABI with and without risk factors in acute ischaemic stroke patients and control group.**

| ABI | With risk factors | | Without risk factors | |
|---|---|---|---|---|
| | Stroke | Control | Stroke | Control |
| < 0.9 | 44 | 6 | 2 | 1 |
| > 0.9 | 40 | 65 | 14 | 28 |

*Among control group, 71 subjects had at least one risk factor and 29 subjects had no risk factor while in acute ischaemic stroke patients, 84 subjects had at least one risk factor and remaining 16 were having no risk factors.*

*ABI < 0.9 was noticed in 8.45% control subjects and 52.3% of acute ischaemic stroke subjects within risk factor positive subjects, while ABI < 0.9 was noticed in 3.44% control subjects and 12.5% subjects of acute ischaemic stroke without risk factor subjects. The difference in these values was statistically highly significant (p < 0.001).*

**Table VI: Distribution of acute ischaemic stroke patients according to ABI and NIHSS score at the time of admission.**

| NIHSS score | Total no. | ABI < 0.9 | Percentage | Mean |
|---|---|---|---|---|
| 1 - 4 | 6 | 2 | 33.3% | 0.890 |
| 5 - 15 | 58 | 17 | 29.31% | 0.8623 |
| 16 - 20 | 21 | 13 | 61.9% | 0.8381 |
| 21 - 42 | 15 | 14 | 93.3% | 0.7078 |
| Total | 100 | 46 | 46% | 0.90 ± 0.12 |

*14 (93.3%) acute ischaemic stroke subjects had ABI < 0.9 in the NIHSS score group of 21 - 42 at the time of admission, 13 (61.9%) stroke subjects had ABI < 0.9 in the 16 - 20 NIHSS score group and 17 (29.31%) subjects had ABI < 0.9 in NIHSS score group of 5 - 15. Only 2 (33.3%) subjects had NIHSS score group 1 - 4 at the time of admission.*

*The mean ABI was 0.7078 in 21 - 42 NIHSS score group. The mean ABI was 0.8381, 0.8623 and 0.890 in NIHSS score groups 16 - 20, 5 - 15 and 1 - 4 NIHSS in acute ischaemic stroke subjects, respectively. Linear regression of mean ABI of acute ischaemic stroke patients was seen with increasing NIHSS score.*

Smoking is a risk factor for atherosclerosis. 40% of subjects in the control group and 48% of subjects in the acute ischaemic stroke group were smokers. 10% smoker subjects in control group and 50% smoker subjects in acute ischaemic stroke group were having ABI < 0.9. The mean ABI of smokers and non-smokers, in control group was 1.014 ± 0.11 and 1.062 ± 0.113, whereas in ischaemic stroke group was 0.903 ± 0.131 and 0.907 ± 0.109, respectively. Our study results were similar to studies done by Pil Wook Chung *et al*, Milionis *et al*, Janine Gronewold *et al*; their studies showed no significant difference in the severity of acute ischaemic stroke subjects, between smokers and non-smokers.

In this study, 31% subjects in control group and 24% subjects

in acute ischaemic group were diabetic. The mean ABI of diabetic subjects in control and acute ischaemic stroke group was 1.01 ± 0.10 and 0.88 ± 0.13, respectively. ABI < 0.9 was present in 12.9% diabetic control subjects and 58.33% diabetic ischaemic stroke subjects, respectively while 4.34% non diabetic control subjects and 42.10% non diabetic ischaemic stroke subjects had ABI < 0.9. Markus *et al* showed prevalence of low ABI in subjects with or without diabetes as 40% and 29%, respectively. Low ABI was associated with older age, hypertension, and presence of other vascular diseases. Lee *et al* in showed prevalence of low ABI with DM and non DM as 41.2% and 30.4%, respectively[14].

19% subjects in control group and 12% subjects in acute ischaemic stroke group had IHD. 15.7% IHD subjects in control group and 58.3% IHD subjects in acute ischaemic stroke group had ABI < 0.9. The mean ABI of IHD and non-IHD subjects, in control group was 0.982 ± 0.10 and 1.057 ± 0.113 respectively whereas in ischaemic stroke group it was 0.87 ± 0.12 and 0.907 ± 0.11, respectively. Sander *et al* showed same results and no significant association seen with IHD as a predictor of ischaemic stroke[17]. Millionis *et al* also showed the same results.

In this study, mean serum total cholesterol level in control and acute ischaemic stroke subjects was 174.7 ± 11 and 172.3 ± 34.9 mg/dl, respectively. No subjects in control group and 16 subjects in acute ischaemic stroke group had total cholesterol > 200 mg/dl. In which 43.7% subjects (7 out of 16) in ischaemic stroke group had ABI < 0.9[14].

Out of 100 subjects in the control group, 71 subjects had at least one risk factor and 29 subjects had no risk factor while in 100 acute ischaemic stroke subjects, 84 subjects had one risk factor and remaining 16 subjects had no risk factor. Out of 71 risk factor positive subjects in control group, 6 (8.45%) subjects had ABI < 0.9 and rest 65 (91.5%) subjects had ABI > 0.9. Out of 84 risk factors positive subjects in acute ischaemic stroke group, 44 (52.3%) subjects had ABI < 0.9 and rest 40 (47.6%) subjects had ABI > 0.9. 3.44% (1 out of 29) risk factor negative subjects in control group had ABI < 0.9 while 12.5 (2 out of 16) risk factor negative subjects in acute ischaemic stroke group had ABI < 0.9. These results suggest that some new hidden risk factors may be responsible for lower ABI in conventional risk factor negative group.

A low ABI reflects the combined effect of many risk factors over time and once atherosclerosis has developed, would be expected to be a better predictor than any one risk factor alone.

8% out of 100 patients had NIHSS score at the time of admission in the range of 5 - 15, 21% patients had NIHSS score in the range 16 - 20 and 15% patients had NIHSS score in the range of 21 - 42; only 6% had a NIHSS score of

1 - 4. The mean NIHSS score at time of admission was 13.35 ± 6.10 and range was 2 to 26. 14 (93.3%) acute ischaemic stroke subjects had ABI < 0.9 in NIHSS score group of 21 - 42 at the time of admission, 13 (61.9%) stroke subjects had ABI < 0.9 in 16 - 20 NIHSS score and 17 (29.31%) subjects had ABI < 0.9 in NIHSS score group of 5 - 15; only 2 (33.3%) subjects had ABI < 0.9 in NIHSS score group 1 - 4 at the time of admission. The mean ABI was 0.7078 in the 21 - 42 NIHSS score group. The mean ABI was 0.8381, 0.8623 and 0.890 among NIHSS score groups 16 - 20, 5 - 15, and 1 - 4 in acute ischaemic stroke subjects, respectively.

Linear regression of mean ABI of acute ischaemic stroke patients was seen with increasing NIHSS score. The observations of Chun Yi Li *et al* found nearly similar mean NIHSS value 10.0 ± 7.0 at the time of admission and a higher NIHSS value (NIHSS > 7) in patients with ABI < 0.9. Lee *et al* also found significantly higher NIHSS score values in abnormal group of ABI at the time of admission. Alvarez *et al* found a significant negative correlation between NIHSS score and low ABI at the time of admission in ischaemic stroke subjects[18]. Sanjay Poliestty *et al* found a high mean NIHSS score of 22.5 in patients with ABI < 0.9.

6 (100%) acute ischaemic stroke subjects had ABI < 0.9 in NIHSS score group of 21 - 42 at the time of discharge, 8 (88.8%) stroke subjects had ABI < 0.9 in 16 - 20 NIHSS score group and 29 (39.1%) subjects had ABI < 0.9 in NIHSS score group of 5-15; only 3 (27.2%) subjects had ABI < 0.9 in NIHSS score group 1 - 4 at the time of discharge. The mean ABI was 0.6533 in 21 - 42 NIHSS score group. The mean ABI was 0.7575, 0.8491 and 0.8666 among NIHSS score group, 16 - 20, 5 - 15, and 1 - 4 in acute ischaemic stroke subjects, respectively. A strong negative, statistically significant correlation was found between ABI and NIHSS score at the time of discharge.

Only 28.26% (13 out of 46) subjects of acute ischaemic stroke with ABI < 0.9 migrated to lower NIHSS score groups at the time of discharge. On the other hand, 49.29% (25 out of 54) subjects of acute ischemic stroke with ABI > 0.9 migrated to lower NIHSS score groups at the time of discharge. Subjects with ABI < 0.9 had higher or same NIHSS score group at time of discharge.

**Table VII: Correlation between ABI and NIHSS score among patients of acute ischaemic stroke at the time of admission.**

| | |
|---|---|
| Pearson correlation co-efficient | -0.579 |
| P value | 0.001** |
| N | 100 |

*A negative; moderately strong and statistically significant correlation was found between ABI and NIHSS score at the time of admission.*

**Table VIII: Distribution of acute ischaemic stroke patients according to ABI and NIHSS score after 24 hours of admission.**

| NIHSS score | Total no | ABI < 0.9 | Percentage | Mean ABI |
|---|---|---|---|---|
| 1 - 4 | 6 | 2 | 33.33% | 0.890 |
| 5 - 15 | 63 | 20 | 31.74% | 0.8614 |
| 16 - 20 | 16 | 10 | 62.5% | 0.8295 |
| 21 - 42 | 15 | 14 | 93.33% | 0.7078 |
| Total | 100 | 46 | 46% | 0.90 ± 0.12 |

Subjects with ABI > 0.9 had migrated to a lower NIHSS score group at the time of discharge, while subjects with ABI < 0.9 remained in higher or same NIHSS score group. 8 patients (5 males + 3 females) with acute ischaemic stroke and ABI < 0.9, dead. Thus, our observations are suggesting that abnormal ABI was associated with severe ischaemic stroke.

Our observation of low ABI with higher NIHSS score in acute ischaemic stroke subjects is supported by the study of Chun Yi Li *et al* on high-risk of future events in acute stroke with ABI < 0.9. NIHSS score at admission and at time of discharge was higher in the patients with ABI < 0.9[20]. Only 24.4% of 41 patients with an ABI < 0.9 had favourable outcomes at 6 months after the index stroke, whereas more than > 50% patients with an ABI > 0.9 had favourable outcome at 6 months. Lee *et al* observed initial stroke severity, as measured by mean initial NIHSS score, was higher in patients with abnormal ABI (6.61 ± 6.56) compared to those with normal ABI (4.36 ± 4.90). Poor stroke outcome was associated with older age, hypertension, smoking and initial higher NIHSS score[15]. Alvarez *et al* in a follow-up study, found that initial higher NIHSS score was associated with low ABI. ABI < 0.9 was an independent predictive factor for new vascular events and functional outcome after 1 year of follow-up[18]. Sanjay Polisetty *et al* in their study found that severity of

ischemic stroke was significantly higher with low ABI and initial higher NIHSS score[20].

**Table IX: Distribution of acute ischaemic stroke patients according to ABI and NIHSS score at the time of discharge.**

| NIHSS score | Total no | ABI < 0.9 | Percentage | Mean |
|---|---|---|---|---|
| 1 - 4 | 11 | 3 | 27.2% | 0.8666 |
| 5 - 15 | 74 | 29 | 39.1% | 0.8491 |
| 16 - 20 | 9 | 8 | 88.8% | 0.7575 |
| 21 - 42 | 6 | 6 | 100% | 0.6533 |
| Total | 100 | 46 | 46% | 0.90 ± 0.12 |

**Table X: Correlation between ABI and NIHSS score among acute ischaemic stroke subjects at the time of discharge.**

| | |
|---|---|
| Pearson correlation co-efficient | -0.596 |
| P value | 0.001** |
| N | 100 |

Low ABI values had a significant greater predictive value for a subsequent severe ischaemic stroke. A low index reflects the combined effect of many risk factors over time and once atherosclerosis has developed, would be expected to be a better predictor than any one risk factor alone. In our study, the prevalence of older age, hypertension, higher BMI and waist to hip ratio was significantly higher in ABI < 0.9 patients than patients of acute ischaemic stroke who had ABI > 0.9. These results showed that ABI is inversely related to traditional risk factors for ischaemic stroke and represents a marker for atherosclerotic changes in other vascular beds. Indeed, after adjustment of major stroke risk factors, an inverse linear relationship was found between ABI and severity of acute ischaemic stroke.

**Table XI: Migration of acute ischaemic stroke subjects between NIHSS score groups at time of discharge.**

| NIHSS score | Total no at admission | ABI < 0.9 | Total no at discharge | ABI < 0.9 | Migration of subjects from other NIHSS group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of subjects (ABI > 0.9) with same score | No of subjects (ABI > 0.9) score increase | No of subjects (ABI > 0.9) score decrease | No of subjects (ABI < 0.9) with same score | No of subjects (ABI < 0.9) score increase | No of subjects (ABI < 0.9) score decrease |
| 1 - 4 | 6 | 2 | 11 | 3 | 4 | 0 | 4 | 2 | 0 | 1 |
| 5 - 15 | 58 | 17 | 74 | 29 | 25 | 0 | 20 | 17 | 0 | 12 |
| 16 - 20 | 21 | 13 | 9 | 8 | 0 | 0 | 1 | 8 | 0 | 0 |
| 21 - 42 | 15 | 14 | 6 | 6 | 0 | 0 | | 6 | 0 | 0 |
| Total | 100 | 46 | 100 | 46 | 29 | 0 | 25 | 33 | 0 | 13 |

**Fig. 1:**



**Fig. 2:**



**Fig. 3:**



**Fig. 4:**



**Fig. 5:**



**Fig. 6:**
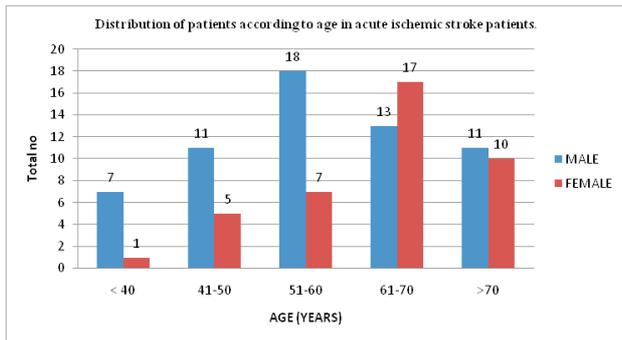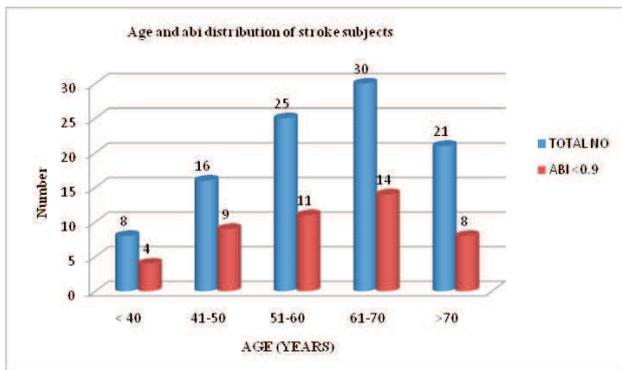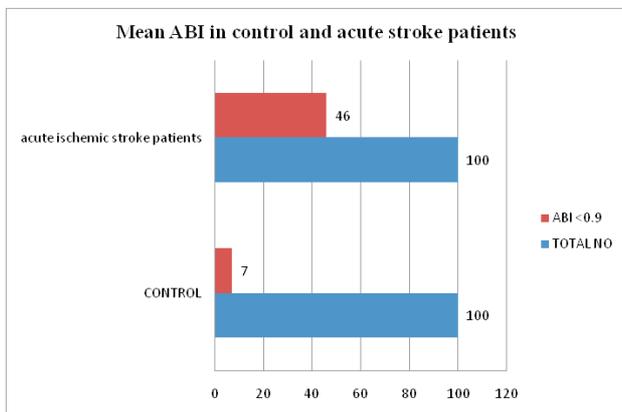
## Conclusion

In our study, patients with low ABI presented with more severe ischaemic stroke. Nonetheless, our findings support the notion that ABI determination is a simple, cost-effective, non-invasive screening tool, which may be used for risk stratification of patients, of acute ischaemic stroke, who could benefit from intensified management of hypertension, diabetes dyslipidaemia, as well as from lifestyle modification, such as smoking cessation and exercise programs. ABI can be easily measured, even in a primary care setting, and used as part of assessment of stroke risk in individuals.
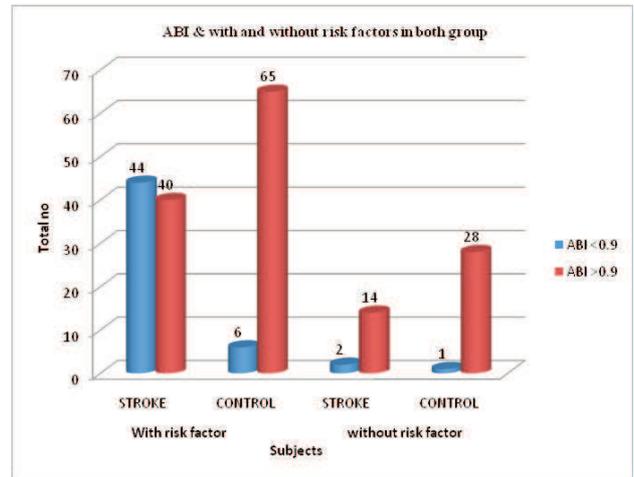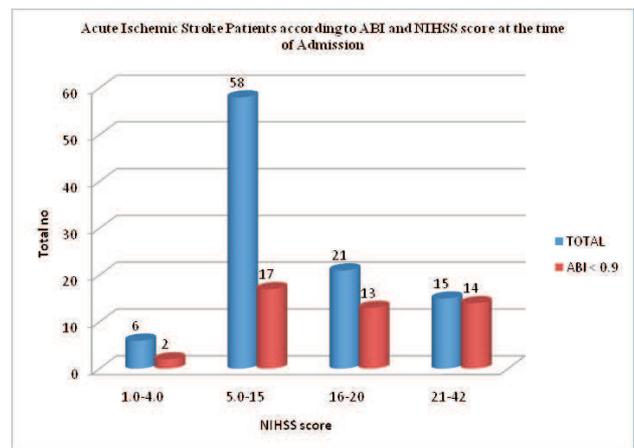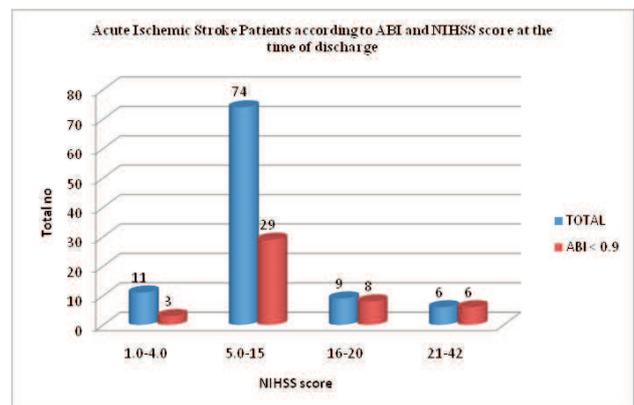
**Limitation:** Our study group was small. Since the study
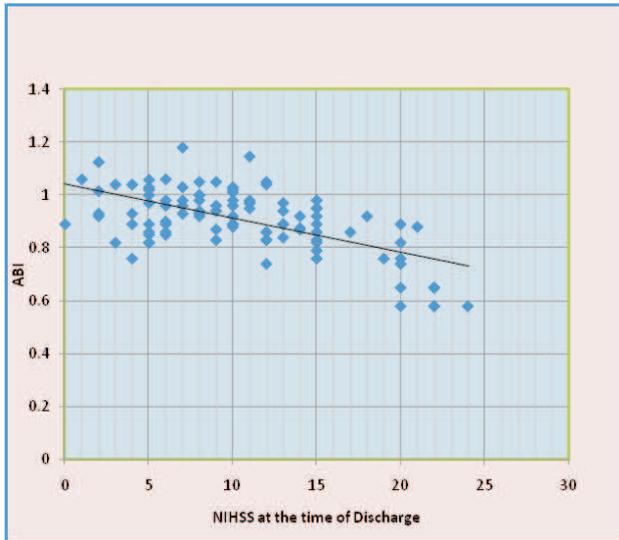
**Fig. 7:**

was case-control in design, the clinical endpoints were not followed. This study did not use invasive techniques like arteriogram to confirm the diagnosis of PAD.

Our study was carried out in a tertiary centre, where the cases are either serious or referred. Our study may thus be biased towards more serious cases. Our study did not include recently emerging risk factors, such as fibrinogen, homocysteine, C-reactive protein and lipoprotein-a (due to non availability in our institute), which may have prognostic value in PAD patients.

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> *"You may be disappointed if you fail,*
> *but you are doomed if you don't try."*
>
> — BEVERLY SILLS.

# A Study of Gestational Diabetes Mellitus, its Prevalence, Risk Factors and Complications in a Tertiary Care Hospital

*D Trivedi\*, V Chavda\*\*, K Patel\*\**

## Abstract

*Background: Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable severity with onset or first recognition during pregnancy. Women with GDM are at increased risk for adverse obstetric and perinatal outcomes. Hence, early detection and management are imperative ensure better maternal and foetal outcomes.*

*Aims: This study was done to evaluate the prevalence of GDM using Diabetes in Pregnancy Study group in India (DIPSI) criteria and compose the feto-maternal outcomes among women with GDM versos those without GMD in a Tertiary Hospital.*

*Materials and method: This study was carried out in 210 patients between 24 and 28 weeks of gestation, attending the antenatal clinic. These patients were given 75 g oral glucose, irrespective of meals and their plasma glucose was estimated at 2 h. Patients with plasma glucose values >= 140 mg/dl were labeled as GDM and the rest as control or non-GDM group. All patients were followed-up till delivery to assess their maternal and foetal outcomes.*

*Results: The prevalence of GDM in this study was 10.95%. Maternal and fetal complications in the GDM group were much higher than in the non-GDM group.*

*Conclusion: GDM, as a disease entity, adversely affects maternal and fetal outcomes. The awareness, early detection, prevention and control of modifiable risk factors is vital to reduce the burden of diabetes and reverse maternal and foetal outcomes.*

*Key words: DIPSI criteria, gestational diabetes, pregnancy, female.*

## Introduction

Gestational diabetes mellitus (GDM) is emerging as a serious public health problem. It is defined as "carbohydrate intolerance of variable severity with onset or first recognition during the pregnancy"[1,2]. The current definition of GDM, was first proposed by the National diabetes data group (NDDG) in 1979, although that group used the term "impaired glucose tolerance (IGT)" rather than "carbohydrate intolerance of varying severity". The latter term was introduced at the Second International Workshop-Conference on Gestational Diabetes in 1985.

The prevalence of diabetes is increasing globally and these numbers include women with GDM[3]. The 1997 WHO estimates of the prevalence of diabetes in adults predicted a rise of than 120%, from 135 million in 1995 to 300 million in 2025, worldwide, which include GDM also[4]. Women with GDM are at increased risk of diabetes in future as are their children and the subsequent generations[5].

Although it has been studied extensively for more than 30 years, there is no consensus on specific screening strategies, criteria for screening, or even whether diagnosis and treatment have an effect on foetal outcome[6].

The prevalence of GDM may range from 1 - 14% of all pregnancies depending on the population studied and the diagnostic tests employed. GDM may develop at any time during pregnancy[7]. Numerous studies have demonstrated that women with GDM manifest increased rates of still births, perinatal mortality, macrosomia and congenital malformations[8,9].

It is commonly recommended that the glucose challenge be administered at 24 - 28 weeks of gestation, however, a number of investigators have explored the effect of advancing gestation on screening test function[9]. Jovanovich *et al* performed a cross- sectional study of 999 prenatal patients, administering the glucose screening test at the first prenatal visit. There was an increasing likelihood of gestational diabetes as pregnancy progressed; suggesting that the screening test performed early in pregnancy is likely to miss affected individuals[9].

The WHO expert group recommended that all pregnant women should be screened at the beginning of third trimester of pregnancy using OGT.

The data regarding prevalence of GDM and the number of women affected are important to allow for rational planning

*\*Associate Professor, \*\*3rd Year Resident, Department of Medicine, GMERS Medical College,*
*Sola, Ahmedabad - 380 007, Gujarat.*
*Corresponding Author: Dr D Trivedi, Associate Professor, Department of Medicine, GMERS Medical College,*
*Sola, Ahmedabad, Gujarat, Tel: 09428510076, E-mail: drdiptitrivedi@icloud.com.*

and allocation of resources and the preventive strategies that may be undertaken in future. As there is wide variation between different regions and communities in india, multiple studies are needed to observe the pattern of GDM. The present study was, therefore, undertaken to study the prevalence of GDM it is risk factors and complications in women attending a Tertiary Hospital at GMERS Medical College and Sola Civil Hospital in Ahmedabad.

### Diagnostic criteria (Box 1)

There are a number of country-specific guidelines on diagnosis and treatment of GDM. These include American diabetes association (ADA) guidelines, WHO guidelines, DIPSI guidelines and IADPSG guidelines, Controversy and confusion still exists, because of these different guidelines for the diagnosis of GDM.

**Box 1: Definition of GDM by different criteria.**

| Criteria | Sample time | Fasting/ non fasting | Glucose load (geos) | Fasting mg/dl | 1 hr mg/dl | 2 hr mg/dl | 3 hr mg/dl |
|----------|-------------|----------------------|---------------------|---------------|------------|------------|------------|
| ADA | F, 1 hr, 2 hr, 3 hr | Fasting | 100 | > 95 | > 180 | > 155 | > 140 |
| WHO | F, 2 hr | Fasting | 75 | > 126 | – | > 140 | – |
| IADPSG | F, 1 hr, 2 hr | Fasting | 75 | > 92 | > 180 | > 153 | – |
| DIPSI | 2 hr | Non Fasting | 75 | – | – | > 140 | – |

### DIPSI (a modified version of WHO) (Box 2)

It is a one-step procedure, with a single glycaemic value, to diagnose GDM in the community. In the antenatal clinic, a pregnant woman is given a 75 g oral glucose load, irrespective of whether she is in the fasting or non-fasting state. A venous blood sample is collected at 2 hours for estimating plasma glucose by the GOD- POD method[10,11].

**Box 2: DIPSI criteria for diagnose of GDM.**

| Critaria | In pregnancy | Outside pregnancy |
|----------|--------------|-------------------|
| 2 hour ≥ 200 mg/dl | Diabetes | Diabetes |
| 2 hour ≥ 140 - 199 mg/dl | GDM | IGT |
| 2 hour ≥ 120 mg/dl | DGTT | – |

## Materials and method

### Study site

The study was performed GMERS Medical College and Hospital, Sola, Ahmedabad, Gujarat.

### Study population

This study included pregnant women (estimated gestational age between 24 - 28 weeks) who took antenatal visit at

sola Civil Hospital, Ahmedabad during April 2014 to April 2016 if they fulfilled the inclusion criteria described below.

### Study design

Prospective, observational type of study.

