



MPS Chawla

## From the Editor

It is indeed a moment of great honour for me to assume charge as Editor of Journal, Indian Academy of Clinical Medicine, one of India's widely read premier medical journal for practicing internists, post-graduate students, medical teachers and researchers. I have been associated with the Journal for more than a decade, first in the capacity of Secretary and then as Associate Editor and it has helped me tremendously in my professional growth. I feel humbled and honoured to have been entrusted with this daunting, yet academically enriching task of encapsulating in each issue the nectar of distilled scientific knowledge from all spheres of clinical medicine which helps clinicians to tackle challenges in their day to day practice.

My immediate predecessor, Dr DG Jain needs no introduction. He has been associated with the Journal ever since its revamp by Dr (Prof.) AK Agarwal. He has been brilliant in managing the Journal and I believe he will always be there to support me.



Sumeet Singla

It is with great pleasure that I welcome on board Dr Sumeet Singla as Associate Editor and Dr Saurabh Srivastava as Editorial Secretary. Dr Sumeet Singla is professor of medicine at Maulana Azad Medical College, New Delhi and Dr Saurabh Srivastava is professor of medicine at School of Medical Sciences and Research, Sharda University, Greater Noida. I am sure that their dynamism and commitment will help in the growth and outreach of the Journal.

I would like to express my deep gratitude for all the distinguished referees and reviewers for graciously giving their invaluable time in the form of expert advice, guidance and suggestions which have helped the Journal in maintaining high standards. My sincere thanks are due to all other team members who continue to work backstage and help in giving shape to the Journal.

Members of the Governing Body of IACM have always been very encouraging and supportive and I expect the same amount of co-operation from them.

Finally, the Journal continues to look forward to the stimulating indulgence of its readers who have always been a source of inspiration with their constructive criticism and the authors who contribute by sending Original Articles, Review Articles, Case Reports, Images in Clinical Medicine, etc.

I pray that Journal continues to grow and help in the teaching of art of clinical medicine.



Saurabh Srivastava

– MPS Chawla

drmpsawla@gmail.com

# C O N T E N T S

**Journal, Indian Academy of Clinical Medicine • Vol. 18, Number 1, January-March, 2017**

*Contains 72 pages from 1 to 72 (inclusive of all advertisements)*

<b>Letter</b>	<b>From the Editor</b> ..... 1 <i>MPS Chawla</i>
<b>Update</b>	<b>New Evidence Generated in 2016</b> ..... 7 <i>MPS Chawla</i>
<b>Viewpoint</b>	<b>Healthy Heart Syndrome</b> ..... 12 <i>BM Hegde</i>
<b>Original Articles</b>	<b>Study of Plasma Fibrinogen Levels in Type 2 Diabetes Mellitus and its Association with Microalbuminuria and Glycaemic Control</b> ..... 14 <i>Pankaj Kumar Saini, Manoj Saluja, SR Meena, Shyam Bihari Meena, Naveen seervi, Prashant Shringi</i> <b>Hepatic Dysfunction in Patients of Dengue Viral Infection in Kota Region</b> ..... 18 <i>Naveen Seervi, SR Meena, Manoj Saluja, Shyam Bihari Meena, Prashant Shringi, Pankaj Kumar Saini</i> <b>Echocardiographic Study of Left Ventricular Changes in Patients Suffering from Chronic Obstructive Pulmonary Disease in a Tertiary Care Centre</b> ..... 22 <i>Gouranga Santra, Nabendu Karji</i> <b>Dynamic Changes in Serum Phosphorus Level During Treatment of Diabetic Ketoacidosis and Predicted by Degree of Metabolic Acidosis on Presentation</b> ..... 26 <i>Ravindra Kumar Tiwari, Archana Gokhroo, Kishor Phepale, Rajesh Jain, Pavan Kumar V</i> <b>Cardiological Complications in Cerebrovascular Accidents</b> ..... 29 <i>Suman Ghosh, Animesh Deb, Anup K Bhattacharya</i> <b>Hepatic Osteodystrophy - A Study on The Prevalence of Osteoporosis in Cirrhosis of Liver and its Correlation with Severity of Liver Disease</b> ..... 36 <i>Aanchal Arora C, Rajesh Manocha G, S Prasad</i>
<b>Case Reports</b>	<b>Autosomal Non-dominant Hereditary Spherocytosis in a Young Female from West Bengal: An Unusual Entity</b> ..... 40 <i>Ayan Basu, Bisakh Bhattacharya, Yogiraj Roy, Mehebubar Rahman, Dewan Koushik, Rama Prosad Goswami</i> <b>Fat Embolism Syndrome with Cerebral Involvement: A Case Report and Review of Literature</b> ..... 43 <i>M Narang, Alex Babu, Ashutosh Kumar</i> <b>A Case of Sjogren Syndrome Presenting as Hypokalaemic Paralysis and Respiratory Arrest due to Renal Tubular Acidosis – Case Report</b> ..... 47 <i>Nitya Nand, Sameer Aggrawal, Nisha Batra, Rajiv Jain, Virender Chauhan, Manoj Yadav</i> <b>Dengue Encephalitis: Needs more Emphasis in Dengue Prone Areas</b> ..... 50 <i>Kripa Shanker Jhirwal, Hemant Mahur, DP Singh</i>

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<b>Case Reports</b>	<b>Magnetic Resonance Imaging in Endomyocardial Fibrosis with Massive Left Ventricular Endocardial Calcific Deposits</b> 52 <i>Simmi Aggarwal, Gagandeep Singh, Himanshu Khutan, Yash Paul Samberia, Ravinder Garg</i> <b>A Case of Human Parvo Virus B 19 Infection with Erythroid Hypoplasia and Idiopathic Thrombocytopenic Purpura in an Immunocompetent Child</b> 55 <i>P Ganesh, YS Raju, D Swaroopa, A Krishna Prasad</i> <b>Acute Cerebellar Demyelination: An Unusual Complication of Antituberculous Drugs</b> 58 <i>Vivek Pal Singh, Anil Vardani, RK Singal, Atul Bhasin, NM Agarwal, RN Saini</i> <b>Malarial Hepatopathy-Experience at a Tertiary Care Center of North India</b> 60 <i>Parveen Malhotra, Yogesh Sanwariya, Ajay Chugh, Hemant Dahiya, Naveen Malhotra, Vani Malhotra</i> <b>An Unusual Cause of Dysphagia</b> 63 <i>Parveen Malhotra, Yogesh Sanwariya, Hemant Dahiya, Ajay Chugh, Vani Malhotra, Naveen Malhotra</i> <b>Dengue Fever Presenting as Cerebellar ataxia</b> 64 <i>Rajesh Deshwal, CA Tukaram</i> <b>A Rare Case of Osler Weber Rendu Disease – A Case Report</b> 66 <i>Nitya Nand, Savio Dsouza, Nisha Batra, Virender Chauhan, Manoj Yadav</i>
<b>Images</b>	<b>Achondroplasia: An Important Cause of Stunted Growth</b> 68 <i>G Garg, A Gogia, A Kakar</i>
<b>Announcements</b>	<b>List of JIACM Reviewers (2016)</b> 13 <b>Form for (Rule 8), 2017</b> 35 <b>Advertisement Tariff of the Journal, Indian Academy of Clinical Medicine (JIACM)</b> 42 <b>Invitation for Nominations for Oration Awards for 2017</b> 46 <b>Invitation for Papers (Platform/Poster) for IACMCON-2017, Kolkata, W.B.</b> 49 <b>Instructions to Authors</b> 65 <b>Format for Nomination for IACM Oration Awards</b> 69 <b>Abstract Form for IACMCON-2017, Kolkata, W.B.</b> 70 <b>Application Form for IACM Membership/Fellowship</b> 71

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**Dr. MPS Chawla**

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*Headquarters :*

Post-Graduate Department of Medicine, Sarojini Naidu Medical College, Mahatma Gandhi Road, Agra - 282 002 (U.P.)

## **Editorial/Mailing Address**

4/19 B, Jangpura B, New Delhi - 110 014

Tel.: (011) 23361252

**E-mail: [iacmjourn@gmail.com](mailto:iacmjourn@gmail.com)**

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## New evidence generated in 2016

**MPS Chawla\***

As a new feature the editorial team has introduced the concept of reporting the results of trials which have the potential to change clinical practice.

### Cardiology

1. Dehmer SP, Maciosek MV, Flottemesch TJ *et al.* Aspirin for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: a decision analysis for the US Preventive Services Task Force. *Ann Intern Med* 2016; 164: 777-86.

This study is decision analysis using a CVD microsimulation model based on evidence reviews. *It showed that aspirin therapy improved overall quality of life for most men and women when it was initiated at age 40 to 69 years for lifetime use, unless otherwise contraindicated.* The benefit was concentrated in the higher-risk groups, with 10-year CVD risk greater than 10%.

2. Køber L, Thune JJ, Nielsen JC *et al.* DANISH Investigators. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. *N Engl J Med* 2016; 375: 1221-30.

This trial randomly assigned 1,116 patients who had heart failure not from ischemic heart disease to receive either an ICD or usual care. In both groups, 58% of patients got CRT. Implantation of an ICD compared with usual care did not provide an overall survival benefit over a median follow-up of 67.6 months. Adverse events associated with device implantation included a 5% infection rate in the ICD group and a 22% mortality rate. *Hence the practice of ICD implantation for non ischemic cardiomyopathy should be stopped immediately.*

3. Leibowitz M, Karpati T, Cohen-Stavi CJ *et al.* Association between Achieved Low-Density Lipoprotein Levels and Major Adverse Cardiac Events in Patients with Stable Ischemic Heart Disease taking Statin Treatment. *JAMA Intern Med* 2016; 176: 1105-13.

This population-based observational cohort study addressed the question of whether there is clinical benefit in trying to decrease LDL-C levels beyond 1.810 mmol/l (70 mg/dl) in patients with CAD. It found that targeting an LDL-C level less than 2.586 mmol/l (< 100

mg/dl) achieves the same cardiovascular risk reduction as more aggressive targets. There was no reduction in MACEs with achievement of a level less than 1.810 mmol/l (< 70 mg/dl). *This study cautions regarding aggressive lowering of LDL-C levels as adverse effects of statins increase with higher doses.*

4. Lonn EM, Bosch J, López-Jaramillo P *et al.* HOPE-3 Investigators. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *N Engl J Med* 2016; 374: 2009-20.

HOPE-3 (Heart Outcomes Prevention Evaluation) is an international trial that included 12705 people (age  $\geq$  65 years for women and  $\geq$  55 years for men) without known CVD who were considered to be at intermediate risk by virtue of having at least 1 risk factor. In a 2  $\times$  2 factorial design, each participant was randomly assigned to receive daily rosuvastatin (10 mg) or placebo, plus daily candesartan/hydrochlorothiazide (16 mg/12.5 mg) or placebo. At baseline, the mean LDL-C level was 3.310 mmol/l (128 mg/dl) and mean blood pressure was 138/82 mm Hg. During a median follow-up of 5.6 years, key findings were that rosuvastatin lowered the mean LDL-C level by 0.905 mmol/l (35 mg/dl) and that antihypertensive drugs lowered the mean systolic/diastolic blood pressure by 6/3 mm Hg. The first co-primary outcome (cardiovascular-related death, nonfatal stroke, or nonfatal myocardial infarction) occurred less frequently with rosuvastatin than placebo (3.7% vs. 4.8%, respectively). Overall, candesartan/hydrochlorothiazide did not lower the incidence of the first co-primary outcome compared with placebo (4.1% vs 4.4%, respectively); however, it did lower the incidence in the subgroup with the highest baseline systolic blood pressure (> 143 mm Hg; 4.8% vs 6.5%). *Overall, outcomes with rosuvastatin plus candesartan/hydrochlorothiazide were not statistically significantly better than outcomes with rosuvastatin alone. There was no benefit on mortality for rosuvastatin compared with placebo.*

5. Song M, Fung TT, Hu FB *et al.* Association of Animal and Plant Protein Intake with All-Cause and Cause-Specific Mortality. *JAMA Intern Med* 2016; 176: 1453-63.

This prospective cohort study of 131 342 US health

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\*Professor, Department of Medicine, PGIMER and Dr. RML Hospital, New Delhi - 110001.

care professionals included 64.7% women from the Nurses' Health Study (1980 to end of follow-up on 1 June 2012) and 35.3% men from the Health Professionals Follow-up Study (1986 to end of follow-up on 31 January 2012). Food-frequency questionnaires were used to assess animal and plant protein intake every 4 years. The cause of death was validated through death certificate or medical records.

Animal protein intake was not associated with all-cause mortality [hazard ratio (HR), 1.02 per 10% energy increment (EI) (95% CI, 0.98 to 1.05)] but was associated with higher cardiovascular mortality [HR, 1.08 per 10% EI (CI, 1.01 to 1.16)]. *Plant protein, was associated with lower all-cause mortality [HR, 0.90 per 3% EI (CI, 0.86 to 0.95)] and lower cardiovascular mortality [HR, 0.88 per 3% EI (CI, 0.80 to 0.97)].*

## Haematology and Oncology

1. Connolly SJ, Milling TJ Jr, Eikelboom JW *et al.* ANNEXA-4 Investigators. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *N Engl J Med* 2016; 375: 1131-41.

Novel oral anticoagulants are being increasingly prescribed and recommended as first-line treatment in patients with venous thromboembolism. However, until recently, no antidote was available to reverse these agents in patients who present with life-threatening bleeding. Idacuricizumab has been recently shown to be effective in the treatment of such bleeding in patients taking dabigatran, an oral direct thrombin inhibitor.

This trial was conducted to study the role of andexanet alfa in patients with acute major bleeding who were receiving factor Xa inhibitors. This multicenter, prospective, open-label study enrolled 67 adult patients with acute major bleeding within 18 hours after administration of a factor Xa inhibitor. Patients received a bolus dose of andexanet alfa, followed by a 2-hour infusion. Factor Xa activity decreased by 89% (95% CI, 58% to 94%) in the rivaroxaban group and 93% (CI, 87% to 94%) in the apixiban group after the bolus dose of andexanet alfa and remained stable during the 2-hour infusion. At 12 hours after infusion of andexanet alfa, clinical hemostasis was adjudicated as excellent or good in 79% of patients (CI, 64% to 89%). Thrombotic events occurred in 18% of patients during 30-day follow-up. *Use of andexanet alfa may prove to be a major breakthrough in the treatment of life-threatening bleeding in patients on factor Xa inhibitors.*

2. Ataga KI, Kutlar A, Kanter J *et al.* Crizanlizumab for the

Prevention of Pain Crises in Sickle Cell Disease. *N Engl J Med* 2017; 376: 429-39.

This double-blind, randomised, placebo controlled, phase 2 trial sought to clarify the role of P-selectin blockade through the use of crizanlizumab to prevent pain in sickle cell disease. 198 adult patients with sickle cell disease were randomly assigned to receive high-dose crizanlizumab (5 mg/kg), low-dose crizanlizumab (2.5 mg/kg), or placebo for 52 weeks. *Crizanlizumab at high doses led to less frequent painful crises and an increased time to first crisis without an increase in serious adverse events, regardless of whether patients were receiving hydroxyurea.*

3. Chai-Adisaksopha C, Hillis C, Siegal DM *et al.* Prothrombin Complex Concentrates versus Fresh Frozen Plasma for Warfarin Reversal. A Systematic Review and Meta-Analysis. *Thromb Haemost* 2016; 116: 879-90.

This systematic review and meta-analysis included 13 studies (5 randomised and 8 observational) to assess the efficacy and safety of PCCs versus FFP for warfarin reversal in patients presenting with major bleeding or in need of emergent surgery. The primary end point was all cause 30-day mortality. Use of PCCs was associated with a significant reduction in all-cause mortality compared with FFP [odds ratio (OR), 0.56 (CI, 0.37 to 0.84);  $P = 0.006$ ]. *Compared with FFP, PCCs can lead to effective, efficient, and timely warfarin reversal without an increase in risk for venous thromboembolism.*

4. Wei Y, Ji XB, Wang YW *et al.* High-dose Dexamethasone vs Prednisone for Treatment of Adult Immune Thrombocytopenia: A Prospective Multicenter Randomised Trial. *Blood* 2016; 127: 296-302.

This prospective multicenter, randomised, controlled, open-label trial was done to compare high-dose dexamethasone (40 mg for 4 days for 1 or 2 cycles) with prednisone (1 mg/kg of body weight for 4 weeks, then tapered over 4 to 6 weeks) in adults with ITP whose platelet counts were less than 30,000 cells/ $\mu$ l. The primary end-points were initial and sustained responses, as defined by standard accepted criteria. Compared with prednisone, high-dose dexamethasone resulted in higher rates of overall (82% vs 67%; OR, 2.05;  $P = 0.044$ ) and complete (51% vs 26%; OR, 2.8;  $P = 0.011$ ) responses. The time to initial response was shorter in the high-dose dexamethasone group than the prednisone group (3 vs 6 days;  $P < 0.001$ ). *Sustained responses did not differ between the groups, occurring in 40% of patients receiving high-dose dexamethasone and 41% receiving prednisone ( $P > 0.20$ ). Weight gain and cushingoid appearance were more frequent with*

prednisone.

5. Heddle NM, Cook RJ, Arnold DM *et al.* Effect of Short-Term vs Long-Term Blood Storage on Mortality after Transfusion. *N Engl J Med* 2016; 375: 1937-45.

This large, multicenter, randomised, controlled trial with 31 497 patients compared transfusion of the freshest RBCs in inventory [short storage group; mean, 13 days (SD, 7.6)] with RBCs that had been in inventory for longer periods [long storage group; mean, 23.6 days (SD, 8.9)]. The primary end-point of in-hospital mortality was 9.1% in the short storage group and 8.7% in the long storage group [OR, 1.05 (CI, 0.95 to 1.16);  $P > 0.20$ ]. Results also did not differ in the 3 prespecified high-risk groups: cardiovascular surgery patients, intensive care patients, and patients with cancer. *This study supports transfusion of blood stored for longer periods (but still within blood bank standards) in both high-risk and generalised hospital patients.* This is encouraging news for blood banks, which continue to struggle to ensure an adequate inventory of blood products and meet the demands for services that have previously requested the freshest blood available.

## General Internal Medicine

1. Lindson-Hawley N, Banting M, West R *et al.* Gradual versus Abrupt Smoking Cessation: A Randomised, Controlled Non-inferiority Trial. *Ann Intern Med* 2016; 164: 585-92.

*Clinicians can advise patients interested in smoking cessation that compared with quitting gradually, quitting abruptly is more likely to lead to abstinence at 4 weeks and 6 months.*

2. Bibbins-Domingo K. US Preventive Services Task Force. Aspirin use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2016; 164: 836-45.

The decision to use aspirin for the primary prevention of cardiovascular events and colorectal cancer is most beneficial in patients aged 50 to 59 years who have a 10% or greater risk for cardiovascular disease during the next 10 years. *Aspirin seems to reduce the incidence of colorectal cancer after 10 years and to reduce mortality from colorectal cancer after 20 years, but its use is not recommended for the primary prevention of colorectal cancer alone because the benefits do not outweigh the harms.*

3. Albert RK, Au DH, Blackford AL *et al.* Long-Term Oxygen Treatment Trial Research Group. A Randomised Trial of

Long-term Oxygen for COPD with Moderate Desaturation. *N Engl J Med* 2016; 375: 1617-27.

This trial was done at 42 centers and involved 738 participants (mean age, 68.8 years; 73% male). The first group of participants (57%) had a resting oxygen saturation of 89% to 93% and were randomly assigned to receive no oxygen or 2 L of continuous oxygen per minute by nasal cannula. The second group (43%) had an oxygen saturation of 80% to 90% during a 6-minute walk and were randomly assigned to receive no oxygen or to individually adjusted oxygen doses during exercise and sleep. The following outcomes were measured during 18 months of follow-up: mortality, hospitalisations, COPD exacerbations, quality of life, anxiety, depression, and functional status. *No differences were found between the groups that did and those that did not receive oxygen.*

## Critical Care Medicine

1. Keh D, Trips E, Marx G *et al.* SepNet Critical Care Trials Group. Effect of Hydrocortisone on Development of Shock Among Patients with Severe Sepsis: The HYPRESS Randomised Clinical Trial. *JAMA* 2016; 316: 1775-85.

Treatment with hydrocortisone is currently recommended for patients with sepsis and refractory or vasopressor-dependent shock<sup>23</sup>. Although improved haemodynamics and more rapid reversal of shock has been consistently demonstrated, data on a potential mortality benefit with this approach remain controversial. This double-blind, randomised, controlled trial conducted in 34 ICUs aimed to determine whether hydrocortisone therapy prevents the development of shock in septic patients without shock. The investigators randomly assigned 380 patients with sepsis, evidence of organ dysfunction, and absence of shock to receive either placebo or hydrocortisone, 200 mg/d, for 5 days, followed by a taper for 6 more days. The primary end-point was occurrence of shock within 14 days. The 2 groups did not differ statistically in the primary end-point; 36 of 170 patients (21.2%) in the hydrocortisone group and 39 of 170 patients (22.9%) in the placebo group developed shock [difference, - 1.8% (CI, - 10.7% to 7%);  $P = 0.70$ ]. Mortality at 28 days also did not differ between groups [8.8% vs 8.2%; difference, 0.5% (CI, - 5.6% to 6.7%);  $P > 0.20$ ]. More hyperglycaemic episodes occurred in the hydrocortisone group [90.9% vs 81.5%; difference, 9.4% (CI, 2.4% to 16.4%);  $P = 0.009$ ].

*This trial argues against the use of adjunctive hydrocortisone therapy in patients with sepsis without shock.*

2. Roberts JA, Abdul-Aziz MH, Davis JS *et al.* Continuous versus Intermittent  $\beta$ -lactam Infusion in Severe Sepsis. A Meta-analysis of Individual Patient Data from Randomised Trials. *Am J Respir Crit Care Med* 2016; 194: 681-91.

The investigators assessed 3 randomised, controlled trials of intermittent versus continuous  $\alpha$ -lactam dosing in a total of 632 patients. Rates of hospital mortality and clinical cure for the continuous and the intermittent infusion groups were 19.6% versus 26.3% [relative risk, 0.74 (CI, 0.56 to 1.00);  $P = 0.045$ ] and 55.4% versus 46.3% [relative risk, 1.2 (CI, 1.03 to 1.40);  $P = 0.021$ ], respectively.

*This trial provides rationale for further research regarding continuous infusion of concentration-dependent antibiotics such as  $\beta$ -lactams in severe sepsis.*

3. Qureshi AI, Palesch YY, Barsan WG *et al.* ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Haemorrhage. *N Engl J Med* 2016; 375: 1033-43.

This study was designed to determine whether rapidly lowering the systolic blood pressure to an intensive target of 110 to 139 mm Hg in patients with an acute hypertensive response to ICH improved outcomes compared with a standard target of 140 to 179 mm Hg. Patients with supratentorial ICH less than 60 cm<sup>3</sup>, a Glasgow Coma Scale score of 5 or more, and at least 1 SBP reading of 180 mm Hg or greater were randomly assigned to the intensive or standard blood pressure target. Treatment was initiated within 4.5 hours after symptoms and continued for 24 hours. Intravenous nicardipine was the initial blood pressure lowering agent used in all patients. Enrollment was stopped at 1,000 participants because of futility. *The primary outcome of death or moderately severe to severe disability (modified Rankin scale score of 4 to 6) at 3 months was observed in 186 of 481 patients (38.7%) in the intensive treatment group and 181 of 480 patients (37.7%) in the standard treatment group [relative risk, 1.04 (CI, 0.85 to 1.27)]. The percentage of patients with hematoma expansion also did not differ between groups.*

## Hospital Medicine

1. Uranga A, Espana PP, Bilbao A *et al.* Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A Multicenter Randomised Clinical Trial. *JAMA Intern Med* 2016; 176: 1257-65.

This multicenter, randomised, non-inferiority trial sought to substantiate the IDSA guidelines by randomly assigning

312 community dwelling, immunocompetent adults to receive either a minimum of 5 days of antibiotic therapy, followed by discontinuation if body temperature was 37.8 °C or less and there was no more than 1 CAP-associated sign of clinical instability, or usual care at the physician's discretion. The primary outcome was improvement or resolution of signs and symptoms of CAP without further antibiotics at day 10 and day 30 from hospital admission. *This trial supports the existing IDSA recommendations for 5 days of antibiotic treatment in clinically stable, afebrile patients with CAP after hospitalisation. These recommendations have the potential to reduce costs, antibiotic-related adverse events, and antibiotic resistance without differences in cure.*

2. Seymour CW, Liu VX, Iwashyna TJ *et al.* Assessment of Clinical Criteria for Sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315: 762-74.

This study developed criteria using data from 12 community and academic hospitals in Pennsylvania and externally validated them in 165 hospitals. The development and validation samples included 148 907 and 706 399 adults with a first episode of suspected infection, respectively. Investigators compared the prediction accuracy for in hospital mortality of the 2001 SIRS system ( $\geq 2$  SIRS criteria) with the Sequential Organ Failure Assessment (SOFA) (score  $> 2$ ); the modified Logistic Organ Dysfunction System (score  $> 2$ ); and the quick SOFA (qSOFA), a newly developed assessment that optimised the quality and completeness of predictor variables and model parsimony. A qSOFA threshold included at least 2 of the 3 following criteria to be present: respiratory rate of 22 breaths/min or greater, altered mentation, and systolic blood pressure of 100 mm Hg or less. *For non-ICU patients, the predictive accuracy of qSOFA for mortality was superior to that of the 2001 SIRS criteria (area under the receiver operating characteristic curve, 0.81 vs. 0.76;  $P < 0.001$ ) and similar to that of the other more complex models.*

## Pulmonary Medicine

1. Gibson P, Wang G, McGarvey L *et al.* CHEST Expert Cough Panel. Treatment of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report. *Chest* 2016; 149: 27-44.

Unexplained Chronic Cough is defined as a cough persisting for more than 8 weeks that remains unexplained despite appropriate evaluation and therapeutic trials. *Gabapentin and multimodal speech pathology-based cough suppression are recommended for treatment of UCC.*

2. McEvoy RD, Antic NA, Heeley E. SAVE Investigators and Co-ordinators. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnoea. *N Engl J Med* 2016; 375: 919-31.

Patients with moderate-to-severe OSA and a known diagnosis of coronary artery or cerebrovascular disease were randomly assigned to receive CPAP plus usual care or usual care alone, with a mean follow-up of 3.7 years. The primary end-point was death from cardiovascular causes, myocardial infarction, hospitalisation for unstable angina, heart failure, stroke, or transient ischemic attack. Secondary end-points included health-related quality of life, daytime sleepiness, and other cardiovascular outcomes.

1,359 patients were assigned to receive CPAP plus usual care and 1,358 were assigned to receive usual care. Adherence to CPAP was 3.3 hours (SD, 2.3) per night, with a reduction in apnoea-hypopnoea events from 29 to 3.7 events/h. *Compared with the usual care control group, CPAP treatment did not prevent cardiovascular events, despite good control of the apnoea-hypopnoea events. However, there was a significant improvement in the secondary end points of health-related quality of life, daytime sleepiness, snoring, and anxiety or depression.*

## Rheumatology

1. Nissen SE, Yeomans ND, Solomon DH *et al.* PRECISION Trial Investigators. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. *N Engl J Med* 2016; 375: 2519-29.

In this randomised, multicenter, double-blind, non-inferiority trial, 24,081 patients with either RA or osteoarthritis received celecoxib, ibuprofen, or naproxen. Patients either were at risk for or had a history of cardiovascular events. Mean treatment duration was 20.3 months (SD, 16), and mean duration of follow-up was 34.1 months (SD, 13.4). The primary outcome was time to first event: death from a cardiovascular cause. In the intention-to-treat cohort, this outcome occurred in 188 patients (2.3%) receiving celecoxib, 201 (2.5%) receiving naproxen, and 218 (2.7%) receiving ibuprofen [hazard ratio (HR) for celecoxib vs naproxen, 0.93 (95% CI, 0.76 to 1.13); HR for celecoxib vs ibuprofen, 0.85 (CI,

0.70 to 1.04);  $P < 0.001$  for non-inferiority for both comparisons]. The on-treatment analysis showed similar results ( $P < 0.001$  for non-inferiority). *Celecoxib had a lower risk for gastrointestinal side-effects and is non-inferior to ibuprofen or naproxen regarding cardiovascular safety.*

2. Cosman F, Crittenden DB, Adachi JD *et al.* Romosozumab Treatment in Post-menopausal Women with Osteoporosis. *N Engl J Med* 2016; 375: 1532-43.

This phase 3, international, randomised, double-blind, placebo-controlled, parallel-group trial involved 7,180 women with osteoporosis at the hip or femoral neck. Patients received romosozumab or placebo for 1 year, and then all patients received 1 year of open-label denosumab (a monoclonal antibody inhibiting RANKL). At 1 year, 16 of 3,321 patients (0.5%) in the romosozumab group versus 59 of 3,322 (1.8%) in the placebo group developed new vertebral fractures [risk ratio, 0.27 (CI, 0.16 to 0.47);  $P = 0.001$ ]. *In year 2, the cumulative incidence of new vertebral fracture was 0.6% of the original romosozumab group compared with 2.5% in the original placebo group [risk ratio, 0.25 (CI, 0.16 to 0.40);  $P = 0.001$ ].* Adverse events, including hyperostosis, cardiovascular events, and cancer, were similar between the groups.

3. Villiger PM, Adler S, Kuchen S *et al.* Tocilizumab for Induction and Maintenance of Remission in Giant Cell Arteritis: a Phase 2, Randomised, Double-Blind, Placebo-controlled Trial. *Lancet* 2016; 387: 1921-7.

In this trial, 20 patients received tocilizumab and prednisolone and 10 patients received placebo and prednisolone. The primary end point was the proportion of patients who achieved complete remission of disease (defined as a prednisolone dosage of 0.1 mg/kg per day) at week 12. Patients were followed for 1 year. Patients who received tocilizumab and prednisolone were more likely than those receiving placebo plus prednisolone to reach complete remission [17 of 20 (85%) vs 4 of 10 (40%), respectively; risk difference, 45% (CI, 11% to 79%);  $P = 0.03$ ]. *Tocilizumab recipients were more likely than placebo recipients to have relapse-free survival at 52 weeks and a lower cumulative prednisolone dose. Rates of adverse events were similar in each group.*

## Healthy Heart Syndrome

**BM Hegde\***

***"Plato is my friend,  
Aristotle is my friend,  
but my greatest friend is truth."***

– Isaac Newton.