### Sample size

In an earlier study, done at various centers, the prevalence of gestational diabetes mellitus was found to be 16.55[3]. Assuming this prevalence, with 5 per cent confidence interval, at level of significance of 95%, a sample of 206 eligible subjects was required. The sample size was calculated using Cochrane equation[12]. (Cochrane 1963: 75):-

$$n = \frac{Z^2 pq}{e^2}$$

$$n = \frac{Z^2 x(P)x(1-P)}{e^2}$$

P = prevalence 16.55% (previous study)

Z = confidence limit = 1.96 (95% confidence level)

e = confidence interval (margin of error) expressed as decimal 0.05 = +5

### Study period

From April 2014 to April 2016

### Selection criteria

#### Inclusion criteria

All pregnant women (24 - 28 weeks) who will take antenatal visit at Sola Civil Hospital, Ahmedabad during this period were included for screening and all those found having abnormal plasma glucose value (> 140 mg/dl) as for DIPSI critaria considered as having GDM.

#### Exclusion criteria

1. All diabetic women who became.

2. Major chronic diseases like molignancy, tuberculosis, congestive cardiac failure, renal failure and advanced liver failure.

3. Those patients not willing to consent or those wasting to opt out from the study anytime later.

## Methodology

The study protocol was approved by the Institutional Ethics Committee.

The present prospective study was conducted on all antenatal women (between 24 - 28 weeks of gestational

age) who visited ante-natal clinics (OPD) in the Sola Civil Hospital, Ahmedabad, which is attached with GMERS Medical College during the period of study. They were evaluated for demographic pattern and for presence of GDM, according to DIPSI recommended method, and followed-up to determine the outcomes of pregnancy as per a pre-designed proforma.

## Statistical method

Chi-square test was used to test the difference between two proportions

P value < 0.05 = statistically significant

P value < 0.01 = highly significant

Odds ratios were calculated for different risk factors

All statistical analyses were performed using Microsoft Excel and SPSS software.

## Observations and discussion

Total 210 antenatal women were randomly selected during this study period; GDM was diagnosed in 23 (10.95%) women based on DIPSI Criteria. The remaining formed the non-GDM group.

GDM prevalence has been reported variably worldwide, and differently, among racial and ethnic groups. Prevalence is higher in Blacks, Latino, Native Americans, and Asian women, than in White women.

In India, in a study done in 1981[13] the prevalence of GDM was found to be 7.62 per cent. In a random survey performed in various cities in India in 2002 - 2003, the prevalence of GDM was 16.2 per cent in Chennai, 15 per cent in Thiruvananthapuram, 21 per cent in Alwaye, 12 per cent in Bangalore, 18.8 per cent in Erode and 17.5 per cent in Ludhiana[14]. An overall GDM prevalence of 16.55 per cent was observed. In a study done at a tertiary care hospital in Maharashtra, the prevalence of GDM was found to be 7.7 per cent and 13.9 per cent women were found to have a single abnormal value on OGTT[15]. Use of different criteria for diagnosis of GDM in various studies may be responsible for different prevalence rate of GDM. In India, it is difficult to predict any uniform prevalence pattern because of wide differences in living conditions, socio- economic levels dietary habits and lack of data.

In our study, (Table I) prevalence of GDM increased significantly with increasing age. A similar association has been seen in earlier studies[15-17]. In our study, the odds of a woman > 25 years developing GDM were 3.72. Similarly Seshiah et al[17] reported an odds ratio of 2.1 for women > 25 years of age.

**Table I: Distribution of age groups in study population.**

| Age (years) | Number of participants (%) | No of GDM patients N (%) N = 23 |
|---|---|---|
| 16 - 20 years | 8 (3.8%) | 0 (0) |
| 21 - 25 years | 79 (37.61%) | 3 (3.79) |
| 26 - 30 years | 106 (50.47%) | 16 (15.09) |
| > 30 years | 17 (8.09%) | 4 (23.52) |

Table II shows that out of 26 patients with BMI > 25 Kg/m², 14 patients (53.84%) had GDM. In comparison, 9 patients (4.89%) with BMI < 25 Kg/m² developed GDM. So, other risk factors also play an important role, besides obesity.

Gomez et al[18] found that 50% of women with GDM had obesity. This may be due to increased demands on maternal metabolism during pregnancy from excess weight, resulting in imbalances in hormonal carbohydrate regulation mechanisms, and insulin sensitivity. Nilofer[19] found obesity as a risk factor in 88.89% of GDM patients. In our study, a significant proportion of subjects with GDM were overweight (60.86%).

**Table II: Distribution of BMI in study population.**

| BMI (Kg/m²) | No of patients (210) | GDM | Non-GDM |
|---|---|---|---|
| < 18.5 | 80 | 3 (3.75%) | 77 (96.25%) |
| 18.5 - 24.9 | 104 | 6 (5.76%) | 98 (94.24%) |
| > 25 | 26 | 14 (53.84%) | 12 (46.16%) |

Table III shows distribution of the study population based on their socio-economic status according to Kuppuswamy classification. This classification divides population into five classes based on their education, occupation and income. The prevalence of GDM was found to be higher in women belonging to upper and upper middle class (4/11, 36.36% and 10/43, 23.25% respectively). Rajput et al[20] found an association between GDM with higher socio-economic status. Higher association of GDM with upper class is seen in our study also. This may be because of fast developing economy of India since last 20 years and people are consuming more junk food as compared to traditional foods. This association could also be related to multiple factors such as higher maternal age, BMI and more sedentary lifestyle in women of higher socio-economic status.

In our study, distribution of GDM according to parity was found to be as below. 8/75 (10.66%) of study population with zero parity had GDM. 14/106 (13.20%) with single parity had GDM and 1/19 (5.26%) with parity of 2 had GDM.

**Table III: Comparison of socio-economic status as a risk factor in GDM and non-GDM population.**

| Socio-economic status | GDM (%) N = 23 | Non-GDM (%) N = 187 |
|---|---|---|
| Upper class | 4 (17.39) | 7 (3.74) |
| Upper middle class | 10 (43.47) | 33 (17.64) |
| Lower middle class | 4 (17.39) | 65 (34.74) |
| Upper lower class | 4 (17.39) | 72 (38.50) |
| Lower class | 1 (4.34) | 10 (5.34) |

Table IV shows the comparison of prevalence of all risk factors between GDM and non- GDM population. Family history of diabetes mellitus, age > 25 years, past history of GDM, family history of HTN, socio-economic status, previous history of macrosomic baby and BMI > 25 kg/m$^2$ were significantly associated with GDM group (P < 0.05). History of GDM in previous pregnancy was present in one woman only (4.34%) and developed GDM again.

Family history of diabetes mellitus has been reported to be associated with higher chances of developing GDM[21,22]. In our study, 6 (26.08%) per cent of women with GDM had positive family history of diabetes mellitus. Seshiah et al[17] observed a significant association between family history of diabetes mellitus and occurrence of GDM among pregnant women.

**Table IV: Comparison of prevalence of risk factors in GDM and non-GDM population.**

| Risk factors | Non-GDM No (%) n = 187 | GDM No (%) n = 23 | $\chi^2$ (p value) |
|---|---|---|---|
| Age > 25 years | 120 (64.17) | 20 (86.95) | 4.7849 (< 0.05) |
| BMI > 25 Kg/m$^2$ | 12 (6.41) | 14 (60.86) | 55.9799 (< 0.01) |
| Family history of diabetes mellitus | 13 (6.95) | 6 (26.08) | 9.113 (< 0.01) |
| Family history of HTN | 10 (5.34) | 5 (21.73) | 8.2966 (< 0.01) |
| Past history of GDM | 0 | 1 (4.34) | 8.1693 (< 0.01) |
| Previous history of macrosomic baby | 0 | 1 (4.34) | 8.1693 (< 0.01) |

Table V shows calculated odds ratios for risk factors found to be positively associated with GDM. McGuire et al[22] observed an odds ratio of 23 for women with prior GDM.

Table VI shows the distribution of associated complications such as pregnancy-induced hypertension (PIH), vaginal candidiasis, and abruptio placentae. The prevalence of all these complications was higher in the GDM group than in the non-GDM group, with statistical significance (P < 0.05).

Our study revealed that the most common complications seen in GDM mothers were PIH (26.08%) followed by vaginal candidiasis (17.39%). Gajjar et al found that the most common maternal complication seen in GDM mothers was

gestational hypertension (36.4%) followed by abruptio placentae (20%)[23].

**Table V: Odds ratio for risk factors found to be associated with GDM.**

| Risk factors | Odds Ratio | 95% CI Lower | 95% CI Upper | p value |
|---|---|---|---|---|
| Age > 25 years | 3.72222 | 1.0667 | 12.9890 | < 0.05 |
| BMI > 25 Kg/m$^2$ | 27.3438 | 9.6797 | 77.2421 | < 0.001 |
| Family history of diabetes mellitus | 4.7240 | 1.5914 | 14.0229 | < 0.01 |
| Family history of HTN | 4.9167 | 1.5139 | 15.9682 | < 0.01 |
| Socio-economic status (upper middle class) | 3.5897 | 1.4506 | 8.8834 | < 0.01 |
| Previous history of macrosomic baby | 25.0000 | 0.9885 | 632.2451 | = 0.05 |
| Past history of GDM | 25.0000 | 0.9885 | 632.2451 | = 0.05 |

**Table VI: Comparison of maternal complications in GDM and non-GDM population.**

| Complications | Non-GDM No (%) N = 187 | GDM No (%) N = 23 | $\chi^2$ (p value) |
|---|---|---|---|
| Pregnancy induced HTN | 27 (14.43) | 7 (26.08) | 3.8622 (< 0.05) |
| Abruptio placentae | 5 (2.67) | 3 (13.04) | 6.0101 (< 0.05) |
| Vaginal candidiasis | 11 (5.88) | 4 (17.39) | 4.0901 (< 0.05) |
| PROM | 10 (5.34) | 4 (17.39) | 4.7745 (< 0.05) |
| Shoulder dystocia | 1 (0.53) | 1 (4.34) | 3.1568 (> 0.05) |
| PPH | 25 (13.36) | 5 (21.73) | 1.1718 (> 0.05) |

*PROM: Premature rupture of membranes; PPH - Post-pertion haemorrhage.*

Table VII shows statistical correlation between delivery outcomes in women, with and without GDM. Prevalence of cesarean delivery and assisted vaginal delivery was statistically higher in GDM group than in non-GDM group (P < 0.01).

Gajjar[23] found a cesarean rate of 19.5% in the GDM patients. Cesarean delivery rate in our study was 60.86%, amongst the GDM patients, with the most common indication being arrest of labor. This is quite high, probably because in our set-up more number of high-risk patients with GDM delivered by ceserean section hence, lesser number of high-risk patients are given trial of labour.

Table VIII shows the foetal outcomes in the study group. The prevalence of stillbirths, macrosomia, and neonatal intensive care unit (NICU) admissions was higher in the GDM group than in the non-GDM group, with statistical significance (p < 0.05). The prevalence of hypoglycaemia and hyperbilirubinaemia was higher in GDM than in non-GDM group, but it did not reach statistical significance.

**Table VII: Comparison of maternal outcome in GDM and non-GDM population.**

| Maternal outcome | Non-GDM No (%) N = 187 | GDM No (%) N = 23 | $\chi^2$ (p value) |
|---|---|---|---|
| Cesarean section | 52 (27.80) | 14 (60.86) | 10.3883 (< 0.01) |
| Spontaneous vaginal delivery | 132 (70.58) | 6 (26.08) | 18.0021 (< 0.01) |
| Assisted vaginal delivery | 3 (1.60) | 3 (13.04) | 9.656 (< 0.01) |

**Table VIII: Comparison of foetal outcome in GDM and non-GDM population.**

| Foetal outcome | Non-GDM No (%) N = 187 | GDM No (%) N = 23 | $\chi^2$ (p value) |
|---|---|---|---|
| Stillbirths | 1 (0.53) | 2 (8.69) | 9.6866 (< 0.01) |
| Macrosomia | 9 (4.81) | 5 (21.73) | 9.4304 (< 0.01) |
| Hypoglycaemia | 7 (3.74) | 2 (8.69) | 1.2245 (> 0.05) |
| Hyperbilirubinaemia | 8 (4.27) | 3 (13.04) | 3.1702 (> 0.05) |
| NICU admission | 21 (11.22) | 6 (26.08) | 4.0349 (< 0.05) |

In one study in Brazil[24] the incidence of hypoglycaemia and hyperbilirubinaemia were 16.3% and 6.1%, respectively.

## Conclusion

GDM should be taken seriously as the offspring may develop DM in future, and so will be a major health concern for future generations. In addition to traditional risk factors, in modern mothers-changing lifestyle, stress, late marriage are important and modifiable risk factors. Interventions done at pre-primordial level can lend new hope in the fagnt against diabetes for upcoming generations.

## Recommendation

We would like to suggest that by increasing sample size of the age group > 25 years may open new avenues in the field of GDM. This requires larger number of patients in future studies.

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# Sodium Valproate Versus Topiramate for Prophylaxis of Migraine Among Children and Adolescents: A Randomised Trial

*Ramakant Yadav\*, TP Singh\*\*, SK Shukla\*\*\**

## Abstract

*Objective: Migraine is a common health problem in children and adolescents, resulting in missing school days. This study compares the efficacy and safety of sodium valproate and topiramate in preventing migraine among children and adolescents.*

*Materials and method: In this randomised, double-blind clinical trial 88 children with migraine (8 - 16 years of age) were equally allocated to receive sodium valproate (10 - 20 mg/kg per day) or topiramate (1 - 2 mg/kg per day). The primary efficacy measure was reduction in 50% or more headache days, in comparison to baseline headache frequency per month. Secondary efficacy measures were headache related disability, migraine intensity and duration. Efficacy measures were recorded at the baseline and at 12 weeks of treatment.*

*Results: A total of 82 patients were included in the trial, 40 in the sodium valproate group and 42 in the topiramate group. At 12 weeks, the percentage of patients who had a relative reduction of 50% or more in the number of headache days was 75.0% in the sodium valproate group and 70.0% in the topiramate group. The monthly migraine frequency, headache related disability, intensity and duration were significantly decreased in both the sodium valproate and topiramate groups when compared to the baseline. No significant difference was observed between these two groups in terms of reduction of frequency, headache related disability, severity and duration of attack. Weight gain, abdominal pain and somnolence were the main side-effects in sodium valproate group and weight loss, fatigue and loss of appetite in topiramate group.*

*Conclusion: Sodium valproate and topiramate were found effective for the prevention of paediatric migraine. Both drugs were well tolerated.*

*Key words: Sodium valproate, migraine, paediatric, topiramate, prevention.*

## Introduction

Migraine is a common health problem in children and adolescents[1,2,3]. Migraine affects children and adolescents in their daily activities and school performances, as well as causes school absenteeism[3,4]. The prevalence of migraine headaches among children and adolescents aged between 5 to 15 years ranges from 2.7 - 10.6%[3]. The prevalence increases with age and is reported to be up to 28% in adolescents, aged 15 to 19 years[3,6]. Migraine headaches show a male predominance in children, with female predominance in adolescence and adulthood[3,5].

Management of migraine headaches in children and adolescents consists of behavioural treatments, acute treatments, and preventive treatments[7]. Preventive management is recommended when the frequency of migraine attacks is three of more per month or the migraine attacks are significantly disabling, as assessed by a scoring system such as the Paediatric Migraine Disability Assessment Scale[8,9]. In 1988, Sorensen reported the potential efficacy of sodium valproate in migraine prophylaxis[10]. Sodium valproate is considered as a first-line therapy for migraine prophylaxis in adults and several open label and retrospective studies have suggested that it may be effective in the paediatric population[11].

Topiramate has been approved for use in migraine prevention in adults in Europe and by the FDA[12]. Randomised, double-blind, placebo-controlled studies showed the effectiveness of topiramate in significant reduction of monthly migraine frequency in children and adolescents[13]. Some studies have showed the effectiveness of topiramate in reducing monthly migraine frequency in children[14-17]. We conducted a randomised, double-blind clinical trial to evaluate the efficacy and safety of sodium valproate and topiramate as preventive treatments for migraine headaches among children and adolescents, residing in a rural area.

## Materials and method

A prospective randomised, double-blind clinical trial to

*\*Professor and Head, Department of Neurology, \*\*\*Professor, Department of Community Medicine, Uttar Pradesh University of Medical Sciences (UPUMS), Saifai, Etawah, Uttar Pradesh,*
*\*\*Professor, Department of Medicine, Sarojini Naidu Medical College (SNMC), Agra, Uttar Pradesh.*
*Corresponding Author: Dr Ramakant Yadav, Professor and Head, Department of Neurology, UP University of Medical Sciences, Saifai, Etawah, UP, Tel: 09415181190, E-mail: rkyadav_2003@yahoo.com.*

compare the efficacy of sodium valproate and topiramate as prophylaxis for paediatric migraine was conducted in a tertiary care teaching hospital of Uttar Pradesh University of Medical sciences (UPUMS). The patients were recruited from out patient services of the Neurology department. Eighty eight patients, 8 - 16 years of age, with common migraine as defined by the 2004 international headache society criteria were enrolled in our study from 2012 to 2015. The study was approved by local ethics committee. A complete history of the patients, including migraine characteristics and general medical history was recorded, along with a general and neurological examination.

The inclusion criteria were as follows:

1. Children and adolescents, aged 8 - 16 years, diagnosed with migraine (without aura) according to the International Headache Society criteria[18].

2. More than 4 migraine attacks per month.

The exclusion criteria were as follows:

1. Focal neurologic deficit

2. Severe adverse effects related to the study treatment drugs, as also their contraindications.

3. Known concomitant serious disease (hepatic, renal, cardiovascular, or thyroid disease).

In the 4 weeks prospective baseline period, the previous medications of patients for migraine, either for preventive or acute treatment, were halted. The frequency, intensity, duration and headache related disability of the migraine patients was recorded. Each patient was given a diary to record the frequency and intensity and duration of each migraine.

Patients who completed the prospective baseline phase of the study entered the double-blind have and were then randomised into two treatment groups. One group of participants received sodium valproate as the preventive treatment for migraine (the valproate group); and the other group of participants received topiramate (the topiramate group). Sodium valproate and topiramate tablets were provided in similar packages.

The sodium valproate group was administrated at a dose of 10 - 20 mg/kg per day and topiramate group was administrated at a dose of 1 - 2 mg/kg body weight per day for 12 weeks. Adjustment of the dose of valproate sodium and topiramate, in presence of intolerability or occurrence of serious side-effects related to the treatment drugs, was considered. Patients were permitted to take analgesics for abortive treatment of acute migraine attacks throughout the study.

Patient information of the characteristics of migraine attacks (including the frequency, intensity and duration of attacks) during the double-blind phase were recorded using diaries. Each patient was provided with a diary for 90 days, in which all migraine attack characteristics like duration and intensity of attacks were recorded. The Paediatric Migraine Disability Assessment Scale (PedMIDAS), which assesses the effect of migraine on school, home, play and social activities was used to determine headache related disability at baseline and at the end of the trial.

Follow-up visits were scheduled at 4, 8 and 12 weeks. At each visit, the diaries were checked and information collected. Patients were evaluated using detailed questionnaires for occurrence of side-effects.

## Efficacy measures

To measure the efficacy of sodium valproate and topiramate treatments, the frequency, intensity of migraine attacks, headache related disability and 50% responder rate to the treatments were evaluated. All required data for calculating the intended measures was based on information obtained from the diaries.

Frequency of migraine attacks was defined as the mean number of migraine attacks that fulfilled the IHS criteria for migraine without aura in each 4 week period. The intensity of attacks was graded on a 0 - 3 scale 0 = Normal, 1 = Mild, 2 - Moderate, 3 = severe[19]. Migraine intensity was defined as the mean intensity of migraine attacks per each 4 week period. Headache related disability was assessed by PedMDAS score ( range 0 - 240) with score of 0 - 10 indicate No disability, 11 - 30 mild disability, 31 - 50 moderate disability and > 50 severe disability[8].

A 50% responder rate was defined as the percentage of patients who had a migraine frequency that was reduced greater or equal to 50%.

## Safety measures

At each visit safety of the treatment drugs was assessed by asking the patients' for side-effects during the last 4 weeks using a detailed questionnaire. The relation of side-effects to treatment drugs was also assessed at each visit by interviewing the patients. Special attention was paid to the occurrence of sleepiness, decreased appetite, weight loss, weight gain and vomiting.

## Statistical analysis

The evaluation of the efficacy and safety of treatments was based on information obtained from the diaries, and patient history. Descriptive statistics were calculated for the treatment group and total population, separately. The

comparison between the baseline values and 12 weeks values during the double-blind phase was performed using paired t test. In order to analyse the treatment comparability, a student's t test was done for independent samples. Results were expressed as mean ± SD and p < 0.05 was considered statistically significant. Data was analysed using SPSS software, version 24.

## Results

In this study, a total of 88 participants fulfilled the inclusion criteria. Six patients were excluded, 2 due to lack of consent and 4 lost to follow-up. Eighty two patients (42 male and 40 female) enrolled in the study, with a mean age of 10.95 (range, 8 - 16) years. At baseline, the mean ± SD of monthly migraine frequency was 6.96 ± 1.469, monthly migraine intensity was 2.23 ± 0.790 and mean PedMIDAS score was 45.60 ± 12.66. Participants were randomly allocated into two treatment groups (sodium valproate n = 40; topiramate n = 42). There were no statistically significant differences between the treatment groups, regarding the participant age, the baseline mean of monthly migraine frequency, migraine related disability (PedMIDAS) and migraine intensity. (Table I) represents demographic data and baseline characteristics of the study participants.

**Table I: Characteristics of the patients at baseline.**

| Characteristics | All patients | Sodium valproate group | Topiramate group |
|---|---|---|---|
| 1. Age (years) | 10.95 ± 2.93 | 10.90 ± 3.02 | 11.00 ± 2.87 |
| 2. Gender Female – no (%) | 82 (48.78) | 40 (45) | 42 (52.38) |
| 3. PedMIDAS (score) | 45.60 ± 12.66 | 45.62 ± 12.48 | 45.59 ± 12.99 |
| 4. Frequency of headache (per month) | 6.96 ± 1.46 | 6.87 ± 1.45 | 7.04 ± 1.49 |
| 5. Intensity of headache (score) | 2.23 ± 0.79 | 2.15 ± 0.76 | 2.30 ± 0.81 |

At 12 weeks, the percentage of patients who had a relative reduction of 50% or more in the number of headache days was 75.0% in the sodium valproate group and 70.0% in the topiramate group. The reduction in the mean of monthly migraine intensity was also significant for both groups (sodium valproate; p < 0.0001, 95% CI 0.99 to 1.46; topiramate: p < 0.0001, 95% CI 1.08 to 1.50) compared with the baseline values. The PedMIDAS score significantly decreased in both groups (sodium valproate; p < 0.0001, 95% CI 22.01 to 28.94; topiramate: p < 0.0001, 95% CI 20.68 to 27.27) when compared with baseline score. The reduction in monthly migraine frequency, intensity and disability showed no significant differences for the sodium valproate group versus the topiramate group (Table II).

**Table II: Efficacy results after 3 months of preventive therapy.**

| Parameters | Sodium valproate group | Topiramate group |
|---|---|---|
| 1. ≥ 50% relative reduction in headache frequency - no. (%) | 30 (75) | 30 (71.42) |
| 2. PedMIDAS score | | |
| At baseline | 45.62 ± 12.48 | 45.59 ± 12.99 |
| At week 12 | 20.15 ± 7.13 | 21.61 ± 6.98 |
| 95% CI | 22.01 to 28.94 | 20.68 to 27.27 |
| P value for patients (comparison with baseline) | 0.0001 | 0.0001 |
| 3. Headache frequency | | |
| At baseline | 6.87 ± 1.45 | 7.04 ± 1.49 |
| At week 12 | 2.30 ± 1.32 | 2.42 ± 1.38 |
| 95% CI | 3.93 to 5.22 | 4.16 to 5.03 |
| P value for patients (comparison with baseline) | 0.0001 | 0.0001 |
| 4. Headache intensity | | |
| At baseline | 2.15 ± 0.76 | 2.30 ± 0.81 |
| At week 12 | 0.92 ± 0.69 | 1.02 ± 0.74 |
| 95% CI | .99 to 1.46 | 1.08 to 1.50 |
| P value for patients (comparison with baseline) | 0.0001 | 0.0001 |
| 5. Headache duration | | |
| At baseline | 6.95 ± 1.85 | 6.60 ± 2.50 |
| At week 12 | 4.62 ± 3.43 | 3.92 ± 2.59 |
| 95% CI | 1.25 to 3.40 | .76 to 3.29 |
| P value for patients (comparison with baseline) | 0.0001 | 0.0001 |

## Safety measures

Treatment related adverse effects were reported in 6 patients in the sodium valproate group, which were mild somnolence in 2, weight gain in 3 and abdominal pain in 1. In the topiramate group, 5 subjects experienced mild treatment related adverse effects that included mild appetite loss in 2, weight loss in 2 and fatigue in 1. No serious side-effects were reported in either treatment groups.

The analysis revealed no statistically significant differences between the sodium valproate group and topiramate group for treatment related adverse effects.

## Discussion

In this study, we evaluated the frequency, intensity, duration and headache related disability of monthly migraine attacks among children and adolescents aged 8 - 16 years at baseline and after 12 weeks treatment period. The results

of patients receiving sodium valproate or topiramate treatment were compared at baseline and after 12 weeks of treatment. The frequency of probable adverse effects related to sodium valproate and topiramate treatment and safety of the treatments were evaluated.

In this study both sodium valproate and topiramate treatments resulted in significant reduction in the frequency and intensity of monthly migraine attacks, and headache related disability from the baseline through 12 weeks of treatment. The percentage of patients who had a relative reduction of 50% or more in the number of headache was 75% in the sodium valproate group and 71.42% in the topiramate group, in comparison of baseline period, with 12 weeks of treatment. Sodium valproate was effective in producing more than 50% reduction in migraine attacks in 48 - 78% of patients in other studies[22-24] which was comparable with our study. A reduction of 50% frequency in the topiramate treatment varies in different studies, from 43.1 - 95.2%[13,14,16]. There are some studies in Iran that show the efficacy and safety of topiramate for the prophylaxis of childhood migraines[20,21]. In our study, the intensity of headache and headache related disability (PedMIDAS) also improved in both valproate and topiramate groups, when compared with baseline which was in agreement with other studies[13,17].

With regard to safety both treatments were well tolerated and no life-threatening side-effects were reported. The frequency of side-effects in our study was 13.4%, in sodium valproate group and 15% in topiramate group, which were mild and similar to other studies. The side-effects related to topiramate administration varied considerably among studies from 14 - 18%. The most frequently reported side-effects were weight loss, anorexia, abdominal pain, sedation, paresthesias, and difficultiy in concentration[13-17]. No dropouts occurred in our study due to adverse effects.

To the best of our knowledge, the current study is the first that compares the effectiveness of sodium valproate and topiramate treatment as a prophylaxis of migraine headaches among children and adolescents residing in rural areas. A limitation of our study was that it had no placebo group.

## Conclusion

Sodium valproate and topiramate demonstrated efficacy in prevention of migraine headaches in children and adolescents. Both drugs were well tolerated and safe.

**Conflict of interest:** The authors declare no conflicts of interest.

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# Evaluation of Serum Uric Acid Level Among Stroke Patients in A Tertiary Care Hospital of North Bengal, India

*Sutanay Bhattacharyya\*, Saikat Datta\*\*, Sharmistha Bhattacherjee\*\*\**

## Abstract

*Introduction: Stroke is the third most common cause of death and the second most common cause of cognitive impairment. Well established risk factors associated with stroke are: age, hypertension, diabetes mellitus, dyslipidaemia, smoking, carotid artery stenosis and atrial fibrillation. But the role of elevated serum uric acid, as an independent risk factor for stroke, has been controversial.*

*Objectives: The current study was done to assess the prevalence of hyperuricaemia, and the factors associated with it, among stroke patients admitted to Medicine Department at NBMCH.*

*Methods: A descriptive study, with cross-sectional design, was conducted from May to June 2014 among 96 patients admitted within 72 hours of stoke, confirmed by neuroimaging techniques. Hyperuricaemia was defined as serum uric acid level of more than 7 mg/dl for males, and more than 6 mg/dl, for females. Data was organised and presented by applying principles of descriptive statistics.*

*Results: 28.1% of the stroke patients were found to be hyperuricaemic. Patients of ischaemic stroke had higher degree of hyperuricaemia than haemorrhagic stroke. Hyperuricaemia was significantly higher among hypertensives and diabetics, in patients above 80 years, in male patients, in smokers and, those with a negative family history of stroke.*

*Conclusion: The study concludes that the association of hyperuricaemia and hypertension in stroke patients points towards a possibility of hyperuricaemia being an important risk factor for cerebrovascular accidents. Further studies are required to further establish the role of uric acid in stroke patients, especially in the current geographical setting.*

*Key words: Stroke, hyperuricaemia, ischaemic, haemorrhagic.*

## Introduction

Cerebrovascular accident or stroke is the third most common cause of death and the second most common cause of cognitive impairment in elderly people worldwide[1]. Stroke causes rapid deterioration in brain function due to alteration in the blood supply to the brain. Stroke is of two types: haemorrhagic and ischaemic. The latter accounts for more than eighty per cent of the cases[2]. Haemorrhagic stroke is due to leakage of blood, with subsequent compression of adjacent part of brain while, ischaemic stroke is due to reduced blood supply to a part of the brain. Irrespective of its cause, stroke is an acute emergency and can lead to progressive neurological damage, and eventually death, if not treated early[3].

Various risk factors for stroke have been described. In a multi national case-control study, various disease conditions like, high blood pressure, previous stroke or transient ischaemic attack, high cholesterol, heart disease, diabetes and sickle cell disease were described as risk factors for stroke. Other lifestyle related conditions like unhealthy diet, lack of physical exercise, obesity, smoking and excessive alcohol consumption were also attributed to the causation of stroke[4]. Well established risk factors associated with stroke are: age, hypertension, diabetes mellitus, dyslipidaemia, smoking, carotid artery stenosis and atrial fibrillation[2]. But, the role of elevated serum uric acid as an independent risk factor for stroke has been controversial. Uric acid (end product of the purine catabolic pathway) is one of the most abundant anti-oxidants in human plasma, with very potent free radical scavenging activity. Simultaneously, it also acts as a prothrombotic agent by stimulating platelet aggregation. This has led to conflicting theories regarding the role of hyperuricaemia in pathogenesis of stroke. There have been reports of association of increased uric acid with established risk factors of stroke, such as elevated serum triglycerides and low density lipoproteins[5]. Contradictory results have also been recorded where uric acid exerts neuroprotective effect, due to its anti-oxidant property, and is associated with better outcome[6].

*\*Resident, Department of Medicine, Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital, New Delhi - 110 029,*
*\*\*Associate Professor, Department of Medicine, \*\*\*Assistant Professor, Department of Community Medicine, North Bengal Medical College, Sushrutanagar, Darjeeling - 734 012, West Bengal.*
*Corresponding Author: Dr Saikat Datta, Professors' Quarters A-5, North Bengal Medical College, Sushrutanagar, Darjeeling, WB, Tel: 09433175684, E-mail: dr_saikat@rediffmail.com.*

Given the association of increased serum uric acid with various well established risk factors (components of metabolic syndrome) and contradictory results obtained about the direct association of uric acid, it is important to replicate the study in different populations. No concrete evidence is present whether uric acid promotes or prevents the development of stroke, or simply acts as a marker of associated risk factors. It is particularly important to determine its association in the present study population, where stroke is highly prevalent, so that appropriate interventions can be taken. The level of intervention will depend on the outcome of the study, and may vary from uric acid monitoring in high-risk patients to administration of uric acid lowering agents or uric acid analogues. Variation in uric acid levels among ischaemic and haemorrhagic stroke can further throw light on the mechanism and importance of hyperuricaemia in stroke patients. With this background, the objective in the present study was to investigate the serum uric acid level among ischemic and haemorrhagic stroke patients admitted in North Bengal Medical College and Hospital, West Bengal. To the best of our knowledge, no such study has been carried out among patients from the Eastern part of the country. The outcome will help not only to clarify the role of uric acid as a risk factor/marker for stroke and its possible mechanism of action, but also inform about possible therapeutic interventions.

## Aims and objectives

Cerebrovascular accidents are associated with high morbidity and disability, with subsequent increase in mortality. Thus, it is very important to understand the risk factors for such a disease, in order to reduce its chance of occurrence. The importance of uric acid as a risk factor is controversial. So, in order to determine the role of uric acid in stroke patients, the aims and objectives of the current study are:

1. To study the prevalence of hyperuricaemia among stroke patients admitted in Medicine Department at North Bengal Medical College and Hospital (NBMCH).

2. To evaluate factors associated with hyperuricaemia, such as elevated blood pressure and diabetes mellitus; history of any significant illness; addiction; among ischaemic stroke and haemorrhagic stroke, and demographic variables among the study population.

## Materials and method

- **Study type and design:** The present study was a descriptive, cross-sectional design.

- **Study period:** May 2014 to June 2014.

- **Study setting:** The study was conducted in the indoor ward of the Medicine Department at North Bengal Medical College and Hospital, Darjeeling, West Bengal.

- **Study population:** Cases of stroke, admitted within 72 hours of the event, in the indoor wards of Medicine department during the study period were included in the study.

  1. **Inclusion criteria:** According to World Health Organisation stroke is defined as 'a syndrome of rapidly developing clinical signs of focal or global neurological disturbance lasting for more than 24 hours'. Cases confirmed by neuroimaging techniques (CT scan brain or MRI brain) were selected for the study.

  2. **Exclusion criteria:** Patients with the following conditions were excluded from the study:

     ❖ Patients having a confirmed cardiac source of emboli (atrial fibrillation, valvular heart disease).

     ❖ Past history of any vascular disease such as previous stroke, angina, myocardial infarction.

     ❖ Patients receiving drugs affecting serum uric acid levels like diuretics.

     ❖ Patients suffering from active infections, malignancy or any liver or renal disease.

     ❖ Confirmed cases of gout.

     ❖ Patients who were too sick and/or refused to give consent.

- **Sampling**

  ○ **Sample size:** In a similar study, done in Iran, by Mehrpour *et al* the prevalence of hyperuricaemia in acute ischaemic stroke patients was 47%[6]. Taking this into consideration the sample size was calculated using the formula:

  $$n = (Z_\alpha)^2 P(1-P)/d^2$$

  where n is the sample size,

  $Z\alpha$ is the standard normal variate (at $\alpha = 0.05$ level is 1.96),

  P is the proportion of hyperuricaemia in stroke patients = 0.47,

  Q = 1-P = 0.53, and

  d is the absolute precision = 0.1

  Applying the formula, the sample size came out to be 96.

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- ❖ Sampling technique: After analysis of records of previous one year of patient admissions to indoor wards of General Medicine, North Bengal Medical College and Hospital, it was seen that, on an average, 2-3 patients suffering from cerebrovascular accidents are admitted, per day, in the three indoor wards. Data was collected from all the patients, six days a week, to get the final sample size of 96.

- ● Study tools

  - ❖ Medical records of the patient were evaluated for:

    1. Demographic data, such as age and gender.

    2. Addiction history, in the form of tobacco consumption (semi-quantitative estimation of tobacco was determined).

    3. History of diseases with known association with stroke such as diabetes mellitus, hypertension other cardiovascular diseases.

    4. Any medication received for stroke.

    5. Other relevant data available.

  - ❖ Disposable syringes for drawing blood samples.

  - ❖ Test tubes of appropriate sizes for collecting and transporting the samples to the laboratory.

  - ❖ Automated analyser for uric acid estimation.

  - ❖ Stethoscope and sphygmomanometer for measuring the blood pressure.

- ● Study technique: All the patients fulfilling the inclusion criteria were recruited for the study. Clinical history of the patients was evaluated, by interview as well as from medical records available in the hospital. Physical examination of the patients was done, including blood pressure determination. Neuroimaging techniques were used for confirmation of diagnosis, as well as for determining the type of stroke, that is, haemorrhagic or ischaemic. Interpretation was done by experts.

  Blood samples were separately drawn from each of the stroke patients. The samples collected in plain vials (without EDTA) were then transferred to the laboratory in the Department of Biochemistry and appropriate tests performed. Serum uric acid estimation was done using automated analyser by the PAP/Uricase method in the laboratory. The uric acid levels were noted for each patient separately. Hyperuricaemia was defined as serum uric acid level more than 7 mg/dl for men and 6 mg/dl for women[3].

- ● Data analysis: After collecting all data, entry was done in Microsoft Excel. Data was organised and presented by applying principles of descriptive statistics. Categorical data was analysed using Chi-square test and continuous variables analysed using t-test and ANOVA, wherever applicable. Appropriate statistical software was used for analysis.

- ● Ethical considerations: Prior consent was taken from the Institutional Ethics Committee. An informed consent form, translated into local language, was used to take the informed consent of the patients. Anonymity and confidentiality was ensured.

- ● Variables used in the study: Variables used in the study were as follows:

  A. Profile variables

  - ❖ Age: Patient's age was enquired and recorded in number of completed years and was confirmed from available records.

  - ❖ Gender: Recorded as male and female.

  - ❖ Family history of stroke: Whether the patient's first degree relative had an episode of stroke, previously.

  - ❖ Smoking history: A person was said to be a smoker if he/she had smoked tobacco/tobacco product at least once for six months prior to the day of interview[7].

  - ❖ Hypertension: According to the 7th Joint National Committee, hypertension was defined as systolic blood pressure of more than 140 mm of Hg and diastolic blood pressure of more than 90 mm of Hg. Patients with past use of anti-hypertensives were also included[8].

  - ❖ Diabetes mellitus: Patients with fasting plasma glucose of more than or equal to 126 mg/dl or random plasma glucose of more than or equal to 200 mg/dl were included as diabetics[9].

  - ❖ Medication received: It was inquired whether the patients received any medication or not, after being admitted.

  - ❖ Type of stroke: Neuroimaging techniques, including CT scan and MRI, was used to evaluate whether a patient had ischaemic or haemorrhagic stroke. The results were interpreted by experts.

  B. Hyperuricaemia: Patient was said to have hyperuricaemia, if serum uric acid level was more than 7 mg/dl in case of males, and 6 mg/dl in case of females.

## Result

The present study was conducted among 96 patients, diagnosed as stroke, and admitted in the medicine wards of North Bengal Medical College.

### Profile of the study population

Half of the stroke patients were in the age group of 40 - 59 years, while majority of them were males (53.1%). 75% of them did not have a family history of stroke. 39.5% of the patients were smokers. While more than half of the study population (64.6%) had hypertension, the numbers of diabetics were comparatively less (31.2%). Out of these, 17.7% of the hypertensives and 30% of the diabetics were diagnosed for the first time on presentation. Mean baseline blood pressure was found to be 140/85 mm of Hg. All the hypertensive patients had hypertension prior to the occurrence of stroke. Most of the patients (78.1%) had received medication for stroke before their blood samples were drawn. Majority of the study population (61.5%) had haemorrhagic stroke, as diagnosed by neuroimaging techniques (Tables I and II).

### Table I: Socio-demographic correlates of hyperuricaemia (N = 96).

|  | Hyperuricaemia | | Total | Statistics |
|---|---|---|---|---|
|  | Present | Absent |  |  |
| Age in years |  |  |  |  |
| 20 - 39 | 2 (28.5%) | 5 (71.5%) | 7 (100%) | $\chi^2 = 0.618$ |
| 40 - 59 | 14 (29.2%) | 34 (70.8%) | 48 (100%) | p = 0.892 |
| 60 - 79 | 10 (25.6%) | 29 (74.4) | 39 (100%) |  |
| 80 and above | 1 (50%) | 1 (50%) | 2 (100%) |  |
| Gender |  |  |  |  |
| Male | 14 (37.8%) | 37 (62.2%) | 51 (100%) | $\chi^2 = 0.024$ |
| Female | 13 (28.9%) | 32 (71.1%) | 45 (100%) | p = 0.875 |
| Family history of stroke |  |  |  |  |
| Present | 6 (25%) | 18 (75%) | 24 (100%) | $\chi^2 = 0.154$ |
| Absent | 21 (29.2%) | 51 (70.8%) | 72 (100%) | p = 0.694 |
| Smoking |  |  |  |  |
| Smoker | 14 (36.8%) | 24 (63.2%) | 38 (100%) | $\chi^2 = 2.364$ |
| Non-smoker | 13 (22.4%) | 45 (77.6%) | 58 (100%) | p = 0.124 |
| Total | 27 (28.1%) | 69 (71.9%) | 96 (100%) |  |

### Prevalence of hyperuricaemia

28.1% of the stroke patients were found to be hyperuricaemic. Mean serum uric acid level was 5.33 mg/dl (Fig. 1).

### Table II: Clinical correlates of hyperuricaemia (N = 96).

|  | Hyperuricaemia | | Total | Statistics |
|---|---|---|---|---|
|  | Present | Absent |  |  |
| Type of stroke |  |  |  |  |
| Haemorrhagic | 12 (20.3%) | 47 (79.7%) | 59 (100%) | $\chi^2 = 4.590$ |
| Ischaemic | 15 (40.5%) | 22 (59.5%) | 37 (100%) | p = 0.032 |
| Hypertension |  |  |  |  |
| Present | 22 (35.5%) | 40 (64.5%) | 62 (100%) | $\chi^2 = 4.689$ |
| Absent | 05 (14.7%) | 29 (85.3%) | 34 (100%) | p = 0.030 |
| Diabetes mellitus |  |  |  |  |
| Present | 12 (40%) | 18 (60%) | 30 (100%) | $\chi^2 = 3.034$ |
| Absent | 15 (22.8%) | 51 (77.2%) | 66 (100%) | p = 0.081 |
| Medication received on admission |  |  |  |  |
| Yes | 20 (26.7%) | 55 (73.3%) | 75 (100%) | $\chi^2 = 0.360$ |
| No | 7 (33.3%) | 14 (66.7%) | 21 (100%) | p=0.548 |
| Total | 27 (28.1%) | 69 (71.9%) | 96 (100%) |  |
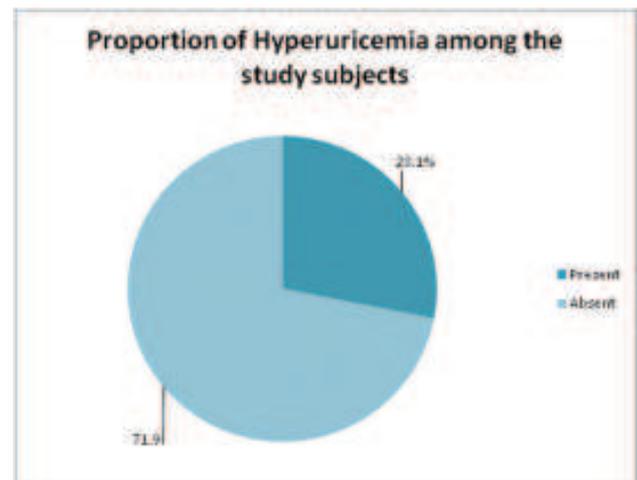


**Fig. 1:** Pie chart showing the prevalence of hyperuricaemia.

### Factors associated with hyperuricaemia

Half of the patients (50%) above the age of 80 years were found to be hyperuricaemic, while 25.6% of the patients in the age group of 60 - 79 years were hyperuricaemic. Hyperuricaemia was found to be more common in males than females, though the association was not statistically significant.

It was seen that 29.2% of the stroke patients who had a negative family history of stroke and 25% of the patients with a positive family history of stroke were hyperuricaemic. The uric acid levels were more elevated in those with a history of smoking.

Hyperuricaemia was common in hypertensive patients and, the association was found to be statistically significant. Diabetic patients had a higher level of uric acid, compared to their non-diabetic counterparts.

In Table II, it was seen that 33.3% of the patients who did not receive medication prior to the drawing of the blood samples, and 26.7% of those who had received medication before the drawing of the blood samples, were found to be hyperuricaemic.

The proportion of hyperuricaemia was more in patients having ischaemic stroke (40.5%), than the patients having haemorrhagic stroke (20.3%). The difference was found to be statistically significant (Tables I and II).

## Discussion

The role of elevated serum uric acid level has remained a controversial one. Contradictory theories exist, regarding the importance of hyperuricaemia, in stroke patients. The present study attempts to investigate the prevalence of hyperuricaemia in stroke patients, the factors associated with hyperuricaemia and, whether there is any difference between uric acid levels among haemorrhagic and ischaemic stroke.

The prevalence of hyperuricaemia in stroke patients, both haemorrhagic and ischaemic, in the present study was 28.1%. Mean serum uric acid level was 5.33 mg/dl. The finding in the present study is similar to a study done by Bansal et al[10], on 50 patients suffering from ischaemic stroke, where the prevalence of hyperuricaemia was found to be 30%. In another study done in Iran, the prevalence of hyperuricaemia was comparatively higher (47.3%)[6]. The variation in the results could be due to different study population, different racial factors or different methods of estimating uric acid level, or a combination of the above.

The association of hyperuricaemia with other established risk factors of stroke was also determined. No significant relationship was found between the age of the patient and hyperuricaemia (p-value = 0.892). Although 50% of the stroke patients above 80 years had stroke, no definite conclusion can be drawn since the age group (above 80 years) had only two patients. Compared to this finding, Mehrpour et al[6] found a negative relationship, and Conen et al[11] found a slightly positive association between serum uric acid levels and age of the patients. In the present study, no significant association was found between gender of the patient and prevalence of hyperuricaemia, although men had higher serum uric acid levels (p-value = 0.875). Freedman et al[12], found a significant relationship between age and uric acid levels in ischaemic stroke patients, with men showing significantly higher level of serum uric acid

levels than women. Hyperuricaemia was found in higher percentages of stroke patients who did not have a family history of a similar episode, although no significant association was found (p-value = 0.694). This was evaluated keeping in mind whether any genetic factors play a role in the occurrence of hyperuricaemia in stroke patients. To the best of our knowledge, no literature was found regarding this topic. Stroke patients who had a positive smoking history were found to have greater prevalence of hyperuricaemia than non-smokers. No significant association was found (p-value = 0.124). Smoking, as a risk factor for stroke, is well established with the risk being almost doubled in case of ischaemic stroke[13]. However, similar to our study, other studies also did not find any significant relationship between smoking and elevated uric acid level[6,14].

In our study, a positive, significant, association was found between hypertension and hyperuricaemia in stroke patients (p-value = 0.030). Hyperuricaemia has been found to be an independent risk factor for the occurrence of stroke in patients with isolated systolic hypertension[15,16]. Other studies have also found increased uric acid levels in hypertensive patients who suffered from an attack of stroke. Thus, the association of hyperuricaemia with hypertension (which itself is a well known risk factor for stroke) favours the possibility of it being a potential independent risk factor. In our study, although the prevalence of hyperuricaemia was higher in diabetics than non-diabetics stroke patients, no significant association was found (p-value = 0.081). Similarly, Mehrpour et al[6] also found no significant association between hyperuricaemia and diabetes mellitus in stroke patients. However, contrary findings also exist. Giuseppe et al found hyperuricaemia as an important risk factor for occurrence of stroke in patients with type 2 diabetes mellitus[17]. Another study in Finland also found hyperuricaemia to be a strong predictor of stroke in middle-aged, non insulin dependent diabetes patients[18]. A variation in the above findings was seen in the study by Chammaro et al[19] where serum uric acid level was inversely related with fasting blood sugar in acute ischaemic stroke patients. No positive relationship was found between treatment received on admission and hyperuricaemia (p-value = 0.548). None of the drugs used for management of stroke significantly affected serum uric acid level. Although recombinant tissue plasminogen activator was given to 16.4% of the ischaemic stroke patients admitted in an Iranian hospital, no significant difference in serum uric acid level was found between those who received the treatment, and those who did not[5].

In our study, a significant association was found between ischaemic stroke and hyperuricaemia (p-value = 0.032). Our finding is similar to the findings in other studies. However, majority of the studies have focused on the

association of serum uric acid level with ischaemic stroke. Kim *et al*[10] found hyperuricaemia to modestly increase the risk of both ischaemic and haemorrhagic stroke. Mehrpour *et al*[6] did not find any significant difference in serum uric acid level between the two types of stroke. In another study, hyperuricaemia was found to have a slightly higher risk for ischaemic than haemorrhagic stroke[20]. However, further studies on the role of hyperuricaemia, in haemorrhagic stroke alone, are required before reaching further conclusions.

There are few limitations to our study. Firstly, the sample size is small. Secondly, as it is a cross-sectional study, we could not find the incidence of stroke. Subsequently, the role of uric acid as a risk factor, or as a passive marker, of stroke cannot be differentiated. Thus, there is a need to conduct multicentric cohort studies, with larger sample sizes for further validating the results obtained in our study.

## Conclusion

Prevalence of hyperuricaemia was significantly higher among ischaemic stroke patients, than haemorrhagic stroke. The independent significant association of hyperuricaemia with ischaemic stroke could be an indicator of serum uric acid level being an independent risk factor for ischaemic stroke. However, longitudinal cohort studies are required to differentiate between the role of uric acid as a risk factor, or a passive marker of stroke.

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"*No human thing is of serious importance.*"

– PLATO.

# REVIEW ARTICLE

# Small Fibre Neuropathy – Revisited Nerve Disorders

*A Pandey\*, PK Maheshwari\*\*, M Chaturvedi\*\*\**

## Abstract

*Small fibre neuropathy (SFN) is a major cause of neuropathic pain in the hands and feet, especially in the elderly. Pain is often described as severe burning, pricking or stabbing type. Systemic causes include Diabetes mellitus, dysthyroidism, vitamin B12 deficiency, sarcoidosis, HIV, antiretroviral therapy, Celiac disease, Sjögren syndrome, Fabry's disease, Hereditary Sensory Autonomic Neuropathy, and many others. The affected nerve fibres are the small-diameter myelinated A-delta fibres and unmyelinated C fibres, which mediate pain, thermal sensation, and autonomic function. Large fibres are not affected. Evaluation includes, a thorough history and examination. Laboratory studies should include CBC, BUN, electrolytes, LFT, thyroid function studies, fasting glucose, B12, ESR, HIV1 and 2, ANA. EMG and NCV. QSART may show a lack of sweating in response to acetylcholine. Skin biopsy is a useful tool. Treatment options include anticonvulsants, antidepressants, anti-inflammatory medications, immunosuppressants, lidocaine, opioids, topical agents, nerve blocks, nerve stimulators, physical therapy, acupuncture, relaxation, and meditation techniques.*

*Key words: Small fibre neuropathy, dysaesthesias, nerve conduction studies, electromyography, QSART, skin biopsy*

## Introduction

Neuropathic pain is one of the most common reasons for a patient seeking medical attention. When such patients are investigated using electromyography, nerve conduction studies, quantitative sensory testing, and extensive serologic evaluation, many will not have any identifiable abnormalities. Such patients may be misdiagnosed as neuromas, fasciitis, fibromyalgia[1], restless leg syndrome[2], or a psychosomatic disorder. In such patients, the question of a small fibre neuropathy should be entertained.

Peripheral neuropathies involve different types of nerve fibres. The large, myelinated A-alpha and A-beta fibres convey proprioception and touch. Small fibres include myelinated A-delta fibres and unmyelinated C fibres, which innervate skin (somatic fibres) and autonomic fibres. Together, they mediate pain, thermal sensation, and autonomic function. Most peripheral neuropathies affect nerve fibres of all sizes. Such neuropathies are referred to as mixed fibre neuropathies (MFN). Many patients present with large fibre neuropathies characterised by numbness, tingling, weakness, loss of deep tendon reflexes, and abnormal electrophysiologic studies. Patients with SFN typically present with neuropathic pain, numbness and paraesthesias. Pain tends to be a prominent symptom, and often has a burning quality. In most cases of SFN, sensory symptoms are symmetrical, length dependent, and persistent. However, a number of SFN patients will manifest atypical features, such as non-length-dependent symptoms[3], and multifocal numbness.

## Clinical presentation

The majority of patients with peripheral neuropathy exhibit evidence of large fibre involvement. Large fibres mediate motor function, position, and vibration sensation. Patients with large fibre neuropathies often present with numbness, tingling, and weakness. Neurological examination reveals distal weakness, diminished deep tendon reflexes, reduced vibratory and position senses. Diagnosis is confirmed by electrophysiologic abnormalities, such as slowed motor and sensory conduction velocities, reduced motor and sensory action potential amplitudes, and denervation on the electromyography.

In many patients, the impairment is purely or predominantly in small nerve fibres. SFN usually presents with painful sensations and numbness in feet. It affects the small, unmyelinated nerve fibres that convey pain and temperature sensations from receptors in the skin, and mediate autonomic functions[4,5]. Symptoms usually follow a length-dependent pattern, or stocking-glove distribution, but in some conditions like Sjögren syndrome, Celiac disease, and paraneoplastic syndrome can present a form of SFN that is non-length-dependent[3]. Symptoms can occur anywhere in the body, including the feet, arms, legs, trunk, face, or even the mouth[6,7]. Symptoms typically start in the toes, and then slowly ascend to the legs, hands and arms. Sensory symptoms are prominent. Pain is of C-fibre type; burning, superficial, often described as stabbing or aching pins and needles or cramping in calves and feet. Pain may be associated with paraesthesiae like tingling or numbness,

*\*Associate Professor, \*\*Professor and Head of Department, \*\*\*Professor, Department of Medicine,*
*Sarojini Naidu Medical College and Hospital, Agra, Uttar Pradesh.*
*Corresponding Author: Dr Anjana Pandey, Associate Professor, P.G. Department of Medicine, SNMC, Agra, UP,*
*E-mail: docapg@gmal.com.*

that typically affects the limbs in a distal-to proximal pattern. Symptoms are usually worse at night, and often affect sleep. Some patients may not have pain, but have a feeling of tightness in the feet.