The prestigious medical Journal, the *Lancet*, had a good study published on the heart status of the aboriginals in the Amazon forests in the Bolivian territory. They are the Tsaimane (pronounced as chee-mah-nay). As in all our reductionist studies, they measured the coronary calcium level as a surrogate marker of coronary artery disease, which also is not a true measure of coronary artery disease. Be that as it may, the Tsaimane tribe lived away from what we call civilisation and led a hunter-gatherer egalitarian life, without the touch of modern monetary economy, with its accompanying "Wall-street greed". These people are not supposed to get precocious heart attacks and premature death. Both inferences are, at the moment, only presumptions!

The study authors claim that since they eat hunter-gatherers' diet of fruits, cereals like rice and maize, and also fish with occasional meat of monkeys, piranha and large rodents they hunt<sup>1</sup>. They walk a lot to get their food daily, average being about 17,000 steps, in contrast to the western healthy advice of 10,000 steps. They live together in large communes without the "I" (illness concept) but with the "we" (wellness concept). They do not have banks and money in circulation. They share what they get, with due consideration for everyone in the commune. In short, they have no negative thoughts of greed, pride, jealousy, on-upmanship, living as one large family.

As usual, in our reductionist cross-sectional research, we seem to lose the woods while counting the trees! See how the conventional pundits reacted to the findings. Tim Chico, consultant cardiologist and reader in cardiovascular medicine at the University of Sheffield, told *The Independent* that we shouldn't "romanticise the Tsaimane existence", adding that "two-thirds of them suffer intestinal worms and have a very hard life, without fresh water, sewerage, or electricity". We think it is a hard life, but they are very happy indeed. Intestinal worms are supposed to increase our immune strength! Another comment is still romantic: "Surely, somewhere in the middle is the place to be. It's up

to each of us to find that healthy balance." As I said above, we have missed the woods for the trees. The woods are beautiful, dark and deep and we shall not miss the woods in this study.

Our evolution and even our diseases are environmental and not genetic or due to minor things like what we eat, how we eat it, where we live, what our abdominal girth is, our weight, our blood pressure, sugar, cholesterol, etc. The so-called risk factors in our venerated risk factor hypothesis, in reality, do not have much effect on our illness or wellness. Non-availability of fresh water, sewerage and electricity are not risk factors either. These are important in the 18th century Newtonian world view, which is reductionistic. As the common saying goes, it is not what you eat that kills as long as you do not over eat; it is *what eats you that kills you* – your negative thoughts!

In the 21st Century quantum world view, matter is not made out of matter but is made out of energy. In that context the human body is just the holographic projection of our mind, the consciousness. Our mind is the canvas on which our thoughts are projected. Mind is not inside the brain! *The real environment of our body is our mind. Therefore, it is the mind that determines why one is healthy at a given time or is ill at any other time.* While food, exercise and water, etc., are important for good health, the real kingpin in the game of our health and disease is our mind! If the Tsaimane tribe are healthier than us and have no heart disease, it is because the environment of their body (their mind) is happy, contented and has no negative feelings. That hidden truth was missed by the researcher while they went in search of inconsequential details about their living.

An old study of the Innu community of the islands off the coast of Labrador coastal town (*The Failure of Scientific Medicine: Davis Inlet as an Example of Socio-political Morbidity*) in Canada published in 1987 so graphically showed how the Innus, an aboriginal race, who lived with no knowledge of the so called civilisation and the monetary economy of mainland Canada, lived an egalitarian hunter-gatherer existence without sewerage, electricity and clean water, but with profound happiness, caring and sharing what they hunted and gained. They lived happily like a large single family<sup>2</sup>. Their records on stone and leaves showed

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**\*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.**



that their only causes of death were old age and predation! They were not heir to any illness that the civilised world suffered from up until 1732 when, for the first time, a barter company from mainland Canada, The Hudson's Bay Company, set up a shop in Innus land starting the barter economy which soon led to the monetary economy and Innus became rightful citizens of mainland Canada. Now Innus are heir to every disease that Caucasian Canadians are heir to, from common cold to cancer, ten years precociously compared to Caucasian Canadians. What changed for the Innus was the introduction of the monetary economy with all its attendant ills! William Wordsworth was right, when in 1802, he wrote:

*The world is too much with us; late and soon,  
Getting and spending, we lay waste our powers;  
Little we see in Nature that is ours;  
We have given our hearts away, a sordid boon!*

The essence of the wisdom in these two studies, somewhat similar in character, and their message is the same. When you sell your heart (soul) to the Devil you will have to get heart attacks more frequently. The Innus and Tsaimanes have had their hearts with them and they had not sold their hearts to the Devils of the monetary economy. It is not because of what they ate or what they did that mattered as much *as what ate them* (their negative thoughts resulting from the monetary greed). Our Western medical science can only answer "how" one gets a disease or "how much." Our positive sciences cannot answer the question "why" does one get any disease at any given time? So spake Nobel Laureate Charles Sherrington in 1895 at the age of 38 in his acceptance speech after he was appointed Professor of Physiology at the Liverpool University.

Let us not get lost in the Newtonian world view of the 18th Century. Quantum world view allows us to comprehend much more than what we can grasp with our five senses. *The latter allows us to know that the real environment of diseases is the human mind.* If we can mind our mind we can mend most diseases without outside intervention. Healing, finally, is due to our own built-in immune system. Long live mankind on this planet? Please take note that *"knowledge advances not by repeating known things (as was done by the researchers in this Bolivian study), but by refuting false dogmas."* Reductionistic science in human affairs must give place to holistic science.

***"Wise men talk because they have something to say;  
fools, because they have to say something."***

– Plato.

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## Study of Plasma Fibrinogen Levels in Type 2 Diabetes Mellitus and its Association with Microalbuminuria and Glycaemic Control

Pankaj Kumar Saini\*, Manoj Saluja\*\*, SR Meena\*\*\*, Shyam Bihari Meena\*\*\*\*, Naveen Seervi\*, Prashant Shrangi\*

### Abstract

**Objectives:** This study was undertaken to estimate plasma fibrinogen levels and its association with microalbuminuria and glycaemic control in patients with type 2 diabetes mellitus in addition to assessment of risk factors such as obesity, hypertension, smoking, and dyslipidaemia.

**Materials and Methods:** Plasma fibrinogen levels (Clauss method) were estimated in 60 type 2 diabetic patients and 30 age, sex, and body mass index matched controls. Plasma fibrinogen levels were correlated with various parameters-like microalbuminuria (urine albumin to creatinine ratio), glycosylated haemoglobin (ion exchange High Performance Liquid Chromatography), age, sex, body mass index, hypertension, smoking, and dyslipidaemia.

**Results:** Mean plasma fibrinogen level in cases was high ( $380.03 \pm 101.07$  mg/dl) as compared to controls ( $244.43 \pm 61.27$  mg/dl) which was found to be statistically highly significant ( $p < 0.0001$ ). Fibrinogen levels were associated with age ( $p = 0.003$ ), body mass index ( $p = 0.016$ ), total cholesterol ( $p = 0.003$ ), LDL ( $p = 0.012$ ), triglycerides ( $p = 0.015$ ), HDL ( $p = 0.013$ ), microalbuminuria ( $p < 0.0001$ ) and glycaemic control ( $p < 0.0001$ ) in diabetics. But, no correlation was found with sex ( $p = 0.154$ ), hypertension ( $p = 0.167$ ), and smoking ( $p = 0.283$ ) in cases. In controls plasma fibrinogen level was associated with age ( $p = 0.004$ ) and body mass index ( $p = 0.0008$ ). Multi variable linear regression analysis showed body mass index ( $p = 0.003$ ), microalbuminuria ( $p < 0.05$ ), glycaemic control ( $p = 0.0008$ ), and total cholesterol ( $p = 0.043$ ) to be independent variables for hyperfibrinogenaemia.

**Conclusion:** Patients with type 2 diabetes mellitus had a higher plasma fibrinogen level. Fibrinogen level was significantly associated with microalbuminuria and glycaemic control.

**Keywords:** Type 2 diabetes mellitus, fibrinogen, microalbuminuria, glycaemic control.

### Introduction

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia. Patients with type 2 diabetes mellitus have been reported to be at increased risk of developing cardiovascular related diseases. The increase in cardiovascular morbidity and mortality rates appears to relate to the synergism of hyperglycaemia with other cardiovascular risk factors. Individuals with insulin resistance and type 2 diabetes mellitus have elevated levels of plasminogen activator inhibitors (especially PAI-1) and fibrinogen, which enhances the coagulation process and impairs fibrinolysis, thus favouring the development of thrombosis<sup>1</sup>.

Patients with diabetes are prone to arterial thrombosis due to persistently activated thrombogenic pathways and impaired fibrinolysis. The presence of high plasma levels of CRP and fibrinogen are predictive for vascular complications and cardiovascular death in patients with diabetes<sup>2</sup>.

Fibrinogen is a strong and independent cardiovascular risk factor. Its plasma concentration predicts cardiovascular events in both the general population, and non diabetic

patients with clinical vascular disease. Plasma fibrinogen may also be increased in type 2 diabetes, thus suggesting that hyperfibrinogenaemia could contribute to the excess cardiovascular morbidity and mortality in this disease<sup>3</sup>.

Fibrinogen strongly affects hemostasis, blood rheology, platelet aggregation and endothelial function. The hemorheological consequences of hyperfibrinogenaemia might act at various levels; by reducing blood flow, by predisposing to thrombosis, and by enhancing atherogenesis<sup>4</sup>.

Microalbuminuria has been recognised as an important biomarker to predict micro and macrovascular diabetic complications<sup>5</sup>. Poor glycaemic control has been reported to be associated with increased vascular complications in diabetics<sup>6</sup>.

In view of above concepts and due to paucity of similar studies, this study has been undertaken to study plasma fibrinogen levels in patients with type 2 diabetes mellitus and its association with microalbuminuria and glycaemic control in addition to assessment of various risk factors such as age, obesity, hypertension, smoking and dyslipidaemia.

\*Post-Graduate Resident, \*\*Associate Professor, \*\*\*Senior Professor, \*\*\*\*Assistant Professor, Department of Medicine, Government Medical College, Kota - 324 001, Rajasthan.

## Materials and methods

The source of data were patients of type 2 diabetes mellitus attending outdoor or admitted at Govt. Medical College and MBS Hospital, Kota during the study period from November 2013 to November 2014. Patients of type 1 diabetes mellitus, patients with acute and chronic infections, renal disease, endocrine disease, malignancy, and patients on warfarin, steroids, hormone replacement therapy were excluded from the study. The method of collection of data was purposive sampling technique and it was a case-control study. Sample size of the cases were sixty patients attending outdoor or admitted at Govt. Medical College and MBS Hospital, Kota who were diagnosed as type 2 diabetes mellitus, newly detected or already on treatment. Controls were selected from non-diabetic healthy attendants accompanying the patients at MBS hospital, Kota with no history of diabetes mellitus or hypertension or ischaemic heart disease who were age, sex and body mass index matched to the cases. A detailed history and clinical examination was done pertaining to various risk factors and relevant laboratory investigations were done in both diabetic patients and in controls. The various parameters which were studied included age of the patient (years), sex, body mass index ( $\text{kg}/\text{m}^2$ ), smoking, blood pressure (mmHg), plasma fibrinogen level (mg/dl), glycosylated haemoglobin (%), microalbuminuria, total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride level. Plasma fibrinogen was estimated by clot based assay, Clauss method. Microalbuminuria was measured by urine albumin to creatinine ratio. Spot urine microalbumin was measured by immunoturbidimetric analysis. Urine creatinine was measured by spectrophotometry. Glycosylated haemoglobin was measured by Ion exchange high performance liquid chromatography method. Fasting blood sample was collected for lipid profile. Total cholesterol, HDL and triglycerides were directly assessed by standard enzymatic methods. LDL cholesterol was estimated using direct enzyme clearance method. Blood Sugar level, plasma fibrinogen level, microalbuminuria, glycosylated haemoglobin, complete blood count, ESR, C-reactive protein, blood urea, serum creatinine and serum lipid profile were measured in cases and controls.

## Results

In this study, 60 patients with type 2 diabetes mellitus were studied and compared with 30 age, sex, and body mass index matched controls in relation to plasma fibrinogen levels. Fibrinogen levels were correlated with age, sex, body mass index, microalbuminuria, glycaemic control, hypertension, smoking and lipid profile. The patients were divided into four age groups, viz., 40 - 50 years, 51 - 60 years, 61 - 70 years and 71 - 80 years for analytical purpose.

According to body mass index patients were divided in three groups, i.e., 18 - 25, 26 - 30 and  $>30$ . Mean age of cases was 56.5 years and mean age of controls was 56.2 years. Males and females were equal in number in cases and controls (M:F = 1:1). Mean body mass index was 27.46 in cases and 27.2 in controls. Maximum patients (30) had duration of diabetes more than 5 years with mean duration of 7.5 years. Mean plasma fibrinogen level in cases was high ( $380.03 \pm 101.07$  mg/dl) when compared to controls ( $244.43 \pm 61.27$  mg/dl) and it was found to be statistically highly significant ( $p < 0.0001$ ) (Table I).

**Table I: Clinical and biological parameters of diabetic patients and controls.**

	Diabetic patients	Controls	P value	Significance
Subjects	60	30	-	-
Mean age (years)	$56.5 \pm 9.33$	$56.2 \pm 9.76$	0.87	NS
Sex (M/F)	30/30	15/15	-	-
Body mass index ( $\text{kg}/\text{m}^2$ )	$27.46 \pm 3.68$	$27.20 \pm 3.92$	0.73	NS
Fibrinogen (mg/dl)	$380.03 \pm 101.07$	$244.43 \pm 61.27$	$< 0.0001$	Significant

It was found in cases that as age advances fibrinogen also increases and it was statistically significant ( $p = 0.003$ ). In controls also fibrinogen showed positive correlation with age ( $p = 0.004$ ). In cases males had higher mean fibrinogen level than females, but it was not statistically significant ( $p = 0.154$ ). In controls also fibrinogen level did not show significant association with sex ( $p = 0.082$ ). Fibrinogen level showed positive correlation with body mass index in cases ( $p = 0.016$ ) and controls ( $p < 0.0001$ ) (Table II, Table V).

**Table II: Correlation of plasma fibrinogen level with various parameters in diabetics.**

S.no.	Parameter	N	Fibrinogen level	Pvalue	Significance
1.	Age group (years)			0.003	Significant
	40 - 50	19 (32%)	$343.26 \pm 76.96$		
	51 - 60	25 (42%)	$361.92 \pm 84.5$		
	61 - 70	12 (20%)	$432.83 \pm 121.53$		
	71 - 80	4 (6%)	$509.5 \pm 96.52$		
2.	Sex			0.154	NS
	Male	30 (50%)	$398.77 \pm 123.97$		
	Female	30 (50%)	$361.3 \pm 68.48$		
3.	Body mass index ( $\text{kg}/\text{m}^2$ )			0.016	Significant
	18 - 25	16 (27%)	$333.6 \pm 79.75$		
	26 - 30	32 (53%)	$379.9 \pm 96.72$		
	$> 30$	12 (20%)	$442.2 \pm 111.4$		

Fibrinogen level was high in patients with microalbuminuria ( $429.2 \pm 93.59$  mg/dl) when compared to patients without microalbuminuria ( $323.8 \pm 78.24$  mg/dl) and it was found to be statistically significant ( $p < 0.0001$ ). Patients with poor glycaemic control had higher fibrinogen level ( $429.1 \pm 94.87$  mg/dl) when compared to patients with adequate glycaemic control ( $301.1 \pm 45.84$  mg/dl) and it was statistically significant ( $P < 0.0001$ ) (Table III).

In diabetic hypertensive patients mean fibrinogen level was high when compared to diabetic normotensive patients but it was statistically not significant ( $395.3 \pm 98.37$  vs.  $358.7 \pm 102.92$ ,  $p = 0.169$ ). In smokers mean fibrinogen level was high when compared to non smokers but it was statistically not significant ( $419.8 \pm 126.7$  vs.  $372.1 \pm 94.67$ ,  $p = 0.283$ ) (Table III).

**Table III: Correlation of plasma fibrinogen level with various parameters in diabetics.**

S.no.	Parameter	N	Fibrinogen level	P value	Significance
1.	HbA1C (%)			<0.0001	Significant
	≤ 6%	23 (38%)	$301.1 \pm 45.84$		
	> 6%	37 (62%)	$429.1 \pm 94.87$		
2.	Microalbuminuria			< 0.0001	Significant
	Present	32 (53%)	$429.2 \pm 93.59$		
	Absent	28 (47%)	$323.8 \pm 78.24$		
3.	Hypertension			0.169	NS
	Hypertensives	35 (58%)	$395.3 \pm 98.37$		
	Normotensives	25 (42%)	$358.7 \pm 102.92$		
4.	Smoking			0.283	NS
	Smokers	10 (17%)	$419.8 \pm 126.73$		
	Non smokers	50 (83%)	$372.1 \pm 94.68$		

Plasma fibrinogen levels significantly correlated with total cholesterol ( $p = 0.003$ ), HDL cholesterol ( $p = 0.013$ ), LDL cholesterol ( $p = 0.012$ ) and triglyceride level ( $p = 0.015$ ) (Table IV).

Multi variable linear regression analysis showed body mass index ( $p = 0.003$ ), microalbuminuria ( $p < 0.05$ ), glycaemic control ( $p = 0.0008$ ) and total cholesterol ( $p = 0.043$ ) to be independent variables for hyperfibrinogenaemia.

**Table IV: Correlation of plasma fibrinogen level with serum lipid profile in diabetics.**

	Total cholesterol		LDL		HDL		Triglycerides	
Lipid groups (mg/dl)	<200	>200	<130	>130	>40	<40	<150	>150
Mean fibrinogen (mg/dl)	342.6	420.1	347	411	339.4	403.6	347.8	410.2
P value	0.003		0.012		0.013		0.015	
Significance	Significant		Significant		Significant		Significant	

**Table V: Correlation of plasma fibrinogen level with various parameters in controls.**

S.no.	Parameter	N	Fibrinogen level	P value	Significance
1.	Age group (years)			0.004	Significant
	40 - 50	9 (30%)	$199.33 \pm 52.74$		
	51 - 60	12 (40%)	$241.83 \pm 48.94$		
	61 - 70	7 (23%)	$282.86 \pm 53.46$		
	71 - 80	2 (7%)	$328.5 \pm 16.26$		
2.	Sex			0.082	NS
	Male	15 (50%)	$263.93 \pm 50.56$		
	Female	15 (50%)	$224.9 \pm 66.37$		
3.	Body mass index (kg/m <sup>2</sup> )			< 0.0001	Significant
	18 - 25	13 (44%)	$193.69 \pm 40.4$		
	26 - 30	10 (33%)	$257.9 \pm 35.51$		
	> 30	7 (23%)	$319.43 \pm 23.39$		

## Discussion

The results from our study showed plasma fibrinogen levels to be significantly high in patients with diabetes as compared to controls. Bruno G *et al*<sup>6</sup> found fibrinogen levels to be significantly high in patients with diabetes. Jain A *et al*<sup>7</sup> found higher fibrinogen levels in diabetic patients as compared to controls. Similar results were obtained by Ganda OP *et al*<sup>8</sup>. Fibrinogen has an independent effect on cardiovascular mortality suggesting that both endothelial dysfunction and chronic inflammation are involved in the excess cardiovascular mortality of type 2 diabetic patients<sup>5</sup>.

Plasma fibrinogen levels showed an increasing trend with age. Bruno G *et al*<sup>6</sup> reported positive association of fibrinogen levels with age. No significant association was found between fibrinogen and sex. Jain A *et al*<sup>7</sup> also did not find any association between sex and fibrinogen.

In our study fibrinogen level showed significant association with body mass index. Study by James J *et al*<sup>13</sup> also showed fibrinogen to increase with body mass index. Similarly, association between body mass index and fibrinogen was found by Jain A *et al*<sup>7</sup>.

In our study mean fibrinogen level was high in patients with poor glycaemic control. The correlation between glycaemic control and fibrinogen levels could be due to (a) glycosylated fibrinogen is less susceptible to plasmin degradation (b) relative insulin deficiency in diabetics results in differential protein synthesis, i.e., 29% decrease in albumin synthesis and 50% increase in fibrinogen synthesis<sup>14</sup>. In the study of Bruno G *et al*<sup>6</sup> fibrinogen level was significantly associated with haemoglobin A1c value. Another study by Ceriello A<sup>15</sup> suggested that hyperfibrinogenaemia is one way by which hyperglycaemia activates coagulation. Therefore, both epidemiologic and

clinical findings support the hypothesis that poor glycaemic control may lead to thrombophilia, a condition that might be involved in the increased cardiovascular risk in patients with diabetes.

Plasma fibrinogen levels were significantly high in patients who had microalbuminuria, compared to those with no proteinuria. Michaelle Della Vestra *et al*<sup>11</sup> found higher fibrinogen levels in patients with microalbuminuria and overt proteinuria compared to those with no proteinuria. Similar results were obtained in studies by Jain A *et al*<sup>7</sup>, Ghada ZA Soliman<sup>8</sup>, which suggest that the positive association seen between albumin excretion rate and fibrinogen level could explain the increased cardiovascular related morbidity and mortality in diabetic patients with microalbuminuria and macroalbuminuria.

In the present study, higher levels of fibrinogen were seen in hypertensive patients compared to normotensives, however, it was not statistically significant. Higher levels of fibrinogen were seen in hypertensive patients compared to normotensives in studies by Lee AJ *et al*<sup>10</sup>, Mistry P *et al*<sup>12</sup> and Jain A *et al*<sup>7</sup>.

No significant association was found between fibrinogen levels and smoking. Our results were consistent with the study done by Jain A *et al*<sup>7</sup> in which they found no significant association between fibrinogen level and smoking.

Fibrinogen levels were significantly associated with total cholesterol, LDL cholesterol and triglyceride level. Fibrinogen levels had inverse association with HDL cholesterol. In a meta analysis by Ernst *et al*<sup>16</sup> positive associations were seen between fibrinogen levels and total cholesterol, triglycerides, LDL levels and inverse associations between HDL and fibrinogen levels. Similar results were obtained by Ghada ZA Soliman<sup>8</sup>.

## Conclusion

It has been shown that diabetes is a procoagulant state. The pathophysiology of this procoagulant state is not completely understood. Hypercoagulability, as evidenced by increased fibrinogen levels, may contribute to the procoagulant state observed in patients with diabetes. This procoagulant state may contribute to atherosclerosis which is the major cause of cardiovascular related morbidity and mortality.

Fibrinogen levels were significantly higher in microalbuminuric diabetic patients with poor glycaemic control. Microalbuminuria represents a sensitive marker of cardiovascular disease and it has been recognised as a powerful predictor of cardiovascular related morbidity and

mortality. It can be concluded that hyperfibrinogenaemia may precede the onset of clinical vascular complications and therefore it could be a possible mechanism of the increased cardiovascular risk in patients with type 2 diabetes mellitus.

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## Hepatic Dysfunction in Patients of Dengue Viral Infection in Kota Region

Naveen Seervi\*, SR Meena\*\*, Manoj Saluja\*\*\*, Shyam Bihari Meena\*\*\*\*, Prashant Shringi\*, Pankaj Kumar Saini\*

### Abstract

**Introduction:** Dengue viral infection is an important mosquito-borne arboviral disease in many tropical and subtropical countries, including India. We encountered an outbreak of dengue infection in the recent past in the Kota region of Rajasthan. Hepatic dysfunction was very common in these patients. So we planned to a study of hepatic dysfunction in these patients and its impact on severity of illness.

**Material and methods:** We analysed 117 serologically confirmed (IgM ELISA positive) hospitalised cases of dengue of age more than 10 years. They were grouped into DF, DHF and DSS (according to 1997 WHO criteria). Detailed history and clinical examination were done. Various liver function tests were ordered. All patients underwent ultrasound study of abdomen.

**Results:** Out of these 117 cases, 65 (55.56%) were male and 52 (44.44%) were female. Fever was present in all cases. Bodyache, myalgia, pain abdomen and vomiting were common symptoms. Hepatomegaly was the most common clinical sign observed (73.5%). Mean values of AST were 158.2, 202.3 and 348.8 IU/L ( $p < 0.0001$ ); mean values of ALT were 93.5, 100.4 and 284.8 IU/L ( $p < 0.0001$ ); mean values of ALP were 116.3, 140.8 and 220.1 IU/L ( $p = 0.0003$ ) in DF, DHF and DSS groups, respectively. Mean values of INR were 1.08, 1.24 and 1.27 in DF, DHF and DSS groups, respectively ( $p = 0.0001$ ). On ultrasound, ascites was seen in 21 (32.3%), 25 (78.1%) and 16 (80%) ( $p = 0.0001$ ); pleural effusion was seen in 21 (32.3%), 23 (71.9%) and 14 (70%) ( $p = 0.0002$ ); gall bladder wall thickening was seen in 31 (47.7%), 22 (68.8%) and 15 (75%) ( $p = 0.0346$ ) in DF, DHF and DSS groups, respectively.

**Conclusion:** Hepatic dysfunction is very common with dengue viral infection. The degree of hepatic injury is proportional to morbidity degree and mortality in these patients. Hepatomegaly, raised liver enzymes, prolonged prothrombin time, ascites, pleural effusion and gall bladder wall thickening can be used as predictors of the severity of dengue viral infection.

**Key words:** Dengue viral infection, hepatomegaly, liver enzymes, prothrombin time, ascites, pleural effusion, gall bladder.

### Introduction

Dengue virus infection is a major and important public health problem in many South-East Asian countries and also in more than 100 countries of the tropical and subtropical region<sup>1,2</sup>. It is the most common arboviral disease transmitted globally. It is caused by four antigenically distinct dengue virus serotypes (DEN 1, DEN 2, DEN 3 and DEN 4)<sup>3</sup>. Recently, we encountered many outbreaks in several regions of the country. Hepatic injury with dengue infection has been described since 1960<sup>4</sup>. The degree of liver dysfunction in patients with dengue infection varies from mild injury with elevation of transaminase activity, hepatomegaly (tender/non tender) to severe injury with jaundice and fulminant hepatic failure<sup>1</sup>. In patients with dengue fever, elevated bilirubin level and transaminase values suggest poor outcome<sup>5</sup>. The liver dysfunction could be a direct viral effect or an adverse consequence of dysregulated host immune response against the virus<sup>6</sup>. As there is an upsurge in the dengue epidemic in India, the increased incidence of hepatic dysfunction may clinically simulate to viral hepatitis or enteric hepatitis and malaria. It is thus important to differentiate dengue from these

conditions. Awareness of these manifestations of hepatic involvement in dengue may be helpful in arriving at an early diagnosis and avoiding morbidity and mortality.

### Aims and objectives

Large clinical studies documenting hepatic involvement in dengue infection are scarce. In the recent past, we encountered one such dengue outbreak in the Kota region of Rajasthan. Along with the typical manifestations of dengue viral infection, we documented many patients with impaired liver functions. So we planned to study liver function abnormalities in patients admitted with dengue viral infection at Govt. Medical College, Kota and to determine role of hepatic dysfunction as predictor of the severity of disease in these patients.

### Materials and methods

This prospective cohort study was conducted in the Department of Medicine, Government Medical College and associated group of hospitals, Kota during the study period from August 2013 to November 2014. All the clinically

\*Post-Graduate Resident, \*\*Senior Professor and Head, \*\*\*Associate Professor, \*\*\*\*Assistant Professor, Department of Medicine, Government Medical College, Kota - 324 001, Rajasthan.

suspected cases of dengue infection, aged more than 10 years, as per the WHO guidelines were screened and 117 serological confirmed cases (by dengue IgM capture ELISA) were included in this study. Cases with pre-existing liver disease, viral hepatitis, malaria, and enteric fever were excluded from the study. All of the patients underwent detailed history and clinical examination. CBC, various liver function tests, and ultrasound study were done in all patients. Descriptive statistics, one way ANOVA, and chi-square test (for trends) were applied for analysis of results.

## Results

A total of 117 seropositive cases formed the study subjects. Out of these 65 patients had DF, 32 had DHF and 20 had DSS (classified according to 1997 WHO guidelines). Fever was the most common presenting symptom and was present in 100% cases. Next to fever, bodyache/myalgia (52.14%), pain abdomen (50.43%) and vomiting (43.59%) were the common symptoms. Hepatomegaly was the most common clinical sign and was seen in 73.5% of total cases (64.6%, 78.1% and 95% cases of DF, DHF and DSS, respectively). The incidence of jaundice was (4.27%) among cases.

Elevated AST was observed in 91.45% of cases (86.1%, 100% and 95% of cases of DF, DHF and DSS, respectively). Elevated ALT was observed in 81.2% of cases (75.4%, 84.4% and 95% of cases of DF, DHF and DSS, respectively). Elevated levels of ALP was seen in 41.5% of cases of DF, 65.6% cases of DHF and 70% cases of DSS. Abnormal values of prothrombin time were observed 3.1%, 15.6% and 20% cases with DF, DHF and DSS, respectively ( $p < 0.05$ ).

On ultrasound study, ascites was seen in 32.3%, 78.1% and 80% cases of DF, DHF and DSS, respectively. Pleural effusion was seen in 32.30%, 71.9% and 70% cases of DF, DHF and DSS, respectively. Gall bladder wall thickening on USG was seen in 47.7%, 68.8% and 75% cases of DF, DHF and DSS, respectively. There were two deaths in our study. Both of these cases presented with DSS. Both deaths were secondary to multi-organ involvement, shock, and hepatic dysfunction.

As depicted Table I, we analysed the mean values of various liver function tests and compared these by one way ANOVA. We observed mean S. bilirubin (total) was 0.79, 1.0 and 1.3 mg/dl in DF, DHF and DSS groups with statistically significant difference between these groups, respectively ( $p < 0.05$ ). Mean AST values were 158.2, 202.3 and 343.8 IU/L and mean ALT values were 93.5, 100.4 and 284.4 IU/L in DF, DHF and DSS, respectively with statistically significant difference ( $p < 0.05$ ). Mean values of AST were more than mean values of ALT in all three groups. Mean ALP values were 116.3, 140.8 and 220.1 IU/L in DF, DHF and DSS groups,

respectively with statistically significant difference ( $p < 0.05$ ). We did not observe significant difference in values of S. albumin in three groups ( $p > 0.05$ ). Mean values of S. globulin were 2.76, 2.61 and 2.46 g/dl in DF, DHF and DSS groups, respectively with significant difference between these groups. Mean values of INR were 1.08, 1.24 and 1.27 in three groups, respectively, with significant difference statistically. Mean APTT were 30.55, 31.5 and 31.5 seconds in DF, DHF and DSS groups, respectively, without significant difference statistically.