Examination usually reveals diminished pain and temperature perception, allodynia (perception of non-painful stimuli as being painful), and hyperalgesia (perception of painful stimuli as being more painful than expected) in the affected area. Vibration sensation can be mildly reduced in the toes. Motor strength, tendon reflexes, and proprioception, however, are largely preserved.

Autonomic fibre involvement may lead to dry eyes, dry mouth, orthostatic dizziness, constipation, bladder incontinence, sexual dysfunction, and sweating disturbances[8]. Examination may show orthostatic hypotension and skin changes. The skin over the affected area may appear atrophic, dry, shiny, discolored, or mildly oedematous as a result of sudomotor and vasomotor abnormalities.

## Aetiology

1. Diabetes mellitus and glucose intolerance are the most common cause of SFN[9] Research suggests that even prediabetes is a risk factor for small fiber neuropathy, and impaired glucose tolerance neuropathy may represent the earliest stage of diabetic neuropathy[10,11]. The overall prevalence of neuropathy is 66% in type 1 and 59% in type 2 diabetes. Neuropathy can be broadly divided into symmetric and asymmetric types, although a great deal of overlap exists between these categories. Symmetric neuropathies may present as small-fibre involvement (e.g., dysaesthesias in the feet) or autonomic dysfunction (e.g., impotence), but often both occur together; examination usually reveals additional evidence of large-fibre involvement, and of an underlying generalised neuropathy. By far, the most common form of diabetic neuropathy is a length-dependent diabetic sensorimotor polyneuropathy (DSPN). DSPN is a mixed neuropathy with small- and large-fibre sensory, autonomic, and motor nerve involvement in various combinations, although sensory and autonomic symptoms are more prominent than motor ones.

   Several recent studies have found a high prevalence of impaired glucose tolerance in patients with sensory peripheral neuropathy, with a rate of up to 42%, in cases initially thought to be idiopathic, compared with 14% in the general population[11,12]. Impaired glucose tolerance more often had SFN whereas those with diabetes more often had polyneuropathy involving both small and large fibres[12].

2. Hereditary causes: Include Fabry's disease[13,14], Tangier's disease, Hereditary sensory autonomic neuropathy, and Hereditary amyloidosis.

3. Dysthyroidism: One prospective study showed that patients with hypothyroidism have symptoms and findings compatible with SFN[15].

4. Leprosy[16]: In leprosy patients, usually there is extensive sensory loss followed by impaired motor function because of invasion of muscular nerves where they lie closest to the skin (the ulnar nerve is the most vulnerable). There is loss of sweating in areas of sensory loss, but the autonomic nervous system is otherwise unaffected. In distinction to other polyneuropathies, tendon reflexes are usually preserved in leprosy, despite widespread sensory loss.

5. Nutritional deficiency

6. Idiopathic[17]

7. HIV infection[18] and antiretroviral therapy for HIV. HIV distal sensory symmetric polyneuropathy presents as a painful, predominantly SFN. This syndrome cannot be distinguished reliably from neuropathy caused by antiretroviral drugs (nucleoside reverse transcriptase inhibitors); its onset with respect to exposure to the offending drugs may be the only clue. Most patients present with painful burning, tingling, and numbness in the feet. Symptoms are typically bilateral, gradual in onset, and worse at night. Both large myelinated and small unmyelinated nerve fibres are affected. A toxic neuropathy follows exposure to specific dideoxynucleosides (d4T, ddI, and especially ddC), particularly in advanced HIV disease. Sural nerve biopsy shows severe axonal destruction, most prominently in unmyelinated fibres, along with mitochondrial abnormalities.

8. Neurotoxic drug exposure[19]

9. Inflammatory bowel disease[20,21], and Celiac disease[21].

10. Sjögren syndrome[22].

11. Immune mediated diseases-lupus[23,24], scleroderma[25], mixed connective tissue disease[26].

12. Sarcoid[27]

13. Vasculitis[28,29]

## Laboratory tests

1. Complete blood cell count

2. Fasting glucose, glycosylated haemoglobin, glucose tolerance test

3. Erythrocyte sedimentation rate

4. Thyroid profile

5. Antinuclear antibody, dsDNA antibodies, Sm antibodies to evaluate lupus erythematosus, scleroderma, mixed connective disease

6. Angiotensin-converting enzyme (ACE) level, chest radiogram and biopsy to evaluate sarcoidosis

7. Vitamin B12, B6 and B1 level

8. Gliadin and transglutaminase antibodies, duodenal biopsy to evaluate celiac disease

9. Serological tests for HIV-1

10. Small and large bowel biopsy to evaluate inflammatory bowel disease

11. Biopsy of skin, nerve and muscle, ANCA, HCV, RF to evaluate vasculitis

12. Skin scrapings and nerve biopsy for leprosy

13. Alpha-galactosidase A activity to evaluate Fabry's disease

14. Biopsy, free light chains and transthyretin mutation for amyloidosis

15. Urine and blood toxin level.

## Nerve conduction studies and electromyography

Routine nerve conduction studies and electromyography assess the function of large nerve fibers only, and are thus normal in SFN.

Biopsy of sural nerve (cutaneous nerve): an invasive procedure, can confirm SFN. However, it has a disadvantage that it leaves a permanent area of sensory deficit and quantification of small nerve fibres in a sural nerve biopsy is not routinely available.

Some patients with SFN also have a concomitant autonomic neuropathy, and therefore autonomic nervous system testing can provide objective confirmation in some cases. Autonomic function can be assessed by measuring heart rate and blood pressure responses, and assessment of sudomotor function by Quantitative sudomotor axon reflex testing (QSART), and Quantitative sensory testing (QST).

## Quantitative sudomotor axon reflex testing

QSART is an autonomic study that measures sweat output in response to acetylcholine, which reflects the function of post-ganglionic sympathetic unmyelinated sudomotor nerve fibres. Electrodes are placed on the arms and legs to record the volume of sweat produced by acetylcholine iontophoresis. A mild electrical stimulation on the skin allows acetylcholine to stimulate the sweat glands. The output is compared with normative values. The test is very sensitive to drugs that can affect sweating such as antihistamines and antidepressants, and such drugs must be discontinued 48 hours before the study.

One prospective study showed that 67(72.8%) of 92 patients with painful feet had abnormal results on QSART, i.e., low sweat output[30].

## Quantitative sensory testing

Research suggests that when quantitative sensory testing (warm and cold thermal perception threshold, heat and cold pain, and pressure sense) was tested at the at forearm and distal leg, patients noticed a greater loss of sensory fibre function in the distal leg compared to the forearm. Cold and warm perception thresholds, and heat pain perception, were significantly elevated in neuropathy patients in the distal leg, compared with control subjects, but no significant difference for any of the quantitative sensory measures was seen between the groups in the forearm. This indicates that the small-fibre function was more impaired in the distal leg than the forearm in these groups of patients[31].

## Skin biopsy

Skin biopsy is a minimally invasive procedure. Specimens are taken from the distal leg, distal thigh, and proximal thigh, using a 3 mm disposable punch, under sterile technique. It is sufficient to obtain biopsies from only a single limb. Having proximal and distal biopsy sites helps determine whether a neuropathy is length-dependent or non-length dependant. The procedure takes only 10 to 15 minutes. The biopsy technique to obtain the skin samples is easily learned and can be performed quickly. The wound leaves minimal scarring. Skin specimens are routinely obtained by punch biopsy at the foot, calf, or thigh, under local anaesthesia. In length-dependent neuropathies, such as toxic neuropathies, the epidermal nerve fibre density is more severely reduced distally at the foot or calf, but in sensory neuronopathy or multifocal neuropathy, the nerve fibre density may be preferentially reduced proximally at the thigh[3].

Biopsy specimens are immunostained using an antibody against protein gene product (PGP) 9.5. Protein gene product (PGP) 9.5 is a ubiquitin hydrolase that can serve as a pan-axonal and pan-neuroendocrine marker[32]. This allows visualisation and quantification of unmyelinated C-fibres and possibly myelinated A-delta fibres, in the epidermis. The diagnosis of SFN can be established if the

intraepidermal nerve fibre density (IENFD) is lower than normal. Nerve fibre density may be normal in the early stage of SFN, but in this setting skin biopsy often shows abnormal morphologic changes (axonal swelling, abnormal nerve fibre orientation, very fine calibre axons, excessive or complex nerve fibre branching) in the small fibres, especially large swelling, and repeat biopsy in 6 to 12 months may be considered. The diagnostic efficiency of skin biopsy is about 88%. For diagnosing SFN, it is more sensitive than quantitative sensory testing, and more sensitive and less invasive, than sural nerve biopsy.

A retrospective study using skin biopsy with IENFD detected abnormalities in 88.1% of 67 patients who had symptoms suggestive of sensory neuropathy but normal nerve conduction studies compared with 10% of healthy controls[33]. Skin biopsy with IENFD was abnormal in 81% of patients clinically diagnosed with mixed large and small fibre neuropathy. SFN is most easily and reliably diagnosed by skin biopsy, demonstrating a reduction in the epidermal nerve fibre density[34]. The sensitivity of skin biopsy in diagnosing SFN was 88.4%, in comparison to 54% for clinical examination, and 49% for QST, with a specificity of 95 to 97%[35,36].

## Diagnostic criteria for SFN[35]

### Inclusion criteria

At least two abnormal results from the following:

(i) Clinical signs of small fibre impairment-pinprick and thermal sensory loss and/or allodynia and/or hyperalgesia, and the distribution is consistent with peripheral neuropathy (length or non-length dependent neuropathy);

(ii) QST-abnormal warm and/or cooling threshold at the foot;

(iii) Skin biopsy-reduced IENFD at the distal leg.

### Exclusion criteria

(i) Any sign of large fibre impairment-light touch and/or vibratory and/or proprioceptive sensory loss and/or absent deep tendon reflexes;

(ii) Any sign of motor fibre impairment-muscle wasting and/or weakness;

(iii) Any abnormality on sensorimotor nerve conduction study.

## Treatment

Treatment of SFN should be to target the underlying cause and alleviate the neuropathic pain. Cause-specific treatment

is a key in preventing SFN, or slowing its progression.

### Optimised glycaemic control

The DCCT and the UKPDS, have shown that good control can prevent or delay the onset of diabetic peripheral neuropathy. As glucose dysmetabolism is most often associated with SFN, tight glycaemic control and lifestyle modification with diet control, weight control, and regular exercise are very important in these patients.

Since impaired glucose tolerance neuropathy may represent the earliest stage of diabetic neuropathy, the neuropathy at this stage may be reversible with lifestyle intervention and improvement of impaired glucose tolerance.

A prospective 3-year study, suggest that lifestyle intervention significantly improved impaired glucose tolerance, reduced the body mass index, and lowered total serum cholesterol levels[36]. Changes in these metabolic variables were accompanied by significant improvement of neuropathy as evidenced by significantly increased intraepidermal nerve fibre.

### Aldose reductase inhibitors (ARI)

The aldose reductase inhibitors prevent conversion of glucose to sorbitol in presence of hyperglycaemia. Therefore, it prevents the polyol pathway cascade. ARIs are alreastat, tolerestat, epalrestat, sorbinil, and zopolrestat. The results of more than 20 clinical trials conducted in past 15 - 20 years on the effect of a variety of aldose reductase inhibitors generally have been disappointing[37].

### Gamma linolenic acid (GLA)

Gamma linolenic acid (GLA) is an important constituent of neuronal membrane phospholipids as well as a substrate for prostaglandin E and prostacyclin formation, which may be important for preservation of nerve blood flow. In diabetic patients, conversion of linolenic acid to GLA and subsequent metabolism is impaired, possibly contributing to the pathogenesis of diabetic neuropathy. A recent trial used GLA for one year and this resulted in significant improvements in both clinical measures as well as electrophysiologic test results[38].

Other measures like advanced glycation end products (AGE), N-acetyl-L-carnitine, gangliosides, and human intravenous immunoglobulin are still under trial.

### Treatment of other causes

Identify the cause and treat it to prevent and slow the progression of SFN. Treatment of sarcoidosis, autoimmune disease, and coeliac disease improved the symptoms of

SFN resulting from these conditions.

## Treatment modalities for neuropathic pain

**Topical:** local anaesthetic, capsaicin

**Local:** transcutaneous electrical nerve stimulation (TENS), accupuncture, thermal (heat, cold), vibration, massage

**Blocks:** somatic (nerve, plexus, root), sympathetic (ganglia, or regional)

**Central** spinal cord stimulation (SCS), deep brain stimulation (DBS)

**Spinal drugs:** epidural or intrathecal (local anaesthetics, opioids)

**Systemic drugs:** TCAs, anticonvulsants, opioids, NSAIDs, SSRIs

**Surgery:** decompression

**Psychological:** behavioural measures, pain management programs

**Rehabilitation**

## Drugs for neuropathic pain

**Anticonvulsants:** Commonly used anticonvulsants are carbamazepine, clonazepam, phenytoin, and gabapentin. The drugs are more effective in lancinating pain. When initiating carbamazepine, it is advisable to begin with a low dose of 100 mg and then increase gradually, until there is significant relief of symptoms or side-effects are encountered. Complete blood counts and liver functions should be checked at the onset, and then on a monthly basis, over the first three months because leukopenia is a common complication.

Gabapentin should be started at a dose of 300 mg/day and gradually increased until symptomatic relief occurs or until a maximum dose of 2,400 mg per day is reached. side-effects: sedation, dizziness, peripheral oedema, weight gain.

Pregabalin (150 - 600 mg per day) , similar to gabapentin but less sedating.

Topiramate: 25 - 400 mg per day

## Antidepressants

Tricyclic anti-depressants (TCA) are the most commonly used drugs for pain relief in peripheral neuropathy. Double blind trials of the tricyclic anti-depressants have demonstrated significant benefits in reducing pain that is burning, aching, sharp, throbbing, or stinging. The use of amitriptyline is contraindicated in patients with heart block, recent myocardial infarction, heart failure, urinary tract

obstruction, orthostatic hypotension, and narrow angle glaucoma. It should be started at low doses of 10 to 20 mg every night and increased gradually until pain control is achieved or dose limiting side-effects occur.

Achievement of pain relief may require as much as 150 mg of the drug per day for 3 to 6 weeks. Withdrawal from amitriptyline must be gradual so as to prevent rebound insomnia. These drugs act on the central nervous system, preventing the reuptake of norepinephrine and serotonin at synapses involved in pain inhibition.

Amitriptyline 20 - 150 mg per day

Nortriptyline 20 - 150 mg per day

Desipramine 20 - 200 mg per day

Duloxetine 60 - 120 mg per day

Side-effects: Sedation, weight gain, anticholinergic effects, sexual dysfunction, arrhythmia (side-effects most prominent with amitriptyline).

## Topical anaesthetics

5% lidocaine patch is preferred if the painful area is small. Use the patch to cover the painful area, 12 hours on and 12 hours off. If it does not provide relief within 1 week, it should be discontinued.

Side effects: local oedema, burning, erythema. 0.075% capsaicin patch three or four times a day, causes burning.

## Opioids

Tramadol 100 - 400 mg per day. It can be started at 50 mg, two to four times a day, as needed.

Side-effects: sedation, dizziness, seizure, nausea, constipation

Nonsteroidal anti-inflammatory drugs and selective serotonin reuptake inhibitors are typically less effective than the other drugs, mentioned.

## TENS

The patient controls a pocket-size device that sends electrical signals to leads placed on affected areas.

Alternative therapies for small fibre neuropathy, such as meditation, yoga, and accupuncture, have yet to be studied.

## Treatment for nerve regeneration

The agents used for nerve regeneration are known as neurotrophic factors. A neurotrophic factor is defined as a naturally occurring protein that is released by target tissues of responsive neurons, binds to specific receptors and is retrogradely transported to the cell body where it regulates

gene expression through the actions of second messenger systems[39].

A large number of neurotrophic factors that exert effects on specific neuronal populations in the peripheral nervous system have been discovered. Some of these factors may prove useful for the treatment of diabetic peripheral neuropathy. All neurotrophic factors are still under trial, and none of them is available for clinical use. Among the most promising are members of the neurotrophin gene family nerve growth factor (NGF), brain derived neurotrophic factors, neurotrophin, insulin like growth factor, and glial cell derived neurotrophic factor.

## Prognosis

Most patients with SFN experience a slowly progressive course, with symptoms and signs spreading proximally over time.

In one study, only 13% of 124 patients with SFN showed evidence of large-fibre involvement over a 2-year period. Neuropathic pain worsened in 30% and resolved spontaneously in 11%. Most patients with SFN require chronic pain management. Again, treatment of the underlying cause is important and can improve the prognosis.

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*"I never had a policy;*
*I have just tried to do my best each and every day."*

– Abraham Lincoln.

# A Case Scenario Justifying the World AIDS Day 2016 Slogan 'Hands up for HIV Prevention'

*Matin Ahmad Khan\**

## Background

Latest data shows that the decrease in new HIV infections among adults has plateaued. The UNAIDS Prevention gap report depicts that, worldwide, an estimated 1.9 million adults have become infected with HIV every year for at least the past five years and that the number of new HIV infections has started to rise in some regions of the world. This report also says that HIV prevention efforts will have to be rejuvenated if the world is to stay on track to end the AIDS epidemic by 2030. In its warm-up to World AIDS Day 2016, the UNAIDS gave the 'Hands up for HIV Prevention' slogan for World AIDS Day 1st December, 2016 which explores different aspects of HIV prevention and how they address specific groups of people, such as adolescent girls and young women, key populations and people living with HIV.

The need of bracing up different issues relating to prevention has never been so pronounced-like use of Condoms, VMMC (Voluntary Medical Male Circumcision), EMTCT (Elimination of Mother-to-Child Transmission) or PPTCT (Prevention of Mother-to-Child Transmission), PrEP (Pre-Exposure Prophylaxis), Investment in HIV Prevention and Treatment as Prevention (TasP). We will try to examine a case scenario cutting across the different modalities of HIV prevention. Looking into this case scenario, we shall be able look into different modalities and the importance of HIV prevention, and thus justifying the slogan 'Hands up for HIV Prevention'.

## Case scenario in question

### *(This question was asked to me in a site for response)*

*'I am in a relationship with a positive man with undetectable viral load. I am negative. We refrain from oral and anal sex. Last night while self stimulating ( masturbating), some of his semen got on my hand and I had an open cut. I have not been able to sleep. I do have a question. Since we are in a monogamous relationship and he is undetectable? Should I get tested on same frequency. Going for testing freaks me out. I have not been tested since 3 months after his diagnosis which was three years ago'.*

## Introduction

The scenario (A non-HIV patient getting exposed to semen of a HIV positive man with an undetectable viral load – VL on the hand having an open cut) is an interesting, educative and unique case scenario as it involves almost all issues related to HIV prevention, i.e., scanty information – with holding his/her name and gender possibly due to stigma/ discrimination issues forwarded by the questioner, and issues involving responses to various situations in sero-discordant couples (magnetic couples), exposure in an unique non-occupational yet non-sexual mode, counselling and testing issues, initiating nPEP (Non-occupational Post-Exposure Prophylaxis) and PrEP (Pre-Exposure Prophylaxis), TasP (Treatment as Prevention) and HTPN 052 Study. The importance of answering this kind of scenarios lies in the fact that it would help many – including the questioner itself.

It is a case of providing inadequate information (about his/ her gender, the HIV-infected partner being on ART or not, size and depth of cut in his/her hand, which part of the hand – palm or dorsum, time elapsed since injury and has asked question about his/her going for testing of HIV at the frequency specified as per country Guidelines.

With whatever little information we have from this person's history, it is to be advised to him/her that though probability of transmission is extremely low, but due to paucity of information provided and just to be very sure, about non-transmission of the virus, notwithstanding the improbability of spread, he/she should go for testing as per the country guidelines.

Considering all the issues involved, it is suggested that HIV-antibody tests are to be done for the questioner as per the country's testing guidelines. This will enable the questioner not only to gain psychological peace of mind but also by knowing the status – whether negative or positive, to help him/her to lead healthy life. Though we expect the result to be negative, considering low risk, but, it is to be remembered that decreased risk is not no risk. Effective cART that drives the viral load to undetectable levels significantly decreases any chance of HIV transmission;

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*\*Consultant and HIV Medicine Specialist and Associate Professor, Dept of Biochemistry Patliputra Medical College, Dhanbad, Jharkhand - 825 006.*

however, it does not eliminate the risk completely, so one should always adopt 'safest sexual practices'. That's the critical point in a discordant scenario.

**Strategies based on action by uninfected individual to prevent infection are:**

Education/behaviour change, condoms, male circumcision, microbicides, PrEP (Pre-exposure prophylaxis), vaccines and possibly 'PEP (Post-exposure prophylaxis).

**Strategies to block transmission based on action by infected individual to reduce infectiousness/prevent virus release are:**

Prevention of mother-to-child transmission, treatment of positive partner in discordant couples, treatment as prevention (TasP) – TasP for all, TasP for higher VL, TasP for higher CD4, and more rapid clinical linkage to ART.

Out of the above mentioned, there could be various options in this scenario for prevention of further transmission (TasP, PrEP, nPEP – Non-occupational post-exposure prophylaxis). We presume, the positive partner is on ART, as that person is undetectable, so his (positive partner) taking ART, will be acting as treatment as prevention (TasP) in this scenario.

If this questioner decides to take ART for his/her benefit, to reduce the chances of transmission, subject to fulfilling certain conditions, then this will be called PrEP (pre exposure prophylaxis).

Of course in both the set ups (PrEP, nPEP), the questioner has to go for 'Tests at base-line and subsequent times, more so when the questioner decides to start ART as PrEP, because the moment he/she becomes positive after initiating PrEP, then he/she has to stop two drug regimen used as PrEP and further initiate ART as per the guidelines for HIV-infected persons.

This is a question involving many issues about the transmissibility of HIV infection under sero-discordant scenarios. The questioner's HIV-acquisition risks are extremely low (theoretically) and unwarranted and we will try to put his/her fears to rest by examining the issues involved in this case critically and coming up with scientifi explanations.

## Discussion

### Issues involved

We will critically examine the issues involved in this scenario as follows:

### The first issue

Basic science tells us that HIV/AIDS is not readily contracted and hence the word 'Acquired' we find in the acronym

'AIDS'! One has to put in extra labor to 'acquire' it.

In order for infection to occur, three things must happen:

- One must be exposed to semen, vaginal secretions, blood or breast milk, and
- The virus must get directly into one's bloodstream through some fresh cut, open sore, abrasion, etc., and
- Transmission must occur, directly from one person to the other, very quickly (the virus does not survive more than a few minutes outside the body).

No matter what the circumstances are, if one thinks about these three criteria for transmission, he/she should be able to determine whether he/she is at risk for HIV or not.



**Fig. 1:** Pre-exposure prophylaxis (PreP).

### The second issue

The questioner has not mentioned how old the cut was and where (palmer/dorsal side). It may be presumed, the cut was in the process of healing when the questioner asked this question, which means that even though the cut was still visible, there was probably no direct access to the blood stream. There would have to be open, active sores and then enough fluids for there even to be a remote chance.

As we know that chances of transmission in intact skin are zero but through mucous membranes are not zero. So, palmar side exposure has more risk than dorsal side, if it is not intact.

Blood contains the highest concentration of virus, followed by semen, followed by vaginal fluids. Breast milk can also contain a high concentration of the virus, but transmissibility depends on 'Who and How'?

*It is not enough to be in contact with an infected fluid to become infected. Instead, it will require prolonged and sustained contact.* Healthy, unbroken skin does not allow HIV to get into the body. HIV can only enter through an open cut or sore, or through contact with the mucous membranes in the anus and rectum, the genitals, the mouth, and the eyes. The vulnerability of the mucous membrane can be increased by inflammation, rough sex, the location and thickness of the mucous membrane and

STIs.

It's important to note that unless there is something unusual and undeniable as an open sore on the skin, there is no risk from semen on the skin. There is no risk from casual contact either. Also, mutual masturbation and frottage are not considered HIV transmission risks (a no risk activity – not a very low risk activity!) as long as there are no active bleeding cuts on one's person.

We can have look at the individual risks and calculate the probability.

**Risk of HIV transmission following an exposure from a known HIV-positive individual.**

| Type of exposure estimated risk of HIV transmission per exposure | (%) |
|---|---|
| Blood transfusion (one unit) | 90 - 100 |
| Receptive anal intercourse | 0.1 - 3.0 |
| Receptive vaginal intercourse | 0.1 - 0.2 |
| Insertive vaginal intercourse | 0.03 - 0.09 |
| Insertive anal intercourse | 0.06 |
| Receptive oral sex (fellatio) | 0 - 0.04 |
| Needlestick injury | 0.3 (95% CI 0.2 - 0.5) |
| Sharing injecting equipment | 0.67 |
| Mucous membrane exposure | 0.09 (95% CI 0.006 - 0.5) |

*(CI = confidence interval).*

### *The third issue*

The gender of the questioner has not been mentioned, and the questioner is in relationship with a positive C male, making them a 'magnetic couple' (sero-discordant) which certainly puts one at additional risk of transmission (how so ever small-if the questioner is a female and having 'vaginal sex' with HIV + male without protection).

**Here are certain facts about sexual transmission of HIV in discordant situations:**

- Stage of Illness of PLHIV – (HIV levels in blood are almost 10-times higher during the acute phase of infection, as many as 50% of new infections may occur through sex or sharing needles with someone who has just recently been infected).

- During inflammation, immune cells are brought to the area to fight infection. These immune cells include dendritic cells, which may transport HIV to the lymph nodes, and CD4+ cells (the cells that HIV infects).

- In an HIV-positive person, inflammation of the genital tract or rectum increases the viral load in the genital or anal fluids, even though it does not increase the blood viral load. This is because inflammation at a site usually brings more infected immune cells to the area. When these cells become active to fight infection, they unwittingly make more copies of HIV.

- If an HIV-negative person has inflammation, a larger number of immune cells will arrive at the site to fight off the cause of the inflammation. This means there is a greater chance that HIV, (if in this period he/she has sex with an infected partner) which will come into contact with these cells and infect them.

- Fidelity (faithfulness)/monogamous in relationship/ marriage also affects the transmission as one could never be able to figure out the person's HIV status, one is going to have sex with as HIV (and not AIDS! – there is difference between HIV and AIDS) is not visible and recognisable by one's physical appearance.

- These things may not apply in this case as it is a kind of
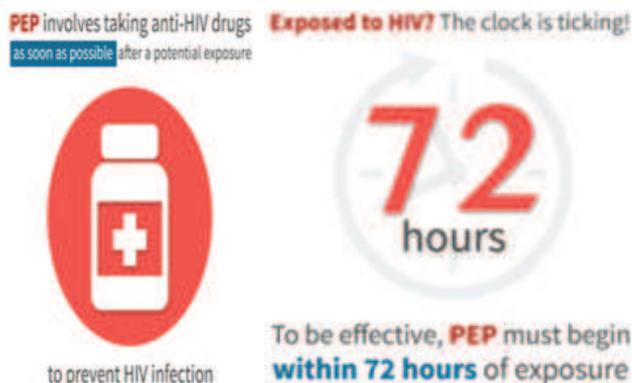


*Fig. 2: Basics of Post-Exposure Prophylaxis (PEP). (PEP – if used is during occupational exposure, if used during non-occupational exposure called nPEP).*



*Fig. 3: Basics of Post-Exposure Prophylaxis (PEP). Treatment as Prevention (TasP) or Treatment for Prevention (T4P).*

a non-sexual exposure in non-occupational setup in sero-discordant couple.