**Table I: Comparison of liver function tests between DF, DHF and DSS groups.**

Parameter	DF (n = 65)	DHF (n = 32)	DSS (n = 20)	p value
Mean S. bilirubin (T) (mg/dl) (range)	0.79 (0.3 - 1.6)	1.0 (0.5 - 3.3)	1.3 (0.6-3.4)	0.0006
Mean AST (IU/L) (range)	158.2 (18 - 719)	202.3 (60 - 460)	343.8 (32 - 874)	< 0.0001
Mean ALT (IU/L) (range)	93.5 (18 - 719)	100.4 (24 - 253)	284.8 (28 - 806)	< 0.0001
Mean ALP (IU/L) (range)	116.3 (56 - 373)	140.8 (62 - 360)	220.1 (65 - 750)	0.0003
Mean S. albumin (g/dl) (range)	3.43 (2.4 - 4.2)	3.47 (2.6 - 4.4)	3.39 (3.0-3.8)	0.7171 (ns)
Mean S. globulin (g/dl) (range)	2.76 (1.5 - 3.4)	2.61 (1.7 - 3.5)	2.46 (1.6 - 3.3)	0.0198
Mean PT (INR)	1.08	1.24	1.27	0.0001
Mean APTT (seconds)	30.55	31.5	31.5	0.1024 (ns)

**Table II: Comparison of ultrasound findings in DF, DHF and DSS groups.**

Parameter	DF (n = 65)	DHF (n = 32)	DSS (n = 20)	p value
Ascites	21/65 (32.3%)	25/32 (78.1%)	16/20 (80%)	p= 0.0001
Pleural effusion	21/65 (32.3%)	23/32 (71.9%)	14/20 (70%)	p = 0.0002
GB wall thickening	31/65 (47.7%)	22/32 (68.8%)	15/20 (75%)	p = 0.0346

GB: Gall bladder.

As depicted in Table II, we analysed incidence of ultrasonographic features like ascites, pleural effusion and gall bladder wall thickening by chi-square test (for trends). Ascites was seen in 32.3%, 78.1% and 80% cases, pleural effusion was seen in 32.30%, 71.9% and 70% cases and gall bladder wall thickening was seen in 47.7%, 68.8% and

75% cases of DF, DHF and DSS, respectively. We observed all three features were significantly more common in DSS and DHF groups, as compared to DF group.

## Discussion

The clinical and biochemical impact of dengue viral infection was studied on 117 serologically confirmed cases of dengue viral infection during a recent outbreak in 2013 in Kota region of Rajasthan. Hepatomegaly is one of the commonest clinical sign of dengue infection. Hepatomegaly is more frequent and is commoner in patients with DHF than in those with DF<sup>7</sup>. Association of hepatomegaly with cases of dengue infection has been quite variable, the incidence varying from 43% to 98%<sup>8,9</sup>. In our study, hepatomegaly was seen in 73.5% of total cases. The incidence of hepatomegaly was more in shock cases as compared to non-shock cases.

Liver dysfunction with mildly elevated liver enzymes has been reported. Dengue infection leads to involvement of liver parenchyma which releases these markers into the blood<sup>10</sup>. In the acute phase of the disease, an increase occurs in aminotransferases, the levels of which subsequently decrease, as the liver recovers<sup>11</sup>. Most of the studies showed that unlike other viral infections, in dengue the rise of AST is usually more than ALT<sup>12,13</sup> and is believed to be due to release of AST from the damaged myocytes, RBCs, kidney and brain tissue also. In our study we observed AST values more than that of ALT values in all three groups. There was a statistically significant difference in between all three groups in values of AST as well as ALT ( $p < 0.05$ ). Like the AST and ALT, raised S. alkaline phosphatase (ALP) was also seen more commonly in DSS, followed by DHF, DF ( $p < 0.05$ ). All these findings indicate that raised liver enzymes can be used as predictor for the severity of dengue viral infection.

Five (4.27%) cases had clinical jaundice. Out of this 5 cases of 3 were in DSS group (15%), 2 (6.3%) in DHF group. Majority of the previous studies reported jaundice in less than 5%<sup>11,14</sup>. The mean total serum bilirubin of these 5 patients was 3.2 mg/dl. Jaundice occurs more in complicated than in uncomplicated cases. Jaundice in dengue infection has been associated with fulminant hepatic failure and is a poor prognostic sign<sup>15</sup>.

Prothrombin time depends on clotting factors II, V, VII and X, alone or in combination. These factors are synthesised in the liver. Abnormal PT indicates abnormal coagulopathy. It is seen more frequently in cases with severe dengue because increased hepatic cell damage would have caused decreased production of clotting factors, resulting in prolonged PT. Abnormal values of prothrombin time were observed 3.1%, 15.6% and 20% cases with DF, DHF and

DSS, respectively ( $p < 0.05$ ) inferring that altered coagulation profile manifested by prolonged prothrombin time is observed significantly higher in dengue haemorrhagic and dengue shock cases, in comparison to classical dengue fever.

Ultrasound findings of ascites, pleural effusion and gall bladder thickening (acalculous cholecystitis) were observed more in DHF and DSS cases as compared to DF group. Srivenu etha *et al* also observed ascites more common in DSS and DHF groups as compared to DF group<sup>10</sup>. These findings suggest that, like the biochemical markers of liver injury, these ultrasound findings can also be used as predictors of severity of dengue viral infection.

## Conclusion

In our study, we observed that hepatic injury is very common in patients with dengue viral infection. Care must be taken in patients presenting with fever and abnormal liver profile to not make a mistaken diagnosis of viral hepatitis, malaria and enteric fever, etc. Hepatomegaly was the commonest clinical sign in these patients. We observed that degree of hepatic injury (evidenced by raised liver enzymes and abnormal prothrombin time) was proportional to the morbidity and mortality in these patients. We also observed that signs of plasma leakage (ascites and pleural effusion) and gall bladder wall thickening were more in DHF and DSS cases as compared to DF.

Our study concludes that hepatomegaly, raised liver enzymes, prolonged prothrombin time, ascites, pleural effusion and gall bladder wall thickening may be used as predictors of severity of dengue viral infection. However, larger studies may be required to confirm these findings.

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## DIAMICRON XR 60

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## Echocardiographic Study of Left Ventricular Changes in Patients Suffering from Chronic Obstructive Pulmonary Disease in a Tertiary Care Centre

Gouranga Santra\*, Nabendu Karji\*\*

### Abstract

**Introduction:** Right ventricular changes are common in chronic obstructive pulmonary disease (COPD) but controversy has existed regarding the left ventricular changes. We studied left ventricular changes by echocardiography in COPD patients.

**Method:** We enrolled patients with clinical features of COPD. Patients with bronchiectasis, cystic fibrosis, bronchiolitis obliterans and other cardiovascular and systemic diseases were excluded. A control group was selected without history of smoking, asthma, occupational exposure and features of COPD. We matched age, sex, and socio-economic status of control and study groups. All cases and control under went echocardiography.

**Result:** Out of 60 patients of COPD, ten (17%) patients had left ventricular hypertrophy (LVH). Regarding left ventricular systolic function, mean ejection fraction was slightly elevated but was not statistically significant. An impairment of left ventricular diastolic function was noted in 90% patients. Most of them showed decrease in E velocity and the mean E velocity ( $59.86 \pm 5.28$  cm/sec) was significantly decreased from control value ( $69.25 \pm 8.76$  cm/sec) ( $p < 0.05$ ). 'A' velocity was increased ( $65.26 \pm 8.15$  cm/sec) significantly than control value ( $52.75 \pm 7.04$  cm/sec) ( $p < 0.05$ ). E/A ratio was  $< 1$  in most cases (54 patients). In the study group, mean E/A ratio ( $0.896 \pm 0.10$ ) was significantly lower than control group ( $1.32 \pm 0.11$ ) ( $p < 0.05$ ).

**Conclusion:** COPD is commonly associated with left ventricular diastolic dysfunction (90% cases). LVH is not uncommon (17%). LV systolic dysfunction is not found. A larger study will be more helpful to identify the left ventricular changes in COPD.

**Key words:** Chronic obstructive pulmonary disease, left ventricular hypertrophy, diastolic dysfunction.

### Introduction

Large numbers of patients suffer from chronic obstructive pulmonary disease (COPD) in their active period of life. The numbers of COPD patients are increasing, with ageing of population. So there is need to highlight different aspects of the disease, to decrease the morbidity and mortality of affected people. Right ventricular changes are common in COPD but controversy has existed regarding the left ventricular changes. Studies regarding left ventricular changes in COPD are few<sup>1-15</sup>. We have tried to detect changes in left ventricle of COPD patients, using echocardiography and echo-doppler study.

### Material and methods

We enrolled COPD patients from the out-patient clinic and indoor of Department of General Medicine, over a period of six months. For selection of patients, inclusion criteria included: 1) history of chronic cough for three consecutive months for more than two years, breathlessness, prolonged smoking or working in a polluted environment; 2) examination findings like wheeze, ronchi, coarse crepitations, hyperinflation of lungs; 3) radiological features indicating

hyperinflation of lungs, i.e.,  $\uparrow$  translucency, flattening of diaphragm,  $\downarrow$  peripheral vascular markings, enlarged pulmonary artery and its branches with peripheral pruning; 4) pulmonary function test showing FEV1  $< 80\%$  of predicted and FEV1/FVC  $< 70\%$  of predicted. Exclusion criteria included: 1) history suggestive of valvular and congenital heart diseases, coronary artery and pericardial diseases; 2) presence of systemic diseases, i.e., hypertension, diabetes, hypothyroidism, chronic kidney disease and connective tissue diseases; 3) addiction to alcohol or other drugs that could independently cause cardiac changes; 4) a number of specific causes of COPD, i.e., cystic fibrosis, bronchiectasis, bronchiolitis obliterans; 5) ECG evidence of ischaemia (patients with nonspecific ST-T changes in ECG, though quite common in COPD, were excluded because of possible ischaemia); and 6) echocardiographic evidence of regional ventricular wall motion abnormality, akinesia, hypokinesia, dyskinesia or evidence of cardiomyopathy. A control group was selected from patients attending General Medicine department, having no history of smoking, asthma, occupational exposure, and no symptoms and signs of COPD and without any change suggestive of COPD in chest X-ray, or pulmonary function test. We matched age, sex, and socio-

\*Associate Professor, Department of Medicine, Midnapore Medical College, Midnapore - 721 101, West Bengal,

\*\*Associate Professor, Department of Medicine, RG Kar Medical College, Kolkata, West Bengal.

economic status of control and study groups.

All patients in our study underwent echocardiography and echo-doppler study. The echocardiographer was blinded to cases and control. Patients were subjected to echocardiography, approximately, at the same time in morning to minimise changes due to variations of sympathetic activity. The parameters assessed were anatomy of left ventricle, left ventricular internal diameter in diastole and systole [LVID (d) and LVID (s)], left ventricular posterior wall thickness (LVPWT), interventricular septal wall thickness in systole [IVS (s)] and diastole [IVS (d)].

The measurements obtained by M-mode echocardiography including ejection fraction and fractional shortening were used to assess LV systolic function.

$$\text{Fractional shortening} = \frac{\text{LVID (d)} - \text{LVID (s)}}{\text{LVID (d)}} \times 100$$

$$\text{LV ejection fraction} = \frac{(\text{LVIDd})^3 - (\text{LVIDS})^3}{(\text{LVIDd})^3} \times 100$$

Mitral flow velocities were recorded by doppler study. E-peak [peak velocity of early rapid diastolic filling (cm/sec)], A-peak [peak velocity of late diastolic filling (cm/sec) during atrial contraction] and E/A ratio were calculated. (E/A ratio is normally  $1.6 \pm 0.5$ . Normal peak velocity is greater with early diastolic flow. In patients with impaired LV relaxation, peak-E velocity is reduced while peak-A velocity is increased

and E/A ratio is altered).

We calculated LV mass by using Devereux regression equation and body surface area (BSA).

$$\text{Left ventricular mass index} = \frac{0.83 [(\text{LVIDd} + \text{LVPWT} + \text{IVS})^3 - (\text{LVIDd})^3] + 0.6}{\text{BSA (sq.M)}} \text{ Gm}$$

Echocardiographic criteria for left ventricular hypertrophy (LVH) included: 1) IVS(d) or LVPWT(d) > 1.1 cm; and 2) LV mass index: > 111 gm/m<sup>2</sup> in female and > 135 gm/m<sup>2</sup> in male.

All procedures in the study were in accordance with the ethical standards of responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was taken from all patients for being included in the study.

Statistical methods: We used standard statistical methods for data analysis. Echocardiographic findings were expressed as mean  $\pm$  standard deviation. Echocardiographic values of two groups were compared by Student's 't' test. P-value < 0.05 was considered as statistically significant.

## Results

Averages of 2-D, M-mode and doppler values of left ventricular dimensions and functions are tabulated and compared (Table I).

**Table I: Comparison of left ventricular dimensions and functions of cases and control.**

Echocardiography findings	Study group (n = 60)	Control group (n = 40)	P values
a) LV systolic function			
i) Ejection fraction (EF %)	58.75 $\pm$ 7.10 (SD = 7.10)	56.4 $\pm$ 8.217 (SD = 8.217)	P > 0.05
ii) Fractional shortening (FS %)	32.16 $\pm$ 6.48 (SD = 6.48)	34.66 $\pm$ 5.85 (SD = 5.85)	P > 0.05
b) LV diastolic function			
i) E-peak velocity cm/sec	59.86 $\pm$ 5.28 (SD = 5.28)	69.25 $\pm$ 8.76 (SD = 8.76)	P < 0.05
ii) A-peak velocity cm/sec	65.26 $\pm$ 8.15 (SD = 8.150)	52.75 $\pm$ 7.04 (SD = 7.04)	P < 0.05
iii) E/A ratio	0.896 $\pm$ 0.10 (SD = 0.10)	1.32 $\pm$ 0.11 (SD = 0.11)	P < 0.05
c) LV cavity dimension			
i) LVID(d)cm/BSA	4.13 $\pm$ 0.79 (SD = 0.79)	3.7 $\pm$ 0.5 (SD = 0.5)	P < 0.05
ii) LVID(s)cm/BSA	2.81 $\pm$ 0.78 (SD = 0.78)	2.3 $\pm$ 0.31 (SD = 0.31)	P < 0.05
iii) LVPWT(s) cm/BSA	1.186 $\pm$ 0.11 (SD = 0.11)	0.96 $\pm$ 0.21 (SD = 0.21)	P < 0.05
iv) LVPWT(d) cm/BSA	1.07 $\pm$ 0.15 (SD = 0.15)	0.93 $\pm$ 0.21 (SD = 0.21)	P < 0.05
v) LV Mass gm/m <sup>2</sup>	106.84 $\pm$ 30 (SD = 30)	74.82 $\pm$ 30.96 (SD = 30.96)	P < 0.05
d) IVS(s) cm/BSA	1.2 $\pm$ 0.14 (SD = 0.14)	0.91 $\pm$ 0.16 (SD = 0.16)	P < 0.05
e) IVS(d)cm/BSA	1.06 $\pm$ 0.24 (SD = 0.24)	0.86 $\pm$ 0.11 (SD = 0.11)	P < 0.05

Abbreviations: LV-left ventricle; LVID(d) - left ventricular internal diameter in diastole; LVID(s) - left ventricular internal diameter in systole; LVPWT(s) - left ventricular posterior wall thickness in systole; LVPWT(d) - left ventricular posterior wall thickness in diastole; IVS(s) - interventricular septal wall thickness in systole; IVS (d) - interventricular septal wall thickness in diastole.

Regarding systolic function of left ventricle, mean ejection fraction ( $58.75 \pm 7.10$ ) among cases was slightly elevated than among controls ( $56.4 \pm 8.217$ ) but the difference was not statistically significant ( $P > 0.05$ ).

Impairment of LV diastolic function was noted. The mean E velocity ( $59.86 \pm 5.28$  cm/sec) among cases was significantly decreased than controls ( $69.25 \pm 8.76$  cm/sec) value. 'A' velocity was also noted to be increased ( $65.26 \pm 8.15$  cm/sec) significantly as compared to controls ( $52.75 \pm 7.04$  cm/sec) value. E/A ratio was less than one in most (54) cases. In the study group, mean E/A ratio ( $0.896 \pm 0.10$ ) was significantly lower than control ( $1.32 \pm 0.11$ ) value ( $p < 0.05$ ). Left-ward shift of septum and flattening of IVS was present in 54 (90%) patients.

We considered LVH when LVPWT (d) and IVS (d) were  $> 1.1$  cm and exceeded the limit of LVH through Devereux formula. Eighteen patients had LVPWT (d) and IVS (d)  $> 1.1$  cm. Out of 18 patients, ten patients (17%) had increase in both IVS and LVPWT and exceeded the limit of LVH by Devereux formula. Other eight patients didn't exceed the limit of LVH by Devereux formula.

## Discussion

**Left ventricular systolic dysfunction:** Normal LV systolic function was seen in all of our patients at rest. We found normal ejection fraction ( $58.75 \pm 7.10\%$ ) ( $SD = 7.10$ ) and fractional shortening ( $32.16 \pm 6.48\%$ ) ( $SD = 6.48$ ) in COPD patients and values were not significantly different from control group ( $P > 0.05$ ). Previously, a hypothesis was postulated that hypoxia, hypercapnoea, and acidosis can depress LV systolic function and may lead to LV failure. In an Indian study, LV systolic dysfunction was reported in 7.5 % of COPD patients<sup>1</sup>. However, an earlier study by radionuclide ventriculography had shown a normal to supranormal ejection fraction in chronic cor-pulmonale patients due to COPD<sup>2</sup>. Jardin *et al*, also had shown normal systolic function in advanced COPD patients by echocardiography<sup>3</sup>. Poddar *et al* showed that LV systolic function is usually not disturbed in COPD, even after development of cor-pulmonale, but LV systolic dysfunction may be frequently associated with COPD, when overt right heart failure develops<sup>4</sup>.

**Left ventricular diastolic dysfunction:** Doppler study revealed diastolic dysfunction in majority [54 out of 60 (90%)] of our patients. In our study, 'E'-peak velocity was  $59.86 \pm 5.28$  cm/sec in cases and  $69.25 \pm 4.38$  cm/sec among controls ( $P < 0.05$ ). 'A' peak velocity was  $65.26 \pm 8.15$  cm/sec in cases and  $52.75 \pm 7.04$  cm/sec ( $p < 0.05$ ) among controls.

Prevalence of LV diastolic dysfunction is very high in COPD patients, varying with the severity of the disease<sup>1,5,6</sup>. Different

studies have shown that septum-mediated ventricular interdependence is the operating factor causing decreased diastolic compliance of left heart in cor-pulmonale<sup>5,7,8</sup>. Chronic RV pressure overload induces LV filling impairment despite a normal systolic phase due to septal leftward shift<sup>9</sup>. Chronic hypoxaemia may also lead to abnormalities of myocardial relaxation and lung hyperinflation may lead to stiffening of parietal pleura and thus of the wall of cardiac fossa<sup>1</sup>. LV diastolic dysfunction may also be due to compression of the left ventricle resulting from the limited space within the cardiac fossa and pericardium as well as decreased pulmonary venous return and also correlates with the severity of pulmonary hypertension<sup>1,5,10,11</sup>. In our study 90% of the patients had diastolic dysfunction as well as both LVID (d) and LVID (s) were increased.

**Left ventricular hypertrophy:** In our study, we found LVH in 17% patients. Autopsy studies done in the past have shown the presence of LVH in COPD patients<sup>12</sup>. To determine left ventricular involvement in patients with chronic cor-pulmonale, right and left ventricular weights, wall thickness, myocyte degeneration and percentage of fibrosis, 18 autopsied hearts were examined by Kohana *et al*<sup>13</sup>. It was seen that walls of both ventricles were significantly thickened and myocyte diameters of both ventricles were significantly greater in COPD and it was concluded that left ventricle was involved pathologically in patients with chronic cor-pulmonale. Dragnov V *et al* have studied 507 patients with chronic cor-pulmonale and, in 62.2% of them, LVH was found<sup>12</sup>. In an Indian study, LVH was seen in 22.5% of COPD patients<sup>1</sup>. Severity of pulmonary hyperinflation, as measured by residual lung volume seems to be associated with greater LV mass in COPD patients<sup>14</sup>. The cause of LVH is uncertain though hypoxia, hypercarbia, acidosis, and increased intrathoracic pressure might play some role<sup>15</sup>. LVH is usually not seen in COPD patients with mild hypoxaemia<sup>16</sup>.

There are limitations in our study. We could not rule-out the possibility of ischaemic heart disease, having only used history, ECG and echocardiography (as treadmill test, coronary angiography or autopsy studies were not done). It was also not possible to rule out early hypertrophic cardiomyopathy. Echocardiographic assessment is difficult in COPD patients because of lung hyperinflation and there may be inaccuracies.

## Conclusion

LV diastolic dysfunction is seen in a majority of COPD patients. LVH is also common. LV systolic dysfunction is not seen. Larger studies are needed to confirm the association of LVH and other left ventricular changes, purely due to COPD.

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# Dynamic Changes in Serum Phosphorus Level During Treatment of Diabetic Ketoacidosis and Predicted by Degree of Metabolic Acidosis on Presentation

Ravindra Kumar Tiwari\*\*, Archana Gokhroo\*, Kishor Phepale\*\*\*, Rajesh Jain\*, Pavan Kumar V\*\*\*

## Abstract

*Changes in serum phosphate during treatment of diabetic ketoacidosis (DKA) are not well characterised, although it is known that serum phosphate falls with treatment. We sought to define the nature of these changes and whether the severity of acidosis on admission influenced the severity of subsequent hypophosphataemia. We retrospectively reviewed data on 50 patients with confirmed DKA presenting to our unit between December 2012 and July 2014. At presentation, 66% of patients were hyperphosphataemic. Serum phosphate fell during the course of treatment in all episodes (mean absolute fall  $3.98 \pm 0.816$  mg/dl). The mean serum phosphorus level was  $1.7 \pm 0.612$  mg/dl. Ninety percent of nadir phosphate levels were hypophosphataemic ( $< 2.5$  mg/dl), and 12% were severely hypophosphataemic ( $< 1.0$  mg/dl). Mean initial bicarbonate differed significantly between those with serum phosphates  $< 1.5$  mg/dl ( $9.57 \pm 1.79$ ) and those with serum phosphates  $\geq 1.5$  mg/dl ( $14.935 \pm 2.375$ ,  $P = 0.0031$ ). Similar significant difference were noted between those with nadir phosphates less than and more than 1.0 mg/dl respectively ( $7.22 \pm 1.71$  and  $13.32 \pm 2.88$ ,  $P < 0.01$ ).*

*The initial hyperphosphataemia is reflective of intravascular volume depletion and consequent renal impairment. The severity of subsequent hypophosphataemia can be predicted by the degree of metabolic acidosis on presentation. As hypophosphataemia is associated with a number of clinical sequelae, including respiratory muscle weakness, rhabdomyolysis, haemolysis and increased mortality, clinicians should recognise the likelihood of this biochemical derangement in DKA patients presenting with profound metabolic acidosis.*

## Introduction

Diabetic ketoacidosis (DKA) is one of the most common medical emergencies in the world. The patient may present with a wide range of manifestations like ketosis, ketoacidosis, ketoacidotic pre-coma and coma<sup>1</sup>, but often these manifestations are submerged in the clinical presentation of the precipitating illnesses. Phosphate depletion is common in diabetic ketoacidosis. Intracellular phosphate is lost as a result of acidosis, and increased renal phosphate excretion. During treatment with insulin, phosphate is taken up intracellularly with resultant hypophosphataemia.

The severity of subsequent hypophosphataemia can be predicted by the degree of metabolic acidosis on presentation<sup>2</sup>. Hypophosphataemia is associated with a number of clinical sequelae, including decreased cardiac output, respiratory muscle weakness, rhabdomyolysis, central nervous system depression, seizures, and coma, acute renal failure, and haemolysis<sup>3-10</sup>.

## Aims and objectives

1. To assess serum phosphorus levels in patients of type 2 diabetes mellitus with ketoacidosis.

2. To assess serum bicarbonate levels in patients of type 2 diabetes mellitus with ketoacidosis.
3. To correlate initial bicarbonate levels with subsequent serum phosphorus levels in patients of type 2 diabetes mellitus with ketoacidosis.

## Materials and methods

### Source of data

The study was conducted on 50 patients with type 2 diabetes mellitus with ketoacidosis, admitted at JLN Hospital Ajmer during December 2012 to July 2014.

### Inclusion criteria

1. Patients who gave written informed consent.
2. Patients with diabetic ketoacidosis.
3. Patients with type 2 diabetes mellitus.
4. Patients who were  $> 18$  years age.

### Exclusion criteria

1. Patients who did not give written informed consent.
2. Patients with malnutrition, malabsorption syndromes.
3. Patients on diuretics, steroids, phosphate binding

antacids.

4. Patients with renal transplantation.
5. Patients with hyperparathyroidism.
6. Patients with pancreatitis, burns, volume expansion.
7. Patients who were alcoholics.
8. Respiratory alkalosis – hyperventilation, panic attacks, salicylate poisoning.
9. Rapid cellular uptake – refeeding syndrome, leukaemic blast cell crises, hungry bone syndrome.
10. Patients with type 1 diabetes mellitus and other causes of ketoacidosis.

### Statistical analysis

Depending upon the data available, appropriate statistical test were applied, qualitatively by chi-square, and quantitatively by t-test.

### Methodology

Serum phosphorus levels were estimated on day one, after 24 hours of admission or worsening of patient's condition, and at discharge/final outcome. It was correlated with initial serum bicarbonate level. The following investigations were carried out:

1. Haematological and biochemical investigations:
  - a) Hb%, WBC count-total and differential.
  - b) Blood sugar estimation was done.
  - c) Serum electrolytes by flame photometry.
  - d) Blood urea estimation.
  - e) Serum creatinine.
  - f) Serum bicarbonate.
  - g) Serum phosphorus.
2. ABG: Arterial blood gases estimation
3. Urine: For routine and microscopy and culture and sensitivity
4. Urine for ketone bodies
5. X-ray chest
6. ECG

### Observations

**Table I: Reduction of serum phosphorus level during treatment of DKA.**

	On admission mean $\pm$ SD	After 24 hours of treatment	Mean reduction
Serum phosphorus level (mg/dl)	5.68 $\pm$ 1.266	1.7 $\pm$ 0.612	3.98 $\pm$ 0.816

**Table II: Relation b/w serum bicarbonate levels and subsequent serum phosphorus level.**

Serum phosphorus level (mg/dl)	Number of patients	Serum bicarbonate level (mEq/l)	P-value
< 1.5	22	9.57 $\pm$ 1.79	0.0031
$\geq$ 1.5	28	14.935 $\pm$ 2.375	

**Table III: Relation b/w serum bicarbonate levels and subsequent serum phosphorus level.**

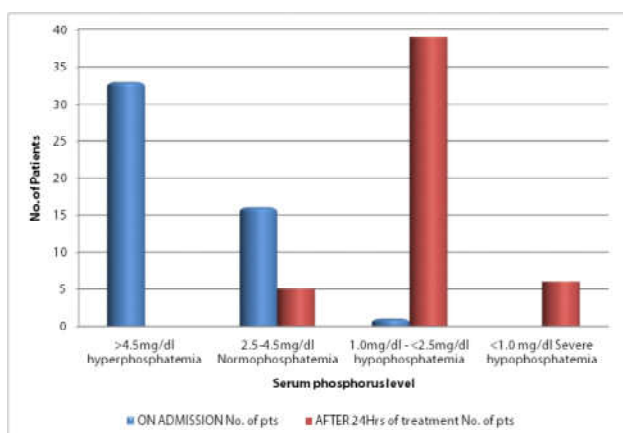
Serum phosphorus level (mg/dl)	Number of patients	Serum bicarbonate level (mEq/l)	P value
< 1	6	7.22 $\pm$ 1.71	0.01
$\geq$ 1	44	13.32 $\pm$ 2.88	

### Result

1. The average age of our patients was 48.22  $\pm$  12.48 years.
2. Male: Female ratio was 1: 1.172.
3. Infection was the most common precipitating factor, followed by irregular treatment.
4. Most of the patients presented with vomiting, abdominal pain, fever dehydration, and acidotic breathing.
5. On admission, serum phosphorus level (mean  $\pm$  SD) was 5.68  $\pm$  1.266 mg/dl. During treatment of DKA, mean absolute fall in serum phosphorus level was 3.98  $\pm$  0.816 mg/dl, and mean serum phosphorus level was 1.7  $\pm$  0.612 mg/dl (Table I).
6. Mean initial bicarbonate differed significantly between those with nadir phosphates < 1.5 mg/dl (9.57  $\pm$  1.79) and those with nadir phosphates  $\geq$  1.5 mg/dl (14.935  $\pm$  2.375, P = 0.0031) (Table II).

If we consider a lower limit of serum phosphorus level, (1 mg/dl) similar significant difference in initial bicarbonate levels was seen. Mean initial bicarbonate level differed significantly between those with nadir phosphates < 1.0 mg/dl (7.22  $\pm$  1.71) and those with nadir phosphates  $\geq$  1.0 mg/dl (13.32  $\pm$  2.88, P = 0.01) (Table III).

7. So, the severity of subsequent hypophosphataemia can be predicted by the degree of metabolic acidosis at presentation. As profound hypophosphataemia can be associated with serious complications, early recognition and correction while managing a patient of diabetic ketoacidosis is important to reduce the morbidity and mortality.



**Fig. 1:**

- Mortality rate was 4% (2 patients). Severe hypophosphataemia was present in both the patients and both patients were comatose and severely acidotic at the time of presentation.

## Conclusions

- Most DKA patients have hyperphosphataemia on presentation which is reflective of intravascular volume depletion and pre-renal renal impairment, but during treatment most of the patients developed hypophosphataemia.
- The severity of subsequent hypophosphataemia can be predicted by the degree of metabolic acidosis on presentation.