### The fourth issue

The probability of HIV transmission with nearly any type of exposure is directly correlated with viral load. Recently there have been studies that show that in sero-discordant couples (one being HIV-positive and the other negative) if the positive partner is on antiretroviral medications, has an undetectable viral load, and no other STI's (sexually transmitted infections) present, then the likelihood of HIV transmission is small. (The famous Swiss Federal Commission Report and HTPN 052 Trial) *HTPN 052 Trial – A Game Changer*, showed 96% reduction in HIV transmission between sero-discordant partners when HIV-infected partner began ART immediately. Even CDC, in its campaign for 'Act against AIDS Campaign' says that at VL 50,000 or more copies/ml, projected 26 new infections related to sexual intercourse. In contrast, at VL, 3,500 copies/ml, the projected number of new infections drops to 2.

Shedding of virus in the male genital tract is not uncommon, even in men with consistently undetectable plasma HIV RNA, and the timing and frequency of this shedding appear to be unpredictable. Furthermore, previous studies have shown no clear association between the presumed penetration of specific antiretroviral into the genital tract and the likelihood of detectable virus in semen.

Three studies, all with small number of subjects, have demonstrated that effective ART can reduce VL in serum, to undetectable level. However, reduction in HIV in serum does not always lead to reductions of HIV in genital secretions to undetectable levels.

The threshold level of genital-tract HIV necessary for transmission is not known. HIV transmission can be "very likely", between magnetic couples, even when the positively charged person is on effective combination antiretroviral therapy (cART-combined anti retroviral therapy) that has driven his HIV plasma to viral load undetectable levels, are overestimating the risk considerably.



**Fig. 4:** *Treatment as Prevention (TasP or T4P).*

### The fifth issue

While we are on the topic of "undetectable" viral loads (VL), here some basics to clear common misunderstandings about this term:

- 'Undetectable' means the HIV plasma viral load is below the lower limit of detection for the particular test assay that is being used. Early viral load tests could only detect viral load above 10,000 copies per ml. Newer tests were able to test down to 500 copies of the virus per milliliter of plasma. The even newer ultrasensitive viral load assays can test all the way down to 25 or 50 copies/ml.

- 'Undetectable does not mean cured! There is no cure for HIV/AIDS as of now, though this has become a chronic treatable and manageable disease just like high blood pressure (hypertension) and high blood sugar level (diabetes); you have to gulp' medicines for life.

- Undetectable does not mean noninfectious (that you cannot transmit the virus to others)! We have cases documenting HIV transmission from a man with an undetectable viral load to his HIV-negative wife via unprotected vaginal sex. There are also cases of mother-to-child transmission, despite the mother having an undetectable viral load, though undetectability certainly decreases the risk of transmission.

- Undetectable does not mean the virus cannot be detected anywhere in the body. Despite having an undetectable viral load in the blood (plasma), the virus would still be readily detectable in other tissues and body compartments, but the ability to transmit decreases considerably from a HIV patient who is undetectable.

- Effective combination antiretroviral therapy does not kill the virus! Rather it merely suppresses viral replication. Consequently, if someone with an undetectable viral load on combination antiretroviral therapy stops taking his drugs, the virus will soon start reproducing again and the viral load will skyrocket to levels near to where the viral load was before treatment was begun. That's why the compliance/adherence to ART regimen must be at least 95% if not total (100%).

### The sixth issue

Newer research has shown that antiretrovirals (ARVs) can be used by uninfected persons to prevent HIV before an exposure (called PrEP) and after a non occupational exposure (called 'nPEP'). In this set up (sero-discordant), one must be aware be aware about the availability of the options – I believe the positive partner is on ART, as he is undetectable, then this ART is acting as 'Treatment as prevention (TasP/T4P). If it is decided that the questioner

should take ART after this exposure for fixed number of days (as this exposure comes within the time period of 72 hours) then this becomes 'nPEP', that is *'Non Occupational Post-Exposure Prophylaxis*.

If this questioner decides to take ART for his/her benefit, to reduce the chances of transmission, subject to fulfilling certain conditions then this will be called ' *PrEP (Pre-Exposure Prophylaxis*). Of course in both the set ups (PrEP, nPEP), the questioner has to go for 'Testing' at base-line and subsequent times as per the protocol of the country, more so when the questioner decides to start ART as PrEP, because the moment he/she becomes positive after initiating PrEP, then he/she has to stop two drug regimen used as PrEP and further initiate ART as per the guidelines for HIV-infected persons.

### The seventh issue

*Treatment as prevention (TasP)* is the use of combination antiretroviral therapy (ART) in HIV-positive individuals to preserve their health and reduce the risk of transmitting the virus. Anti-retroviral therapy (ART) initiation has been shown to dramatically reduce HIV transmission in discordant heterosexual couples prompting revisions to treatment eligibility criteria. Responding to this, new guidelines recommend starting ART either at HIV diagnosis, or at CD4 counts of $\geq$ 500 cells/mm$^3$. In June 2013, the World Health Organisation updated its ARV guidelines to reflect treatment and prevention benefits – and suggests that countries offer ART to all HIV-positive individuals with CD4 cell counts of 500 or below, and to specific groups (pregnant or breastfeeding women, HIV-positive people in serodiscordant couples) regardless of CD4 cell count. In 2016, the WHO guidelines have been further revised to TREAT ALL peson infected with HIV irrespective of CD 4 count or clinical stage.

### The eight issue:

*Stigma and discrimination*

This issue has psycho-social dimensions. The questioner has not come up physically to seek help (has chosen to seek advice through mail) and has provided inadequate/ insufficient information possibly due fear of rejection/ ostracism/fear of discrimination or stigmatisation.

HIV stigma and related discrimination remain key barriers to dealing effectively with the HIV stigma and can deter people at risk, from being tested for HIV and deter HIV-positive people from accessing appropriate treatment and care. It also remains the key obstacle for HIV-positive people disclosing their status to friends and family, employers and work colleagues, health care providers, insurance companies, landlords, and sexual partners for fear of being treated less favourably, or being out-rightly rejected or abused often on moral grounds culminating into to rejection, which prevents them from seeking advice openly to as HIV/AIDS is often linked to behaviour resulting in people being labeled as immoral, more so when there are homosexual activities involved (as we presume in this case).

## Conclusions

HIV serodiscordant relationships are among the most vulnerable. It is not uncommon getting exposed to body fluids of an HIV-infected partner in a sero-discordant (magnetic couples) set ups. This is an interesting case scenario cutting across many issues about the transmissibility of HIV infection in such cases.

**Learning points/take home messages**

- No one is immune from HIV.
- HIV is still stigmatised and discriminated (though decreased) in societal terms.
- HIV sero-discordant relationships are among the most vulnerable to acquiring HIV by sexual transmission, and diagnosing it is key to HIV prevention.
- HIV negative partners in discordant couples are at high risk of infection.
- Viral load (VL) is important in transmission, but it changes over time.
- VL is proportional to acquisition of HIV through any route.
- Undetectable VL reduces the risk of transmission of HIV. But undetectablility does not mean no risk or no infection.
- Effective risk reduction options exist (PrEP, nPEP).
- Disclosure is important for HIV prevention.
- Treatment for the HIV-positive partner also is highly effective in reducing the risk of transmission to the HIV-negative partner ( called treatment as prevention – TasP or T4P).
- Combined, treatment and consistent condom use are likely to offer greater protection than either one alone.

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# Chronic Daily Headache with Recurrent Episodic Neurological Manifestations due to Idiopathic Hypertrophic Cranial Pachymeningitis - A Case Report with Review of Literature

*Geeta A Khwaja\*, Vijay Ghuge\*\*\*\*, Ashish Duggal\*\*\*\*, Abhilekh Srivastava\*\*\*\*, Vikram Bohra\*\*\*\*, Neera Chaudhury\*\*, Debashish Chowdhury\*\*, Sanjay Pandey\*\*\**

## Abstract

*Idiopathic hypertrophic pachymeningitis (IHPM) is a rare chronic fibrosing inflammatory disease of unknown aetiology that needs to be differentiated from other secondary causes of hypertrophic pachymeningitis. We report a case of chronic daily headache of 9 years duration, with a history of seizures, recurrent episodes of diplopia and deafness in the right ear due to cranial IHPM. Multiple non-contrast CT/MRI brain scans done in the past failed to detect the pachymeningitis and the patient was misdiagnosed and treated as a case of TBM with no relief. Diagnosis of pachymeningitis was established by contrast MRI brain. Infectious, inflammatory, infiltrative, neoplastic and other disease processes were excluded by relevant investigations and the patient showed a good clinical and radiological response to steroid therapy. This case report discusses the aetiopathogenesis, clinical profile, outcome and treatment of IHPM along with a brief review of literature.*

## Introduction

A variety of infectious, inflammatory, infiltrative, neoplastic and other disease processes can cause diffuse thickening of the dura mater. Idiopathic Hypertrophic Pachymeningitis (IHPM) is a rare, chronic fibrosing, inflammatory disease of unknown aetiology and remains a diagnosis of exclusion[1]. Chronic headache and cranial neuropathies are common neurological manifestations of cranial pachymeningitis. We report a case of chronic daily headache, with recurrent episodic neurological manifestations, due to cranial IHPM and good response to steroid therapy.

## Case history

A 47-year-old non-diabetic, non-hypertensive male reported to us in November 2013, with a 9 years history of chronic daily headache, accompanied by 2 - 3 episodes of seizures 8 years back. He also complained of recurrent, short lasting, 8 to 9 episodes of diplopia in the last 8 years, and deafness in the right ear since last 2 years. Around 8 years back, he developed acute onset, mild-to-moderately-severe daily headache which was holocranial and nonpulsatile in nature. It was not associated with vomiting, photophobia, phonophobia or any diurnal or postural variation. The headache was however, occasionally associated with nausea and disturbed his sleep. Over the last 9 years, the patient had been consuming around 3 to 4 tablets of 50 mg of diclofenac, per day for pain relief. On 2 or 3 occasions

however, in the course of illness he had a short febrile illness that abated with some treatment. There was however, no history of prolonged fever, loss of appetite, weight loss or any systemic disturbances.

About 7 years back, the patient had 2 or 3 episodes of generalised tonic-clonic seizures within a few days and was treated with phenytoin for a period of around one year. There was no seizure recurrence while on medication or after stopping the drug, over the last 7 years. There was no history of forgetfulness, cognitive impairment or any change in behaviour or personality.

In the last 8 years the patient also complained of recurrent short lasting episodes of diplopia, which would last for around one to one and a half months, and then resolve spontaneously without any specific treatment. Diplopia was more marked on right lateral gaze and not accompanied by any ptosis or obvious restriction of eye movements, visual impairment or worsening of the headache. He had suffered 8 - 9 such episodes at around intervals of one year, in the last 8 years, the last episode being around 2 months prior to admission, in September 2013.

About 5 years back (in November 2008), he was diagnosed as having Tubercular meningitis (TBM) following a NCCT Scan head (reported as normal) and CSF study (140 cells/mm^{3} - 40% polymorphs and 60% lymphocytes, protein - 311 mg/dl, sugar - 31 mg/dl) done in a private hospital. He received four drug antitubercular treatment (ATT-

*\*Director Professor, \*\*Professor, \*\*\*Associate Professor, \*\*\*\*Senior Resident, Department of Neurology, G.B. Pant Hospital, New Delhi - 110 002.*

*Corresponding Author: Dr Geeta A Khwaja, Room No. 501, Department of Neurology, Academic Block, 5th Floor, GIPMER, New Delhi - 110 002, E-mail: geetakhwaja@hotmail.com.*

rifampicin, isoniazid, pyrazinamide, ethambutol) for almost 3 years, w.e.f. November 2008 to December 2011, but without any relief in the headache or other symptoms which persisted despite therapy. A second CSF examination done in December 2011, revealed elevated protein only (no cells, protein - 122 mg/dl and sugar - 82 mg/dl).

About 1 year back (in January 2012), around one month after stopping ATT, he developed a sudden impairment of hearing in the right ear followed by complete deafness over the next few weeks. There was no history of any other cranial nerve palsy, motor weakness, loss of sensation in the limbs or any other significant illness in the past.

Over the course of the last 9 years, four non-contrast CT scans head done in November 2005, November 2008, December 2011 and September 2013 were reported as normal. An MRI brain without contrast, done in February 2012 was also reported as normal (Fig. 1A and B).

On clinical examination, at the time of presentation to our centre, the patient was fully conscious and alert. There were no signs of meningeal irritation. Higher mental functions were normal. On cranial nerve examination, visual acuity was normal in both the eyes. Fundus examination was normal. He had a mild partial right 6th and complete right 8th nerve palsy (sensorineural hearing loss). Other cranial nerves were intact. Motor system was normal with preserved deep tendon reflexes and flexor plantar response. Sensory and cerebellar examination were normal.

On laboratory evaluation, haemogram, blood counts, ESR (15 mm/hr) and routine blood chemistry including blood sugar, LFT, KFT were normal. Blood examination was negative for VDRL, HIV, hepatitis B surface antigen (HbsAg), antibodies to hepatitis C virus (anti HCV). Workup for vasculitic profile was negative for ANA, DsDNA, P-ANCA, C-ANCA, RF. ASO titre, CRP, serum calcium and ACE and TFT levels were in the normal range. ECG, X-ray chest, HRCT chest, and ultrasound abdomen were normal. VEP was normal in both eyes. BERA was normal on the left side but not recordable on the right side.

On CSF examination (November 2013), there were 3 cells/mm$^3$ (all lymphocytes, no malignant cells), protein was mildly elevated to 146 mg/dl while sugar was 68 mg/dl (corresponding blood sugar 102 mg/dl). CSF was negative for Gram, AFB and India ink stain. CSF culture (bacterial, fungal and AFB) and analysis for TB PCR and cryptococcal antigen was negative.

Non-contrast MRI brain done in November 2013 appeared normal. However, post-Gadolinium enhanced T1W-MRI images revealed diffuse, prominent, nodular dural thickening along the posterior falx and tentorium cerebelli (hypointense on T2 W images) suggestive of cranial pachymeningitis (Fig. 1C, D, E and F). Diffuse calvarial thickening was also noted in the bilateral fronto-parietal regions. MRI vemography was normal.
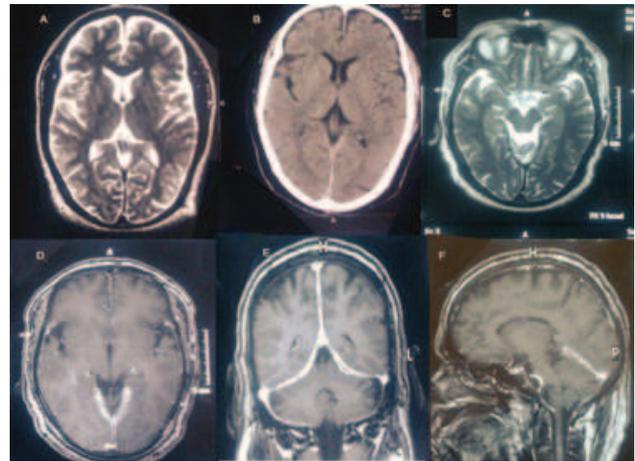


*Figs. 1:* Pre-treatment MRI: (A) Normal T2-Weighted axial MRI images 8 years after disease onset, (B) Normal NCCT head 9 years after disease onset, (C) T2 axial MRI images at the time of initial presentation showing hypointense signal in the tentorium, corresponding T1-weighted post-gadolinium images (D, E, F) show nodular thickening of tentorium cerebelli and posterior falx suggestive of cranial pachymeningitis.

In view of a history of chronic daily headache of 9 years duration, accompanied by episodic neurological manifestations with cranial nerve palsies, only mildly elevated proteins on CSF, and an MRI picture suggestive of pachymeningitis, a diagnosis of cranial pachymeningitis was made. In view of a lack of response to ATT in the past and a negative workup for other secondary causes of pachymeningitis (inflammatory, infective, neoplastic and connective tissue disorders), a diagnosis of idiopathic hypertrophic cranial pachymeningitis (IHCPM) was entertained. A dural biopsy was planned but refused by the patient.

Diclofenac was slowly tapered-off and stopped over a period of one week. Gabapentin (300 mg twice a day) and Amitriptyline (25 mg at bedtime) were started, but did not provide any significant relief in headache. Subsequently, the patient was treated with IV Methyl-prednisolone (1 gm/day) for a period of 5 days and then shifted to oral steroids in a dose of 60 mg/day for a period of one month. The headache subsided within 3 days of starting steroids but the patient developed an acute onset left-sided partial hearing loss around 3 weeks after initiating steroids and while still on 60 mg of prednisolone per day. The steroids were subsequently, gradually tapered to a dose of 20 mg/day over a period of the next 3 months. On the last follow-up in March 2014, the headache had not recurred over the three and a half months follow-up period but there was no improvement in the right or left-sided hearing loss. A follow-

up plain and contrast CT head (March 2014) was normal. Post-contrast MRI brain (March 2014) revealed only minimal dural enhancement (Fig. 2 A, B and C).
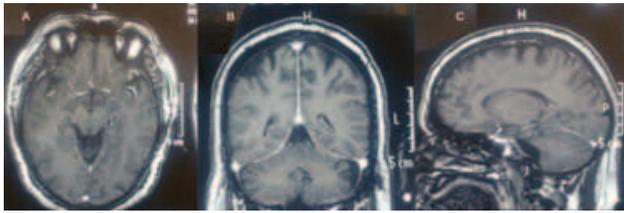


*Figs 2:* Follow-up contrast MRI brain after treatment with steroids – axial (A), coronal (B) and sagittal (C) cuts show minimal dural enhancement.

## Discussion

Idiopathic hypertrophic pachymeningitis (IHPM) is a rare, autoimmune, chronic fibrosing inflammatory disease of unknown aetiology[1]. IHPM is characterised by marked diffuse thickening of the duramater with progressive neurological deficits due to compression of anatomic structures by the thickened inflamed meninges. It may involve the cerebral or spinal dura mater, or both locations simultaneously[2-4]. Charcot and Joffrey (1869) were the first to describe its medullary version while Naffziger and Stern (1949) were the first to report the cranial variant of IHPM[5-7]. Till 2007, there were only 65 documented cases of IHPM in the English literature[8]. There are only 13 reported cases of IHPM in the Indian literature till date[8-13].

IHPM is seen in all ages and both sexes. Chronic progressive or recurrent symptoms are common and depend upon the location of inflammatory lesions and compression of adjacent nervous structures[14]. Spinal IHPM is characterised by inflammatory hypertrophy of spinal cord dura mater. It is more common in the cervical and thoracic region but can affect the entire spine. Radiculopathies, limb paresis and sphincter disturbances are common manifestations. There is only one case report of spinal IHPM in Indian literature[11]. In cranial IHPM, the inflammatory process is located most frequently at the skull base. Chronic headache and cranial neuropathy are common manifestations, as was the case with our patient. Cranial nerve palsies are caused by compression of the exit zone of nerve roots by the hypertrophic basal pachymeningitis[15]. The eighth cranial nerve is most frequently involved, as was observed in our patient, followed by the optic, ocular and lower cranial nerves[16,17]. Lesions of cranial nerves VI to XII and cerebellar ataxia are seen with inflammatory lesions located in the cerebellar tentorium, base of the posterior cranial fossa, clivus and foramen magnum[2,3,6,18,19]. Painful ophthalmoplegia and visual impairment may be seen with dural inflammation in the base of anterior cranial fossa, cavernous sinus, optic canal, and superior orbital fissure area.

The Tolosa-Hunt syndrome (THS) is sometimes considered to be a local, peri-cavernous form of IHPM[14,20].

The pattern of dural involvement in cranial IHPM can be divided into two subgroups with good clinical and imaging correlation[14]. Cranial nerve II, III, IV, V, and VI neuropathy correlates with involvement of cavernous sinus, optic canal and superior orbital fissure. Cranial nerve V, VII, VIII, IX, and X palsies correlate with thickening of falco-tentorial dura. Our patient had history of episodic right 6th and persistent 8th cranial nerve palsies due to involvement of the falco-tentorial dura. Cases with IHPM can be subdivided into two groups: those without inflammatory signs and those with inflammatory signs including fever, increased erythrocyte sedimentation rate, leukocytosis, and increased CRP[1]. The inflammatory group has a worse prognosis[6,14]. Our patient did not have any evidence of inflammatory signs and responded well to therapy.

Clinically, headache (88% cases), cranial nerve palsy (62% cases) and ataxia (32% cases) are frequent[16]. Headache, nausea and vomiting are common at disease onset[14]. Headache may be the only symptom for many years in a small percentage of patients[22]. Visual deterioration/ blindness and retro-orbital pain may occur due to optic neuropathy[7,9,23]. Hearing impairment due to VIII cranial nerve involvement is frequent, as was the case with our patient[17]. Cranial nerves V, VII, IX, X, and XII are involved with equal frequency[17]. Papilloedema may develop in up to 26% cases[16]. Cerebellar ataxia is due to thickened and adherent pachymeninges of the posterior fossa[17]. Less common manifestations of IHPM include: diabetes insipidus with hypophysitis, dural venous sinus occlusion or thrombosis, internal carotid artery occlusion, intracranial haemorrhage and obstructive hydrocephalus[9,14,24-28]. Symptoms and signs documented in 65 cases of IHPM include: headaches - 91%, lesions of cranial nerves - 77%, cerebellar ataxia - 11%, epileptic seizures - 8%, diabetes insipidus - 5%, hypopituitarism - 2% and psychotic manifestations in 2% cases[2,3,10,16,18,29]. Besides headache and cranial nerve palsies, 2 or 3 episodes of generalised tonic-clonic seizures within one year of disease onset were reported by our patient also.

The cause of IHCP remains speculative, from infectious agent, mucopolysaccharidosis and intrathecal toxin to fibrosclerotic disease[17]. Recently, the autoimmune background of diseases has been underlined. The co-occurrence of IHPM with other autoimmune diseases like rheumatoid arthritis, Wegener's granulomatosis, lupus erythematosis, temporal arteritis, other connective tissue diseases and Hashimoto's disease supports the hypothesis. Genetic factors may also predispose to the development of an immune mediated disorder. The use of

immunosuppressive medicines in the treatment of IHPM supports the theory of immunological aetiopathogenesis of the disease[2,3,18,20,30,31]. Some evidence suggests that IHPM may be related to the newer disease entity called IgG4 related sclerosing disease[32,33].

A variety of infectious, inflammatory, infiltrative, neoplastic and other disease processes can cause diffuse thickening of the dura mater (Table I). IHPM is a diagnosis of exclusion. Other causes of pachymeningitis, i.e., neurosarcoidosis, neurosyphyllis, tuberculosis, rheumatoid pachymeningitis, Wegener's granulomatosis, en plaque meningioma and dural carcinomatosis need to be excluded by relevant investigations, as was done in our case also[34].

Diagnosis of IHPM is based upon, neuroimaging (CT Scan head/MRI brain), CSF examination, and a dural biopsy to rule-out the secondary causes of pachymeningitis. On non-contrast CT Scan head, the inflamed thickened dura may or may not appear hyperdense. Strong, intense and marked enhancement of the tentorium, falx, and prepontine region (> 2 mm) may be seen after contrast administration. In our case, non-contrast CT scans of head, done on several occasions, after the onset of the headache were found to be normal. On MRI brain, the inflamed thickened dura may appear iso-intense or hypo-intense on T1W images and hypo-intense with or without a hyperintense border on T2W images in IHPM[7,17]. After Gadolinium administration, the lesions undergo a significant post-contrast intensification, as was observed in our case also. Thickening is better appreciated in the coronal and sagittal images. Two forms of lesions may be seen – planar and tumour like. Linear thickening of the falx and tentorium is the most common finding. Focal nodular, pseudotumoral thickening of dura mater, due to inflammatory infiltrations may simulate a dural mass[35]. Localised cerebral or cerebellar white mater changes may be caused by venous congestion due to poor sinus drainage[17]. Other associated findings include mastoid effusion, sinus abnormality, cavernous sinus involvement, white motter oedema, and hydrocephalus. Imaging in IHCP can remain negative for up to 2 years after disease onset[17].

CSF examination may reveal lymphocytic pleocytosis in one fourth and elevated protein in two-third of the cases with IHPM. CSF may be normal in one-fourth of the patients[16]. In our case also the CSF proteins were found to be elevated. An elevated ESR may be found in up to 88.8% cases but was within the normal range in our case[16]. A dural biopsy is usually required to confirm the diagnosis and to exclude other causes of IHPM. Biopsy from an accessible site with CT or MRI documented enhancing and thickened dura mater is more likely to yield a positive aetiological diagnosis[36]. Pathological findings consist of a thickened fibrous dura mater. Chronic inflammatory cell infiltrate consisting of lymphocytes, plasma cells, histiocytes, and less frequently granulocytes is the usual finding on histopathology[2,3,14,16,18]. Granulomatous findings have been noted in about 10% of the reported cases[17,23,37]. A dural biopsy could not be performed in our patient, but the significant clinical and radiological improvement soon after starting steroids, supported and confirmed the diagnosis of IHCPM.

Immunosuppressive therapy is the treatment of choice in IHPM. Steroids are the mainstay of therapy. In an analysis of 65 cases with IHPM, 83% (54/65) of the cases were treated with steroids[1]. Steroid therapy is effective in alleviating symptoms and arresting progression of IHCP, as was the case with our patient[7,9]. Rarely patients may worsen while on steroids[9]. In our case, the headache subsided completely soon after starting steroids and did not recur over a 3 and a half month follow-up period, but a fresh left-sided 8th cranial palsy developed while the patient was still on a high daily dose of steroids. Up to 50% to 66% cases may fail to respond or become dependent on steroids[14]. In refractory cases or those with steroid related side-effects immunomodulators such as azathioprine, methotrexate and cyclophosphamide can be used[38]. Surgical excision is an option for patients with mass effect due to thickening of skull base dura, unresponsive to steroid therapy[17]. Symptomatic hydrocephalus requires ventriculoperitoneal shunting. Decompression of the optic nerve may be considered in patients with rapidly deteriorating vision.

Complete recovery is rare in IHPM. Spontaneous resolution of both clinical symptoms and signs, and dural thickening has been reported[39]. The disease is often progressive, with remissions and relapses as was observed in our case[1]. Response to steroids, steroid dependency, and remitting and relapsing course have been documented[17,27,39]. Most patients experience recurrence after stopping treatment and require prolonged treatment[14]. Death is most often due to obscuration of large sinuses or compression of the hypothalamus and brain stem by inflammatory dural infiltrations[2,3,40]. Among the 33 patients with IHPM gathered from the literature by Parney et al, full remission without steroid dependence was seen in 26% cases, steroid dependent partial or complete remission in 15% cases, progressive course inspite of steroid therapy in 15% cases, and death regardless of treatment in 32% cases[16].