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## Cardiological Complications in Cerebrovascular Accidents

Suman Ghosh\*, Animesh Deb\*\*, Anup K Bhattacharya\*\*\*

### Abstract

*Cerebrovascular accident (CVA) or stroke is the second most common cause of death after ischaemic heart disease all over the world, according to Global Burden of Diseases (GBD). CVA and cardiovascular diseases share several common aetiological factors, so CVA patients may develop cardiovascular complications or vice-versa. Even American Heart Association (AHA) and American Stroke Association (ASA) work together because of these common aetiological factors and to prevent both cerebrovascular as well as cardiovascular complications. There are also reports showing post-CVA patients developing cardiovascular complications, and even death.*

*Based on these observations we took 100 post-stroke patients in our study who did not have any cardiovascular ailments before or documented earlier. We monitored these patients at the time of first visit, followed subsequently at 3 and 6 months interval. These patients were evaluated by various non-invasive tests (e.g., blood pressure records, serial ECG monitoring and 2D-echocardiography) as well as by doing markers of cardiac myocyte injury (troponin-T).*

*Among 100 patients, we found 16 patients developed cardiac arrhythmias, 11 developed congestive heart failure (CHF), 10 developed significant ST-T changes and pathological Q-wave on serial ECGs, raised troponin-T levels were seen in 13 patients, 46 patients developed various 2D-ecocardiographic abnormalities (e.g., regional wall motion abnormalities, concentric left ventricular hypertrophy, diastolic dysfunction, and congestive heart failure with low ejection fraction) at the time of first visit as well as on follow-up studies.*

**Key words:** Cerebrovascular accidents, atrial fibrillation, regional wall motion abnormality, computer tomography scan, troponin-T.

### Introduction

In 2001, it was estimated that cerebrovascular diseases (stroke) accounted for 5.5 million deaths world wide, equivalent to 9.6% of all deaths (WHO, 2002)<sup>1</sup>. The situation is no less severe in India. A recent community survey in the Eastern Indian city of Kolkata showed that the average annual incidence of stroke was 145 per 100,000 persons per year (Das *et al*, 2007)<sup>2</sup>. Based on physiological background cerebro-vascular accident/strokes are either of ischaemic (or) of haemorrhagic type. Mortality rate of ischaemic stroke has been reported to be lower (25.9%) as compared to haemorrhagic stroke (49.2%) (Andersen *et al*, 2009)<sup>3</sup>. Stroke patients are more susceptible to medical complications like cardiac complications, pneumonias, venous thromboembolism, fever, pain, dysphagia, bowel and bladder difficulties, and depression (Kumar *et al*, 2010)<sup>4</sup>. Among these, cardiac complications have been the most common and have interested researchers (Haddad *et al*, 2011; Wira *et al*, 2011)<sup>5,6</sup>. Several studies have shown that patients with transient ischaemic attack (TIA) and haemorrhagic stroke have a high prevalence of asymptomatic CAD.

The cardiac mortality rate in patients of acute stroke has been shown to range between 0.5% to 6.2% over a follow-up period ranging from 4 days to 6 months (Albers *et al*,

2001)<sup>7</sup>. This can be explained as stroke and cardiovascular diseases share common risk factors and pathological mechanisms and coronary artery disease (CAD) is an important cause of death in patients with cerebrovascular disease (Adams *et al*, 2003)<sup>8</sup>.

Keeping in view the high short-term mortality and commonality of risk factors, it is essential that a multifactorial assessment of cardiovascular complications in post-stroke patients should be studied with respect to time of follow-up using different non-invasive methods. The present study is an attempt in that direction.

### Aim and objectives

The present study was carried out with an aim to evaluate the cardiovascular complications in post-stroke patients with the following objectives:

- To monitor any cardiovascular event by various non-invasive methods like ECG 2D- echocardiography in patients after stroke at different follow-up periods, e.g., on first visit, 3 months and 6 months.
- To motivate all post-stroke patients to undergo regular monitoring for any cardiovascular event for prevention of any cardiological complication as a consequence of cerebral insult.

\*Junior Resident, \*\*Associate Professor, \*\*\*Professor, Department of General Medicine, MGM Medical College and LSK Hospital, Kishanganj - 855 107, Bihar.

## Materials and methods

This observational study was carried out at the indoor and out-patient departments of Medicine, Neurology and Emergency or Casualty ward of Mata Gujri Memorial Medical College and LSK Hospital, Kishanganj during a one year period from January 2014 to June 2015. Study was done in a population of adults, between 40 - 80 years of age, with confirmed diagnosis of cerebro-vascular accident/stroke clinically as well as radiologically. The inclusion exclusion criteria were as follows:

### Inclusion criteria

- Age 40 years and above.
- Either sex
- Clinicoradiologically confirmed diagnosis of new onset/ history of stroke of any type (parenchymal, haemorrhagic or ischaemic).

### Exclusion criteria

- Patients having a history of heart disease prior to stroke.
- Patients having a history of chest pain, shortness of breath, syncope or dizziness which was not evaluated earlier.

**Ethical approvals:** The approval for the study was obtained from Institute's Ethical Committee.

**Sample size:** A total of 100 patients were enrolled for this study.

## Methods

At enrollment, the following information was noted for all those patients who fulfilled the inclusion criteria after obtaining an informed consent:

- Demographic information.
- Clinical/medical history including history of heart disease, history of symptoms of cardiac abnormalities, psychiatric status and presence of comorbidities such as hypertension and diabetes.
- Personal addictions, viz., smoking/tobacco use.
- Family history.
- Physical examination.
- Haemodynamic assessment – including pulse (rate, rhythm, volume, character, condition of arterial wall), respiratory (rate and rhythm), systolic and diastolic blood pressure.
- Cardiovascular examination.
- Systemic examination.
- CNS evaluation, including CT scan, to diagnose the type of stroke.

- ECG
- 2-D echo evaluation (ejection fraction, RWMA, valves arrhythmia).
- Cardiac troponin-T level estimation during the acute episodes.

## Results

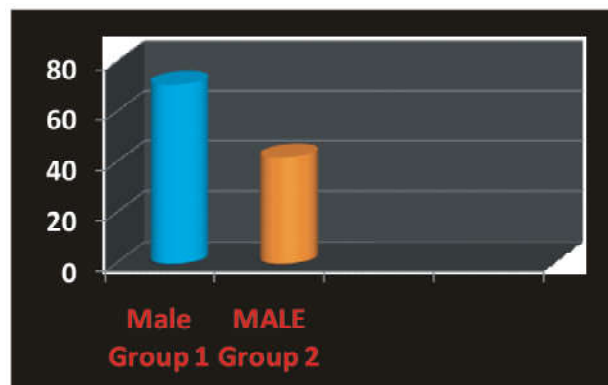
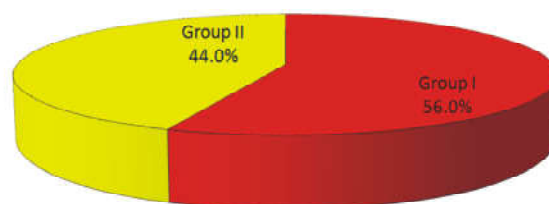
The present study was carried out with an aim to evaluate the cardiac complications in post-stroke patients. A total of 100 post-stroke patients were enrolled in the study. All underwent cardiac evaluation with three approaches – electrocardiographic (ECG) evaluation, cardiac troponin-T estimation and 2-D echocardiography at the time of first visit, 3 months after, and 6 months after presentation.

On the basis of comprehensive cardiac evaluation, the patients were divided into two groups. Table I shows group-wise distribution of cases:

**Table I: Distribution of cases according to group.**

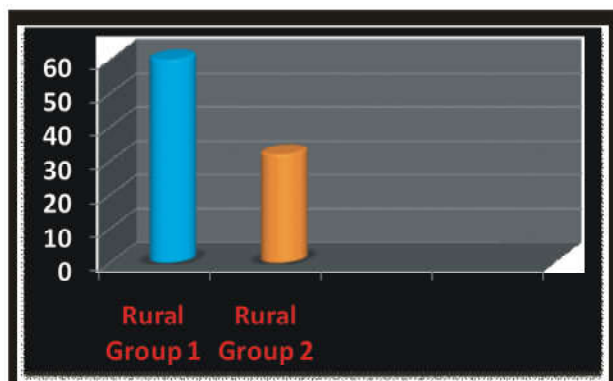
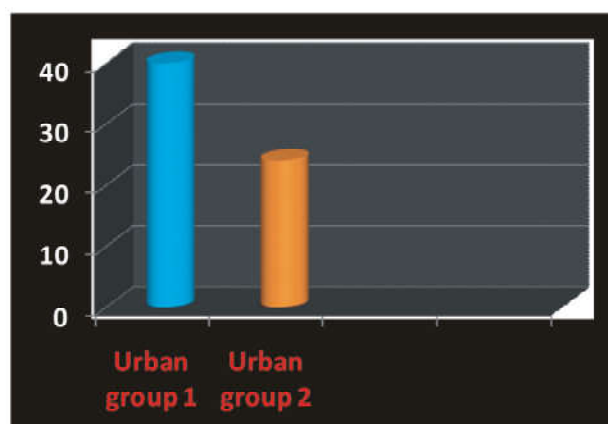
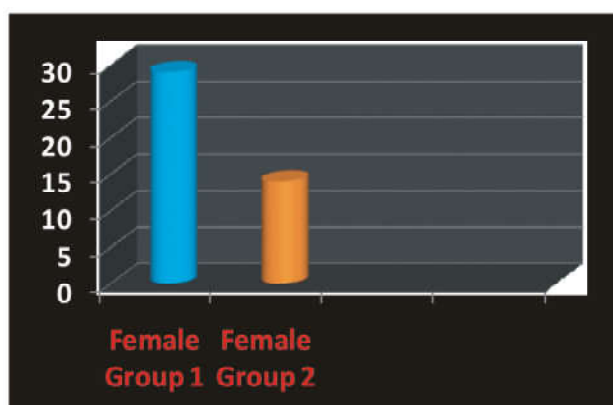
S.n.	Group	Description	No. and (%) of cases
1.	I	Post-stroke patients developing cardiac abnormality	(56%)
2.	II	Post-stroke patients with no cardiac abnormality after the event.	(44%)

Out of 100 patients enrolled in the study, a total of 56 (56%) had cardiac abnormality. These patients subsequently comprised group I of the study. Remaining, 44 (44%) patients did not have cardiac abnormality and comprised group II of study.



**Table II: Demographic distribution of patients in the two groups.**

S.n.	Characteristics	Total	Group I (n = 56)	Group II (n = 44)	Significance of difference
1.	Mean age $\pm$ SD (range) in years	56.22 $\pm$ 8.34 (40 - 76)	57.23 $\pm$ 8.88 (40 - 76)	54.93 $\pm$ 8.34 (40 - 76)	t = 1.289; p = 0.201
2.	Gender				$\chi^2 = 0.989$ ; p = 0.320
	Male	71	42	29	
	Female	29	14	15	
3.	Place of residence				$\chi^2 = 0.433$ ; p = 0.511
	Rural	60	32	28	
	Urban	40	24	16	
4.	Religion				$\chi^2 = 10.390$ ; p = 0.001
	Hindu	50	36	14	
	Muslim	50	20	30	



#### **Association of cardiac abnormalities with gender, place of residence, and religion**

Overall, majority of patients were males (71%). Among these 71 males, group I included 42 (75%) as compared to that in group II 29 (65.9%); this difference was not significant statistically ( $p = 0.320$ ). Overall, exactly half the patients were Hindus (50%) and remaining half (50%) were Muslims. However, proportion of Hindus was higher in group I (64.6%) as compared to that in group II (31.8%), and this

difference was significant statistically too ( $p = 0.001$ ). None of the patients had known heart disease or symptoms of heart disease prior to stroke, or any psychiatric co-morbidity.

Out of 48(48%) patients with history of hypertension 33 patients (58.9%) belonged to group-I and 15 patients (34.1%) belonged to group-II ( $p = 0.014$ ). However, diabetes and smoking showed less significant association with cardiac abnormalities ( $p > 0.05$ ). In the present study, patients having two or more risk factors (diabetes, hypertension, smoking) along with high LDL level were considered as having multiple with factors. A total of 27 patients (27%) had presence of multiple risk factors, out of which 18 patients (32.1%) belongs to group-I and 9 patients (20.5%) belongs to group-II. This association was not significant statistically ( $p = 0.191$ ).

Hemiparesis (23 left side and 24 right side) and hemiplegia (23 left side and 18 right side) were the most common findings in both the groups. Monoparesis was seen in 3 cases (2 right side, 1 left side) while monoplegia was seen in 9 (5 left side and 4 right side) cases. Statistically, there was no significant association between CNS findings and cardiac abnormalities ( $p = 0.840$ ).

**Table III: Distribution of patients in the two groups according to medical and personal history.**

S.n.	Characteristics	Total		Group I (n = 56)		Group II (n = 44)		Significance of difference
		No.	%	No.	%	No.	%	
1.	Diabetes	29	29	17	30.4	12	27.3	$\chi^2 = 0.114$ ; $p = 0.736$
2.	Hypertension	48	48	33	58.9	15	34.1	$\chi^2 = 6.090$ ; $p = 0.014$
3.	Smoking	41	41	23	41.1	18	40.9	$\chi^2 = 0.000$ ; $p = 0.987$

**Table IV: Distribution of patients in the two groups according to physical and haemodynamic findings.**

S.n.	Characteristics	Total		Group I (n = 56)		Group II (n = 44)		Significance of difference
		No.	%	No.	%	No.	%	
1.	Neck vein engorgement	8	8	8	14.3	0	0	$\chi^2 = 6.832$ ; $p = 0.009$
2.	Pulse							
	Rate (bpm) in Mean $\pm$ SD	91.22 $\pm$ 15.55		92.25 $\pm$ 16.71		89.91 $\pm$ 11.28		$t = 0.797$ ; $p = 0.427$

Majority of cases (75%) had ischaemic stroke. 25% patients had haemorrhagic CVA, out of which 5 patients had subarachnoid haemorrhage. Proportion of patients with haemorrhagic stroke was much higher in group-I 24 patients (42.9%), as compared to group-II. 1 patient (2.3%).

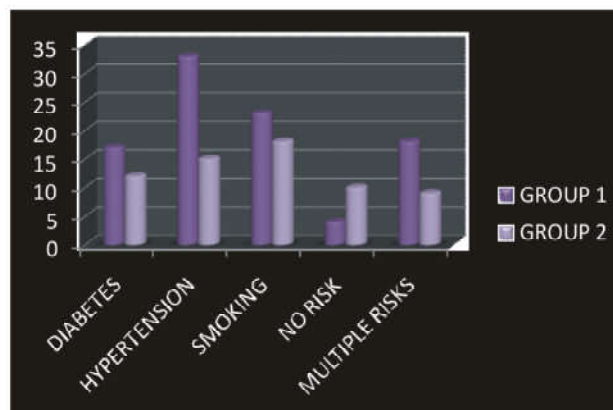
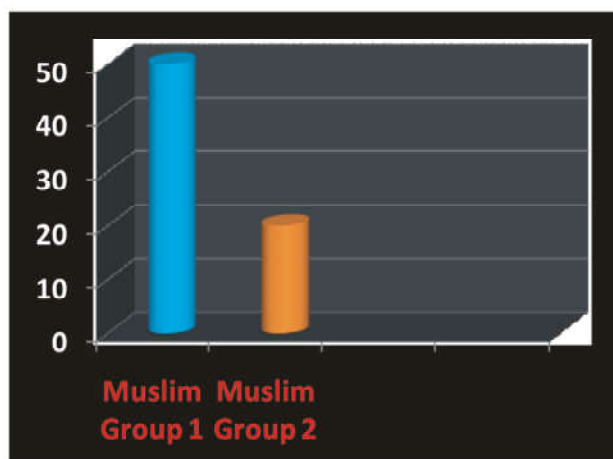
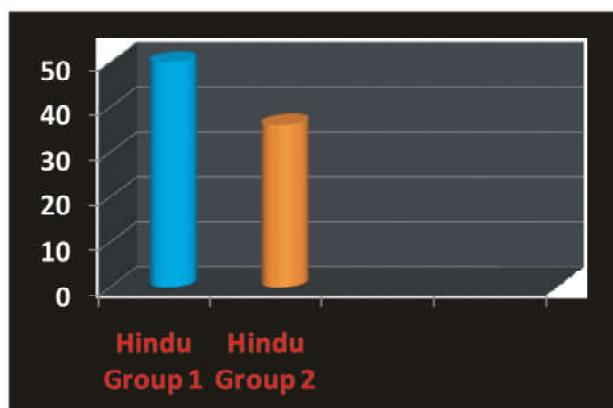
ECG abnormalities were seen in 22 patients – atrial fibrillation

(AF) in 12 (12%), Q wave changes in 5 (5%) and ST-T change in 5 (5%) cases.

**Table V: Distribution of patients in the two groups according to CNS findings.**

S.n.	Finding	Total		Group I (n = 56)		Group II (n = 44)	
		No.	%	No.	%	No.	%
1.	Left side hemiparesis	23	23	14	25.0	9	20.5
2.	Left side hemiplegia	23	23	13	23.2	10	22.7
3.	Left side monoparesis	1	1	0	0.0	1	2.3
4.	Left side monoplegia	5	5	3	5.4	2	4.5
5.	Right side hemiparesis	18	18	9	16.1	9	20.5
6.	Right side hemiplegia	24	24	13	23.2	11	25.0
7.	Right side monoparesis	2	2	2	3.6	0	0.0
8.	Right side monoplegia	4	4	2	3.6	2	4.5

$\chi^2 = 3.455$  ( $df = 7$ );  $p = 0.840$ .



**Table VI: Distribution of patients in the two groups according to CT scan findings.**

S.n.	Finding	Total		Group I (n = 56)		Group II (n = 44)	
		No.	%	No.	%	No.	%
1.	Haemorrhagic	25	25	24	42.9	1	2.3
2.	Ischaemic	75	75	32	57.1	43	97.7

$\chi^2 = 21.645$  (df = 1);  $p < 0.001$ .

**Table VII: Comparison of ECG findings between the two groups.**

S.n.	Finding	Total	
		No.	%
ECG abnormalities			
1.	AF	12*	12
2.	Q Wave	5	5
3.	ST-T Change	5	5
Cardiac troponin-T			
1.	Raised troponin-T	13	13
2D-echo doppler flowmetry			
1.	Low ejection fraction	11	11
2.	Concentric LVH with diastolic dysfunction	45	45
3.	RWMA	10	10
4.	AV Arrhythmia	12*	12

\*Same patients diagnosed as AF by ECG and AV arrhythmia by 2D echo.

### Type of cardiac abnormalities

Raised troponin-T levels were seen in 13 (13%) cases.

On 2D-echo Doppler flowmetry, abnormalities were seen in 46 patients. A total of 45 had concentric LVH with diastolic dysfunction, 10 had RWMA, 6 had AV arrhythmia and 11 patients had low ejection fraction. Multiple abnormalities in echo findings were quite common.

Majority of cases (75%) had ischaemic stroke. 25% patients had haemorrhagic CVA, out of which 5 patients had subarachnoid haemorrhage. Proportion of patients with haemorrhagic stroke was much higher in group-I 24 patients (42.9%), as compared to group-II. 1 patient (2.3%).

ECG abnormalities were seen in 22 patients – atrial fibrillation (AF) in 12 (12%), Q wave changes in 5 (5%) and ST-T change in 5 (5%) cases.

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On 2D-echo Doppler flowmetry, abnormalities were seen

in 46 patients. A total of 45 had concentric LVH with diastolic dysfunction, 10 had RWMA, 6 had AV arrhythmia and 11 patients had low ejection fraction. Multiple abnormalities in echo findings were quite common.

**Table VIII: Follow-up adverse cardiac events.**

S.N.	Finding	Total	
		No.	%
1.	Cardiac arrhythmia	4	4.0
2.	Cardiac arrhythmia with heart failure	2	2.0
3.	Congestive heart failure	5	5.0

On follow-up, adverse cardiac events were noted in 11 patients. Among these 4 cases had cardiac arrhythmia only in the form of atrial fibrillation, premature ventricular and supra ventricular contractions, 2 had cardiac arrhythmia with heart failure while 5 had isolated congestive heart failure.

### Discussion

Cerebrovascular accident or strokes are the major cause of immediate as well as long-term health related consequences in the community. This is reflected as a compromised cerebral activity and at the same time compromised cardio-vascular status.

In the present study, 100 post-stroke patients attending our hospital were enrolled for their detailed cardio-vascular evaluation. A total of 56 out of 100 patients were found to have cardiovascular complications or abnormalities, hence prevalence of cardiovascular complications among post-stroke patients in present study was 56%. According to Prosser J *et al* (2007)<sup>9</sup> cardiovascular complications are the second most common complication in post-stroke patients. In the present study, we focused on cardiological complications. Apart from cardiovascular abnormalities, we also attempted to analyse socio-demographic and clinical parameters in stroke patients to assess their association with cardiovascular abnormalities.

In our study, most patients were below 70 years of age and, as such, age-related increased risk of cardiovascular abnormalities was excluded<sup>3,11</sup>. In our study rural and urban differentiation, in respect of cardiovascular dysfunction among post-stroke patients, did not reveal much difference as most of our patients belonged to rural subgroup.

It was also observed in our study that significantly higher proportion of Hindus, as compared to Muslims, had cardiac abnormalities (OR = 3.86; 95% CI = 1.67-8.81).

In our study, it was also seen that history of hypertension or other cardio-vascular risk factors (diabetes, hypertension, smoking and with LDL level) significantly associated with

cardio-vascular complications in post-stroke patients. This association is also justified by other studies<sup>3,12,13</sup>.

We found in our study 8 patients with neck vein engorgement with cardiac abnormality. We also found 12 patients having irregularly irregular pulse rhythm, while 7 patients had S3 gallop. Increased systolic and diastolic blood pressure levels were found at the time of presentation and follow-up evaluation which also may have been associated with cardiac abnormalities. According to Britton M *et al*<sup>14</sup> 80% patients can have high blood pressure at the time of cerebrovascular accident. Robinson and colleagues demonstrated that an increase in systolic BP by 10 mmHg after stroke was significantly associated with poor outcome due to cardiological complications<sup>15</sup>.

In the present study, the type of cerebrovascular accident/stroke, i.e., (hemiplegia/hemiparesis/monoplegia/monoparesis) did not show a significant difference in risk of cardiological complications. Tsujikawa *et al*<sup>16</sup> showed cardiological complications after stroke did not depend upon site of stroke but upon severity of strokes.

The present study, showed that post-stroke cardiac abnormalities or complications were more in haemorrhagic stroke than ischaemic stroke. Jaikar *et al* (2004)<sup>17</sup> evaluated a total of 60 cerebrovascular accident (CVA) cases associated with ECG changes. 83.3% patients showed abnormal ECG changes. All patients (100%) with cerebral haemorrhage, and subarachnoid haemorrhage had ECG abnormalities, whereas only 64.28% of ischaemic CVA had ECG abnormalities. Generally, mortality rate is higher in haemorrhagic when compared to ischaemic<sup>18</sup> CVA. This can be explained on the basis of cardiac complications or abnormalities which are more common in haemorrhagic CVA than in ischaemic CVA.

In our study, ECG abnormalities were seen in 28 patients, of which atrial fibrillation was seen in 15 (15%) patients, Q-waves were seen in 5 (5%) patients, ST-T changes in 5 (5%) and premature ventricular contractions (PVCs) or ventricular ectopics in 3 (3%) patients at the time of first visit as well as follow-up visits.

Raised troponin-T levels were seen in 13 patients. This finding was also shown by Kerr G *et al* (2014)<sup>19</sup>. According to this study, increased levels of troponin are seen in between 5 - 34% of patients with acute stroke. Increased troponin levels also indicate adverse cardiac outcome. Sudden death associated with CVA, classically known as Takotsubo cardiomyopathy has not been reported in our study probably because of lack of reporting of cases of sudden death associated with cerebrovascular disorders.

On 2D-echocardiography, cardiovascular abnormalities

were seen in 46 patients. 45 patients had concentric left ventricular hypertrophy with diastolic dysfunction, 10 patients had regional-wall motion abnormalities (RWMA), and 11 patients had low-ejection fraction. Cardiac arrhythmia was found in 18 (18%) patients, out of which 15 (83.3%) had atrial-fibrillation, and 3 patients (16.6%) had other ventricular arrhythmia during first presentation and follow-up studies. All these echocardiographic findings have similarities with the finding of Tsujikawa *et al* (2015)<sup>16</sup>.

In our study, we found that 5 patients (5%) developed congestive heart failure (CHF) during follow-up studies. Amaren *et al* (2010)<sup>20</sup> also reported the risk of major coronary events to be 5.1%.

## Conclusion

On the basis of the present study, the following conclusions can be drawn:

1. Prevalence of cardiac abnormalities among post-stroke patients was 56%.
2. Age, gender and place of residence did not show a significant association with post-stroke cardiac abnormalities.
3. Hindus had higher risk of cardiac abnormalities as compared to Muslims (OR = 3.86; 95% CI = 1.67 - 8.81) thereby indicating ethnic variability.
4. Pre-stroke history of hypertension was significantly associated with post-stroke cardiac abnormalities.
5. Absence of risk factors like diabetes, hypertension and smoking reduced the risk of post-stroke cardiac abnormalities.
6. Neck vein engorgement, irregular pulse and post-stroke gallop were less sensitive (10 - 12%) yet highly specific (100%) markers of cardiovascular abnormality in post-stroke patients.
7. No significant difference in rate of cardiovascular abnormality was observed among cases with different types of strokes or lateralisation of CNS involvement.
8. Patients with haemorrhagic stroke had higher incidence of post-stroke cardiac abnormalities as compared to ischaemic stroke.
9. ECG abnormalities were seen in 22%, and raised troponin-T levels were seen in 13% cases. A total of 46% patients had abnormal 2-D echo findings.
10. Atrial fibrillation was the commonest abnormality recorded, followed by premature ventricular and supra ventricular arrhythmias.

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# Hepatic Osteodystrophy – A Study of The Prevalence of Osteoporosis in Cirrhosis of Liver and its Correlation with Severity of Liver Disease

Aanchal Arora C\*, Rajesh Manocha G\*\*, S Prasad\*\*

## Abstract

**Background:** There has been improvement in survival of patients with cirrhosis of liver as a result of advances made in liver transplantation. However, in many patients osteoporosis still remains unrecognised, therefore the clinical significance of hepatic osteodystrophy has increased.

**Aims of study:** To estimate the bone mineral density (BMD) and prevalence of osteoporosis in patients with cirrhosis of liver and to study its correlation with severity of liver disease.

**Methodology:** This is a case control study conducted in the Department of Medicine in VMMC and Safdarjung hospital over a period of two years (2012 - 2014) on 50 patients with cirrhosis of liver and 50 age and sex matched controls, satisfying inclusion and exclusion criteria. Diagnosis of cirrhosis was based on clinical examination and ultrasonographic features. Cases were divided into three groups on the basis of severity of liver disease. BMD was estimated, using DEXA Scan, among the cases and controls. On the basis of results of BMD, cases of cirrhosis were divided into low (Z score  $\leq$  - 2) and normal BMD (Z score  $>$  - 2) groups and the result was correlated with severity of cirrhosis of liver (Child-Pugh Grade).

**Results:** The present study included 50 cases of cirrhosis, mean age  $38.36 \pm 6.3$  years, 44 males and 6 females. The prevalence of osteoporosis was 42% (21 out of 50) in patients with cirrhosis of liver as compared to 20% (10 out of 50) in the control group. The prevalence of low BMD in patients with cirrhosis of liver was 78 % (39 out of 50) as compared to 20% (10 out of 50) in the control group and the difference was statistically significant. Prevalence of low BMD was high in Child-Pugh C as compared to Child-Pugh class B and A ( $p = 0.003$ ).

**Conclusion:** Prevalence of osteoporosis was high among patients of liver cirrhosis and correlated positively with severity of liver disease.

**Key words:** Hepatic osteodystrophy, bone mineral density, cirrhosis.

## Introduction

Cirrhosis is a result of advanced liver disease. It is characterised by replacement of liver tissue by fibrosis and regenerative nodules due to attempted repair of damaged tissue. This results in decreased hepatocellular mass, function and an alteration in blood flow. Hepatocellular failure results in hyperbilirubinaemia, hypoalbuminaemia and prolonged prothrombin time. The Child-Pugh classification is a modified grading system shown to be reliable in predicting survival of patients presenting with variceal bleeding but is also widely used as a method of assessing liver function<sup>1</sup>. Cirrhosis of liver is associated with alterations in bone mineral density and bone mineral metabolism which are defined under the generic term hepatic osteodystrophy (HOD)<sup>2</sup>. In the era of liver transplantation, metabolic bone disease complicating cirrhosis has become a major clinical problem. However in many patients with cirrhosis, osteoporosis remains unrecognised and untreated. For this reason, HOD has become more important.

HOD includes both osteoporosis and osteomalacia<sup>3,4</sup>. A

stronger association has been found between cirrhosis and osteoporosis than between cirrhosis and osteomalacia. Pathogenesis of HOD is multifactorial. Various potential inciting factors that either directly or indirectly alter bone mass are hyperbilirubinaemia, hypogonadism, alcohol, subnormal 25-hydroxyvitamin D<sub>3</sub> levels and concurrent use of drugs-like cholestyramine, furosemide, glucocorticoids and immunosuppressive agents.

Osteoporosis is a disorder characterised by a reduction in bone mass and microarchitectural deterioration of bone tissue, with a resultant increased risk of fracture<sup>4,5</sup>. The prevalence of osteoporosis ranges from 20 - 56%, and inter-individual variations are observed in the relationship to bone density. The fracture rate ranges from 5 - 20%<sup>6</sup>. Metabolic bone disease is directly proportional to duration and severity of chronic liver disease<sup>7,8</sup>.

Keeping in view the high prevalence of metabolic bone disease among cirrhotic patients, and the numerous therapeutic options for bone disease, it is prudent to characterise this condition in order to give these patients a better chance of survival. The prevalence of osteoporosis

\*Senior Resident, \*\*Consultant and Professor, Department of Medicine, Vardhman Mahavir Medical College VMMC and Safdarjung Hospital, New Delhi- 110029.



and metabolic bone disease in cirrhosis of liver has been validated in very few studies in Indian literature<sup>9,10</sup>. In various international studies, the overall incidence has varied from 11 - 48%, with a fracture rate of 3 - 44%<sup>11</sup>. This highlights the need for evaluation of metabolic bone disease in the Indian scenario, hence this study was undertaken.

## Aims and objectives

1. To estimate bone mineral density and prevalence of osteoporosis in patients with cirrhosis of liver.
2. To correlate bone mineral density with severity of cirrhosis.