In conclusion, the diagnosis of IHPM must exclude the secondary causes of pachymeningitis, especially those in which immunosuppressive treatment is not effective or even contraindicated. A contrast CT scan head and MRI brain are essential to diagnose IHPM, as plain scans often appear normal and do not detect the underlying pachymeningitis, as happened in our case. In developing countries, TBM is a difficult diagnosis to exclude as the CSF picture can be cofounding. Polymerase chain reaction (PCR) of CSF for TB

may be helpful in such cases, but majority of the patients will receive ATT by default before an alternate diagnosis of IHPM is considered, as was the case with our patient. A high degree of suspicion is needed to diagnose IHPM, which being a treatable disorder, should not be missed.

## Table I: Causes of hypertrophic pachymeningitis (Sylaja *et al*, 2002).

**Inflammatory and Infective**

Tuberculous meningitis/Tuberculoma en plaque/ Sarcoidosis/Mycosis: Cryptococcus, Histoplasma, Coccidioides/Lyme disease/Syphilis/HTLV-1

**Neoplastic**

Carcinomatous meningitis/Lymphomatous meningitis/ Meningioma en plaque

**Collagen vascular disorders**

Rheumatoid arthritis/Wegener's granulomatosis/mixed connective tissue disease/Orbital pseudotumour/Tolosa-Hunt syndrome/multifocal fibrosclerosis

**Miscellaneous**

Spontaneous intracranial hypotension/chronic haemodialysis/Mucopolysaccharidosis/Chronic intrathecal drug administration

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*"Friends are those rare people who ask how we are,*
*and then actually wait to hear the answer."*

– Ed Cunningham.

# A Case of Splenic Abscess Caused by *Enterococcus faecalis* Infective Endocarditis

C Thakur*, V Sharma**, S Verma***, S Asotra****, V Kumar*

## Abstract

*Splenic abscess is an uncommon clinical condition, having a high mortality rate, up to 47%. The most common causative agents for splenic abscess are Staphylococci, Streptococci, E. coli, Klebsiella, Mycobacterium tuberculosis, Pseudomonas and Salmonella species. There are no standard treatment guidelines for splenic abscesses. Splenic abscesses have been widely treated by antibiotic therapy and splenectomy.*

*Key words: Splenic abscess, Endocarditis, Enterococcus, Splenectomy.*

## Introduction

Splenic abscess is a rare clinical condition. Its incidence in autopsy based studies is 0.14% - 0.7%[1,2]. Untreated splenic abscess is associated with high mortality. Various risk factors include infective endocarditis, diabetes mellitus, and congenital or acquired immunodeficiency[3-5]. It typically results due to seeding from pre-existing endocarditis or other infective focus. There are reports that 3 - 5% of all infective endocarditis cases are complicated by the development of splenic abscess[6]. Clinically, the patient has left upper abdominal pain, fever, nausea, vomiting and anorexia. Imaging by USG and CT of abdomen is suggestive, when correlated clinically. Splenectomy has been considered the gold standard of treatment but recently there has been shift towards spleen preserving techniques. It includes medical therapy targeting the causative organism with antimicrobials, though optimal duration of therapy is yet to be established. We are presenting a rare case of splenic abscess complicating infective endocarditis by *Enterococcus faecalis* in a diabetic patient.

## Case report

A 73-year-old male patient presented to medicine OPD with chief complaints of fever for 1 month. It was associated with chills and rigor. He also had malaise and dull pain in abdomen for the last 10 days.

On examination, he was febrile with a temperature of 101° F. He looked pale and lethargic. His blood pressure was 124/70 mmHg, and heart rate was 112 bpm. On abdominal examination, there was tenderness in the left upper quadrant. No splenomegaly or hepatomegaly was found. Cardiovascular system examination revealed pansystolic murmur in the mitral area radiating anteriorly.

Haematological investigations revealed a total leucocyte count of 18,000/mm3 with a neutrophil count of 84% and lymphocytes 15%. His Hb was 8.0 gm%. The fasting blood sugar was 157 mg% with HB1AC 6.7. HIV was non reactive. Renal and liver function tests were normal.

Ultrasonography (USG) of spleen showed heterogeneous area of size 71 x 70 mm with echogenic debris and shaggy inner wall suggestive of splenic abscess (Fig. 1). USG guided splenic aspirate of 12 ml was sent to the microbiology laboratory for culture and sensitivity testing. Gram staining of the pus sample revealed *gram positive cocci*. On culture small, grey, non-haemolytic colonies on blood agar and small magenta coloured colonies on MacConkey agar were obtained. Gram staining showed *Gram positive cocci*. It was catalase negative. It showed a positive growth in broth containing 6.5% NaCl.

On biochemical reactions, it fermented mannitol, and sorbitol with production of acid and did not ferment arabinose. Aesculin hydrolysis test and VP test were positive. On this basis the isolate was identified as *Enterococcus faecalis* which was sensitive to high level gentamicin, high level streptomycin, doxycycline, chloramphenicol, vancomycin and linezolid and resistant to penicillin. On CT of abdomen, spleen measured 12.1 cm in craniocaudal extent and showed a hypodense lesion of size 82 x 73 mm with craniocaudal extent of 89 mm. It showed a thin anterior, as well as posterior, wall with minimum thickness of 3 mm producing a local bulge on the anterior surface.

*Senior Resident, Department of Microbiology, Dr YSP Government Medical College, Nahan - 173 001, Himachal Pradesh, **Medical Officer, ***Associate Professor, Department of Microbiology, ****Associate Professor, Department of Cardiology, Indira Gandhi Medical College, Shimla, Himachal Pradesh.*
*Corresponding Author: Dr Chaman Thakur, Department of Microbiology, Dr YSP Government Medical College, Nahan-173001, HP, Tel: 08219822419, E-mail: chamanthakur17@gmail.com.*

Transoesophageal echocardiography (TEE) of the patient revealed mitral valve prolapse with moderate-to-severe mitral regurgitation with vegetations over the anterior mitral leaflet (Fig. 2). Three blood samples were drawn at half hourly intervals and were sent for culture. Two out of three samples showed growth of *Enterococcus faecalis* with same sensitivity pattern as above.

A final diagnosis of splenic abscess with infective endocarditis was made.

Initially, the patient was emperically put on piperacillin/tazobactum with metronidazole. The patient did not respond to the treatment and after report of splenic aspirate, he was put on intavenous linezolid. Due to comorbid conditions as old age, diabetes mellitus, anaemia and infective endocarditis he was managed conservatively with introvenous medications for four weeks and was then put on oral linezolid treatment. The patient died despite five weeks of medical therapy.



*Fig. 1: Ultrasonography of spleen showing heterogeneous area of size 71 x 70 mm with echogenic debris and shaggy inner wall suggestive of splenic abscess.*



*Fig. 2: Transoesophageal echocardiography of the patient showing mitral valve prolapse with moderate-to-severe mitral regurgitation with vegetations over the anterior mitral leaflet.*

## Discussion

Splenic abscess is an uncommon clinical condition with an incidence of 0.14% - 0.7% reported in autopsy series. There has been recent sport in case reports due to rising immunocompromised population and better diagnostic facilities[1,2]. The mortality rate is very high, upto 47%, and can reach upto 100% in untreated patients. Appropriate management can decrease the mortality to 14%[7].

Splenic abscess is a rare complication of infective endocarditis. Other causes include conditions leading to immunosuppresion such as diabetes mellitus, malignancies, immunosuppresive drugs and AIDS[3]. Our patient was also diagnosed as a case of diabetes mellitus during hospital stay. Splenic abscess can develop via hematogeneous route, leading to seeding of spleen by embolised vegetation, as in infective endocarditis or due to contiguous infection as in penetrating injury or laprotomy. In our case, the patient had infective endocarditis, so the route of inoculation was most probably hematogeneous.

The commonly reported bacterial pathogens in splenic abscess are *Staphylococci, Streptococci, E. coli, Klebsiella, and Pseudomonas.* Some workers have reported *Mycobacterium tuberculosis*[8] and *Salmonella typhi*[9] also, as a cause of splenic abscess[10].

The patient of splenic abscess presents clinically with fever, left upper abdominal pain, pleuritic chest pain and malaise. The signs are upper quadrant tenderness and splenomagaly with leucocytosis. But in most of the patients there are no localised findings[11]. Due to non-specific presentation the diagnosis of this rare clinical entity is difficult. A high level of clinical suspicion is required in patients with persistent or recurrent fever and sepsis, in spite of adequate antimicrobial treatment. The current imaging techniques are very helpful in making early diagnosis. Ultrasound of the abdomen demonstrates hypoechoic or anechoic lesion(s) in spleen, outlined in most cases by irregular walls. The gold standard for definitive diagnosis is the CT scan which gives a classical appearence of hypodense lesion with peripheral enhancement. It also delineates the exact location of an abscess which also helps in planning therapeutic strategies like percutaneous drainage.

The treatment modalities of splenic abscess are antibiotic therapy in conjunction with splenectomy or percutaneous image guided drainage. Splenectomy is still considered the gold standard of treatment. Though there are studies which favour spleen preserving techniques in the form of image guided drainage of abscess with antimicroial treatment. Laparoscopic approach offers an effective and safe alternative to laparotomy depending on the patient's condition and the individual preference and experience of the surgeon[12]. Ultrasound guided percutanous drainage is an option for patients in a poor general condition in which major surgery is contra-indicated[13]. Our patient's general condition was also not good so he was put on medical treatment, to be followed by surgical intervention later. But, unfortunately, due to comorbid conditions and poor general health, he succumbed. Recent case reports where splenic

abscess, due to *Enterococcus faecalis* was successfully treated surgically (splenectomy)[8] and another case caused by *Salmonella enterica* serotype Typhi was treated by medical management[9].

Surgical treatment should be accompanied by appropriate antibiotic treatment. There are studies which conclude that gram negative bacilli are the predominant cause of splenic abscess whereas some studies have shown Gram positive cocci as the main causative agents. Due to this wide variation, antimicrobial treatment should be based on individual culture and sensitivity reports.

In conclusion, it is to be emphasised that there is high mortality, of not only infective endocarditis, but also of splenic abscess in case of delayed diagnosis. Splenic abscess diagnosis becomes a challenge for the physicians due to non-specific presentation. A high index of suspicion along with abdominal USG and CT in case of abdominal pain and unexplained fever can lead to early diagnosis, treatment and a favourable outcome. The final treatment modality should take into consideration the experience of surgeons, whether the institution is well equipped, and the general condition of the patient.

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*"Who looks outside, dreams.*
*Who looks inside, awakens."*

– CARL GUSTAV JUNG.

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# Primary Sjögren's Syndrome Presenting as Recurrent Hypokalaemic Paralysis

*Prabhat Kumar\*, Nitin Sinha\*\*, RS Tonk\*\*\*, Anindya Ghosh\*\*\*\*, Vaibhav Tandon\*\*\*\**

## Abstract

*Primary Sjögren's Syndrome (SS) is a chronic autoimmune disease characterised by lymphocytic infiltration and destruction of exocrine glands. Renal involvement causing tubulointerstitial nephritis and distal renal renal tubular acidosis (RTA) is well known. However, severe hypokalaemia due to RTA in primary SS causing paralysis is rarely seen. We report the case of a lady who presented with sudden onset flaccid quadriplegia and was found to be having hypokalaemic paralysis. On further evaluation, a diagnosis of SS and distal RTA was made.*

*Key words: Distal RTA, Sjögren's syndrome, hypokalaemic paralysis.*

## Introduction

SS is divided into primary and secondary forms. The clinical hallmarks of SS are keratoconjunctivitis sicca and xerostomia or sicca complex. Extraglandular features in primary SS includes Raynaud's phenomenon, polyarthralgia, fatigue, neuropathy, interstitial lung disease and less frequently renal involvement. Distal RTA causing hypokalaemic paralysis in primary SS is rare with only 19 reported cases so far[1]. We present a case of hypokalaemic paralysis, due to primary SS, and review the literature.

## Case report

A 36-year-old lady presented to emergency department with chief complaints of weakness of all four limbs for last 1 day. Weakness was sudden in onset and involved all four limbs and maximal at the time of onset. There was no history of any convulsions, headache, altered sensorium, bowel and bladder involvement. Also there was no history of fever, loose stools, diuretic use, heavy exertion, high carbohydrate diet, photosensitivity, joint pain, morning stiffness or rash. However, she gave history of dryness of mouth and eyes for last 2 years which was gradually progressive. She was a known case of hypothyroidism for last 3 years and was on regular thyroxine replacement.

She was admitted twice for similar weakness in last one year and diagnosed to be having hypokalaemia, her weakness used to recover after potassium supplementation without any neurological deficit. Potassium levels during her previous episodes of weakness were low. However, the cause of hypokalaemia was never evaluated.

On examination, she was conscious and oriented. Her pulse rate and blood pressure was normal, respiratory rate was 18/minute and single breath count was 25/minute. CNS examination showed normal cranial nerves, hypotonia in all four limbs, power was 2/5 in both proximal and distal muscles of upper and lower limbs. Reflexes were sluggish and plantar response was mute, sensory system examination was essentially normal. Other systemic examination was normal and there were no swollen or tender joints.

Investigations were done which showed serum potassium levels of 2.0 meq/l with normal serum sodium levels, renal function tests, liver function tests and haemogram. Serum TSH level was 1.37 μIU/l. ECG showed U waves with ST changes in leads V5-6.

ABG was suggestive of metabolic acidosis with a pH of 7.28, bicarbonate - 13.4 mEq/l, pCO2 - 22.1 mmHg, sodium - 130 mEq/l, chloride - 107 mEq/l. Anion gap was 10 mEq/l. Urinary pH was 7. Serum ANA and rheumatoid factor were positive, anti-CCP and anti-dsDNA were negative. HbsAg and anti-HCV were negative and complement levels were normal. However, anti Ro and anti La levels were raised in high titres.

USG abdomen showed 2 renal calculi measuring 7 mm and 4.3 mm in left kidney. Nerve conduction study was normal. 2D echocardiograpthy showed mild hypokinesia of LAD territory with an EF of 50%. HRCT chest was normal.

Tear break up time was < 10 seconds in both eyes and Schirmer's test was also positive in both eyes. Lower lip biopsy showed 5 lobules of minor salivary gland, out of which 3 lobules showed periductal infiltrates (> 50) and 1

*\*Senior Resident, \*\*Assistant Professor, \*\*\*Professor, \*\*\*\*Post-graduate Resident, Department of Medicine, PGIMER and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 100 001.*
*Corresponding Author: Dr Prabhat Kumar, 33/22, First Floor, West Patel Nagar, New Delhi - 110 008, Tel: 09968123167, E-mail: drkumarprabhat@gmail.com.*

showed lymphoid aggregate formation with infiltration into the duct. All these findings were consistent with diagnosis of Primary Sjögren's syndrome.

She was given intravenous replacement of potassium chloride and her symptoms started improving gradually. Her power returned to normal within 2 days. She was maintained on oral potassium supplementation. Sodium bicarbonate tablets were given for distal RTA along with calcium tablets. During her hospital stay she developed bilateral parotitis for which NSAID's and oral antibiotics were given. She was discharged on oral potassium supplement and sodium bicarbonate tablets. She was followed up for next 6 months and she never developed any weakness.

## Discussion

SS is an autoimmune disorder characterised by diminished lacrimal and salivary gland function. The overall incidence of SS was estimated at approximately 7 per 100,000 in a 2014 meta-analysis of population-based studies[2]. The highest incidence rates were reported from Asia and Europe. SS can be primary or secondary to other connective tissue disease. Clinical features of SS can be divided into two broad categories, exocrine glandular features and extraglandular features. Extraglandular organs commonly involved are lung, musculoskeletal system, peripheral nervous system, kidney, heart and lymphoreticular system.

The reported prevalence of renal involvement ranges from 2 - 67 per cent, probably due to different definitions of renal involvement[3]. Chronic tubulointerstitial nephritis is the most common renal manifestation resulting in renal tubular acidosis (RTA), nephrogenic diabetes insipidus and hypokalaemia. Glomerular involvement is relatively less common than interstitial nephritis in SS.

Distal RTA (type 1) occurs in 25 per cent of patients of SS, due to defect in distal acidification of urine[4]. Distal RTA patients have normal anion gap metabolic acidosis with urinary pH > 5.5 and hypokalaemia. The mechanisms of distal RTA-induced hypokalaemia include decreased distal tubular Na delivery, secondary hyperaldosteronism, defective H-K ATPase, and bicarbonaturia[5]. Nephrocalcinosis is also common in Distal RTA. Increased calcium phosphate release from bone during bone buffering of retained acid and decreased absorption of calcium from the tubules favours stone formation. Also, high urinary pH causes precipitation of calcium phosphate and reduced citrate

excretion promotes aggregation of calcium crystals. Treatment of Distal RTA includes correction of acidosis by bicarbonate therapy and potassium salt supplementation in hypokalaemic patients. These manifestations are more common in secondary Sjogren's than primary.

Hypokalaemic paralysis is a relatively uncommon but potentially life-threatening clinical syndrome. Most cases are due to familial or primary hypokalaemic periodic paralysis; sporadic cases are associated with numerous other conditions including barium poisoning, hyperthyroidism, renal disorders, certain endocrinopathies and gastrointestinal potassium losses. The age of onset, race, family history, medications, and underlying disease states can help in identifying the cause of hypokalaemic paralysis. Initial therapy of the patient with hypokalaemic paralysis includes potassium replacement and search for underlying aetiology. Further management depends on the aetiology of hypokalaemia, severity of symptoms, and duration of disease. If recognised and treated appropriately, patients recover without any clinical sequellae[6].

Our patient had third episode of hypokalaemic paralysis and, on evaluation, a diagnosis of distal RTA secondary to Primary Sjogren Syndrome was made. After initiating treatment she has not suffered any further episode of hypokalaemic paralysis. Through this case we want to emphasize that all patients of hypokalaemic paralysis should be evaluated for any secondary cause by taking detailed history and appropriate investigations.

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*"Lose your dreams and you might lose your mind."*

– MICK JAGGER.

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# Acute Hepatitis E with Liver Cell Failure and Meningoencephalitis (an Extra-Hepatic Manifestation) in an Apparently Immunocompetent Young Patient

*Harpreet Singh\*, Jasminder Singh\*\*, Ekal Arora\*\*\*, Kiran B\*\*\*\*, Manoj Yadav\*\*\*\*, Neeraj Kumar\*\*\*\**

## Abstract

*Acute liver failure refers to the development of severe acute liver injury with encephalopathy and impaired synthetic function (INR of ≥ 1.5) in a patient without cirrhosis or pre-existing liver disease[1]. Hepatitis E is the most common viral cause of acute liver failure in endemic areas like Indian sub-continent and, in majority of the cases, it is of mild and self-limited variety in an otherwise healthy individual with mortality of 0.07 to 0.6% in non pregnant population. Here we report a case of a 28-year-old male with no known co-morbidities with severe Hepatitis E infection along with meningoencephalitis (extra hepatic manifestation) who had a fatal outcome.*

*Key words: Acute hepatic failure, hepatitis, encephalitis, complications of hepatitis, CSF proteins in hepatic encephalopathy, hepatitis E; liver cell failure; encephalopathy; meningoencephalitis.*

## Introduction

Hepatitis E virus (HEV) is a small non-enveloped single stranded RNA virus with primarily enteric mode of spread. HEV is one of the most common causes of acute viral hepatitis[2]. Although HEV infection has a global distribution, a large majority of its disease burden is in India, Asia, Central America and Africa where it has been estimated to cause over 20 million new infections annually. It generally causes a self-limited acute infection. Nevertheless, acute hepatic failure can develop in a small proportion of otherwise healthy patients (1 - 2%) and upto 20% in cases associated with pregnancy. Apart from hepatic involvement, there are many extra-hepatic manifestations of acute hepatitis E which should be diagnosed, as they can add to the overall mortality. Numerous extra-hepatic manifestations are reported in association with acute or chronic hepatitis E[3]. According to the available data, HEV infection appears to be strongly associated with acute pancreatitis, neurological disorders (with dominant peripheral nerve involvement, most commonly manifested as Guillain-Barré syndrome, followed by neuralgic amyotrophy), haematological diseases (haemolytic anaemia due to glucose phosphate dehydrogenase deficiency, and severe thrombocytopenia), glomerulonephritis, and mixed cryoglobulinaemia. Although causality is uncertain[4], the temporal association between HEV infection and the extra-hepatic manifestations, plus the exclusion of other possible aetiologies suggest that HEV infection may be causal.

## Case report

A 28-year-old young gentleman, non smoker, non alcoholic with no history of any prior co-morbidities presented with complaints of low grade fever, decreased appetite, and recurrent non-bilious vomiting episodes for seven days, yellowish discoloration of eyes for three days and altered sensorium for last one day. There was no history of any blood in vomitus, dark colored stool, loose stools, constipation, pain abdomen, pruritus, abnormal body movements, trauma to the head, any drug intake or any similar illness in the past.

On general physical examination, the patient was unconscious but afebrile with blood pressure 116/72 mm of Hg and heart rate of 78/min. Icterus was present, and there was no cyanosis, clubbing, pedal oedema or lymphadenopathy, and jugular venous pressure was normal. Nervous system examination revealed that pupils were bilaterally equal and sluggishly reactive to light, the motor response was only to painful stimuli with flexor response, generalised hyporeflexia, flexor response on plantar examination and neck rigidity was present. Abdominal examination revealed that liver was just palpable and liver dullness had a span of 12 cm with no evidence of any other organomegaly or free fluid. The clinical examination of cardiovascular and respiratory systems was unremarkable.

Initial laboratory investigations revealed haemoglobin of 13.3 gm%, with raised total leukocyte count of 12,000/mm$^3$ with 83% neutrophils and normal platelet count. Random blood sugar was low (45 mg/dl). Liver function tests are shown in Table I. Renal function tests were normal on admission but deteriorated on day 2 with blood urea of 110 mg/dl and creatinine of 2.4 mg/dl. Serum electrolytes, lipid profile were within normal range. HIV, HbsAg, anti-HCV antibody tests, malaria antigen and peripheral smear

*\*Senior Professor and Unit Head, \*\*Assistant Professor, \*\*\*Senior Resident, \*\*\*\*Resident, Department of Medicine, Pandit B. D. Sharma Post-Graduate Institute of Medical Sciences (PGIMS), Rohtak - 124 001, Haryana.*
*Corresponding Author: Dr Harpreet Singh, 882/23, DLF Colony, Rohtak - 124 001, Haryana, E-mail: drhgs1@rediffmail.com.*

for malaria parasites and dengue antigen and serology and serology for leptospira were negative. IgM for anti-HAV was negative but IgM for anti-HEV was positive. Ultrasound of abdomen showed liver measuring 12 cm in size with fatty infiltration, gall bladder was contracted, pancreas, spleen and bilateral kidneys were normal and there was no free fluid in the abdomen. Chest X-ray, ECG, and CT brain were normal. Blood and urine cultures were sterile and CSF examination was considered in view of history of fever, altered sensorium and neck rigidity and it showed lymphocytic predominance with raised protein suggestive of viral meningitis. CSF by PCR testing for enteroviruses, HSV, VZV, EBV and TB PCR were negative.

The patient was initially administered empirical antibiotics, and parenteral anti-malarials as well, along with mannitol, intravenous fluids, lactulose enema and bowel wash and other supportive measures. He deteriorated further on the 2nd day of admission as his haemoglobin fell from 13.3 gm/dl to 10.1 gm/dl as he started passing black coloured stools and his renal functions became deranged with oliguria. Fresh frozen plasma was given and injection terlipressin was started in view of melena. MRI brain, EEG renal replacement therapy and blood tests for atypical organisms were planned but before further investigations could be undertaken, he collapsed despite best efforts.

**Table I: Liver function tests.**

| Investigations | |
| --- | --- |
| Aspartate aminotransferase (AST) | 1,760 U/l (normal 20 - 40) |
| Alanine aminotransferase (ALT) | 3,870 U/l (normal 20 - 40) |
| Serum bilirubin | 14.3 mg/dl (normal 0.2 - 1.2) (conjugated 9.8 mg/dl) |
| Alkaline phosphatase: | 239 U/l (normal 38 - 85) |
| Serum protein | 6.4 gm/dl |
| A : G ratio | 1.1 |
| PT/INR | 29.8/2.5 |
| Serum ammonia | 220 µmol/l |

## Discussion

Acute liver failure is a clinical syndrome that results from sudden loss of hepatic parenchymal and metabolic functions and manifests as coagulopathy and encephalopathy. Based on the time interval between onset of jaundice and development of encephalopathy liver failure can be hyper acute: < 7 days, acute: 7 days to 4 weeks, and subacute: 4 weeks to 24 weeks. Hepatits E is an important cause of acute viral hepatitis in developing countries like India, with self-limited course but 0.5 to 4 per cent of HEV-infected patients can develop acute hepatic failure as well[5]. Acute hepatic failure with hepatitis E is more likely in those

who are pregnant, malnourished, of advanced age, have serious underlying medical disorders or have pre-existing liver disease, none of which were found in our case.

Virtually all previously healthy patients with hepatitis E infection recover completely with no clinical sequelae but patients who have presenting features such as ascites, peripheral oedema and hepatic encephalopathy, have a poor prognosis and mortality in such cases is exceedingly high (80% in patients with deep coma). In our case, the patient had hepatitis E related acute liver failure with hepatic encephalopathy, and had a increased risk for mortality.

It is rare but well known that there are certain extra-hepatic manifestations of hepatitis E which includes neurological, musculoskeletal, haematological manifestations, renal failure (30 - 70% cases), acute pancreatitis and other immune-mediated diseases. In the present case, the initial CSF findings were suggestive of viral meningitis (an extra-hepatic manifestation of hepatitis E virus), as CSF PCR testing for other viruses was negative. Neurological manifestations of HEV infection were first reported by Sood et al in 2000[6], and these include meningitis, meningoencephalitis, ataxia, pyramidal syndrome, pseudotumor cerebri, acute transverse myelitis, Guillian-Barré syndrome, neuralgic amyotrophy, cranial nerve diseases, Bell palsy – oculomotor palsy. There are very few published reports on increased CSF protein concentration in hepatic coma[7,8]. The standard current textbooks in internal medicine, neurology, and gastroenterology do not address this issue.

This case highlights that patients who develops extra-hepatic manifestations like meningo encephalitis along with acute hepatic failure and hepatic encephalopathy have increased mortality, even. If they do not have any underlying predisposing conditions as stated previously.