## Patients and methods

This was a case-control study conducted in the Department of Medicine in VMMC and Safdarjung hospital. The study was conducted over a period of two years (2012 - 2014) on 50 patients with cirrhosis of liver and 50 age and sex matched controls attending the OPD or admitted in wards and satisfying inclusion and exclusion criteria. Patients aged eighteen years or more, abstaining from alcohol for more than three months prior to the study and diagnosed with cirrhosis of liver on the basis of clinical examination and ultrasonographic features were included in the study. Patients with thyroid disorder, parathyroid disorder, diabetes mellitus, renal failure, malignancy, signs of hypogonadism were excluded from the study. Post-menopausal females and patients on medication with corticosteroids, vitamin D, calcium, oestrogens, calcitonin, bisphosphonates, anticonvulsants, anticoagulants, and sodium fluoride were also excluded from the study. Informed consent was taken from all patients participating in the study. Hospital ethical committee clearance was taken for the study.

The evaluation of subjects included collecting information on age, gender, cause of cirrhosis of liver, duration of disease, alcohol consumption and duration. A general physical and systemic examination was also carried out. Biochemical investigations included complete hemogram, liver function test, kidney function test, blood sugar, thyroid function test, hepatitis B surface antigen, anti hepatitis C antibody, serum calcium and phosphate, and 25 (OH) vitamin D. All blood samples were drawn after overnight fasting. Radiological investigations included ultrasound of the abdomen for the diagnosis of cirrhosis.

Patients diagnosed as cirrhosis of liver constituted the study group and age and sex matched individuals without cirrhosis constituted the control group. For the assessment of severity of cirrhosis study group were divided into 3 groups Child A, B, C as per Child-Turcotte-Pugh classification. Both the groups underwent bone mineral density (BMD) testing. The in-department (DEXA scanner (Osteoscore 3, Platinum) was

used to procure the BMD data subsequent to filling in the pertinent data such as age, sex, height and weight of the subjects in the study and control group. The mean BMD value of the second, third and fourth lumbar vertebrae (lumbar spine BMD) and of the femoral neck of the proximal femur (femoral neck BMD) were used in the present analysis. BMD was expressed in absolute values, T-scores and Z-score. World Health Organisation (WHO) has defined osteoporosis as a T-score below - 2.5 standard deviation (SD).

On the basis of results of bone mineral density, cases of cirrhosis were divided into low (Z-score  $\leq$  - 2) and normal BMD (Z-score  $>$  - 2) groups and the result was correlated with severity of cirrhosis of liver (Child-Pugh Grade).

The data was analysed using SPSS version 17.0. All the results were expressed as mean, standard deviation and statistical significance between means was calculated by student T-test and differences between proportions was assessed by the chi square test where a p value of  $<$  0.05 was considered significant.

## Results

The results were based on the total study population of 100 participants which included 50 cases of cirrhosis and 50 age and sex matched controls. Cases and controls were distributed from the age group 19 - 50 years. Maximum cases were in the age group of 35 - 42 years (43%). Mean age among cases and controls was  $38.36 \pm 6.3$  and  $36.68 \pm 6.16$  years, respectively and the difference between them was statistically insignificant ( $p=0.18$ ). The study comprised of 88% males and 12% females, among both cases and controls (Table I).

**Table I: Distribution of study population by sex and age.**

Total participants	N = 100
Cases	50
Controls	50
Male	88
Female	12
<b>Age groups (years)</b>	
19 - 26	8
27 - 34	30
35 - 42	43
43 - 50	19
<b>Mean age (years)</b>	
Cases	$38.36 \pm 6.3$
Controls	$36.68 \pm 6.16$

Mean BMD in cases and controls was  $0.69 \pm 0.09$  g/cm<sup>2</sup> and

0.97 ± 0.21 g/cm<sup>2</sup>, respectively and the difference was statistically significant (p = 0.0001). Prevalence of low BMD was higher in the cases (78%) as compared to the controls (20%). Prevalence of osteoporosis in cases was 42% and 20% in controls, and the difference was statistically significant (p = 0.017) (Table II).

On the basis of severity of liver disease, the cases were divided into three grades; 54% cases were in Child Pugh grade C, 36% in Child Pugh grade B and 10% in Child Pugh grade A (Table III).

**Table II: Bone mineral density among cases and controls.**

Participants	Cases	Controls	P value
Mean BMD g/cm <sup>2</sup>	0.69 ± 0.09	0.97 ± 0.21	0.0001
Low BMD (Z-score < 2)	39	10	0.0001
Osteoporosis (T-score < - 2.5)	21	10	0.017

**Table III: Case distribution according to severity of liver disease and BMD.**

Cases	N = 50	Percentage %
Child Pugh A	5	10
Child Pugh B	18	36
Child Pugh C	27	54
Normal BMD	11	22
Low BMD	39	78

The cases in the study group were divided into cases with normal BMD and cases with low BMD. On comparison of mean serum calcium levels between the two groups, the difference was statistically insignificant (p = 0.38). Similarly mean serum 25 (OH) vitamin D levels were comparable between the two groups and the difference was statistically insignificant (p = 0.93). On correlation of BMD with severity of liver cirrhosis, 20% Child A cases, 72% Child B cases and 92% Child C cases in the study group had low BMD. The difference in mean BMD between Child A and Child B and between Child A and Child C was statistically significant (p = 0.009 and 0.001 respectively). However difference in mean BMD between Child B and Child C was statistically insignificant (p = 0.6) (Table IV).

## Discussion

HOD is an important complication of chronic liver disease. Osteoporosis and osteomalacia are included under the generic term HOD. The aetiology is multifactorial and pathogenic mechanisms are diverse. Osteoporosis can result in bone fractures with a harmful effect on quality of life. Therefore an assessment of bone mineral density is recommended in patients with cirrhosis of liver. Several

cross-sectional and longitudinal studies have shown, that individuals with cirrhosis have a pronounced loss of bone mineral density (osteoporosis prevalence of 20 - 50%) and a moderately increased rate of osteoporotic fractures (5 - 20%). The purpose of the present study was to estimate bone mineral density in cirrhosis of liver and correlate it with severity of disease, to estimate the markers of bone metabolism and hormonal status, and correlate it with bone mineral density in patients with cirrhosis of liver.

**Table IV: Comparison of BMD with severity of liver disease, serum calcium, serum 25 (OH) vitamin D levels among cases.**

Severity of liver disease	Child Pugh A	Child Pugh B	Child Pugh C	P value
Mean BMD (g/cm <sup>2</sup> )	0.83 ± 0.16	0.69 ± 0.06		0.009
	0.83 ± 0.16		0.68 ± 0.07	0.001
		0.69 ± 0.06	0.68 ± 0.07	0.6
Cases	Normal BMD	Low BMD		
Mean serum calcium (mg/dl)	8.6 ± 1.6	8.1 ± 1.9		0.38
Mean serum 25(OH) vitamin D (ng/ml)	20.2 ± 10.4	20.02 ± 8.2		0.93

The present study included, fifty cases of cirrhosis, mean age 38.36 ± 6.3 years, 44 males and 6 females. Fifty age and sex matched individuals from the general population served as controls. Low BMD (Z-score ≤ - 2) was found in 78% of cases and 20% of controls and osteoporosis (T-score ≤ - 2.5) was found in 42% of cases and 20% of controls and was statistically significant. This is comparable to the Indian data of Sachdev *et al*<sup>9</sup>, in which 64% of cirrhotic patients had low BMD. Mean BMD in the present study in cases and controls was 0.69 ± 0.09 g/cm<sup>2</sup> and 0.97 ± 0.21 g/cm<sup>2</sup>, respectively and the difference was statistically significant (p value = 0.0001).

The prevalence of low BMD of 78 % is in accordance with the study by George *et al* (2009)<sup>10</sup> who have reported low BMD in 68% of Asian Indian patients with cirrhosis of liver. The study was performed on 72 Indian patients with cirrhosis. Low BMD was defined as a Z-score below -2.

Goral *et al* (2010)<sup>6</sup> included 17 female and 38 male patients with liver cirrhosis and 15 female and 15 male controls were included in the study. In the study, osteoporosis was found in 37% of the patients. T- and Z-scores were significantly lower in the cirrhosis group than in controls when bone mineral densities were compared.

Wariaghli *et al*. (2010)<sup>12</sup> included 64 patients with chronic liver disease (mean age 51.66 ± 11.54 years), 48 females and 16 males. Age and sex matched individuals from the general population served as controls. Osteoporosis was evaluated by dual energy X-ray absorptiometry. Prevalence

of osteoporosis in cases was 45.3%, twice as high as in the controls (19.6%) (  $P < 0.001$ ).

Loria *et al* (2010)<sup>13</sup> recruited 35 consecutive patients with chronic liver disease including 8 females and 27 males of overall mean age of  $57 \pm 7$  years, who showed a viral etiology (57%) or alcohol etiology (28%). The prevalence of osteopenia was 26% osteopenia and osteoporosis was 14%.

The study by Sokhi *et al* (2004)<sup>14</sup> determined the bone mineral density (BMD) in different subgroups among pretransplant cirrhotic patients. BMD of the lumbar vertebrae (L) and femoral neck (F) were obtained in 104 consecutive cirrhotic patients. The mean BMD in males ( $n = 54$ ) and females ( $n = 50$ ) at lumbar spine were  $1.28 \pm 0.25$  g/cm<sup>2</sup> and  $1.13 \pm 0.20$  g/cm<sup>2</sup>, respectively ( $P < 0.001$ ). The overall prevalence of osteopenia and osteoporosis was 34.6% and 11.5%, respectively (Table V).

**Table V. Comparison of prevalence of osteoporosis and low BMD in various studies.**

Prevalence of osteopenia and osteoporosis in chronic liver disease of various aetiologies			
References	N	Aetiology	Prevalence of osteopenia/osteoporosis
Goral <i>et al</i> , 2010	55	Child A-B-C cirrhosis Mixed aetiology	Osteoporosis 37%
Wariaghli <i>et al</i> , 2010	64	Cirrhosis Mixed aetiology	Osteoporosis 45.3%
Loria <i>et al</i> , 2010	35	Cirrhosis Viral and alcoholic	Osteoporosis 14% Osteopenia 26%
George <i>et al</i> , 2010	72	Cirrhosis Viral and alcoholic	Low BMD 68%
Sokhi <i>et al</i> , 2004	104	Cirrhosis Mixed aetiology	Osteoporosis 11.5% Osteopenia 34.6%

In the present study, 92% of Child C cases, 72% Child B cases and 20% Child A cases had low BMD. Mean BMD in Child A, Child B, and Child C was  $0.83 \pm 0.16$  g/cm<sup>2</sup>,  $0.69 \pm 0.06$  g/cm<sup>2</sup> and  $0.68 \pm 0.07$  g/cm<sup>2</sup>, respectively and the difference in mean BMD between Child class A and B and that between Child class A and C was statistically significant ( $P$  value 0.009 and 0.001, respectively). However, difference in mean BMD between Child class B and C was statistically insignificant. ( $P$  value = 0.6). Prevalence of low BMD ( $Z$ -score  $\leq -2$ ) was high in Child C, as compared to Child class B and A ( $p = 0.003$ ).

Sokhi *et al*, (2004)<sup>14</sup> included 104 cirrhotic patients who were listed for orthotopic liver transplantation at the time they were enrolled for this study. Child Class C patients had significantly lower BMD values as compared to class B

patients.

A study by Figueiredo *et al*<sup>15</sup>, where 89 patients with noncholestatic cirrhosis and 20 healthy controls were enrolled in a cross-sectional study, the mean BMD decreased significantly with the progression of the liver dysfunction, as measured by Child-Pugh score.

Our data support the findings of other studies that describe an increase in prevalence and severity of osteoporosis with the progression of liver dysfunction<sup>1,16,17</sup>.

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## Autosomal Non-dominant Hereditary Spherocytosis in a Young Female from West Bengal: An Unusual Entity

**Ayan Basu\***, **Bisakh Bhattacharya\*\***, **Yogiraj Roy\*\*\***, **Mehebubar Rahman\*\*\*\***, **Dewan Koushik\*\*\*\*\***,  
**Rama Prosad Goswami\*\*\*\*\***

### Abstract

*Hereditary spherocytosis is a familial haemolytic disorder with marked heterogeneity of clinical features, ranging from a mild asymptomatic condition to severe haemolytic anaemia. Although severe cases can be diagnosed during childhood, less severe cases may go undetected till adulthood. Here we present the case of a 24-year-old lady presenting with features of chronic haemolytic anaemia, not diagnosed in childhood probably due to lack of appropriate investigations or awareness about the disease. Eventually she was diagnosed to be a case of hereditary spherocytosis, but without any positive history or findings in her parents, which leads to the diagnosis of autosomal non-dominant hereditary spherocytosis, an entity not widely reported in eastern India. This is probably the first reported case from West Bengal.*

**Key words:** Hereditary spherocytosis, autosomal non-dominant hereditary spherocytosis, haemolytic anaemia, West Bengal.

### Introduction:

Hereditary spherocytosis (HS) is a type of inherited haemolytic anaemia with marked heterogeneity. Clinical features may vary from asymptomatic to severe haemolytic anaemia. It is a common cause of inherited chronic haemolytic anaemia in northern Europe and North America (1 in 5,000 births) but is relatively uncommon in India<sup>1</sup>.

Majority of the patients (around 75%) exhibit an autosomal dominant mode of inheritance whereas the remainder may be either autosomal recessive inheritance or may arise due to *de-novo* mutation, where family history will be negative for signs and symptoms of the disease.

Here we document a case of a young female presenting with features of chronic haemolytic anaemia, not diagnosed in childhood probably due to lack appropriate investigations or awareness about the disease. Eventually she was diagnosed to be a case of congenital spherocytosis, but her family history was unremarkable and screening for signs and symptoms of the disease in her parents was normal, which leads us to the conclusion of this being a case of non-dominant spherocytosis. To the best of our knowledge, this is probably the first case of non-dominant HS reported from West Bengal.

### Case summary

A twenty-four-year-old female patient, born of non-consanguineous marriage, presented with generalised weakness for last six months along with heaviness of left side of abdomen for the same duration. She also complained

of intermittent yellowish discolouration of sclera and body, for the last one year. She had received blood transfusions, thrice in the past, once after birth and then twice, in the year 2000 and 2014. Her menstrual history was normal. She had history of one intrauterine foetal death at 9 months of gestation. Now she had one healthy male child. There was no history of similar illness in the family.

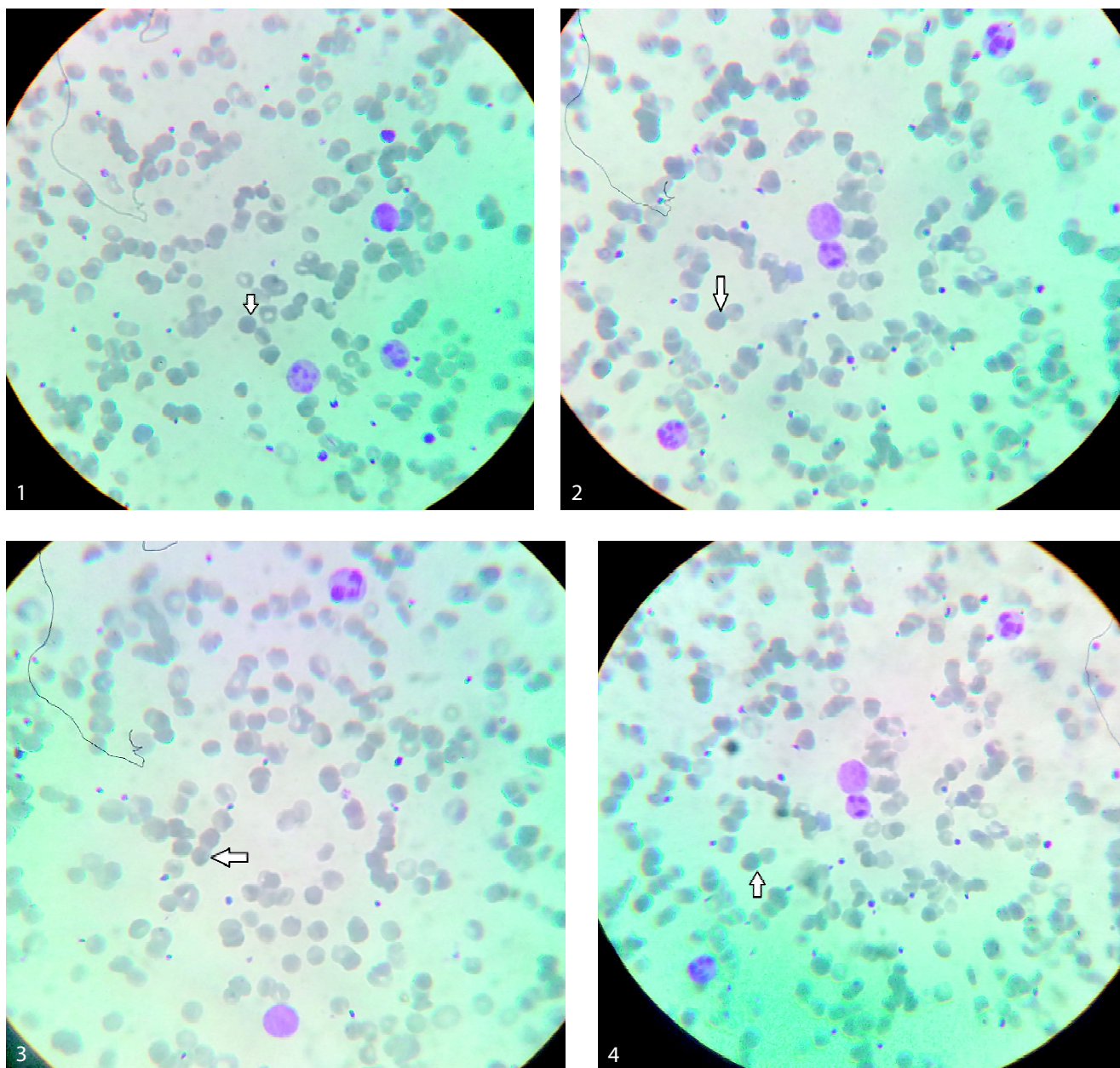
General examination revealed moderate pallor and mild icterus. Systemic examination showed moderate splenomegaly without any hepatomegaly or lymphadenopathy. Other systemic examination was normal.

Laboratory investigations showed Hb 7.7 gm/dl, RBC 2.51 x 10<sup>6</sup>/cumm. PCV 22.6%, MCV 79.2 fl, MCH 30.7 pg, MCHC 37.1 gm/dl, platelet count 2.5 lakhs/cumm, WBC 9,300/cumm. Reticulocyte count was raised at 7.2%. Peripheral blood smear showed plenty of spherocytes (characterised by loss of central pallor), anisocytosis and poikilocytosis (Figs. 1, 2, 3 and 4 white arrow).

LFT showed a picture of unconjugated hyperbilirubinaemia-total bilirubin - 3.5 mg/dl, indirect 2.7 mg/dl, liver enzymes were normal (SGPT 14 IU/L, SGOT 21 IU/L). Ultrasonography of abdomen showed presence of gall bladder stone, normal liver size and architecture, and moderate splenomegaly (17.4 cms). Serology for HIV, HBsAg, and Anti-HCV antibody was non-reactive.

Incubated osmotic fragility test result showed increased osmotic fragility. (Lysis started at 9.0 gm/l of NaCl and 89% lysis occurred at 2.0 gm/l of NaCl). Median corpuscular

**\*RMO Cum Clinical Tutor, \*\*Post-Graduate Trainee, \*\*\*Assistant Professor, \*\*\*\*Associate Professor, \*\*\*\*\*Professor, Department of Tropical Medicine, \*\*\*\*\*Assistant Professor, Department of Laboratory Medicine, School of Tropical Medicine, Kolkata, West Bengal.**



**Fig. 1, 2, 3 and 4:** Peripheral smear showing spherocytes- white arrow.

fragility (MCF) was 6.4 gm/l of NaCl (ref range: 4.65 - 5.9 gm/l of NaCl).

Direct coombs test was negative, G6PD activity was normal, serum ceruloplasmin and serum copper were within normal limits.

On the basis of above investigations, a diagnosis of HS was made.

As there was no history of similar illness in the family, we screened her parents for any signs of the disease but the complete haemogram and incubated osmotic fragility tests

were normal in both. Based on these clinical and haematological findings, we diagnosed it to be a case of non-dominant HS.

## Discussion

HS is an inherited disorder characterised by intrinsic defects in the red cell membrane that render red cells spheroid, less deformable, and vulnerable to splenic sequestration and destruction.

The most common molecular defects are abnormalities



of spectrin and ankyrin which are major components of the cytoskeleton, responsible for RBC shape. The genetic defect responsible for HS include ankyrin,  $\beta$ -spectrin, band 3 protein,  $\alpha$ -spectrin, and protein 4.2<sup>1,2</sup>. Spherical shape of the RBC impairs smooth passage from splenic cord to splenic sinuses and the spherocytic RBCs are destroyed, prematurely in the spleen.

The prevalence of HS is highest in Northern Europe, where rates of one in 5,000 have been reported<sup>1</sup>. An autosomal dominant inheritance pattern is seen in 75% of cases. Although common in West Asia, North Africa and Europe, it is quite rare in India but exact data is not available.

Most studies on autosomal non-dominant HS were from western literature<sup>3</sup>, where it had been shown that *de-novo* mutation occurs in 19% of cases. In 2% of cases, true recessive inheritance was documented, and in 4% of cases, the inheritance pattern could not be elicited. Also, one study in Japan showed that the prevalence of autosomal non-dominant HS was 66%<sup>4</sup>. Occurrence of non-dominant hereditary spherocytosis has not been extensively reported or studied in Indian population<sup>5</sup>.

Panigrahi *et al* had shown that both autosomal dominant and recessive patterns of HS were seen in North India. However, the predominant underlying protein defect in Indian patients needs to be characterised<sup>6</sup>.

Karan *et al* had shown that non-dominant HS does occur in India and should be considered as a diagnosis, when a patient with episodic jaundice and pallor since early childhood, shows microspherocytes in peripheral smear along with raised reticulocyte count, increased osmotic fragility, and normal parental study<sup>7</sup>.

## Conclusion

This case is reported keeping in mind the rarity of this disorder and common lapses in diagnosis and management of such a disorder. The diagnosis of HS should always be considered in a case of anaemia, jaundice, splenomegaly, and gallstone in adults. It is hoped that this report will enhance awareness on the existence of HS in this state and hence, a high index of suspicion and prompt referral to avoid unnecessary use of blood transfusions.

Thus, to conclude autosomal non-dominant HS, although reported from India, has not been extensively studied in terms of its regional distribution and characteristics and, to the best of our knowledge, this is the first case of its kind

reported from West Bengal.

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## **Fat Embolism Syndrome with Cerebral Involvement: A Case Report and Review of Literature**

*M Narang\*, Alex Babu\*, Ashutosh Kumar\**

### **Abstract**

*Cerebral fat embolism is a rare but potentially lethal complication of long bone fractures. Neurological symptoms are variable, and clinical diagnosis is difficult. In this case report, a 26-year-old man suffered acute mental status changes eight hours after a fracture of both bones of right leg. MRI brain was performed forty eight hours after injury which showed multiple non-confluent areas of high signal intensity in T2 weighed sequence, resulting from multiple microemboli.*

*Key words: Fat embolism syndrome, neurological, review.*

*Key messages: 1. Fat embolism syndrome is often missed due to lack of awareness about the disease and its diagnostic criteria. 2. Complete recovery is possible with aggressive supportive treatment.*

### **Introduction**

Fat embolism syndrome (FES) refers to a clinical entity that consists of pulmonary, central nervous system and cutaneous manifestations. It is an uncommon, but potentially life-threatening, complication of long bone fractures. Diagnosis of cerebral manifestation of fat embolism syndrome is highly challenging as the clinical presentation is variable and non-specific: headache, lethargy, irritability, delirium, stupor, seizures, convulsions or coma<sup>1</sup>. Many cases occur as sub-clinical events and remain undiagnosed. Clinical diagnosis of FES can be aided by the presence of respiratory failure, hypoxaemia and cutaneous petechiae.

Neuroradiological diagnosis of cerebral fat embolism is equally challenging. MRI brain is more sensitive and consistently shows multiple small, scattered, non-confluent hyper-intense intracerebral lesions on T2 weighted scan<sup>2</sup>.

### **Case report**

A 26-year-old male who sustained an open fracture of the right tibia and fibula, after a road traffic accident, was admitted to our emergency ward. He did not have any head injury. On admission, the vitals were stable and patient was fully conscious, alert, and oriented. Neurological and other systems examination was normal. X-ray of the right leg showed open fracture involving both bones. He underwent closed reduction with cast immobilisation.

The patient remained normal initially, but after eight hours, he started complaining of shortness of breath and his sensorium started deteriorating. On examination, the patient had tachypnoea, tachycardia, and fever. The arterial blood

gas analysis showed hypoxia (pO<sub>2</sub> was 55 mmHg). The neurological examination revealed Glasgow coma scale score of 5 (eye opening 1, motor response 3, verbal response 1) with normal reaction of both pupils to light. Endotracheal intubation was performed in view of respiratory distress and altered sensorium. The patient was shifted to intensive care unit and mechanical ventilation initiated. His blood investigations were normal except for a raised total leucocyte count of 18,900/mm<sup>3</sup> (90% polymorphs) and high sensitivity C-reactive protein (hsCRP) level of 212.5 ng/ml. The urine test for fat globules was negative but showed trace albuminuria. His coagulation parameters (PT, INR and aPTT) were normal. A chest X-ray showed bilateral pulmonary infiltrates while non-contrast computerised tomography (CT) of brain was normal.

Magnetic resonance imaging (MRI) of brain with contrast enhancement performed on the second day showed multiple tiny lesions in bilateral cerebral white matter, external capsule region, right anterior thalamus, and splenium of corpus callosum, suggestive of cerebral fat embolism. A CT pulmonary angiography showed acute thrombi in few of the sub-segmental branches of bilateral lower lobes, with areas of air space consolidation and few scattered areas of ground glass opacities in bilateral upper lobe suggestive of pulmonary fat embolism. Doppler echocardiography ruled-out patent foramen ovale or shunt lesions.

The patient remained on mechanical ventilation, general supportive care with regular neuro-surgical and orthopaedic evaluation. He was given intravenous dexamethasone injection at a dose of 0.4 mg/kg in three divided doses (to be tapered off after one week). His condition improved

*\*Department of Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi - 110 029*

and on third day he was extubated and put on oxygen through ventimask. His blood parameters and arterial blood gases became normal. On the tenth day, he underwent an external fixation of his fracture and was discharged after twenty days without any pulmonary or neurological sequelae.

## Discussion

Fat embolises in almost every patient with long bone fracture or major trauma, though it is symptomatic in only about 10%. Though bone fractures or major trauma account for the vast majority of FES, it occasionally occurs with burns, pancreatitis, liver disease, sickle cell anaemia, liposuction, parenteral lipid infusion, and other conditions. It typically occurs about 24 hours after injury. Gurd's criteria were proposed in 1974 for the diagnosis of FES (Table I)<sup>3</sup>.

**Table I: Gurd's criteria for diagnosis of fat embolism syndrome (one major and 4 minor criteria, plus fat microglobulinaemia, must be present to formally diagnose fat embolism syndrome).**

### Major criteria

- Petechial rash
- Respiratory insufficiency
- Cerebral involvement

### Minor criteria

- Tachycardia
- Fever
- Fat in retina (visible on fundus)/retinal emboli
- Fat in urine
- Fat in sputum
- Jaundice
- Sudden Anemia
- Sudden thrombocytopenia
- Raised ESR

There are two theories to explain the pathogenesis of FES. According to the "mechanical" theory, free fat particles from the bone marrow enter torn vein sinusoids at the site of the fracture and embolise to the pulmonary arterioles. The "chemical" theory suggests that when fat emboli arise from plasma fat, through some systemic stimulus associated with trauma and other medical conditions, chylomicrons coalesce and fuse to form larger fat globules<sup>4</sup>.

The principal clinical features of FES are respiratory failure, cerebral dysfunction, and skin petechiae. Pulmonary dysfunction is the earliest to manifest and is seen in 75% of patients; it progresses to respiratory failure in 10% of cases. The manifestations include tachypnoea, dyspnoea, and cyanosis; hypoxaemia may be detected hours before the

onset of respiratory complaints. Cerebral changes are seen in 86% of patients with FES. These changes are non-specific, ranging from acute confusion to drowsiness, rigidity, convulsions, or coma. Cerebral oedema contributes to the neurological deterioration.

A non-palpable petechial rash over the chest, axilla, conjunctiva, and neck, that appears within 24 - 36 hours and disappears within a week, occurs in 20 - 50% of patients. Several other signs are non-specific, like tachycardia and pyrexia. Renal changes may include lipiduria, oliguria, or anuria and hepatic damage may manifest as jaundice<sup>5</sup>. The two commonly used diagnostic criteria for fat embolism are Gurd's (Table I) and Shonfeld's criteria (Table II). The one proposed by Gurd and Wilson is commonly used<sup>6,7</sup>.

**Table II: Schonfeld's fat embolism syndrome Index (5 or more points are needed to make a diagnosis).**

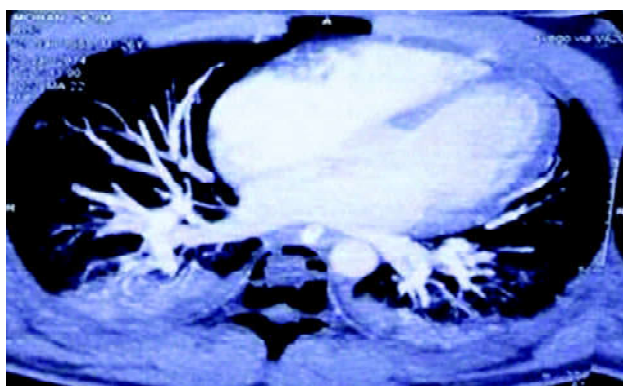
Feature	Points
Petechial rash	5
Lung changes on X-ray: Diffuse alveolar infiltrates	4
Hypoxia	3
Confusion, fever, tachycardia, tachypnoea	1 each

In a study, serum lactate estimation within 12 hours of injury and continuous SaO<sub>2</sub> monitoring, using pulse-oximetry, for at least initial 72 hours were done. A serum lactate of more than 22 mmol/l or even a transient episode of hypoxia on oximetry indicated a higher risk of pulmonary complications<sup>8</sup>. An elevated serum IL-6 level may be useful as an early marker of FES in patients with isolated skeletal trauma<sup>9</sup>.