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# Haemophagocytic Syndrome due to Tuberculosis: A Rare Secondary Outcome of a Common Disease

*Deepti Sharma\*, Indrajeet Uradiya\*\*, Arpit Agarwal\*\*\**

## Abstract

*Haemophagocytic syndrome (HPS) also called haemophagocytic lymphohistiocytosis (HLH), is characterised by a dysregulated activation and proliferation of macrophages, leading to uncontrolled phagocytosis of platelets, erythrocytes, lymphocytes and their haematopoietic precursors throughout the reticuloendothelial system. Mycobacterium tuberculosis-associated HPS is a rare and underdiagnosed association. We report a 20-year-old male patient with unexplained prolonged high grade fever, pancytopenia, splenomegaly and liver dysfunction and was eventually diagnosed as HLH secondary to disseminated tuberculosis. Patient was treated with oral steroid first and then anti-tubercular therapy. Early detection of this rare syndrome prevented fatal outcome of a common disease.*

*Key words: Haemophagocytic lymphohistiocytosis (HLH), disseminated tuberculosis, high grade fever, pancytopenia.*

## Introduction

Haemophagocytic syndrome (HPS) also called haemophagocytic lymphohistiocytosis (HLH), is characterised by a dysregulated activation and proliferation of macrophages, leading to uncontrolled phagocytosis of platelets, erythrocytes, lymphocytes and their haematopoietic precursors throughout the reticuloendothelial system. Mycobacterium tuberculosis-associated HPS is a rare and under diagnosed association. We report a case which was eventually diagnosed as HLH secondary to disseminated tuberculosis.

## Case summary

A 20-year-old Rajasthani young mess-worker presented with fever for last 3 months. He consulted several local doctors and took medications, including ayurvedic medicines, without any benefit.

At the time of admission his – pulse rate was 100/min, blood pressure 100/70 mm of Hg , respiratory rate 20/min, Spo2 98%, and temperature 102 °F, with mild pallor. There was no icterus, cyanosis, clubbing, pedal oedema. Cardiovascular, respiratory and central nervous system examination was unremarkable with normal jugular venous pressure, heart sounds, breath sounds and normal high mental functions, sensory, motor system, cranial nerves examination. Signs of meningeal irritation were absent. Abdominal examination revealed moderate splenomegaly (5 cm from sub-costal margin) and mild hepatomegaly (just palpable).

As our area is endemic for malaria, we started empirical anti-malarial and antibiotic therapy.

His initial investigationa revealed pancytopenia (Hb - 8.4 gm%, TLC - 1,600/mm3, platalet count - 77,000/mm3), MCV - 94 fl, deranged liver functions with raised aspartate transaminase (AST) - 196 IU/l, alanine transaminase (ALT) - 66 IU/l, serum LDH - 4,967 IU/l and with normal serum bilirubin, total protein, A/G ratio, alkaline phosphatase, PT/INR, urine examination, ECG, X-ray chest PA view.

Work-up for the cause of fever, including malarial antibody, scrub typhus, dengue antigen/antibody, HIV, hepatitis B, C were negative. Ultrasonography revealed moderate splenomegaly (15 cms), mild hepatomegaly (13.4 cms) with normal texture and normal portal system.

After 2 days of admission, he developed epistaxis spontaneously (treated with 4 units RDP). Despite continuous empirical treatment patient's fever did not subside (temp 98 - 102 °F). After 7 days of indoor admission patient developed lymphadenopathy (two cervical and two inguinal lymph nodes ranging from 2.5 × 1 cm to 1.5 × 1 cm).

In view of the high grade fever, pancytopenia, lymphadenopathy, moderate splenomegaly there was a strong suspicion for lymphoreticular malignancy and haemophagocytic syndrome and bone marrow aspiration and FNAC from cervical lymph node were done. Bone marrow examination revealed, severe degree of haemophagocytosis; > 10 haemophagocytes/hpf (Fig.1). FNAC of cervical lymph node showed caseous necrosis

*\*Senior Professor, \*\*Post-Graduate Resident, Department of General Medicine, Government Medical College, Kota - 324 005, Rajasthan.*
*Corresponding Author: Dr Deepti Sharma, 1-T-1, Opp. Government Dispensary, Yigyan Nagar, Kota - 324 005, Tel: 09414182588, E-mail: drdeeptisharmakota@gmail.com.*
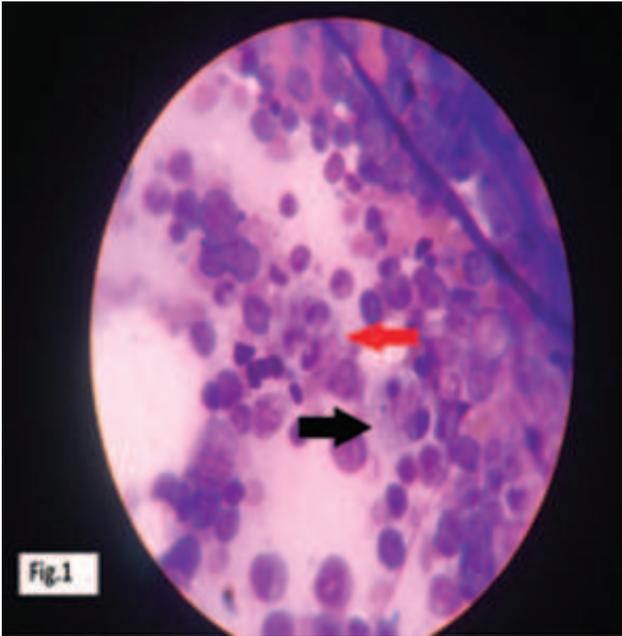
*Fig. 1:* Bone marrow showing haemophagocytes engulfed myeloid cells (red arrow) and erythroid cells (arrow).
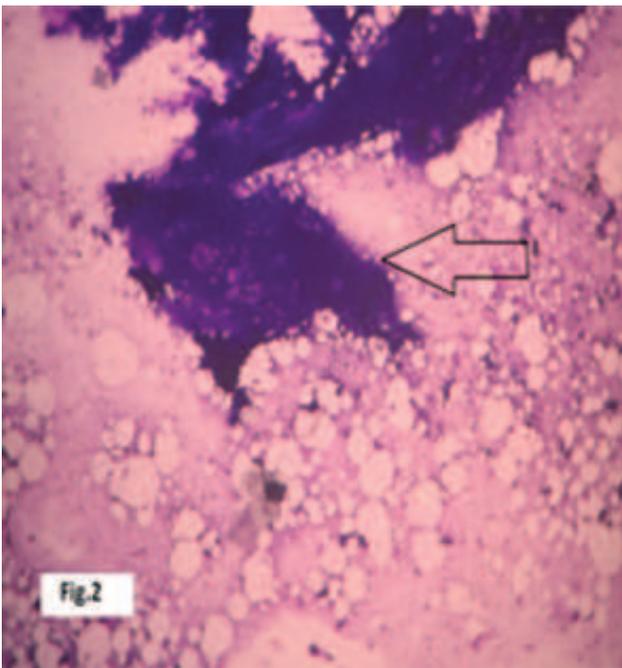


*Fig. 2:* FNAC showing caseous necrosis (arrow).

with absence of epithelioid cells (Fig. 2).

Now we started work up on the lines of haemophagocytic syndrome for which further investigations were done. ESR - 8 mm in 1st hour, borderline raised serum triglyceride level - 173 mg/dl or 1.95 mmol/l (< 150 mg/dl or 1.7 mmol/l), decreased fibrinogen level - 169.10 mg/dl (200 - 400

mg/dl), increased serum ferritin level - 783.4 ng/ml (30 - 400 ng/ml). All of these supportive findings along with previous reports and clinical examination confirmed the diagnosis of haemophagocytic syndrome.

Oral steroid therapy was started and patient responded dramatically. His fever subsided and TLC increased from 1,600/mm3 to 5,100/mm3, platelet counts increased from 77,000/mm3 to 1,90,000/mm3, aspartate transaminase (AST) decreased from 196 IU/l to 73 IU/l, alanine transaminase (ALT) decreased from 66 IU/l to 71 IU/l, serum LDH decreased from 4,967 IU/l to 1,192 IU/l.

To find the cause of haemophagocytic syndrome, we did rheumatoid factor, C-reactive protein, antinuclear antibody (ANA); all of these were negative. There was no history of joint pain or any hereditary disease. Repeat ultrasonography revealed hepato-splenomegaly, ascites along with abdominal lymphadenopathy. Ascitic fluid examination revealed tubercular ascites (total WBC 40 cells/mm3, all lymphocytes, protein 3.4 gm/dl, adenosine deaminase 45 U/l).

For confirming diagnosis of disseminated tuberculosis, we did excisional biopsy of inguinal lymph node and report showed presence of epithelioid cells (Fig. 3). All of these confirmed the diagnosis of disseminated tuberculosis. Finally, we concluded this to be a case of 'haemophagocytic syndrome secondary to disseminated tuberculosis'.

Anti-tubercular was started and patient was discharged on prednisolone 40 mg with advice to review after 7 days.
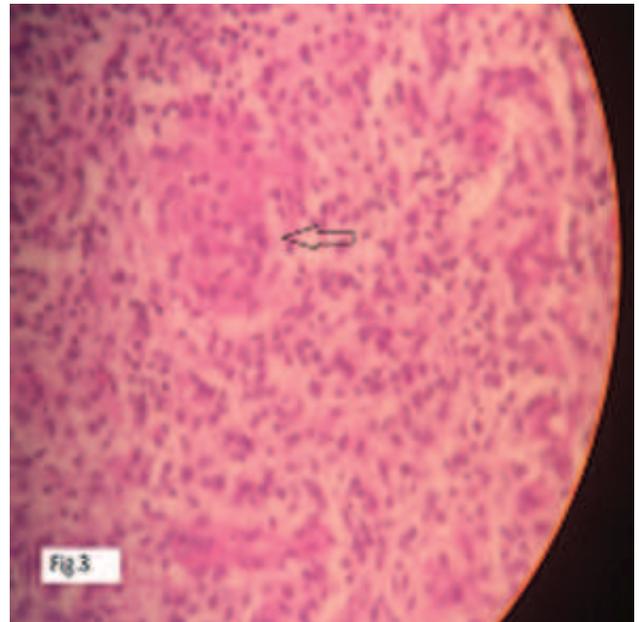


*Fig. 3:* Epithelioid cell granuloma (arrow).

## Discussion

HPS is a life-threatening immune dysregulatory syndrome caused by severe hypercytokinaemia due to a highly stimulated but ineffective immune process. Despite recent gain in knowledge, the pathogenesis of HLH is unclear. However, it is clear that the clinical manifestations of HLH are due to hyperactivation of CD8+ T lymphocytes and macrophages; proliferation, ectopic migration, and infiltration of these cells into various organs; hypercytokinaemia with persistently elevated levels of multiple proinflammatory cytokines, resulting in progressive organ dysfunction that may lead to death.

HLH can be primary (familial or genetic) and secondary. Secondary HLH occurs due to infection, mostly viruses. Where primary HLH is associated with perforin mutation, secondary HLH is associated with production of high levels of activating cytokines by host lymphocytes and monocytes.

There is no test available that can differentiate between primary and secondary HLH. Course of the disease in both groups is not so varied but secondary HLH has good outcome, if detected early[1].

Overall, 3% of all HPS cases are associated with TB[2] and Tseng *et al*[3] found that one-fourth of infection-associated HPS among Taiwanese were due to Mycobacterium tuberculosis.

The proposed scheme for diagnosis of HPS recommends presence of at least five out of following nine criteria[4]:-

a. Fever: peak temperature > 38.5 °C for 7 or more days.

b. Splenomegaly: spleen palpable > 3 cm below the left costal margin.

c. Cytopenia involving two or more cell lines: haemoglobin < 9.0 g/dl, or platelet < 1,00,000/µl, or absolute neutrophil count < 1,000/µl.

d. Hypertriglyceridaemia or hypofibrinogenaemia: fasting triglycerides > 2.0 mmol/l, or more than 3 standard deviations (SD) above the normal value for age, or fibrinogen < 1.5 g/l, or more than 3 SD below the normal value for age.

e. Haemophagocytosis: demonstrated in bone marrow, spleen, or lymph node; no evidence for malignancy.

f. Hepatitis.

g. Low or absent natural killer cell activity.

h. Serum ferritin level > 500 µg/l (although > 3,000 µg/l is a more realistic cut-off to exclude infections and

i. Soluble CD25 (sIL-2 receptor) > 2,400 U/ml (note age-related norms).

Our patient had seven out of these nine criteria. Our centre does not have the facility to test for natural killer cell activity and soluble CD25. HLH due to tuberculosis has high mortality rate (50%). Most of case reports reveal death of the patient[5].

In our experience, judicious case detection and timely management are important. Tuberculosis is very common worldwide, and particularly in India. A search for haemophagocytic syndrome should be done in any patient of tuberculosis who develops high grade fever along with pancytopenia. Our patient responded well to anti-TB treatment; prednisolone was administered only in initial period.

## Conclusion

Although associated with multiple conditions, TB should always be considered as cause of HPS in countries like India where TB is endemic. In spite of high mortality in HLH due to tuberculosis early detection and prompt management may save the life of the patient.

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*"Life is a kind of chess
with struggle, competition, good and evil events."*

– BENJAMIN FRANKLIN.

# Fatal Eosinophilic Cardiomyopathy and Dysphonia: A Case from a Teaching Hospital in Nepal

*RN Das\*, Rajesh Nepal\*\*, Madhav Bista\*\*\*, Madhav Bist\*\*\**

## Introduction

Idiopathic hypereosinophilic syndrome (IHS) is so rare that from 1971 to 1982 in USA only 50 cases were reported, with a prevalence of 1 - 2 per million people[1]. It manifests as persistently high peripheral eosinophilia, causing infiltration and dysfunction of GIT, heart, lungs, pleurae, bone marrow and brain[2]. IHS is diagnosed after excluding clonal proliferation of eosinophils in myeloproliferative disorders and reactive eosinophilic expansion in acute or chronic infective or inflammatory diseases[3]. Though protective, eosinophils can damage vital organs by releasing cytotoxic granules such as eosinophilic major basic protein (MBP), cationic protein (ECP) and neurotoxin (EDN) leading to end-organ damage[4]. In tropics, parasitic infestation remains the chief cause of eosinophilia. IHS rarely involves the heart with significant morbidity and mortality. There are two eponymous hypereosinophilic heart diseases namely, 'Davies disease' or endomyocardial fibrosis, prevalent in the tropics and 'Loeffler's syndrome' or eosinophilic endocarditis, without geographic predilection that have been recorded in medical literature[5]. Present case is of IHS, with dilated cardiomyopathy, which responded to steroids.

## Case presentation

A 40-year-old non-smoker, teetotaler, non-diabetic, normotensive patient from Eastern Nepal was admitted with fever (101 °F), dry cough, and progressive breathlessness for 7 months. Clinically, he had anaemia, tachycardia, apical pansystolic murmur and bibasal crackles. There was no pruritic or vasculitic skin rash, nor was any neurological deficit detected. Routine investigations revealed high peripheral eosinophilia (68%). Total WBC 17,250/cumm and absolute eosinophil counts were 11,212/cumm, respectively. Stool examination revealed no ova, parasite, or cysts. Midnight microfilaria microscopy was negative. Aspergillus precipitin, rheumatoid factor and pANCA tests were negative. Echocardiography showed dilated chambers, thickened IVS and low ejection fraction (35%) (Fig. 1). Chest radiology confirmed cardiomegaly, pulmonary infiltrates and pleural effusion. Routine blood sugar, electrolyte, renal, thyroid and liver function tests

were normal. He was diagnosed as a case of Idiopathic DCM. He was given treatment with oxygen, frusemide and ramipril, with little benefit. On second day of hospital admission, he developed fast atrial fibrillation, low BP, distended jugular veins, hoarse voice and an enlarged tender liver. He had no lymphadenopathy, sternal tenderness or hepatosplenomegaly. Laryngoscopy showed left vocal card paralysis (Fig. 2). Repeat tests showed WBC 16,400/cumm and absolute eosinophil counts 11,152/cumm, respectively. Table I. Bone marrow showed hypercellularity of megakaryocytic and myeloid series and predominance of eosinophilic precursors. No immature cells were found (Fig. 3). The serial investigations have been shown below (Table I).

CECT of thorax confirmed pleural effusion, bilateral alveolar septal thickening and no mediastinal mass. Pleural fluid aspirate showed a protein of 5.2 gm% and eosinophil count of 32%. He was initially treated for congestive heart failure, due to idiopathic dilated cardiomyopathy and was given conventional heart failure treatment. On second admission after a month, he had persistent eosinophilia (65%), atrial fibrillation and hoarse voice. Empirically, he was treated with mebendazole and DEC to treat unidentified parasites



**Fig. 1:** *Dilated cardiomyopathy with thickened IVS.*

*\*HOD, \*\*Assistant Professor, \*\*\*Lecturer, Department of Medicine, Nobel Teaching Hospital, Biratnagar, Nepal.*
*Corresponding Author: RN Das, HOD, Department of Medicine, Nobel Teaching Hospital, Biratnagar, Nepal,*
*Tel: 0779807368588, E-mail: das_drdeepak2004@yahoo.com.*

*Fig. 2: Laryngoscopy: Impaired movement of left vocal cord. No mass or ulcer seen.*
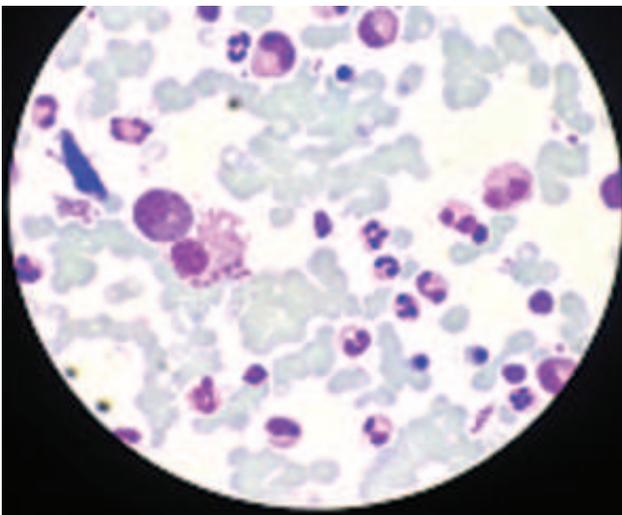


*Fig. 3: Bone marrow showed hypereosinophilia.*

producing persistent eosinophilia, but there was little improvement. After excluding all secondary causes of eosinophilia, a trial dose of corticosteroid (1 mg/kg) was given in the face of heart failure along with diuretics, digoxin, warfarin and ramipril. Eosinophilia reduced significantly from 68% to 65% then 28% and finally 8% within 3 weeks. Patient improved symptomatically but dysphonia persisted. The patient was discharged with relevant medications and advised for follow-up.

## Discussion

Eosinophilia, in a tropical country like Nepal, is a common finding in routine blood testing. Eosinophilia occurs in allergy, autoimmune, bacterial, fungal and parasitic infestation, as a protective immune reaction. Eosinophilia is seen, infrequently, in blood dyscrasias and malignancies. All common causes of peripheral eosinophilia were excluded in the present case (Table II).

In this case, patient had persistent eosinophilia which infiltrated: (i) bone marrow causing anaemia, (ii) pleura causing effusion, and (iii) lungs causing parenchymatous infiltrate, (iv) myocardium causing dilated cardiomyopathy with unusually thickened intraventricular septum. The enlarged left atrium impinged on the left recurrent laryngeal nerve causing Ortner's syndrome. There was no evidence of eosinophilic leukaemia or lymphoma, of physical examination and laboratory tests. In 1957, Bousser *et al*, reviewed 29 cases of hypereosinophilia with various types of clinical manifestations[6]. In 1961, Bentley reviewed a case of "hyper" eosinophilia, thought to be an eosinophilic leukaemia. He also laid down a set of criteria to differentiate 'blastic' form of leukaemia from 'mature' form of hypereosinophilic syndrome[7]. In 1968, Hardy and Anderson first reported IHS[8]. In 1971, Rickles *et al* reviewed 16 cases

## Table I: Serial investigations.

| Date | WBC (per cumm) | Eosinophils (%) | X-ray chest | ECHO | ECG | CECT chest | Laryngoscopy | Bone marrow exam |
|---|---|---|---|---|---|---|---|---|
| 12.12.14 | 16,400 | 11,152 (68) | Cardiomegaly | | ST | | | |
| 10.06.15 | 17,250 | 11,212 (65) | Cardiomegaly, pleural effusion | LA (4.8) (cms) IVS (11) (mm) | ST | | | |
| 12.07.15 | 13,440 | 7,526 (56) | Cardiomegaly pleural effusion, pulmonary infiltrate | LA (5.2) (cms) IVS (12) (mm) | AF | Septal thickening | Left Vocal cord palsy | Myeloid hypercellular marrow; high eosinophil count (> 60%) |
| 13.07.15 | 9,850 | 2,758 (28) | No pleural effusion; pulmonary infiltrate: reduced | LA (5.2) (cms) IVS (12) (mm) | AF | Septal thickening | | |
| 05.08.15 | 7,600 | 608 (8) | No pulmonary infiltrate | LA (5.2) (cms) IVS (12) (mm) | AF (slow) | | | |

*NB: ST: Sinus tachycardia, AF: Atrial fibrillation, IVS: Interventricular septum, LA: Left atrium.*

of hypereosinophilic syndrome, most of which came out to be doubtful eosinophilic leukaemia[9]. After that, many isolated cases with various manifestations were reported across the globe. In 1975, Michael J Chusid et al analysed 14 cases of IHS and published a review article proposing a set of criteria for the diagnosis of IHS, as opposed to eosinophilic leukaemia. He down three criteria, (i) peripheral eosinophilia more than 1,500 cells/cumm for at least six months, (ii) signs and symptoms of end-organ (heart, lungs, gastrointestinal tract, skin, bone-marrow, brain) damage with eosinophilic tissue infiltration/injury and (iii) exclusion of known secondary causes of eosinophilia[10].

**Table II: Common causes of eosinophilia in the tropics.**

| Causes | Pathogenic agents |
|---|---|
| Infection | 1. Helminth: nematodes, cystodes, trematodes (also scabies).<br>2. Bacteria:rebound post-sepsis, Lyme's disease.<br>3. Fungus: aspergillosis. |
| Neoplasia | 1. Lymphoma: Hodgkin or T-cell non-Hodgkin's (secretes IL-5).<br>2. AML-eosinophilic leukaemia.<br>3. CML-hypereosinophilic syndrome. |
| Autoimmune | 1. Atopy: food or drug allergy, asthma, eczema.<br>2. Vasculitis: esp., PAN, rheumatoid arthritis, Churg-Strauss syndrome.<br>3. Addison's disease. |

The present case of a middle-aged male fulfilled all these criteria and was designated as IHS, first to be reported from Nepal having dilated cardiomyopathy and heart failure. IHS can occur from 5 - 80 years, though middle-aged patients (45 to 55) predominate[11] and a literature review showed that more than 90% of cases occurred in males[12]. Though 78% cases of IHS were documented in Caucasians, no study has revealed the true prevalence in Asian population. Present case showed persistently raised eosinophilia over 7 months, with cough and dyspnoea, and was attributed to heart failure.

The eosinophilic pleuro-parenchymal infiltrates were demonstrated in chest imaging and pleural aspirate revealed 32% eosinophils with raised protein (5.2 gm%) reflecting eosinophilic infiltration. The pericardium and myocardium were also infiltrated as evidenced by effusion, chamber dilatation and thickened septum demonstrated by echocardiogram. Laryngoscope revealed immobile left vocal cord. The dramatic reduction of eosinophilia from 68% to 65% and then 56% to 28% and finally 8% along with

symptomatic improvement by steroid administration proved this case to be a rare example of IHS. His hoarse voice persisted. CT neck and thorax did not reveal any mass infiltrating the said nerve. His marrow also showed hypercellularity of megakaryocytes and myeloid series with predominance of eosinophilic precursors. Literature showed small proportion of patients with IHS had mutation of PDGFRA and FIP1L1 genes involving tyrosine kinase fusion protein dysfunction[13]. Though testing for this mutation is now a routine practice in Europe, as its presence indicates response to tyrosine kinase inhibitor 'imatinib', we had no facility to do this in Nepal.

## Conclusion

A Nepali farmer had persistent eosinophilia, infiltrating myocardium, pleurae, lung-parenchyma and marrow. Conventional heart failure treatment did not give him any relief. Though eosinophilia in Nepal is a common laboratory finding, but high index of suspicion for IHS must be kept in multi-organ dysfunction among patients with persistent eosinophilia. Subsequent hospital admissions confirmed IHS after marrow examination, dramatic response of steroid in reducing eosinophilia and relieving patient's symptoms. Mebendazole and DEC had no effect on eosinophilia. The patient was discharged with conventional treatment and advised follow-up. The awareness of IHS among attending physicians in the tropics will avoid misdiagnosis of multi-organ dysfunction, and early detection and institution of proper treatment will save patients.

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*"I have no fear of death.*
*My only fear is coming back reincarnated."*

– TUPAC.

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# Predominantly Ataxic Polyneuropathy Preceding a Recrudescence of Falciparum Malaria

**Geeta A Khwaja\*, Ashish Duggal\*\*, Vijay Ghuge\*\*, Vikram Bohra\*\*, Abhilekh Srivastava\*\*, Neera Chaudhury\*\*\***

## Abstract

*Cerebral malaria is one of the most common and potentially life-threatening complications of P. falciparum malaria. Plasmodium falciparum can not only cause cerebral malaria, but various other neurological complications, both as a presenting manifestation of acute infection and as part of the Post-Malaria Neurological Syndrome (PMNS). Neuropathy is a rare complication of falciparum malaria, and most commonly, has a Guillain-Barré syndrome (GBS) like presentation with predominant motor manifestations. Although sensory symptoms have been variably reported, predominantly sensory ataxic neuropathy is a rare presentation of malarial polyneuropathy. We report such a case of predominantly sensory ataxic neuropathy preceding the recrudescence of falciparum malaria who responded to adequate antimalarials and steroids.*

*Key words: Malaria, recrudescence, sensory ataxic neuropathy, Guillain-Barré syndrome.*

## Introduction

Malarial polyneuritis is a rare complication of malaria, reported mainly from the Indian subcontinent[1]. Although a Guillian-Barré like syndrome is the most common presentation, mononeuritic syndromes have also been reported[2]. Neuropathy can be seen, either in the acute phase of falciparum malaria, or as a part of the post-malaria neurological syndrome. We report a case of acute onset, predominantly sensory, ataxic polyneuropathy preceding a relapse of falciparum malaria.