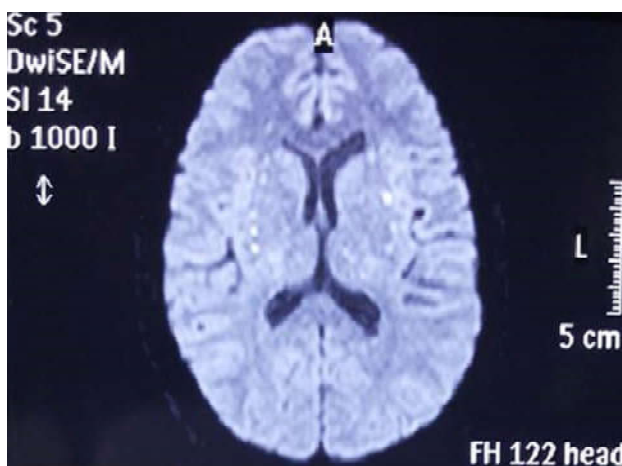
Amongst the laboratory parameters, a sudden and unexplained drop in hematocrit and platelet count could be important pointers towards the diagnosis. The mechanisms underlying thrombocytopenia are unclear but platelet activation by bone marrow emboli with thrombus formation as well as disseminated intravascular coagulation have been proposed as possible pathogenetic processes. Hypoalbuminaemia has been suggested to be due to plasma free fatty acids (FFA) binding to albumin. Besides these, an elevated blood lipase levels, elevated FFA levels and hypocalcaemia (due to binding of free fatty acids to calcium) can also be seen.

Radiological features, which have been described in patients with FES, include chest X-ray findings of bilateral fluffy shadows and the classical multiple flocculent shadows ("snow storm appearance"). These findings can persist up to 3 weeks. The high-resolution CT (HRCT) findings of the lungs in patients of FES showed evidence of bilateral ground-glass opacities and thickening of the interlobular septa, as well as centrilobular nodular opacities. MRI of the brain may





**Fig. 1:** The CT pulmonary angiography showed an acute thrombus in few of the sub-segmental branches of bilateral lower lobes, with areas of air space consolidation.



**Fig. 2:** MRI brain with contrast enhancement showing multiple tiny lesions in bilateral cerebral white matter, external capsule region, right anterior thalamus and splenium of corpus callosum.

reveal characteristic high-intensity signal abnormalities located in the watershed areas perfused by perforating arteries and diffuse anatomic distribution of the lesions on T2WI. Recovery of fat globules in blood (on pulmonary artery catheterisation) and fat droplets within cells recovered by bronchoalveolar lavage (BAL) has been suggested as a rapid and specific method for establishing the diagnosis of the FES, although of uncertain significance<sup>10</sup>.

Ventilation/perfusion imaging of the lungs may be normal or may demonstrate sub-segmental perfusion defects. A study pointed out that pulmonary and systemic fat embolism are not pure mechanical events, so the role of a patent foramen ovale (PFO) is not crucial<sup>11</sup>.

Treatments developed specifically for FES have been largely unsuccessful. Early experiments attempted to use dextrose to decrease free fatty acid mobilisation or ethanol to decrease lipolysis; however, neither has shown clinical benefits. Anticoagulation with heparin was found to be

beneficial in animal models but is no longer commonly used in clinical practice due to the risk of bleeding and unproven benefits.

Corticosteroid therapy has been proposed as a potential therapy for FES by limiting free fatty acid levels, stabilising membranes, and inhibiting complement mediated leukocyte aggregation. A meta-analysis reported no difference in mortality, infection, or avascular necrosis in patients treated with corticosteroids, compared to control patients. While still controversial, some clinicians administer corticosteroids to patients with long-bone fractures as FES prophylaxis. Methylprednisolone is the most commonly used steroid and dosages range from 6 to 90 mg/kg.

Once a patient develops FES, the only proven treatment is supportive care of the involved organ systems. Supplemental oxygen may be required to improve oxygenation. If adult respiratory distress syndrome (ARDS) develops, the patient may require mechanical ventilation while recovering from lung injury. Patients may require intravenous fluid for resuscitation to avoid developing shock. In severe cases, where pulmonary fat embolism causes right ventricular failure, inotropic support with dobutamine may be necessary. Rapid neurological deterioration may develop from increased cerebral oedema. Patients with FES and cerebral oedema may benefit from intracranial pressure monitoring<sup>12</sup>.

FES is associated with multiple long bone fractures and unstable fractures. Hence, an early fixation of long bone fractures within 24 hours is a key step. Prophylactic corticosteroids have been advocated by many authors, though there is no consensus about the dose. Albumin for volume resuscitation is recommended because it helps in restoring euvolaemia and also binds to free fatty acids and reduces further injury. Careful vigilance, with a high degree of suspicion, in high risk patients is vital in early detection of FES. These patients should be monitored continuously for a fall in oxygen saturation. An early initiation of oxygen (and steroids) in desaturating patients might help in reducing the hypoxic insult and sequelae of full blown FES<sup>13</sup>. Placement of inferior vena cava filters to prevent FES has not been sufficiently studied<sup>12</sup>.

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## INVITATION FOR NOMINATIONS FOR ORATION AWARDS FOR 2017

Suggestions are invited from Fellows/Members for the following Orations for the year 2017

so as to reach Dr.T.P.Singh, Hon. General Secretary, Indian Association of Clinical Medicine, on the official Address given below by **30th June, 2017**:

- |   |   |
|---|---|
| <b>1. Prof. B.C. Bansal – Mrs. Uma Bansal Oration</b><br><b>2. Dr. G. S. Sainani – Dr. Mrs. Pushpa G. Sainani Oration</b> | <b>3. Dr. G. B. Jain Oration</b><br><b>4. Founder-President Prof. M. C. Gupta Oration</b> |
|---|---|

- The suggestions are to be made for above Orations to be awarded during IACMCON-2017 (Kolkata). Nomination form is on page 69.
- The suggestions are to be made only by Fellows/Members of the Association, and must be accompanied with reasons for recommending the particular person showing the value of his/her research and accompanied with eight copies of three of his/her best publications. All the relevant papers in connection with suggestions such as Bio-data, list of publications, etc., should be submitted in **EIGHT SETS** by the proposer.
- The recipient of the above awards should deliver a lecture pertaining to his/her work at the Annual Conference of the Association in October 2017.

**Members of the Governing Body of the Association are not eligible to receive the Orations.**

### Eligibility Criteria:

1. The Nominee should have a minimum of 3 years standing in the Association as a Fellow (Kindly mention the Fellowship number and date of award).
  - i. The member should have a standing of minimum three years in the Association.
  - ii. The member should have participated in the annual conferences, scientific programmes, contributed to the *Journal*, and actively engaged in the organisation of the annual conference of the IACM.
  - iii. For Founder-President Dr. M. C. Gupta Oration, the subject of Oration should be related to cardiology.

**Dr. T. P. Singh**, Hony. Gen. Secretary, Indian Association of Clinical Medicine,  
 Post-graduate Department of Medicine, Sarojini Naidu Medical College, Agra - 282 002, U.P.  
 E-mail: iacmnational@rediffmail.com

## A Case of Sjögren's Syndrome Presenting as Hypokalaemic Paralysis and Respiratory Arrest due to Renal Tubular Acidosis – Case Report

Nitya Nand\*, Sameer Aggrawal\*\*, Nisha Batra\*\*\*, Rajiv Jain\*\*\*\*, Virender Chauhan\*\*\*, Manoj Yadav\*\*\*

### Abstract

*We report the case of a young female who presented to us with sudden onset flaccid quadriplegia and respiratory arrest, without any significant past clinical history. She was found to have hypokalaemia and hyperchloraemic metabolic acidosis with a positive urinary anion gap, compatible with distal renal tubular acidosis (dRTA). The patient fully recovered after potassium and alkali replacement. Further investigations revealed Sjögren's syndrome as the underlying cause of dRTA. The complications of dRTA include life-threatening hypokalaemia, chronic renal failure, growth retardation, and osteomalacia. These co-morbidities can be avoided, if the diagnosis is made early, and life-long potassium alkali salt replacement is maintained.*

### Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease, characterised by a progressive lymphocytic infiltration of the exocrine glands, with varying degrees of systemic involvement. Renal involvement is observed in 9% of patients of Sjögren's syndrome. The commonest lesion is tubulointerstitial disease presenting as Fanconi syndrome, dRTA or impairment of renal concentrating ability. Hypokalaemic paralysis, leading to respiratory arrest is a well known, albeit rare complication of severe dRTA from any cause. Cases of SS manifesting for the first time as respiratory arrest caused by hypokalaemia due to dRTA have been rarely reported.

### Case summary

A 24-year-old female, not a known case of any chronic disease, presented to us with sudden onset weakness of all 4 extremities for 1 day duration. There was no history of fever, trauma, loose stools, or vomiting. On examination, the patient was unable to move her head and only eyelid blinking was present. Muscle power was 0/5 in all groups and deep tendon reflexes were absent, but sensations were well preserved. There was no muscle wasting or tenderness. Plantars were not elicitable. Patient had shallow breathing with slightly decreased voluntary respiratory efforts. Her blood pressure was 110/80 mm of Hg and pulse rate was 98/min, irregular with few missed beats. There were no abnormal signs on cardiovascular, respiratory, or per abdomen examination. Within minutes of arrival, patient went in respiratory arrest and was intubated. Lab investigations revealed hypokalaemia (Serum K<sup>+</sup> 2.2 meq/l), metabolic acidosis with pH of 7.120 and bicarbonate concentration (HCO<sub>3</sub><sup>-</sup>) of 10.0 mmol/l. Serum anion gap was within normal range. Investigations revealed urine pH

of 6.0 in presence of metabolic acidosis. ECG showed ventricular ectopics, ST-segment depression with prominent U waves. So, a possibility of hypokalaemic paralysis leading to respiratory failure was considered and RTA was suspected. She was given intravenous potassium chloride and bicarbonate replacement. Patient improved within next 12 hours.

On further interrogation, she gave history of renal calculi few years back, for which she was managed conservatively. There was no history of similar illness in the past. Patient was an unmarried female who achieved menarche at age of 13 years with a normal menstrual cycle, at regular intervals. Based on the above history and investigations, patient was further investigated to look for the cause of RTA.

Renal and liver function tests were within reference range. Urine analysis was negative for albumin, sugar and RBCs. Serum calcium was 9.4 mg/dl, phosphorus was 3.4 mg/dl and albumin was 4.8 g/dl. Viral markers for hepatitis B and C, and human immunodeficiency virus were negative.

In a total urine volume of 2.5 l, urinary potassium excretion came out to be 60.95 meq/day which was definitely high in the presence of hypokalaemia. Urine anion gap was positive and trans-tubular potassium gradient (TTKG = [Urine K<sup>+</sup> / Serum K<sup>+</sup>] / [Urine osmolality / Serum osmolality]) was 15.5. Keeping in mind the urine pH of 6 in the presence of non-anion gap metabolic acidosis, hypokalaemia, and high TTKG, a diagnosis of dRTA was made.

Urinary phosphate excretion was 217.5 mg/day (reference range 400 - 1,300 mg/day). Urinary calcium and citrate excretion were within normal range but validity of the test could not be confirmed as the sample was collected after initiating treatment. Plain skiagram of abdomen did not

\*Senior Professor and Unit Head, \*\*Associate Professor, \*\*\*Resident, \*\*\*\*Senior Resident, Department of Medicine, Pandit B. D. Sharma Post-Graduate Institute of Medical Sciences (PGIMS), Rohtak - 124 001, Haryana.

reveal any evidence of calcification. USG Abdomen showed bilateral normal sized kidneys without any evidence of renal calculi.

A review of the history revealed complaints of dry mouth and gritty sensations in eyes which raised a suspicion of SS leading to dRTA. Schirmer's test was done, which came out to be positive (5 mm at 5 minutes).

Autoantibody screen revealed weakly positive antinuclear antibody titre of 1:40, with coarse speckled pattern. Anti-Ro (SS-A) antibody titre was significantly raised 87.48 units (reference range < 20 units). Anti-La (SS-B) antibody titre was in normal range 4.39 units (reference range < 20 units). This established the diagnosis of SS. Lip biopsy was done but it showed an inconclusive report of hyperplastic epidermis with mononuclear inflammatory infiltrate in the dermis. Further work-up was done to look for other co-existent autoimmune disorders. Thyroid function tests revealed raised TSH of 35.18 uIU/ml (reference range 2.3 - 4.20) decreased free T4 0.69 ng/dl (reference range 0.89 - 1.76) and normal free T3 levels 2.64 pg/ml (reference range 2.3 - 4.2). Anti-thyroid peroxidase antibody was mildly raised 62.30 U/ml. (normal range < 60.00). Rheumatoid factor was > 120 IU/ml (reference range < 14). Anti-cyclic citrullinated peptide antibodies were in low positive range of 9.20 U/ml (reference range < 5).

Patient was initially managed with intravenous potassium chloride and bicarbonate; later on, she was discharged on potassium citrate treatment. She was also prescribed artificial tears and an eye ointment by ophthalmologist. Her potassium level was maintained in normal range during follow-up visits.

## Discussion

SS was described in 1933 by Sjögren as a triad of rheumatoid arthritis, dry eyes and dry mouth. It is an autoimmune disorder characterised by chronic inflammation of the exocrine glands, mainly the salivary and lacrimal, leading to their progressive destruction of resulting in dryness of the mouth and conjunctiva (sicca syndrome). The disease can occur alone as primary SS or it can be associated with other connective tissue diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), mixed connective tissue disease, primary biliary cirrhosis or vasculitis, in which case it is referred to as secondary SS. Renal involvement occurs in about 30% of cases, and is often autoimmune tubulointerstitial nephritis, causing dRTA.

Urolithiasis and dRTA can precede subjective sicca symptoms, and patients with dRTA may have SS in the absence of subjective sicca symptoms. Anti-SS-A antibodies are common in patients with urolithiasis and dRTA. At least

six patients with distal RTA and objective signs of SS, but without subjective sicca symptoms, have been reported. Thus, SS can be diagnosed in dRTA patients even in the absence of subjective sicca symptoms<sup>1</sup>.

This case, where the patient presented with the complaint of quadriparesis and respiratory arrest, is important because it revealed hypokalaemia due to renal tubular involvement in primary SS. Laboratory tests done, when the patient had presented to the casualty, led to the diagnosis type I (distal) RTA accompanied by normal anion gap hyperchloraemic metabolic acidosis, alkaline urine and hypokalaemia. Potassium and then alkali replacement was started for the patient in the casualty, and the symptoms regressed within hours. Later on, she was diagnosed to be a case of primary SS based on revised international criteria for SS.

Hypokalaemia due to dRTA is usually a late manifestation. However, it has been reported in < 2% cases of SS as a presenting manifestation<sup>2</sup>. Paralysis of the extremities is a well known complication of hypokalaemia due to RTA. A prolonged state of severe hypokalaemia may cause muscle weakness to progress, occasionally, into respiratory arrest due to paralysis of the respiratory muscles. Studies have shown no significant difference in the level of serum potassium between the respiratory arrest group and quadriplegia alone group. These results suggest that the progress for respiratory arrest may be influenced by interindividual differences in sensitivity toward hypokalaemia (and presumably also transmembrane K<sup>+</sup> gradient) of respiratory muscles.

There have been few case reports where hypokalaemic periodic paralysis has been investigated and has led to the diagnosis of SS. The first such case report was as early as 1981. India's first such case was reported in 1996 by Thomas *et al*, from CMC Vellore<sup>3</sup>, Tsuboi *et al*, described that periodic paralysis was observed in almost 40% of SS cases associated with dRTA<sup>4</sup>. But hypokalaemic paralysis, with respiratory arrest as a presenting feature, has been documented only in 4 cases<sup>5</sup>. The potassium level in these cases was 1.4 mEq/l and 1.6 mEq/l<sup>7</sup>, while it was 2.2 mEq/l in our case. Although respiratory arrest associated with SS is very rare, this complication is fatal. Most of the dRTA patients presenting with hypokalaemic muscle weakness show good prognosis with immediate respiratory support and potassium supplementation; however, Nimmannit *et al*, described fatal cases of hypokalaemic respiratory failure and ventricular fibrillation due to endemic RTA in Thailand. This indicates that people with hypokalaemic paralysis can have SS, which can be diagnosed early. It is important to pay attention to the co-occurrence of severe hypokalaemia with metabolic acidosis and provide

adequate treatment for this combination in patients with SS.

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## ANNOUNCEMENT

### Invitation for Papers (Platform/Poster) for IACMCON-2017, Kolkata, West Bengal

Scientific papers are invited for Platform Presentation and Poster Presentation during IACMCON-2017 being held from 13th – 15th October, 2017

at ITC Sonar, Kolkata, West Bengal

The Poster Size should be 3 feet x 4 feet (approx.)

**Prizes will be given for Best Platform Presentation and Best Poster Presentation.**

*The abstract of the paper should be mailed to:*

**raju\_ys1197@yahoo.co.in**

Mobile: 09440066482

*The hard copy of the Abstract should be sent to:*

**Dr. Y. S. N. Raju**

*Chairman, Scientific Committee, IACMCON-2017*

**103 Ashoka Lake View Apts, Kundanbagh Begumpet, Hyderabad - 500 010**

**Last date for receiving the Abstracts is 31st August, 2017.**

## Dengue Encephalitis: Needs more Emphasis in Dengue Prone Areas

Kripa Shanker Jhirwal\*, Hemant Mahur\*\*, DP Singh\*\*\*

### Abstract

*Classical dengue fever is commonly seen in children and young adults. It commonly presents with fever, severe headache, body ache, and retro-orbital pain. Unlike other arboviral infections, dengue virus does not usually cause neurological manifestations.*

*We report a 14-year-old girl with dengue encephalitis. Dengue encephalitis should be considered in the differential diagnosis of acute viral encephalitis, especially in countries like India where dengue has assumed epidemic proportions. These undiagnosed cases are at risk of developing complications of dengue haemorrhagic fever.*

### Introduction

Dengue virus is a single-stranded RNA arbovirus belonging to the family flaviviridae. Infection with any of the four types of dengue virus can cause dengue fever, dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). Classical dengue fever is commonly seen in children and young adults. It commonly presents with fever, severe headache, bodyache and retro-orbital pain; hence, the term 'break-bone' fever. Unlike other arboviral infections, dengue virus does not usually cause neurological manifestations. We present a case of dengue encephalitis, which may be the only case of true encephalitis reported from Udaipur, Rajasthan, India.

### Case report

A 14-year-old girl presented to the emergency department of MB Hospital with continuous, high-grade fever for 4 days with severe headache and bodyache. Two days later, she developed difficulty in walking, with falling to one side while standing, and drowsiness. There was no significant past or family history. On examination, the patient was febrile and drowsy. Her pulse, blood pressure and respiratory rate were normal. General physical examination was normal, neurological examination revealed left-sided ptosis with sluggish pupillary reaction to light in that eye. There was gait ataxia with tendency to fall sideways. Other systems were normal.

Her laboratory profile was normal, except for a decreased leukocyte and platelet count and deranged liver profile. IgM capture MAC ELISA technique was used to detect IgM antibodies against the four known strains of dengue virus in the serum of the patient. IgM antibodies against dengue virus were negative. Magnetic resonance (MR) imaging of the brain showed altered signal intensity in brainstem, bilateral thalami, bilateral hippocampi, inferior and middle

cerebellar peduncle, and right frontal cortical gyri, which was suggestive of viral encephalitis. Cerebrospinal fluid (CSF) examination was acellular, with protein of 115 mg/dl (normal range 15 - 50 mg/dl), and glucose of 85.2 mg/dl (normal range 40 - 70 mg/dl). Repeat dengue serology after seven days was positive.

The patient was managed conservatively, with fluid support and continuous monitoring. Her ataxia improved after two days, and she became afebrile. She was discharged after two weeks. On follow-up, the patient was healthy and had no neurological deficit. Dengue serology performed after two weeks showed IgG antibodies in the serum.

### Discussion

Infection by dengue virus is commonly associated with dengue fever, DHF and DSS. However, in recent years, it has been recognised that this virus can also cause neurological manifestations<sup>1-13</sup>. Many neurological manifestations of dengue infection have been described including headache, seizure, depressed sensorium, behavioural disorders, neck stiffness, delirium, paralysis, cranial nerve palsies, and coma. Previously, reports of neurological manifestations in dengue infection had been referred to as encephalopathy rather than encephalitis because attempts to demonstrate direct invasion of the central nervous system (CNS) by dengue virus had failed (1).

Therefore, the pathophysiology of these neurological manifestations was thought to be secondary to prolonged DHF/DSS as opposed to encephalitis, which is defined as a localised invasion of the CNS<sup>2-5</sup>. Various physiological events were thought to lead to encephalopathy such as cerebral oedema<sup>2</sup>, cerebral haemorrhage, hyponatraemia, fulminant hepatic failure<sup>6</sup>, cerebral anoxia, micro-capillary haemorrhage and release of toxic products<sup>7</sup>. Recent reports, however, have demonstrated a possible

\*Final Year Resident, \*\*Associate Professor, \*\*\*Senior Professor and Head, Department of Medicine, RNT Medical College, Udaipur - 313 001, Rajasthan.

neurotropic effect of the virus. Animal studies, done in mice, showed that the virus could break down the blood-brain barrier leading to CNS invasion. Virus-mediated cytokines were found to be responsible<sup>8</sup>. In a study of six cases of dengue encephalitis, the virus was isolated from CSF in four cases. In one patient, virus was detected in CSF by polymerase chain reaction, and in another, IgM antibodies against dengue were present in CSF<sup>9</sup>. In another study of nine cases of encephalitis in patients with dengue, four patients had presence of either the virus or IgM antibodies in CSF<sup>10</sup>, suggesting that the virus can cross the blood-brain barrier directly and invade the brain. In five fatal cases of dengue infection, dengue virus antigen was demonstrated in CNS biopsies by immunohistochemistry<sup>11</sup>. These findings strongly support the hypothesis of direct neuro-virulence of the dengue virus.

Our patient had presented with drowsiness, which is consistent with reports of dengue encephalitis. In a meta-analysis of 355 cases of dengue encephalitis, 47% of patients were drowsy while 21% had seizures<sup>12</sup>. Our patient had no feature suggestive of DHF; neither was the haematocrit raised, nor did the patient have any haemorrhagic manifestations. MR images of the brain showed encephalitis-like changes. CNS imaging studies in cases of dengue encephalitis have shown cerebral oedema as the predominant finding in the majority of patients<sup>9,13</sup>, although a few cases do show encephalitis-like changes. One case of isolated hippocampus involvement has also been reported<sup>14</sup>. Therefore, given the clinical diagnosis of dengue fever along with MR imaging findings of encephalitis and a positive serology, it can be said that this case represents a true case of dengue encephalitis.

Dengue encephalitis should be considered in the differential diagnosis of acute viral encephalitis, especially in countries like India, where dengue has assumed epidemic proportions. Most case series on dengue encephalitis suggest that patients with the disease have a higher tendency to develop DHF/DSS. In one study of six patients, it was shown that all patients developed thrombocytopaenia and five developed characteristic clinical features of DHF/DSS<sup>9</sup>. In another study of eight patients, seven progressed to DHF<sup>15</sup>. Although the neurological recovery was complete in most of the patients, they had increased incidence of DHF/DSS.

In one of the largest meta-analysis of 178 cases of dengue-related encephalopathy<sup>16</sup>, it was shown that outcome was

often very poor (up to 50% mortality). However, most of the deaths were related to DHF/DSS. The mortality in cases of dengue encephalitis is increased, not due to the encephalitis *per-se*, which usually has a benign course, but due to the increased incidence of DHF/DSS. These undiagnosed cases are at risk of developing complications of DHF/DSS. It is therefore, very important for the clinician to be aware of the possibility of dengue infection as a cause of encephalitis.

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# Magnetic Resonance Imaging in Endomyocardial Fibrosis with Massive Left Ventricular Endocardial Calcific Deposits

**Simmi Aggarwal\*, Gagandeep Singh\*\*, Himanshu Khutan\*\*\*, Yash Paul Samberia\*\*\*\*, Ravinder Garg\*\*\*\*\***

## Abstract

*Endomyocardial fibrosis (EMF) is a disease of unknown origin, frequently observed in tropical and subtropical regions. The disease is characterised by formation of fibrous tissue on the endocardium in bilateral or hemilateral ventricles resulting in endocardial rigidity, with valvular involvement, further leading to restrictive cardiomyopathy. We present an asymptomatic 45-year-old male with endomyocardial fibrosis with calcification involving the left ventricle, which was diagnosed on echocardiography and contrast enhanced cardiac magnetic resonance imaging (CEMR) seen as late gadolinium enhancing area. The case highlights the importance of CEMR in diagnosing EMF, as a non-invasive modality.*

**Keywords:** Cardiac MR, endomyocardial fibrosis, restrictive cardiomyopathy.

## Case report

A 45-year-old male of Indian origin, not a known diabetic or hypertensive came to the hospital for routine medical examination. Patient was non-smoker and non-alcoholic. General physical examination was unremarkable with BP of 124/80 mmHg. Cardiac evaluation revealed normal S1 and S2 with no murmur/gallop. Rest of the systemic examination was within normal limits.

Laboratory examination revealed a haemoglobin of 12.9g/dl, a total leukocyte count of 5,800/cumm (with 54.2% neutrophils, 37.1% lymphocytes, 4.8% monocytes, 3.7% eosinophils and 0.2% basophils). The absolute eosinophil count was normal (220/cumm). ECG was s/o LV hypertrophy with strain. X-ray chest revealed a normal cardiac silhouette with normal cardio-thoracic ratio with multiple calcific densities in the cardiac region on left side s/o myocardial calcifications (Fig. 1). Two dimensional echocardiography showed enlargement of left atrium and left ventricle. Left ventricular apex was obliterated with a tissue growth encroaching till mid-cavity. There was no associated valvular dysfunction or pleural effusion and ejection fraction was 50%. CE MR revealed left ventricular hypertrophy obliterating the apex. Hypointensities were seen in the endocardium in left ventricle on T1 and T2 suggestive of calcification with global thickening of left ventricle. CEMR showed delayed enhancement of the endocardium (Figs. 2, 3, 4, and 5). On the basis of clinical and imaging findings, the diagnosis of EMF was made and patient was advised endomyocardial biopsy but he refused and was managed conservatively, and kept on follow-up.

## Discussion

EMF is a progressive restrictive cardiomyopathy, frequently observed in tropical and subtropical regions<sup>1</sup>. It was first described by Davies and Connors and their coworkers in Uganda. It is characterised by fibrous endomyocardial hypertrophy with calcification and small thrombosis in bilateral or hemilateral ventricles, resulting in endocardial rigidity. Artrio-ventricular valves are often involved resulting in valvular incompetence, secondary to papillary muscle involvement and progressive reduction of the cavity leading to restriction in filling<sup>2,3</sup>. The pathogenesis of EMF is not known. An inconsistent eosinophilia is found in patients with EMF and similar endocardial fibrotic changes develop in patients with eosinophilic leukaemia and Loeffler's disease<sup>4,5,6</sup>. In the present case, there was no eosinophilia. Physical findings depend on the extent and distribution of the disease. An elevated jugular venous pressure, ascites and oedema may be present in right ventricular involvement. Pulmonary congestion is present with left-sided disease<sup>7</sup>. Echocardiography is the first-line standard technique for diagnosing EMF<sup>8</sup>. The characteristic findings are obliteration of apex of the involved ventricle, a grossly dilated atrium with a normal-sized ventricle and thickening of the posterior left ventricular wall or anterior interventricular septum in patients with left or right-sided involvement, respectively<sup>2</sup>. In the present case, there was dilatation of left atrium with obliteration of left ventricular apex, with no valvular involvement. CT scan shows a low density area involving the endocardium<sup>9</sup>. However, CT scan was not performed in our patient.

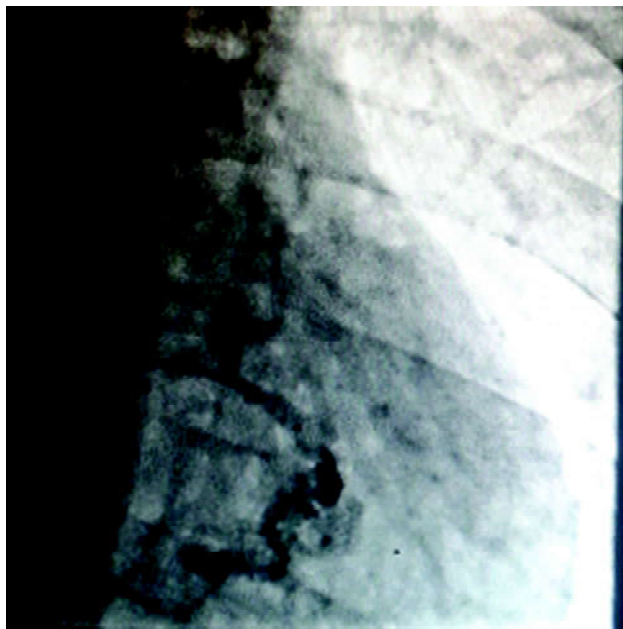
CEMR has a vital role in the diagnosis of EMF. It provides

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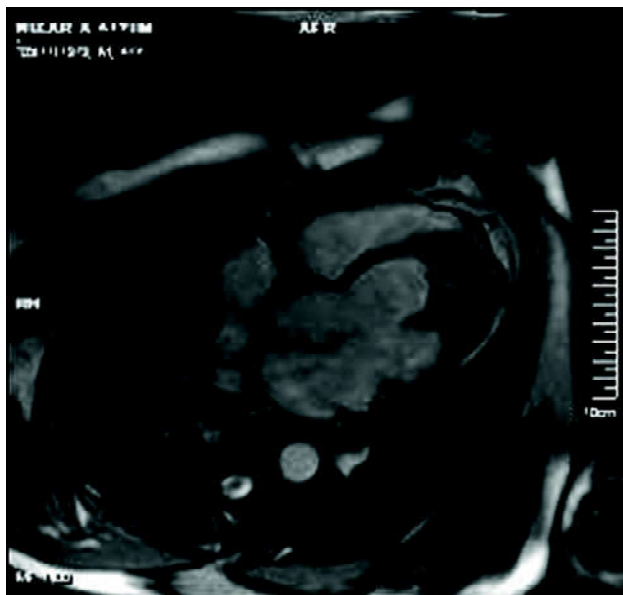
**\*Professor and Head, \*\*\*\*Lecturer, Department of Radio-Diagnosis, \*\*Associate Professor, Department of Cardiology, \*\*\*PG Resident, \*\*\*\*\*Associate Professor, Department of Medicine, GGS Medical College and Hospital, Faridkot, Punjab.**



detailed information of the ventricular morphology and function, including excellent visualisation of the ventricular apex<sup>8</sup>. On T1WI, EMF has been reported as a smooth intermediate signal intensity mass occupying the apex and inlet of ventricle with normal pericardium<sup>9</sup>. Salemi *et al* documented EMF as late gadolinium enhancement (LGE) of the endocardium, seen as continuous area extending from the subvalvular regions to the apex of the ventricles. A three-layered appearance at the apex or the



**Fig. 1:** Fluoroscopy image showing multiple calcified densities in cardiac region on left side.



**Fig. 2:** 4 chamber true-FISP view showing hypointense calcification with thickened myocardium.

'V' sign is typical of EMF with an inner layer showing no perfusion due to thrombus, middle layer showing LGE reflecting fibrous tissue and an outer layer of normal enhancing myocardium. A biopsy may not be required for establishing the diagnosis and late gadolinium enhancing CEMR is the best non-invasive method for confirming EMF<sup>8</sup>. Our patient also showed three layers, i.e., non enhancing calcified endocardium, late gadolinium enhancing endocardium and normal enhancing myocardium, there was no thrombus, hence biopsy was not performed. Amyloidosis, sarcoidosis and sub-endocardial infarction can also cause LGE of the endocardium. Amyloidosis shows global inhomogenous LGE of subendocardium with global increased wall thickness and systolic dysfunction. Cardiac sarcoidosis shows area of myocardial enhancement in the region of granuloma with wall motion abnormalities.



**Fig. 3:** Post-gad 1 min PSIR (phase sensitive inversion recovery) sequence showing normal enhancement of myocardium.



**Fig. 4:** Post-gad 5 min PSIR showing late enhancement of endocardium.



**Fig. 5:** Post-gad 10 min PSIR showing wash out of contrast by myocardium.

Subendocardial infarctions show LGE which is related to coronary artery distribution, there is no apical filling mass, when apex is involved there is associated thinning of ventricular wall with wall motion abnormalities<sup>8</sup>. CEMR can differentiate calcification from acute and subacute thrombus as acute thrombus appears bright on T1 and T2WI and a subacute thrombus appears bright on T1WI and shows low signal on T2WI. A chronic organised thrombus shows low signal on T1 and T2WI due to low water content hence cannot be differentiated from calcification<sup>10,11,12</sup>. Chagas disease also shows fibrous tissue deposition heterogeneously distributed in mid-wall and subepicardium in apical and basal inferolateral regions<sup>13</sup>. Surgical resection of fibrous tissue is the recommended treatment in symptomatic patients. CEMR provides information regarding fibrous tissue distribution and location for surgical procedure. It also helps in post-surgical follow-up, progression and recurrence of EMF.

## Conclusion

This case highlights the importance of CEMR as a non invasive imaging modality for the diagnosis of EMF. So a combination of echocardiography and CEMR can be excellent diagnostic tools in this form of restrictive cardiomyopathy.

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# A Case of Human Parvovirus B 19 Infection with Erythroid Hypoplasia and Idiopathic Thrombocytopaenic Purpura in an Immunocompetent Child

*P Ganesh\*, YS Raju\*\*, D Swaroopa\*\*\*, A Krishna Prasad\*\*\*\**

## Abstract

*Human parvo virus B19 (B19V) is a small (5.5 kb) single stranded DNA virus, with known tropism and cytotoxicity for erythroid progenitors. Human parvovirus B19 infection is associated with various haematological disorders like aplastic crisis, erythroid hypoplasia and idiopathic thrombocytopaenic purpura. Here we are presenting a rare case of parvovirus B19 infection with erythroid hypoplasia and idiopathic thrombocytopaenic purpura occurring simultaneously in a 13-year-old girl, who presented with fever and bleeding manifestations.*

**Keywords:** Parvo virus B19, erythroid hypoplasia, idiopathic thrombocytopaenic purpura.

## Introduction

Human parvovirus B19 (B19V) is a small (diameter ~22 nm), nonenveloped, icosahedral virus with a linear single-stranded DNA genome of ~5,000 nucleotides<sup>1</sup>. B19V exclusively infects humans, and infection is endemic in virtually all parts of the world<sup>1</sup>. Most persons with parvovirus B19 infection are asymptomatic or exhibit mild, nonspecific, cold-like symptoms<sup>2</sup>. Parvovirus B19 usually infects children and causes the classic "slapped-cheek" rash of erythema infectiosum (fifth disease). The virus is highly infectious and spreads mainly through respiratory droplets<sup>2</sup>.

Human parvovirus manifestations depend on immunological and haematological status<sup>3</sup>. Parvovirus B19 infection can trigger an acute cessation of red blood cell production, causing transient aplastic crisis, chronic red cell aplasia, hydrops foetalis, or congenital anaemia. This is even more likely in patients with illnesses that have already shortened the lifespan of erythrocytes (e.g., iron deficiency anaemia, human immunodeficiency virus, sickle cell disease, thalassaemia, spherocytosis)<sup>2</sup>. Chronic B19V infection has been reported in immunosuppressed patients, with persistent anaemia and reticulocytopaenia. Recently, idiopathic thrombocytopaenic purpura (ITP) was reported as a rare complication, in children following B19V infection<sup>4</sup>. Most patients recover completely. Here we are presenting a case of erythroid hypoplasia and idiopathic thrombocytopaenia, occurring simultaneously in an immunocompetent patient with parvovirus B19 infection.

## Case information

A 13-year-old girl student, presented with fever of 5 days duration, epistaxis and spontaneously bleeding gums of one day duration, dizziness and fall, with injury over forehead one day before admission to hospital. The fever

was high grade, intermittent, and was not associated with skin rash or arthralgias. She had dizziness and fall, sustained injury with swelling over left side of forehead. She had subsequent loss of consciousness for 2 - 3 minutes, not associated with involuntary movements and regained consciousness spontaneously. There was no significant past history. On examination, patient had pallor, multiple bilateral cervical lymph nodes, largest measuring 1 x 1 cm, swelling over left side of forehead (likely hematoma). Other systemic examination did not reveal any abnormal findings.

Her initial complete blood counts revealed pancytopenia with haemoglobin - 5.4 g/dl (normal range: 13 - 18 g/dl), total leucocyte count of 3,700 cells/mm<sup>3</sup> (normal range: 4,000 - 11,000 cells/mm<sup>3</sup>) with 62% polymorphs, 25% lymphocytes, 11% monocytes and platelet count of 3,000 cells/mm<sup>3</sup> (normal range 1.5 lakhs - 4 lakhs/mm<sup>3</sup>). In view of cytopaenias with bleeding manifestations, 2 units of packed red blood cell transfusion and 4 units of packed random platelets were initially given. Her serum vitamin B12 levels - 348 pg/ml (normal range 190 - 900 pg/ml) and folate levels were - 4.2 ng/ml (normal range 4 - 15 ng/ml).

Her renal function tests and liver function tests were within normal range. Viral markers were non-reactive for HIV 1/2, negative for anti-HCV, and HBsAg. Smear for malarial parasite and its antigen test was negative. Dengue serology was negative. Blood cultures were sterile. Chest X-ray was normal, ultrasonogram of whole abdomen was normal. Ultrasonogram of neck was suggestive of multiple subcentimetric lymphnodes in cervical, submental and submandibular region. Computed tomography of brain showed left frontal scalp hematoma and no other intra parenchymal haemorrhages.

On day 3 of admission, bone marrow aspiration and biopsy was done which showed normal cellularity with paucity of

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**\*Post-Graduate Student, \*\*Professor and Head, \*\*\*Assistant Professor, \*\*\*\*Professor, Department of General Medicine, Nizam's Institute of Medical Sciences (NIMS), Punjagutta, Hyderabad, Telangana.**

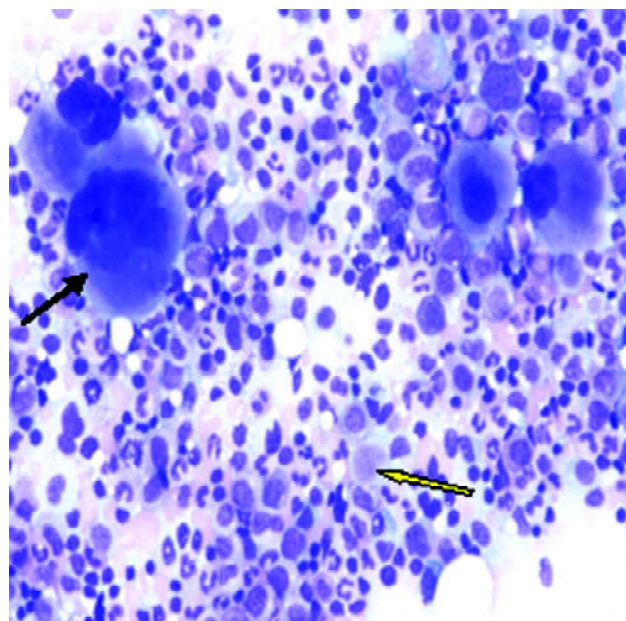
erythroid precursors, myeloid: erythroid ratio 9:1 and giant basophilic pro-normoblasts with intranuclear inclusions (Figs. 2, 3,4), with no further maturation, as well as increased megakaryocytes with few hypolobate forms suggestive of erythroid hypoplasia and idiopathic thrombocytopaenic purpura (Fig. 1). Parvo virus B19 DNA (by nested polymerase chain reaction) was detected in serum. Cervical lymph node biopsy showed reactive hyperplasia.

She was treated with empirical parenteral antibiotics and blood component support. She received pulse steroids of Inj. Methylprednisolone 15 mg/kg for 5 days, later oral prednisone of 1 mg/kg. Her cell counts improved and she undischarged in stable condition. She was on follow-up with low dose prednisone, and after 1 month, her haemogram was completely normal and she was doing well.

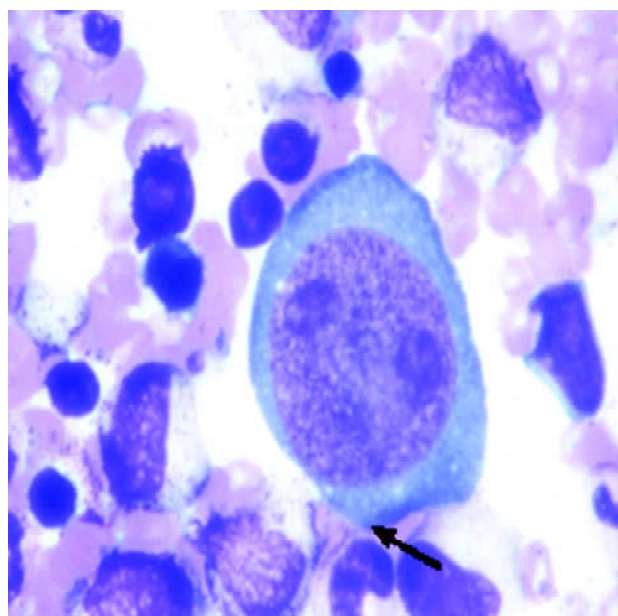
## Discussion

Parvoviruses, members of the family parvoviridae, are small (diameter, ~22 nm), nonenveloped, icosahedral viruses with a linear single-strand DNA genome of ~5,000 nucleotides<sup>1</sup>. B19V exclusively infects humans, and infection is endemic in virtually all parts of the world<sup>1,5</sup>. Transmission occurs predominantly via the respiratory route and is followed by the onset of rash and arthralgia.

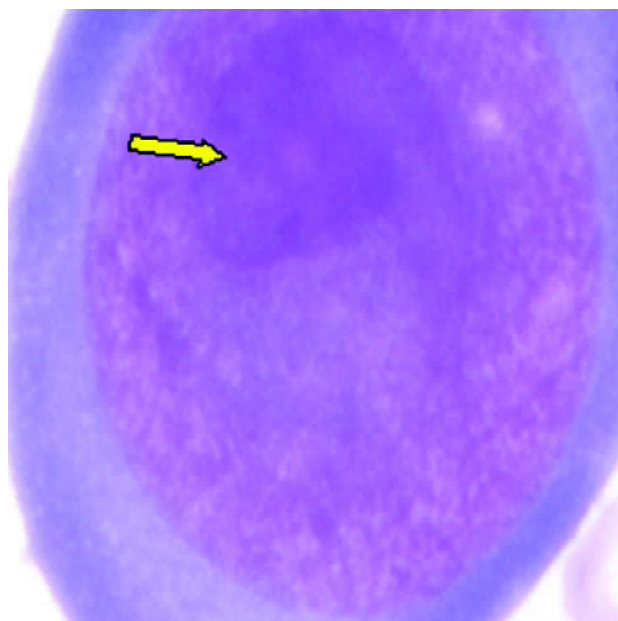
B19V replicates primarily in erythroid progenitors. This specificity is due, in part, to the limited tissue distribution of the primary B19V receptor, blood group P antigen



**Fig. 1:** Bone marrow aspirate is particulate, with normal cellularity for age. There is paucity of erythroid precursors (yellow arrow) with an M:E ratio of 9:1, myeloid maturation is normal. Megakaryocytes are increased with few hypolobate forms (black arrow).



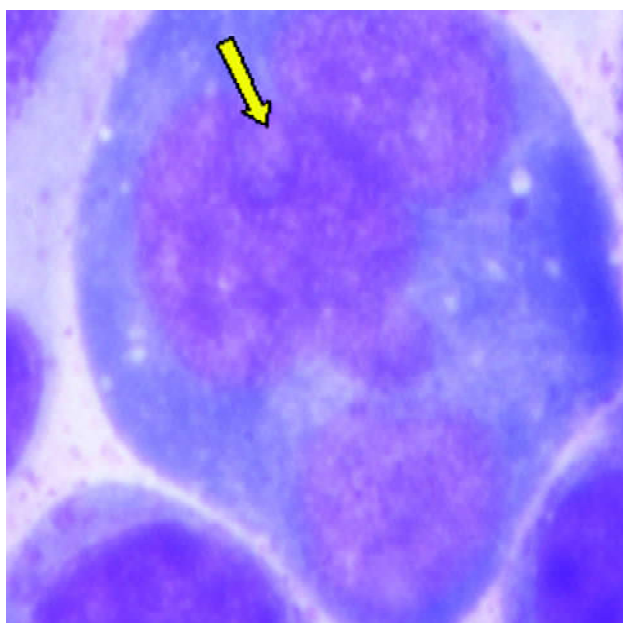
**Fig. 2:** Bone marrow aspirate: Erythroid precursors consist of basophilic normoblasts with no further maturation and show megaloblastoid change with intranuclear viral inclusions and cytoplasmic dog-ear like projections (arrow).



**Fig. 3:** Bone marrow aspirate: Erythroid precursors consist of basophilic normoblasts with no further maturation and show megaloblastoid change with intranuclear viral inclusions (arrow).

(globoside)<sup>1</sup>. Infection leads to high titer viraemia, with  $> 10^{12}$  virus particles (or IU)/ml detectable in the blood at the apex, and virus-induced cytotoxicity results in cessation of red cell production. In immunocompetent individuals, viraemia and arrest of erythropoiesis are transient and resolve as the IgM and IgG antibody response is mounted<sup>1</sup>.





**Fig. 4:** Bone marrow aspirate: Erythroid precursors consist of basophilic normoblasts with no further maturation and show megaloblastoid change with intranuclear viral inclusions (arrow).

Haematologic disorders associated with parvo virus B19 include aplastic crisis, erythroid hypoplasia, idiopathic thrombocytopaenic purpura, haemophagocytosis. B19V infection may rarely cause hepatitis, vasculitis, myocarditis, glomerulosclerosis, or meningitis. Here we are presenting a case of parvovirus B19 associated with erythroid hypoplasia and idiopathic thrombocytopaenic purpura occurring simultaneously in an immunocompetent child, which is a rare combination. We searched literature and few case reports were described about this combination.

Erythroid hypoplasia associated with parvovirus B19 is well established. The usual bone marrow findings in acute parvovirus infections are marked erythroid hypoplasia and occasional giant erythroblasts. Intranuclear inclusions in developing erythroid precursors are rarely described in children or adults with parvovirus infection, although abundant intranuclear inclusions are commonly observed in the placenta and other tissues in infected fetuses<sup>5</sup>.

Many reports have centered on connecting parvovirus B19 infection with childhood idiopathic thrombocytopoenic purpura (ITP). The association is difficult to make because both are rare disorders. Several case reports indicate that parvovirus B19 infection may also cause the development of thrombocytopaenia. Despite recent studies, the frequency and clinical relevance of this association has

remained questionable. B19-induced thrombocytopaenia seems to consist of a central and a peripheral type. Thrombocytopaenia of central origin is due to bone marrow suppression, and the possible cytopathologic effect is underlined by the finding that the NS1 protein, produced by B19, has been found to inhibit megakaryocytic colony formation<sup>3</sup>.

This indicates tissue tropism of B19, beyond the erythroid progenitor cell and shows that viral proteins may be toxic to cell populations that are nonpermissive for viral DNA replication. Destructive thrombocytopaenia of peripheral origin may result from immunologically mediated antiplatelet antibody production, with subsequent excessive platelet clearance in the reticuloendothelial system<sup>3</sup>.

Diagnosis of B19V infection in immunocompetent individuals is generally based on detection of B19V IgM antibodies and B19 DNA detection by PCR<sup>2</sup>. Viral DNA testing is crucial for the diagnosis of parvovirus B19 infection in patients with transient aplastic crisis or in immunocompromised patients with chronic infection. These patients do not test positive for IgM or IgG and remain contagious<sup>2</sup>. No antiviral drug effective against B19V is available, and treatment of B19V infection often targets symptoms only. However, it appears that immunoglobulins, in particular, offer promise as therapy for more severe infections.

**Conclusion:** This case highlights the morphology of human parvovirus B19 infection and its association with simultaneous presentation of erythroid hypoplasia and idiopathic thrombocytopaenic purpura in an immunocompetent child, which is very rare.

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## Acute Cerebellar Demyelination: An Unusual Complication of Anti-tuberculous Drugs

**Vivek Pal Singh\*, Anil Vardani\*\*, RK Singal\*\*\*, Atul Bhasin\*\*, NM Agarwal\*\*, RN Saini\*\***

### Abstract

**Neurotoxicity with first-line anti-tuberculous treatment is relatively uncommon. Central and/or peripheral neurotoxicity, ototoxicity and optic neuritis are well known complications, but cerebellar syndrome is rare. We report a 45-year-old female, who developed cerebellar ataxia after taking four anti-tuberculous drugs for two weeks. Brain magnetic resonance imaging (MRI) revealed toxic demyelination of dentate nuclei of cerebellum. She recovered completely after discontinuation of anti-tuberculous treatment and pulse methylprednisolone therapy.**

**Key words:** Toxic demyelination, cerebellar ataxia, isoniazid, tuberculosis, methylprednisolone.

### Introduction

Neurotoxicity with the first-line anti-tuberculous medications is relatively uncommon in any case, given the number of patients of tuberculosis in India. Yet doctors ought to be aware of the devastating neurotoxicities with anti-tuberculous drugs. Central and/or peripheral neurotoxicity, ototoxicity and optic neuritis are well-known adverse effects of isoniazid (INH), streptomycin (STM) and ethambutol (ETM)<sup>1</sup>. However, cerebellar syndrome by these drugs is rarely reported.

We dismiss a case of acute cerebellar demyelination which developed after two weeks of anti-tuberculous medication and the possible role of INH in cerebellar demyelination. This unusual clinical course should be known to manage the outcome of adverse events due to anti-tuberculous drugs.

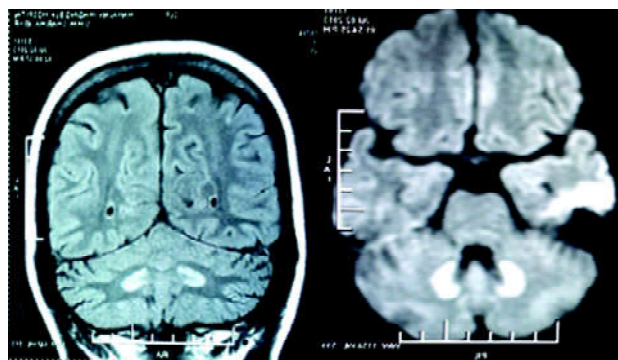
### Case report

A 45-year-old, normotensive, euglycaemic female was admitted with complaints of acute onset imbalance, slurring of speech, generalised weakness and vertigo of three days duration. On examination vitals were normal, with no postural hypotension. GCS was 15/15. She could stand and walk, but with wide-based gait with a tendency to fall either way. Neurological examination revealed horizontal nystagmus to the right and positive cerebellar signs. Fundus examination was normal. There was no history of fever, headache, visual disturbances, seizures or loss of consciousness.

Three weeks prior to admission she was investigated elsewhere for cough with expectoration and low grade fever of one month duration. She had mild anaemia (Hb –

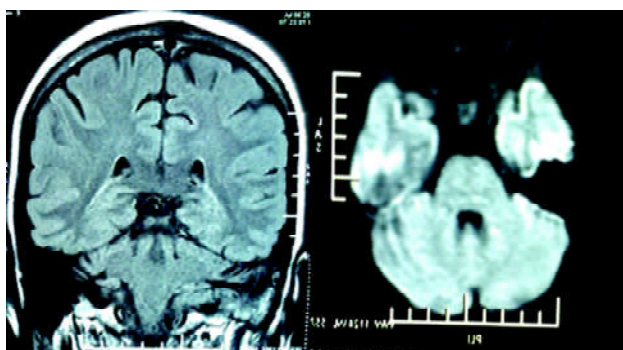
8.1 gm %) along with raised ESR (60 mm in first hour). Mantoux test showed 14 mm induration. Sputum for AFB was positive. Thereafter she was given 4 drug first-line anti-tuberculous drugs with pyridoxine, in appropriate dosage.

She presented to us after regularly taking anti-tuberculous drugs for two weeks. MRI brain was done on emergent basis and it revealed bilateral symmetrical confluent T2/FLAIR hyperintensity with restricted diffusion in the dentate nuclei of cerebellum, suggestive of possibility of toxic demyelination (Fig. 1a). CSF examination for oligoclonal bands, HSV-1 and 2 and TB-PCR was negative. VDRL and HIV 1 and 2 were negative. Routine serologies and biochemistries including vitamin B 12 and TSH were normal. Anti-nuclear antibody and anti-ds DNA were negative. Visual evoked potentials were also normal. In view of acute demyelination of cerebellum she was given pulse methylprednisolone therapy (1 gm/day for 5 days) and ATT was stopped. She had complete clinical recovery within 48 hours and follow-up MRI brain after 5 days revealed resolution cerebellar hyperintensities (Fig. 1b).



**Fig. 1a:** T2/FLAIR hyperintensity with restricted diffusion in the dentate nuclei of cerebellum.

**\*Consultant, \*\*Senior Consultant, Department of Internal Medicine, \*\*\*Principal Consultant and Head, Department of Medicine, BLK Super Speciality Hospital, Pusa Road, New Delhi - 110 005.**



**Fig. 1b:** MRI brain after 5 days showing complete resolution of cerebellar hyperintensities.

Methylprednisolone was gradually tapered off and ATT was reintroduced, with flouroquinolone instead of INH, along with pyrazinamide and rifampicin. Patient completed six months of ATT and remained asymptomatic, with no neurological sequelae.

## Discussion

The differential diagnosis of acute cerebellar dysfunction includes demyelinating, metabolic, infectious, and inflammatory diseases. Cerebellar dysfunction may occur in association with exposure to a wide variety of toxins, including drugs, solvents, and heavy metals. These toxins may adversely affect the cerebellum, directly, or as part of a more generalised encephalopathy. Practically, all drugs given at high enough doses can cause cerebellar dysfunction. The drug-induced cerebellar syndrome is characterised by transient gait ataxia, dysarthria, and nystagmus. Symptoms usually subside with discontinuation of the offending agent<sup>2</sup>.

Out of the first-line anti-tuberculous medications, neurotoxic effects of INH have been reported since the early 1950s, ranging from peripheral neuropathy, encephalopathy, and seizures to psychosis. INH-induced neurotoxicity is a direct effect of inhibition of the phosphorylation of pyridoxine, which results in the decreased production of pyridoxal-5-phosphate, a coenzyme which is required in multiple metabolic functions including neurotransmission via gamma-aminobutyric acid (GABA). Because GABA is one of the primary inhibitory neurotransmitters produced by Purkinje cells of cerebellum, it may be an important mechanism of cerebellar dysfunction

caused by INH toxicity<sup>3,4</sup>.

Pyridoxine, which is traditionally used to prevent and treat INH-induced neuropathy did not consistently reverse the toxicity of multiple INH metabolites formed by hydrolysis, cytochrome P450-dependent oxidation and N-acetyltransferase activity in animal models. In fact, pyridoxine itself has neurotoxicogenic potential with prolonged overdose<sup>5</sup>.

The differential diagnosis of T2 hyperintense, bilaterally symmetrical dentate nuclei includes methyl bromide intoxication, metronidazole toxicity, maple syrup urine disease and enteroviral encephalomyelitis. Multiple sclerosis and acute disseminated encephalomyelitis may present with similar MRI findings, but involvement of the gray matter, a normal CSF, and the temporal profile make these possibilities unlikely<sup>6</sup>.

The close temporal relationship between the onset of cerebellar findings and the initiation of ATT does provide a relationship, albeit non-causal, between anti-tuberculous drugs and cerebellar dysfunction.

To conclude, a diagnosis of INH-induced cerebellar dysfunction should be considered when cerebellar signs develop in patients treated with conventional first-line anti-tuberculous drugs. The recognition of this disorder is important because complete recovery is possible after discontinuation of the offending drug, and appropriate supportive treatment.

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# Malarial Hepatopathy-Experience at a Tertiary Care Center of North India

**Parveen Malhotra\*, Yogesh Sanwariya\*, Ajay Chugh\*, Hemant Dahiya\*, Naveen Malhotra\*,  
Vani Malhotra\***

## Abstract

**Background:** Jaundice is commonly seen in severe malaria (approx. 2.5% of patients), but hepatitis is unusual. Hepatocellular dysfunction varies from mild abnormalities in liver function tests (LFTs) to hepatic failure.

**Aims:** To study the clinical, biochemical profile, complications and outcome in confirmed *Plasmodium falciparum* malaria cases with hepatopathy.

**Material and method:** This retrospective study was carried out in a tertiary care hospital in North India by reviewing case records of slide confirmed cases of *P. falciparum* malaria with biochemical evidence of hepatic dysfunction, admitted between 1/10/2012 to 1/10/2013.

**Results:** A total of 13 patients (all male) with mean age 43.07 years, mean duration of fever prior to hospitalisation 6.5 days, were included. Fever persisted in all the patients after the onset of jaundice. Encephalopathy was present in 38.5% (5) of patients. Hepatosplenomegaly, icterus and anaemia (< 10 gm/dl) were found in 84.61%, 92.30% and 84.61%, respectively. Predominant (> 50%) conjugated hyperbilirubinaemia was found in all the patients, with mean total bilirubin level of 21.06 mg/dl (1.5 - 54). Hyper-hyperbilirubinaemia (> 10 mg%) was associated with renal failure (serum creatinine > 2.0 mg/dl) in 77.8% (7) cases. Mean AST, ALT and ALP levels were 164.84 IU/l (38 - 665), 75 IU/l (43 - 160) and 132.46 IU/L respectively and > 3 times upper limit of normal (ULN) was more common with AST than ALT (53.84% vs 15.38%). Thrombocytopenia was seen in all patients with mean platelet count of 43,853/mm<sup>3</sup>. Most patients had only mild derangement of PT with mean INR of 1.30 (1 - 1.74). Main complications seen were acute kidney injury (88.89%), septicemia (77.79%), acute respiratory distress syndrome (22.22%) and 69.23% required ICU care. Mortality was 38.46% (5), and 53.84% (8) recovered.

**Conclusion:** Malarial hepatitis is a serious complication of patients presenting with *P. falciparum* malaria. Renal dysfunction is more common in those with hyper-hyperbilirubinaemia. Whether this is the cause, or effect, is difficult to hypothesize.

**Key words:** Malaria, malarial hepatitis, renal dysfunction, hyper-hyperbilirubinaemia.

## Introduction

Malaria is one of the most common parasitic infections in our country, with about 2 million confirmed malaria cases and 1,000 deaths, being reported annually. It is more common, especially in North-Eastern states, because of favorable environmental conditions. Currently, changing trends with increase in the incidence and mortality related to *P. falciparum* malaria is being observed<sup>1</sup>. Jaundice is commonly seen in severe malaria (2.5 - 30% of patients). Jaundice in malaria can be due to haemolysis, hepatic dysfunction, co-existent viral hepatitis, chronic liver disease (CLD), septicemia or drug-induced. The majority of cases have either isolated infection with *P. falciparum* or a mixed infection with *P. falciparum* and *P. vivax*. *P. falciparum* malaria affects all age groups with multiple systemic complications which vary in different age groups. Hepatopathy is one of the complications of *P. falciparum* malaria. The manifestations of *P. falciparum* malaria are changing worldwide with respect to clinical presentation and complications<sup>2,3</sup>. In the presence of *P. falciparum*

infection with at least three-fold increase in transaminase levels with or without conjugated hyperbilirubinaemia and in the absence of clinical or serological evidence of viral hepatitis, the diagnosis of malarial hepatopathy is made<sup>4,5</sup>. Malarial hepatopathy is unusual, but a known entity, with its specific histopathological changes and cases with altered liver function test, fulminant hepatic failure, and hepatic encephalopathy have been reported. Hepatic dysfunction in malaria is multifactorial and can be due to micro-occlusion of portal venous branches, endotoxaemia due to systemic infection, intrahepatic cholestasis, hepatic microvillus dysfunction and/or oxidative stress and apoptosis of hepatocytes. Jaundice is the commonest sign of hepatic dysfunction in *P. falciparum* malaria, although tender hepatomegaly is the most common clinical finding. Hepatocellular dysfunction varies from mild abnormalities in liver function tests (LFTs) to hepatic failure. The presence of hepatic dysfunction in patients with *falciparum* malaria indicates a more severe illness, with a higher incidence of complications and a poor prognosis.

**\*Departments of Medical Gastroenterology, Medicine, Anaesthesiology and Critical Care, Gynecology and Obstetrics, PGIMS, Rohtak, Haryana.**



## Aims

To study the clinical, biochemical profile, complications and outcome in confirmed *Plasmodium falciparum* malaria cases with hepatopathy.