## Case report

A 28-years-old male labourer presented to us with a 6 weeks history of sensory loss and mild weakness in the distal parts of both the lower and upper limbs. He first noticed paraesthesiae in the feet and hands, along with an impairment of pain and temperature sensation, which gradually progressed to the mid-thigh and mid-arm region over the next few days. He also complained of a plaster cast sensation in the legs, cotton wool feel of the ground, difficulty in negotiating slippers, slippage of footwear without awareness and a tendency to sway on either side while walking, despite no significant leg weakness. He also developed clumsiness and tremulousness of the hands with difficulty in approaching and manipulating objects and eating food, though he denied any significant weakness of handgrip. Within 3 weeks of the onset of the illness, he was unable to stand or walk unassisted and diagnosed as a case of acute neuropathy and treated with methyl prednisone

for 5 days at some medical centre. Following therapy, he noticed some improvement and was able to walk with one-person support. However, 15 days post-steroids, there was fresh worsening of neurological symptoms along with recrudescence of fever. His history also revealed that about 20 days prior to the onset of the current neurological illness, he had been diagnosed and treated for malaria. On examination, at the time of presentation, the patient was febrile with a temperature of 102 °F. The systemic examination was normal, except for mild pallor and splenomegaly. On neurological examination, the patient was fully conscious, with normal higher mental functions and no cranial nerve deficits. On motor examination, he had hypotonia of all four limbs; power was normal at proximal joints but there was mild distal weakness. All the deep tendon reflexes were absent and plantars were flexor. Sensory examination revealed a 40 - 50% loss of pin-prick and touch sensation in the up to the level of wrist, and up to the level of the knees in the lower limb. Joint position sense was impaired in the toes and thumb. Vibration sense was impaired up to the tibial tuberosity in the lower limbs and up to the radial styloid process in the upper limbs. Romberg's Sign was positive, and the gait was broad-based and cautious, with swaying to either side while walking.

In view of the preceding history of malaria and the patient presenting with a short history of a fluctuating, severe sensory ataxia and a mild distal motor weakness, that worsened during a recurrent febrile bout, a provisional diagnosis of a predominantly sensory (large fiber > small fiber) polyneuropathy preceding a possible relapse of

*\*Director Professor, \*\*Senior Resident, \*\*\*Professor, Department of Neurology, G.B. Pant Hospital, New Delhi - 110 002. Corresponding Author: Dr Geeta A Khwaja, Room No. 501, Department of Neurology, Academic Block, 5th Floor, GIPMER, New Delhi - 110 002, E-mail: geetakhwaja@hotmail.com.*

malaria was entertained.

Investigations revealed haemoglobin of 10.4 g% with a mild microcytic, hypochromic anaemia and the presence of P. falciparum trophozites and gametocytes on peripheral blood smear. Other biochemical parameters including blood sugar, LFT, KFT were normal. Chest X-ray revealed a left lower zone consolidation, while a mild splenomegaly was detected on ultrasound examination of the abdomen. CSF was acellular with mildly elevated protein (148 mg%) and normal sugar levels (58 mg%). Nerve conduction studies (NCS) revealed preserved sural (velocity: 43.3 and 47.3 meters per second; amplitude: 10.3 and 18.9 µV) but absent sensory nerve action potentials (SNAPs) in bilateral median, ulnar, common peroneal and posterior tibial nerves. Motor NCS revealed prolonged distal latencies (range: 6.96 to 11.30 milli sec), low amplitudes (range: 2.61 to 3.37 µV) but preserved velocities (range: 50.9 to 58.1 m/sec) in both median and ulnar nerves with absent CMAPs in bilateral common peroneal and posterior tibial nerves. On the basis of the clinical findings and electrophysiology suggestive of a distal demyelinating neuropathy, a diagnosis of a predominantly sensory ataxic polyneuropathy, preceding a relapse of falciparum malaria, with further worsening during the febrile phase was entertained.

Patient was initially given intravenous artesunate (120 mg twice a day) for 2 days, followed by a combination of oral artesunate (200 mg daily) for 3 days with sulfadoxine-pyrimethamine (1,500 + 75 mg) as a single dose plus doxycycline (100 mg/day) for 7 days. Fever abated within 3 days of initiating antimalarial therapy but due to persistent falciparum gametocytes on his peripheral smear even two weeks post-therapy, primaquine in a single dose of 45 mg was given for parasite clearance. For the management of his ataxic neuropathy, he was also given intravenous methylprednisolone (1 gm IV daily for 5 days) followed by oral steroids in a dose of 60 mg/day. Within a week of starting steroids, there was a significant improvement in his gait and over the next one month he had an almost complete recovery, following which a gradual tapering of the steroids was initiated. A repeat NCS done at this stage, revealed near normal amplitudes and velocities in the previously affected nerves.

## Discussion

Worldwide, malaria affects approximately 1 billion people, with around 1 million deaths, annually[2]. The National Vector Borne Disease Control Program in India reported around 1.6 million cases and ~ 1,100 deaths due to malaria in 2009[3]. Of the four species of plasmodium; P. falciparum is the most notorious, as it can cause severe and complicated malaria in up to 1% cases. Recurrence of malaria is well

known and, in cases with P. vivax and P. ovale infection, is due to a relapse of the original infection as a result of reactivation of dormant hypnozoites in the liver cells. P. falciparum malaria recurrence, on the other hand, can occur by two different mechanisms: reinfection and recrudescence. Reinfection with P. falciparum can occur in highly endemic areas, usually 14 days post-treatment. Recrudescence is defined as re-emergence of malaria due to: incomplete or inadequate treatment; improper choice of medication; drug resistance; an antigenic variation of P. falciparum or multiple infection by different strains[4]. Our case was initially diagnosed and treated as a case of malaria without any accompanying neurological complications, during the first bout of fever. The details of treatment are not available but after an afebrile period of almost 8 weeks, he developed a recrudescence of fever which was however, preceded 6 weeks earlier by a progressive, fluctuating, evolving polyneuropathy. In our case the most likely cause of recurrence of fever was a recrudescence of falciparum malaria due to incomplete or inadequate treatment. A subsequent increase in parasitaemia, probably accounted for the appearance of polyneuropathy and a recurrence of fever with worsening of the neurological deficit.

Cerebral malaria is one of the most common and potentially life-threatening complications of P. falciparum malaria. Neuropsychiatric complications such as confusional state, delirium, hallucinations, personality disturbances, schizophrenia, transient amnesia, dementia, cerebellar ataxia, seizures and neuropathies have also been reported in cases with P. falciparum malaria[2]. These complications may occur as part of the acute infection or rarely as a manifestation of the post-malaria neurological syndrome (PMNS).

Malarial polyneuropathy due to falciparum and vivax infection is rare, but has been reported from the Indian subcontinent. A recent review of literature had shown that there is only one case series of 10 cases from Sudan, and some isolated case reports of malarial polyneuropathy adding up to a total of 29 cases including the present case (Table I). Guillain-Barré syndrome (GBS) is the most common presentation, and usually sets in 3 - 42 days after the onset of fever, with a predominantly proximal weakness[1]. Cases associated with P. vivax have a milder course and a more complete recovery, as compared to those associated with falciparum infection. Mononeuritic syndromes like facial palsy, trigeminal neuralgia, retrobulbar optic neuritis and involvement of ulnar, circumflex and lateral popliteal nerves have also been reported[2]. Although distal sensory loss has been reported in 9 patients, our patient however, had the rare presentation of a predominantly sensory ataxic polyneuropathy with minimal distal weakness. Moreover, the neuropathic symptoms did not develop during the acute

falciparum infection but began 20 days after the defervescence of fever, evolved over the next 5 weeks and further worsened during a recrudescence of fever due to persistent parasitaemia. A demyelinating motor neuropathy has commonly been reported in cases of malarial polyneuropathy[1]. Electrophysiology in our patient revealed, prolonged distal latencies with preserved conduction velocities, suggestive of focal slowing of conduction distally. The decrease in both proximal and distal CMAPs could be due to axonal involvement or a distal conduction block. The fact that there was a significant improvement in the amplitudes after treatment implies that reduction in amplitudes was due to conduction block rather than axonal involvement. There are obvious clinical and electrophysiological similarities with GBS or Miller Fischer Syndrome, but progression of symptoms over a period of 5 weeks makes these diagnostic considerations unlikely. However, response to anti-malarials and steroids clearly point towards an autoimmune mechanism similar to other inflammatory demyelinating neuropathies. Hence a diagnosis of subacute onset predominantly ataxic polyneuropathy due to recrudescence of malaria was made.

**Table I: Neuropathy in malaria.**

| | |
|---|---|
| Total cases | 29 |
| Type of organism | |
| Falciparum | 22 |
| Vivax | 7 |
| Male: female | 18 : 11 |
| Mean age | 12 - 56 years |
| Days from onset | 10.5 days |
| Clinical features | |
| Predominantly motor presentation | 28 |
| Any sensory signs and symptoms | 9 |
| Predominantly sensory presentation | 1 |
| Autonomic manifestations including bladder involvement | 2 |
| Respiratory failure + bulbar weakness | 10 |
| Treatment given | |
| Steroids | 3 |
| IVIG | 4 |
| Plasma exchange | 2 |
| Outcome | |
| Death | 7 |
| Partial recovery | 1 |
| Complete recovery | 21 |

Like other neurological complications of falciparum malaria, neuropathy may also occur as part of the acute infection, or rarely, as a manifestation of the post-malaria neurological syndrome (PMNS). PMNS is a discrete, transient neurological syndrome seen after recovery from severe malarial infection. Criteria for inclusion under this syndrome are: recent symptomatic malarial infection with parasites cleared from blood, full recovery of consciousness in cases of cerebral malaria and the development of new neurological or psychiatric symptoms within two months of acute illness[5]. Although the most common presentations of PMNS are cerebellar ataxia and encephalopathy, other neurological manifestations such as bilateral facial paralysis and polyneuropathy have also been reported[9]. Our patient did not have any evidence of neuropathy during the initial, acute, febrile phase of malaria. Neuropathic symptoms in our patient began 15 - 20 days after defervescence of fever but he cannot be classified as a case of PMNS because of a lack of evidence of clearance of parasites from the blood. Moreover, the neuropathy in our case further worsened during the recurrence of fever due to an active or persistent parasitaemia. This probably also explains the prolonged evolution and persistence of neuropathy (> 5 weeks) in our case. In earlier reports, the symptoms of malarial polyneuritis were self-limiting and resolved within 2 - 6 weeks without any specific treatment; although few cases, particularly those associated with falciparum malaria, have required ventilatory support and treatment with intravenous immunoglobulin or plasma exchange[1]. Adequate treatment of falciparum malaria with antimalarials and clearance of parasites from blood along with a short course of steroids resulted in almost complete clinical as well as neurophysiological recovery in our case.

The pathogenesis of malaria-induced polyradiculoneuritis is not precisely understood, but it can be seen with both falciparum and vivax malaria. It has been suggested that parasitic emboli obstruct the vasa nervosum and cause anoxaemic stagnation, leading to temporary demyelination. Other proposed hypotheses include; release of neurotoxins; associated metabolic and nutritional disturbances; immune-mediated capillary damage; release of free radicals and tumour necrosis factor[6]. Complete recovery after disappearance of parasitaemia has been reported and was also documented in our case.

To conclude, our case highlights a rare but important complication of falciparum malaria. Although there have been reports of polyneuropathy related to malaria, sensory ataxic neuropathy is rare and has not been reported, to the best of our knowledge. Moreover, the neuropathic symptoms did not develop during the acute falciparum infection but began 20 days after the defervescence of

fever, evolved over the next 5 weeks and further worsened during a recrudescence of fever due to persistent parasitemia. As compared to earlier reports, the neurological deficit evolved over a longer period but there was an excellent response to antimalarial therapy and steroids.

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*"Mind means the turmoil, the illness, the disease; mind means the tense, the anguished state.*
*When silence comes, mind disappears; when mind is there, silence is no more.*
*So there cannot be any silent mind, just as there cannot be any healthy disease.*
*Is it possible to have a healthy disease? When health is there, disease disappears.*
*Silence is the inner health; mind is the inner disease, inner disturbance."*

— OSHO, THE ZEN MASTER.

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# Opsoclonus-Myoclonus Syndrome in Adults Secondary to Ebstein-Barr Virus

B Manohar***, Pulin Kumar Gupta*, BMS Lamba*, MPS Chawla*, RS Taneja*, Alka Sharma**, Narender Sharma***, G Sagar***

## Abstract

Opsoclonus myoclonus (OMS) syndrome, also known as opsoclonusmyoclonus ataxia, is a rare neurological disorder of unknown aetiology which appears to be a result of an autoimmune or viral process involving the nervous system. OMS has been described in children (also known as Kinsborne syndrome), occurring usually as a paraneoplastic neurological accompaniment of neuroblastoma with long term neurological, behavioural and developmental squealae. The OMS Literature in adults is largely limited to scattered cases and small case series. In adults, most cases are associated with breast carcinoma or small cell lung carcinoma. Although it is one of the few paraneoplastic syndromes that occurs in both children and adults, the mechanism of immune dysfunction underlying the adult syndrome is quite different. It is hypothesised that a viral infection like Ebstein-Barr, Coxiackie B, Enterovirus, etc., or in some cases Lyme disease may be the inciting cause. OMS is not generally considered an infectious disease, nor it passes genetically. In adults, many patients are left with psychomotor retardation, behavioural and sleep problems. We are reporting a case of "opsoclonus-myoclonus syndrome" after serologically confirmed Ebstein-Barr virus infection. Overall prognosis of this condition is good, like in our patient, who is still alive and is doing his household work and that too without any support but with some psychologically abnormal behaviour and minimal residual physical disabilities.

## Case report

A 60-year-old male, hypertensive since 5 years, chronic alcoholic, non smoker, presented to emergency with history of fever for 4 days, 15 days prior to admission, followed by progressively increasing sudden jerky movements of bilateral upper and lower limbs and abnormal eye movements along with aggressive violent behaviour since last 8 days. All these symptoms were insidious in onset, gradually progressive such that the patient became bedridden within a week of onset. He had difficulty in wearing slippers, eating food, and holding a pen because of these jerky movements. These symptoms were not associated with weakness in limbs. During this phase, the patient also developed difficulty in following gaze on lateral movement, which gradually progressed with difficulty in staring at a fixed point, within next 24 hours. There was no history seizure episodes, bowel disturbances like constipation or incontinence, bladder disturbance like retention or involuntary passage of urine, recent immunisation, tingling and numbness sensation over the body, no difficulty in swallowing or regurgitation or any other symptom suggestive of cranial nerve palsy. No apparent history of high risk behaviour or drug abuse could be elicited.

On examination, the patient was conscious, well behaved and oriented to time, place and person. His general physical examination was normal. His GCS was 15, but he was a bit anxious. Noneurocutaneous markers were seen. On central nervous system examination higher mental functions were normal with no cranial nerves palsies. Motor system examination revealed normal bulk, but hypertonia was present in all 4 limbs along with exaggerated reflexes (grade 4) in all 4 limbs across all joints and power was normal and equal in all 4 limbs. Cerebellar examination and gait could not be checked due to tremors, unsteadiness and incoordination. Bilateral plantars were withdrawl. Sensory system and posterior column sensations were normal. There were rapid, involuntary, saccadic, multidirectional conjugate eye movements, which did not follow a rhythmic pattern. Brief repetitive involuntary, jerky, twitching of muscles groups mainly involving lower limbs but also upper limbs were present. Episodes of dysarthria and mutism were present. Examination of chest and abdomen was normal.

His routine laboratory investigations revealed marked hypergammaglobulinaemia. Rest of the investigations including chest X-ray and ECG were unremarkable. NCCT brain, done in emergency, was normal. MRI brain and brainstem showed age related cerebral atropy with periventricular chronic white matter ischaemic foci. There was no acute infarct/cerebral haemorrhage. Electroencephalogram showed features suggestive of

*Professor, **Assistant Professor, ***Resident, Department of Medicine,
PGIMER, Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.
Corresponding Author: Dr Pulin Kumar Gupta, Professor of Medicine, Room No. 103, Academic Block, PGIMER, Dr RML Hospital, New Delhi - 110 001, Tel: 09899748321, E-mail: guptapulin@yahoo.com.

encephalopathy. Fundoscopy showed red glow with hazy corneal media. Cerebrospinal fluid study showed sugar of 75 mg/dl, protein of 50 mg/dl, 5 cells with all lymphocytes. CSF for ADA, AFB, cryptococcal antigen and India ink, CSF culture Gram stain/acid fast bacilli/fungal culture were also negative. Serum autoimmune encephalitis panel for NMDA antibody/AMPA-R1/AMPA-R2/GABA-B receptor antibody/LGi-1 antibody/CASPR2 antibody was also negative. CECT chest was done to rule-out carcinoma bronchus and it came out to be normal. Blood and urine cultures for bacterial pathogens were negative. His HbsAg, anti-HCV and HIV status was negative. ANA and S. ACE levels were also within normal limits. Since we ruled-out almost all common causes of meninigoencephalitis in india, so CSF viral panel was advised for varicella/HSV/IgM for EBV/CMV/CMV/Measles/Dengue/chikungunya and Japanese Encephalitis. It was all normal execpt IgM for EBV came out to be positive. Subsequently, serum EBV serology was sent and it also came out to be positive in high titres.

Patient was initially, empirically, treated on beta lactam antibiotics and acyclovir for 4 days and later by high dose pulse methylprednisolone for 5 days following the CSF virology reports followed by oral steroids. Clonazepam and haloperidol were added for his aggressive behaviour and psychosis.

Patient was put on Sodium valproate 500 mg twice daily and baclofen for his abnormal movements. Patient slowly improved over next 2 weeks and his rigidity and abnormal movements decreased. After two weeks, patient gradually started doing his daily routine, and was discharged with stable vitals and satisfactory neurological status after 4 weeks.

He has been regularly coming to the OPD every fortnight and is doing well on valproate, haloperidol and clonazepam. Steroids were continued for 1 month at 1 mg/kg and then slowly tapered over next 3 months to 5 mg/kg till date.

## Discussion

The pathology of this condition is unclear. However, there are two proposed meachanisms. The first is that oculomotor neurons of the caudal fastigial nucleus of the cerebellum becomes disinhibited secondary to Purkinje cell dysfunction in the cerebellar vermis[1]. Purkinje cells normally relay inhibitory signals to cells of the fastigial nucleus. Histopathological examination of patients with OMS has demonstrated gliosis and inflammation in cerebellar vermis, supporting this theory. A second potential mechanism is disinhibition of the burst neurons, which are cells that normally generate saccadic eye movements. Burst neurons are normally under tonic inhibition from omnipause cells except during saccades. Disruption of this inhibitory signal may cause the saccadic intrusions seen in ocular flutter or opsoclonus[2].

Opsoclonus is arguably the most distinguishing feature of OMS and must be differentiated from other eye movement disorders such as nystagmus or other saccadic intrusions. Nystagmus is defined by the presence of a slow phase during the eye movement, which may or may not be followed by a fast refixating movement (jerk nystagmus). When only consisting of slow to-and-fro movements, it is known as pendular nystagmus. Saccadic intrusions, opsoclonus included, do not contain a slow phase and consist entirely of rapid movements. Clinically, identifying the slow phase of nystagmus may be challenging and sometimes may only be accomplished using eye movement recordings.

In cases where opsoclonus is either absent or delayed in onset, acute cerebellar ataxia or acute cerebellitis can be easily confused with OMS. Acute cerebellar ataxia represents cerebellar inflammation that typically occurs following infection or immunisation. Patients present with acute truncal and gait ataxia, which is usually benign and self-limited[3]. Eye movement abnormalities may be present in patients with acute cerebellar ataxia as well; however, they will have nystagmus rather than opsoclonus. This is a helpful diagnostic difference and is important because whereas acute cerebellar ataxia is self-limited, OMS requires prompt therapeutic intervention.

OMS has additionally been reported to occur in settings other than paraneoplastic syndrome from neuroblastoma. These cases are typically thought to be "idiopathic" OMS. There is a particular abundance of para- and post-infectious associations reported in the literature, particularly with viral pathogens. Examples of viruses associated with OMS include influenza, West Nile virus, varicella, cytomegalovirus, human herpes virus 6, human immunodeficiency virus, and hepatitis C[4,5,6]. Our case is probably a very rare association of EBV with OMS reported 1st time from this part of the world. There are also reports of antecedent bacterial infections including *Mycoplasma pneumoniae* and salmonella[4,6]. Post-immunisation associations have been reported following varicella, measles, and diphtheria-pertussis-tetanus vaccine administration. Despite these associations, no clear aetiology has been identified. In older children beyond the typical age range for neuroblastoma, OMS may also occur as a post-infectious syndrome.

OMS has also been attributed to toxic or metabolic abnormalities. Examples include phenytoin overdose, hyperosmolar non-ketotic diabetic coma, and cocaine intoxication[7]. Post-traumatic opsoclonus has also been reported in the setting of severe head injury and coma[8].

OMS has been observed in association with other paraneoplastic syndromes, particularly in the setting of small-cell lung carcinoma and adenocarcinoma of breast in adults[7].

Medical treatment of OMS consists of immunosupression. The conventional treatment of both children and adults is either corticosteroids or corticotrophin (ACTH), both of which help in reducing signs and symptoms of OMS. Corticosteroids are given in both a slow taper as well as pulse dosing in relapsing cases[9]. In many cases there is only a partial response to these agents and patient may need long-term treatment due to recurrence of symptoms upon tapering or discontinuation of therapy. More recently, immunomodulatory therapies such as IVIG, rituximab, cyclophosphamide, azathioprine and plasmapheresis have been combined with corticosteroids or ACTH. One prospective, study of 74 OMS patients compared the efficacy of ACTH alone against ACTH in combination with other agents such as IVIG, rituximab, cyclophosphamide, or other chemotherapeutic agents[10]. Regardless of treatment, all patients demonstrated improvement in a standardised neurological motor assessment. Those who received combination therapies, however, had greater degrees of neurological improvement, suggesting that multimodal immunosuppressive therapies may achieve greater therapeutic responses.

Overall, the survival prognosis of children with OMS secondary to neuroblastoma is very favourable. One series of patients with neuroblastoma reported that 90% of patients with OMS presented with non-metastatic disease, whereas non-metastatic disease was present in only 35% of patients without OMS[11]. Despite this excellent prognosis, children with OMS have a more guarded neurological prognosis. OMS can follow a monophasic or multiphasic disease course, with the latter group requiring prolonged immunosuppressive therapy. Approximately 70% of patients are estimated to have some form of residual motor, speech, cognitive or behavioural disturbances[12]. Currently, there are no clinically established laboratory investigations available to predict prognosis or therapeutic response. Most patients experience a relapsing form of OMS, though a minority will have a monophasic course and may be more likely to recover with residual deficits and fortunately the same has happened to our patient till now. Viral infection may play a role in the reactivation of disease in some patients who

had previously experienced remission, possibly by expanding the memory B cell population[13]. Very few case reports of OMS in adults are available, so a further treatment approach is more concerned. Physician should keep an eye on recurrence, which is not a common phenomenon in adults especially after a viral infection. However as per current literature, steroids are the drug of choice and have done a miracle in our patient, who is probably the first case with EBV associated OMS reported from this part of India.

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*"The best way to make your dreams come true is to wake up."*

– PAUL VALERY.

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# Intramedullary Cervical Tuberculoma: Target Sign

*Prabhat Kumar\*, Biswa Ranjan Patra\*\*, Ratnakar Sahoo\*\*\**

A 27-year-old lady, housewife presented with stiffness of both upper limbs and lower limbs for one month. Stiffness started in right upper limb, progressed to right lower limb and then to the left lower and left upper limb. This was not associated with any loss of sensation, bowel and bladder incontinence or back pain. There was associated complaint of fever which was low grade, intermittent, not associated with chills or rigor associated with evening rise, and cough with scanty whitish expectoration for the same duration. The patient also complained of loss of appetite and loss of weight during this period of illness. There was no past history of tuberculosis or contact with tuberculosis or any trauma to head or spine.

On nervous system examination, higher mental function was intact, examination of cranial nerves, spine and cranium was within normal limit. On motor examination, tone was increased in all four limbs, power was decreased in both upper and lower limbs to 4/5. Deep tendon reflexes were exacerbated in upper and lower limbs with well sustained ankle clonus, bilaterally. Plantar reflex was bilaterally extensor with absence of superficial reflexes. All sensations were found to be intact. On respiratory system examination there was stony dullness, decreased air entry and vocal resonance in right interscapular and decreased infrascapular areas of chest.

Chest X-ray revealed right-sided pleural effusion. Pleural fluid analysis showed raised protein levels and 100 cells of which 95% were lymphocytic. ADA of pleural fluid was raised (46 U/l). CSF examination was normal. MRI spine revealed an isointense lesion of size 19 x 8 x 7 mm in cervical spine on T1-weighted sequence which showed peripheral ring enhancement after contrast administration (Fig. 1 - 2). On T2-weighted sequence, lesion showed central hyperintensity and peripheral rim of hypointensity (Target Sign) with upper cervical cord oedema extending upto cervico-medullary junction (Fig. 3). These findings were suggestive of intramedullary cervical tuberculoma on the background of tubercular pleural effusion.

Spinal intramedullary tuberculoma is a rare disease; its incidence among patients with tuberculosis is only 2/ 1,00,000, accounting for only 2% of all cases of tuberculosis of the central nervous system. The ratio of intramedullary

tuberculoma to intracerebral tuberculoma is approximately 1 : 42, and 72% of lesions are located in the thoracic cord[1]. The MRI findings in cases of spinal intramedullary



*Fig. 1:* Sagittal contrast-enhanced T1W image showing a ring enhancing lesion in cervical spine.

*\*Senior Resident, \*\*Post-Graduate Resident, \*\*\*Professor, Department of Internal Medicine, PGIMER and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.*
*Corresponding Author: Dr Prabhat Kumar, 33/22, First Floor, West Patel Nagar, New Delhi - 110 008, Tel: 09968123167, E-mail: drkumar.prabhat@gmail.com*

*Fig. 2: Axial contrast-enhanced T1W image showing a ring enhancing lesion suggestive of tuberculoma.*

tuberculoma can vary during the different phases of tuberculoma. In the early phase, the tuberculoma is characterised by severe infective reactions, poor formation of the gel capsule, and severe oedema around the lesion. During this phase, T1WI and T2WI both show equal signal intensity and they are evenly enhanced after being intensified. As the gel content in the tuberculoma increases, the peripheral oedema is alleviated or may disappear. As a result, T1WI shows equal signal intensity; meanwhile, T2WI shows equal or low signal intensity. After enhanced scanning, there is rim enhancement and low signal in the central region. With the development of caseation, T2WI shows a typical "target sign", which means that it exhibits a range from the low signal target to the high signal rim and also from the center of the low signal rim to the peripheral parts[2-3]. The caseous substance forms the target center, whereas the peripheral infective granulation tissues form the high signal rim.



*Fig. 3: Sagittal T2W image showing intramedullary tuberculoma of cervical spine.*

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> *"The foolish man seeks happiness in the distance,*
> *the wise man grows it under his feet."*
>
> – JAMES OPPENHEIM.

## ABSTRACT FORM, IACMCON-2017

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Signature of the presenting author

*Address for correspondence :*

**Dr. Y. S. N. Raju**
**Chairman, Scientific Committee – IACMCON-2017**
103 Ashoka Lake View Apts, Kundanbagh Begumpet, Hyderabad - 500 010
Mobile: 09440066482, E-mail: raju_ys1197@yahoo.co.in

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