## Materials and methods

This retrospective study was carried out in a tertiary care hospital in North India by reviewing case records of slide confirmed cases of *P. falciparum* malaria admitted between 1/10/2012 to 1/10/ 2013 with biochemical evidence of hepatic dysfunction.

Those cases were included in the study, in whom either serum bilirubin was elevated more than 3 mg/dl with conjugated fraction being more than 50% or rise in serum transaminase levels was more than three times, in the absence of exposure to hepatotoxic drugs or clinical or serological evidence of viral hepatitis.

## Results

A total of 13 patients (all male) were included in the study. Mean age was 43.07 years (range 15 - 72) and mean duration of fever prior to hospitalisation was 6.5 days (range 2 - 12 days). Fever persisted in all the patients after the onset of jaundice. Encephalopathy was present in 38.5% (5) of patients. Hepatosplenomegaly, icterus and anaemia (Hb < 10 gm%) were found in 84.61%, 92.30% and 84.61%, respectively.

Predominant (> 50%) conjugated hyperbilirubinaemia was found in all the patients, with mean total bilirubin level of 21.06 mg/dl (1.5 - 54). Hyper-hyperbilirubinaemia (> 10 mg/dl) was found 69.23% (9) and was associated with renal failure (serum creatinine > 2.0 mg/dl) in 77.8% (7) and mortality in 55.56%. Mean AST, ALT and ALP levels were 164.84 IU/l (38 - 665), 75 IU/l (43 - 160) and 132.46 IU/L respectively and elevation of > 3 upper limit of normal (ULN) was more common with AST than ALT (53.84% vs 15.38%).

Mean total bilirubin, ALT and AST levels at the time of admission (Figs. 1, 2 and 3) were found to be more in those who died as compared to those who got cured. Thrombocytopenia was seen in all patients with mean platelet count of 43,853/mm<sup>3</sup>. Most patients had only mild derangement of PT with mean INR of 1.30 (1 - 1.74).

Main complications seen were acute kidney injury (88.89%), septicaemia (77.79%), acute respiratory distress syndrome (22.22%) and 69.23% (9) required ICU care. Overall Mortality was 38.46% (5) and all of them died in ICU. Presence of septicaemia was associated with a mortality of 57.14%, and 53.84% (8) recovered completely.

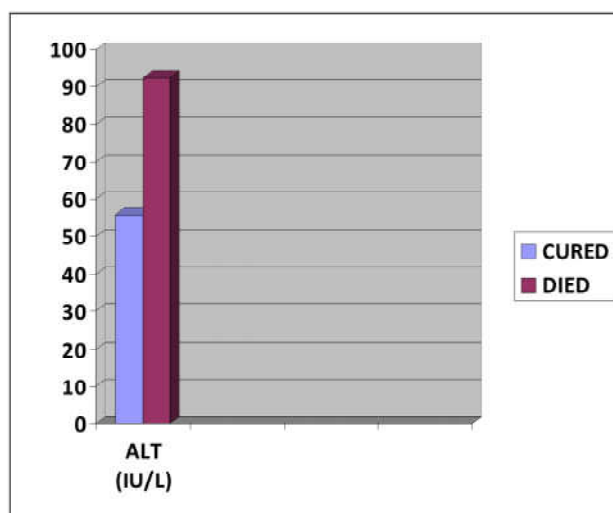


Fig. 1: Mean ALT levels in 2 different sets of patients.

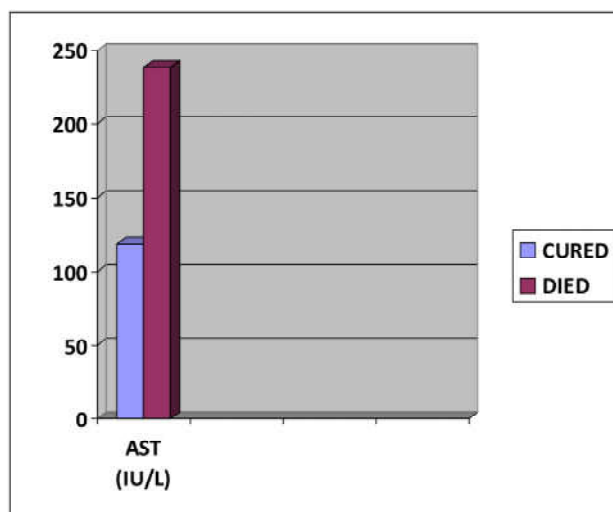


Fig. 2: Mean AST levels in 2 different sets of patients.

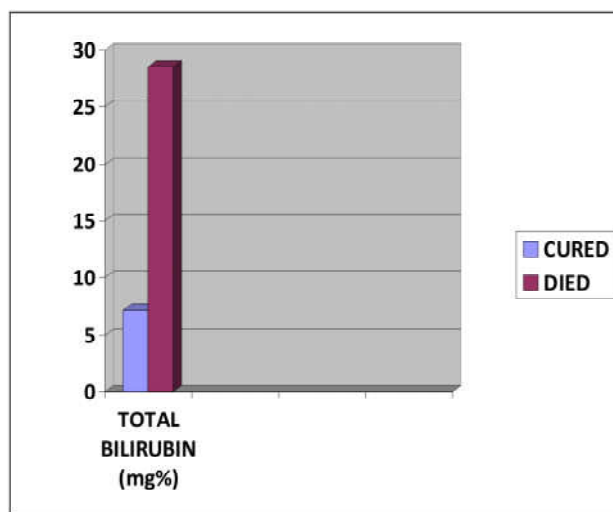


Fig. 3: Mean serum total bilirubin levels in 2 different sets of patients.

## Discussion

Hepatic dysfunction in a case of falciparum malaria has been recognised, and various causes have been attributed for the same. Hepatocyte dysfunction may be because of alteration in vascular flow through the liver, as parasitised red blood cells adhere to endothelial cells, blocking sinusoids and obstructing intrahepatic blood flow. There is evidence of focal hepatocyte necrosis, apoptosis, cholestasis, bile stasis, granulomatous lesions and malarial nodules. The bile stasis is because of impairment of bilirubin transport due to endothelial blockage and disturbance of hepatocyte microvilli. Persistent fever and icterus with hepatosplenomegaly are the commonest finding as supported by the other studies. In a study of 50, peripheral blood film confirmed, cases of *Plasmodium falciparum* malaria with jaundice by Kochar *et al* in 2003<sup>6</sup>, 18 patients had serum bilirubin < 3 mg/dl, 20 patients had serum bilirubin between 3 - 10 mg/dl and only 12 patients had serum bilirubin values of > 10 mg/dl. According to literature, patients of severe falciparum malaria with jaundice rarely have hyper-hyperbilirubinaemia (serum bilirubin levels > 10 mg/dl) but in this study 69.23% patients had hyper-hyperbilirubinaemia and the maximum value was 54 mg/dl. Similar findings were recorded by Anand AC *et al*<sup>4</sup> and Chawla LS *et al*<sup>7</sup>. It has also been observed that higher serum bilirubin levels are associated with increased incidence of acute renal failure and mortality, as in our study.

In a study by Murthy GL *et al*<sup>8</sup> out of 95 patients admitted with falciparum malaria, 20 had evidence of malarial hepatitis. The incidence of complications such as renal failure (60% vs 25%), adult respiratory distress syndrome (35% vs 3%) and septicaemia (20% vs 6%) was significantly higher on compared to them conforment malaria hepatitis.

The mortality too was higher in patients with malarial hepatitis (40% vs 17%). In another study from Thailand, 390 patients with acute falciparum malaria were studied. One hundred and twenty-four patients were jaundiced and had more complications in the form of cerebral malaria, acute renal failure, pulmonary oedema and shock.

## Conclusions

Malarial hepatitis is a serious complication of *P. falciparum* malaria. Renal dysfunction is more common in those with hyper-hyperbilirubinaemia. Whether this is the cause, or effect, is difficult to hypothesize. Higher transaminases and bilirubin levels at the time of admission correlate with higher mortality. Co-existing sepsis is an important cause for mortality in this cohort of patients.

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## An Unusual Cause of Dysphagia

**Parveen Malhotra\*, Yogesh Sanwariya\*, Hemant Dahiya\*, Ajay Chugh\*, Vani Malhotra\*,  
Naveen Malhotra\***

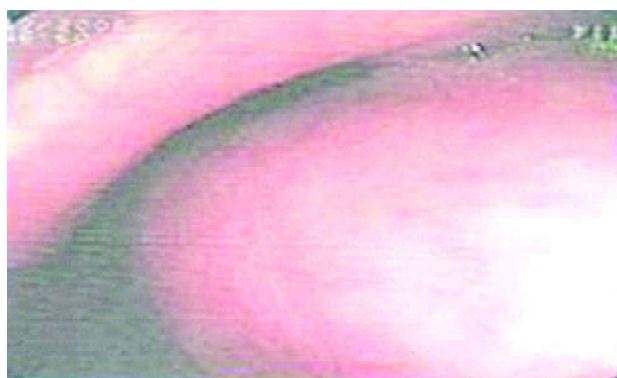
### Case report

We present a case of a 92 years female who was not a known case of any chronic illness, and presented with gradually progressive dysphagia for last one year. There was no history of weight loss, fever, haematemesis or melena. On evaluation, except for mild anaemia, rest of lab parameters and ultrasound abdomen were normal. She was subjected to upper GI endoscopy (Fig. 2) which revealed large posterior pharyngeal bulge with smooth mucosa, non tender and non pulsatile. The rest of the gastrointestinal tract examination was normal. She was thought to be having retropharyngeal mass lesion and was subjected to computed tomography scan of neck and thorax ( Fig. 1 and 3) which revealed severe osteophytic changes in cervical spine with spurs which were causing extrinsic compression over cervical oesophagus. The patient underwent surgical decompression successfully and causative spur was removed.

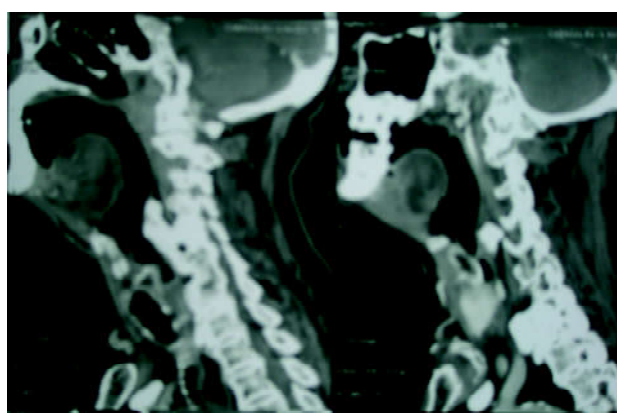
### Discussion

The oesophagus has a close relation to the cervical spine, hence spinal disorders in the neck can interfere with oesophageal function. Extrinsic compression by large anterior osteophytes may occur in cervical spondylosis and, especially in diffuse idiopathic skeletal hyperostosis (DISH, Forestier's disease)<sup>1-3</sup>. In one series, dysphagia was found in 17 - 28% of cases of DISH<sup>4</sup>. The obstruction occurs most commonly at the C5/6 vertebral level and, less commonly, at C4/5, C2/3 and C3/4<sup>1</sup>. Thoracic osteophytes rarely cause dysphagia as the thoracic portion of the oesophagus is relatively mobile and is displaced rather than compressed

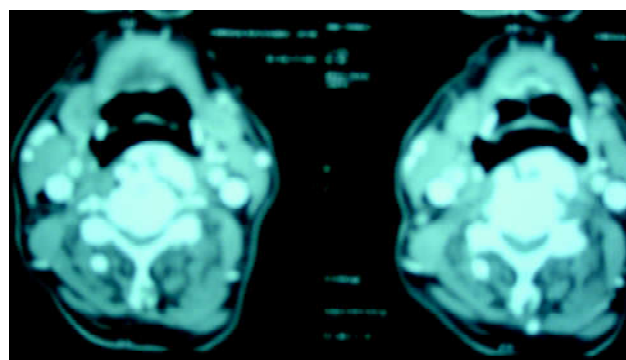
by the hyperostosed spine<sup>5</sup>.



**Fig. 2:** Endoscopy showing large posterior pharyngeal bulge.



**Fig. 3:** CT scan, lateral view, showing large osteophytic spur compressing the oesophagus.



**Fig. 1:** CT Scan Showing compression from osteophytic changes with spur.

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## **Dengue Fever Presenting as Cerebellar ataxia**

**Rajesh Deshwal\*, CA Tukaram\*\***

### **Abstract**

***Dengue infection has risen manifold in India. Varied neurological manifestations have been noted and documented, but acute cerebellitis as a presentation is extremely rare. We report a case, who presented with fever and cerebellar syndrome.***

***Keywords: Dengue fever, cerebellar ataxia, acute cerebellitis.***

### **Introduction**

Dengue is the most common arthropod-borne viral (arboviral) illness in humans. Globally, 2.5 - 3 billion individuals, live in approximately 112 countries, that experience dengue transmission. Annually, approximately 50 - 100 million individuals are infected. The incidence has increased manifold in India due to unplanned urbanisation and migration of population to urban areas. Although initially reported from urban locales, dengue is now being reported from urban and rural backgrounds alike<sup>1</sup>. Dengue is transmitted by mosquitoes of the genus *Aedes*, principally *Aedes aegyptii*. Most of these patients have an uneventful recovery, but others may develop multi-organ dysfunction, along with liver and kidney failure. Still rarer some may develop varied neurological manifestations, but acute cerebellitis is an extremely rare presentation in these patients. We present a patient who reported with pyrexia and cerebellar signs.

### **Case report**

A 76-year-old male resident of Bhagalpur, Bihar presented with history of moderate-grade, intermittent fever and acute onset swaying on either side, while walking along with 3 episodes of fall, of 10 days duration. He also divulged history of headache, body ache, lethargy and loss of appetite. Prior to presentation at our hospital he was admitted and evaluated by a neurologist with MRI brain, CSF analysis and nerve conduction studies which were all reported as normal. Since the patient continued to remain symptomatic despite admission and evaluation, he reported to our hospital. He denied any history of drug intake and toxin ingestion. There was no history of altered sensorium, seizures or cognitive decline. Clinical examination revealed temperature of 100.8 °F, pulse 86/min, regular, BP 134/84 mmHg. No pallor, clubbing, cyanosis, pedal oedema or lymphadenopathy were noted. Patient was conscious and oriented. Higher

mental functions and speech were normal, so were the bulk and tone of the muscles. Power was grade 5 in all limbs. Deep tendon jerks were normal with plantars bilaterally flexor. Joint position and vibration sense were normal. No sensory deficit was noted. Dysdiadochokinesia, and bilateral heel-shin test were positive. Bilateral gait ataxia was present. Broad-based gait, with swaying to either side, was noted. Tandem walking was not possible. Other systemic examination was documented to be normal. Clinical diagnosis of dengue fever with cerebellitis or enteric-fever associated cerebellar ataxia were kept, and investigations were ordered.

Investigations revealed Hb 12.9 gm%, TLC 10,300/cumm (poly morphs 56%), platelet count 2.2 lac/cumm, PCV 34%, blood smear for malarial parasite and paracheck was negative. Dengue IgM was positive and IgG was found negative. Blood sugar (random) 117 mg%, blood urea/S. creatinine 29/1.0 mg%, serum bilirubin 0.6 mg%, AST/ALT 34/30 IU/l, alkaline phosphatase 51 IU/L, serum sodium/potassium 140/4.2 mEq/l. Blood culture was reported as sterile. Fundus examination was normal.

Patient was treated with judicious IV and oral fluids along with symptomatic therapy. He had low grade fever for next 2 days and then became afebrile. His cerebellar signs also improved over the next 7 days and he was discharged, in a walking condition, without any residual disability.

### **Discussion**

Neurological complications have been reported in 0.5 - 6.0% of all dengue patients<sup>2</sup>. Both direct (neurotropism) and immunological mechanisms are responsible for neurological manifestations in dengue infection. Dengue antigen has been detected in the brain in some patients of dengue encephalitis<sup>3</sup>. Acute cerebellitis in relation to virus infection can be primary-infective or post-infective. Acute primary infective cerebellitis mostly occurs due to infections

***\*Consultant, Department of Internal Medicine and HIV Medicine, Apex Immunodeficiency Center, Army College of Medical Sciences and Base Hospital, New Delhi - 110010, \*\*Department of Medicine, Army College of Medical Sciences, New Delhi - 110010.***

such as varicella zoster virus, Epstein–Barr virus, measles, mumps, rubella, herpes simplex virus and coxsackie virus. Post-infectious cerebellitis have been reported following infection with varicella zoster virus, coxsackie virus, Epstein-Barr virus and human immunodeficiency virus. Since fever and cerebellar symptoms started almost together in our patient, it appears to be primary infective cerebellitis. Milinda Withana *et al* had reported a 45-year-old female with almost similar presentation, as our patients. MRI scan of brain was also normal, as was in our patient. Post-infectious cerebellar syndrome has been described following several viral infections, but the association with dengue has been reported in only four instances<sup>6,7</sup>. In these reports, the onset of cerebellar symptoms varied between two days to two weeks after the onset of fever. Of these four patients, the MRI showed hyper-intensity of cerebellum in T2W images in two patients while it was normal in the other two. One of the patients who had cerebellar hyperintensity on imaging had Epstein-Barr virus co-infection. Rajesh Verma *et al* had documented brachial neuritis, encephalopathy, Guillain-Barré syndrome, hypokalaemic paralysis, acute viral myositis, opsoclonus-myoclonus syndrome, myelitis and acute disseminated encephalo-myelitis in a retrospective study of dengue patients<sup>8</sup>.

Literature search shows that this is only the second reported patient of acute cerebellitis due to dengue infection and

clinicians need to be vigilant in picking up this diagnosis.

## Conclusion

Dengue fever presenting as acute cerebellitis should be kept as a differential diagnosis in a patient presenting with cerebellar signs and pyrexia.

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## A Rare Case of Osler-Weber-Rendu Disease – Case Report

Nitya Nand\*, Savio D'souza\*\*, Nisha Batra\*\*, Virender Chauhan\*\*, Manoj Yadav\*\*

### Abstract

*Hereditary haemorrhagic telangiectasia, also known as Osler-Weber-Rendu disease, is an autosomal dominant disorder of fibrovascular tissue. It is characterised by the classic triad of mucocutaneous telangiectasias, recurrent haemorrhages, and familial occurrence. A 65-year-old man presented with purpuric, punctate, tiny macules on the cheeks and tongue. The skin lesions were discovered about 40 years previously. He had a family history of cutaneous telangiectasia and recurrent epistaxis. Also, he had episodes of recurrent epistaxis, gastrointestinal bleeding and anaemia. The gastroendoscopy revealed angiodysplasia of the fundus and body of the stomach.*

**Key words:** Hereditary haemorrhagic telangiectasia, Osler-Weber-Rendu disease.

### Introduction

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disorder of fibrovascular tissue<sup>1</sup>. It is characterised by the classic triad of mucocutaneous telangiectasias, arterio-venous malformations with recurrent epistaxis and haemorrhages, and familial inheritance<sup>2</sup>. Clinically it appears as punctate or splinter-like telangiectasias located on the lips, oral mucosa, upper extremities, nail beds, and trunk<sup>3</sup>. We report here one such case, as it is a rare clinical entity.

### Case report

A 65-year-old man presented to the emergency department with a history of profuse epistaxis with purpuric, punctate, tiny macules on the cheeks and tongue, which had been present for 40 years. He had suffered numerous episodes of mild-to-severe nasal bleeding, of unknown cause, which used to subside spontaneously. He had a history of admission to the Department of Medicine due to severe anaemia, 2 years ago. During his cutaneous examination, we noticed pallor and discoloration, with telangiectasias, in the oral mucosa, cheeks and tongue (Fig. 1). The family history was significant for recurrent epistaxis and telangiectatic lesions in his mother and two siblings, both of them expired due to profuse epistaxis overnight (Fig. 2). No abnormalities were detected on chest X-ray and electrocardiogram. The laboratory work-up at admission revealed the following: WBC - 80,000/mm<sup>3</sup>; platelet count - 207,000/mm<sup>3</sup>; haemoglobin - 6.5 g/dl; ESR - 25 mm/hr; reticulocyte count - 1.5; S. ferritin - 22 (13 ~ 150 ng/ml); serum iron - 34 (50 ~ 150 ug/dl); transferrin saturation - 12% (30 - 50%); vitamin B12 - 1,260 (211 - 911 pg/ml); serum folic acid - 15.2 (> 5.3 ng/ml). Other laboratory work-up was normal, including bleeding time, coagulation time, prothrombin time (PT),

activated partial thromboplastin time (aPTT), Factor VII, Factor IX, vWF and stool for occult blood. Endoscopy of the upper digestive tract indicated multiple gastric and duodenal telangiectasias (Fig. 3).



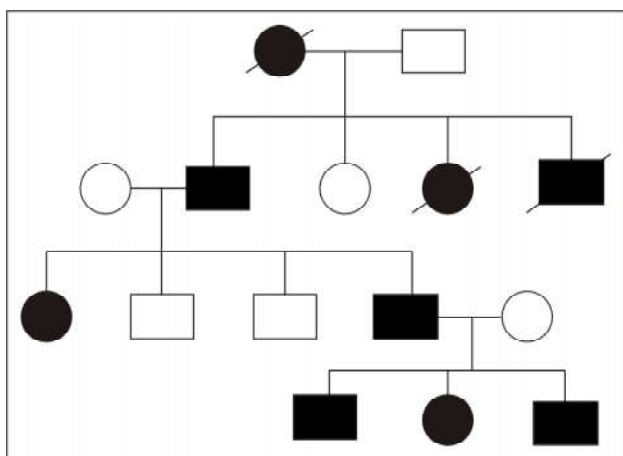
**Fig. 1:** Telangiectasias in undersurface of tongue.

### Discussion

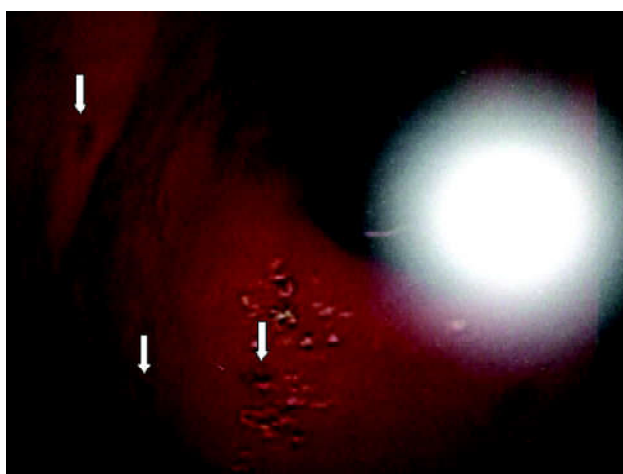
HHT is a hereditary disorder with autosomal dominant transmission, despite the fact that about 20% of the cases do not have a family history. The reported incidence of HHT is approximately 1 per 5,000 ~ 10,000 population, per year. It is thought that the abnormal vessels in HHT develop because of aberrant TGF signalling at some stage during vascular development and homeostasis due to mutations of HHT-associated genes. There are two major types of HHT (HHT1 and HHT2), with disease severity more pronounced in HHT1 compared to HHT2, with an earlier age of onset for epistaxis, the appearance of telangiectasias, and a higher incidence of pulmonary

\*Senior Professor and Unit Head, \*\*Resident, Department of Medicine, Pandit B. D. Sharma Post-Graduate Institute of Medical Sciences, PGIMS, Rohtak - 124 001, Haryana.





**Fig. 2:** Autosomal dominant pattern of inheritance In three generations.



**Fig. 3:** Telangiectasias in the body of stomach.

arterio-venous malformations<sup>4</sup> (AVM). HHT1 can be induced by mutations in the gene, *ENG* (endoglin), encoding endoglin on chromosome 9q33,34. HHT2 can be induced by mutations in the gene, *ALK-1* (activin receptor-like kinase 1), encoding activin receptor-like kinase 1 on chromosome 12q13<sup>5</sup>. These events cause alteration in the elastic and muscle layers of vessel walls, making them more vulnerable to spontaneous rupture and injuries. The diagnosis of HHT is established when three of the following features are present: (1) epistaxis (spontaneous, recurrent nose bleeds); (2) multiple telangiectasias at characteristic sites (lips, oral cavity, fingers, and nose); (3) visceral lesions, such as gastrointestinal telangiectasia (with or without bleeding), pulmonary venous AVM, hepatic AVM, cerebral AVM, spinal AVM; and (4) family history (a first-degree relative with HHT). Our case met four criteria for HHT: recurrent epistaxis, telangiectasias of the fingertips and tongue, GI bleeding combined with anaemia, and first-degree familial tendency.

The clinical manifestations of HHT are known to be variable and age-dependent. Epistaxis is the first manifestation and the most common symptom, but patients may have a variety of serious complications due to vascular involvement of internal organs, such as the gastrointestinal tract, the lungs, and the central nervous system. Pulmonary AVMs, such as right-to-left shunts can result in hypoxaemia. The absence of a filtering capillary bed allows emboli to reach the systemic circulation which may cause cerebral abscesses and stroke. Cerebral AVMs can lead to headaches, migraines, brain abscesses, seizures, paraparesis, ischaemia, strokes, transient ischaemic attacks, and both intracerebral and subarachnoid haemorrhage. Gastrointestinal bleeding can result in iron deficiency anaemia or acute gastrointestinal haemorrhage. Vascular lesions may be present as telangiectasias, AVMs, or aneurysms.

Treatment options for HHT should be considered individually for each patient, owing to the diverse clinical manifestations of this disease. Therapy for the bleeding is primarily supportive and palliative. Management options for cutaneous lesions include electrocauterisation with diathermy, sclerotherapy or laser therapy. Many different types of laser therapy have been used to minimise and/or eliminate these telangiectasias, such as Nd:YAG, IPL, argon, and the tunable dye lasers, all of which have been reported to be effective. Presymptomatic intervention in HHT may substantially affect the outcome. An early diagnosis is essential in high-risk individuals in order to alter their clinical course and prognosis. Patients with a family history of HHT with pulmonary disease are at high-risk of having pulmonary AVMs. Chest CT-scan with pulmonary angiography should be done for surgical treatment planning. MRI is useful for assessing CNS involvement.

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## Achondroplasia: An Important Cause of Stunted Growth

**G Garg\*, A Gogia\*\*, A Kakar\*\*\***

An 18-year-old female presented to us with complaint of short stature. Her mother was also short statured (Fig. 1, 2). On examination she was 120 cm in height, had shortened arms and legs (Fig. 3, 4). Investigations were carried to determine the cause of short stature. Fibroblast growth factor receptor 3 (FGFR 3) receptor mutation for achondroplasia was positive in her case.

Achondroplasia is a skeletal dysplasia that presents with stunted growth and disproportionate limbs.

It is inherited as an autosomal dominant disorder or as a sporadic mutation in approximately 80% of cases<sup>1</sup>. It is caused by mutation in FGFR 3<sup>2</sup>. The resulting mutation causes disturbance of endochondral ossification resulting in short stature midfacial hypoplasia, normal trunk length, prominent lumbar lordosis, genu valgum, trident hand and rhizomelic shortening of arms and legs. The diagnosis can be achieved by plasma FGFR 3 mutation detection. Radiographs of skull and lumbar region can also be helpful. People with achondroplasia generally have normal intelligence. Currently, there is no definitive treatment available for achondroplasia. Although, somatotropin is used to increase the height of the individual before

the onset of puberty. Commonly, people are obese, have recurrent ear infections, recurrent episodes of apnoea. A dreadfully serious complication of achondroplasia is spinal stenosis which can compress spine.

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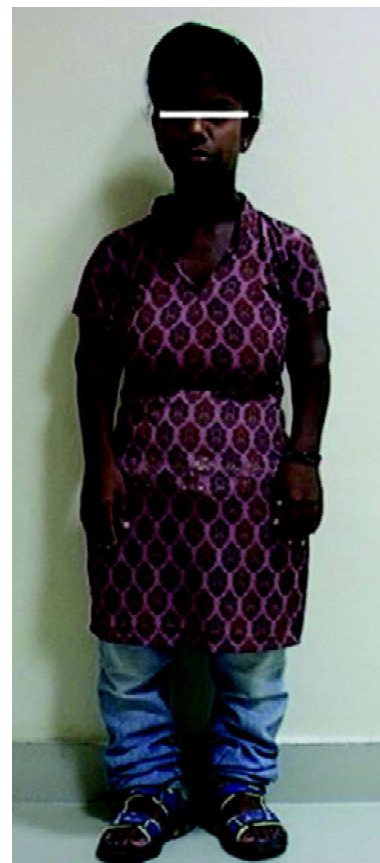
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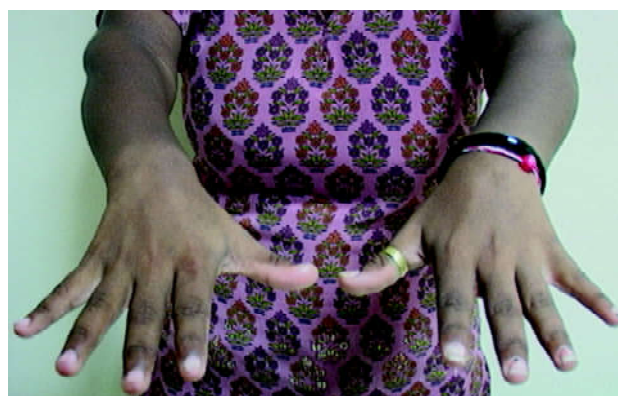
**Fig. 1:** Image showing short stature with disproportionately shortened peripheral limbs.



**Fig. 2:** Image showing shortened upper limbs with trident hand.



**Fig. 3:** Image showing short stature with disproportionate shortening of limbs.



**Fig. 4:** Image showing shortened upper limbs.



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Mobile: 09440066482, E-mail: raju\_ys1197@yahoo.co.in



# Indian Association of Clinical Medicine

Headquarters: P.G. Department of Medicine, S.N. Medical College, Mahatma Gandhi Road, Agra - 282 002, U.P.

## IACM MEMBERSHIP / FELLOWSHIP FORM

No. ....

Date .....

**The Honorary General Secretary,  
Indian Association of Clinical Medicine (IACM)**

**We hereby propose the admission of**

Name (in full): .....

Qualifications: .....

(Branch of Medicine for P.G. Degree)

University: .....

Year of obtaining the first Postgraduate Qualification: .....

Address: .....

.....

..... Pin Code: .....

Phone (with STD code): ..... E-mail: .....

Photograph

**as an Associate Life Member/Life Member/Fellow of the Indian Association of Clinical Medicine.**

*To the best of our knowledge and belief, the above particulars are correct and we consider him/her a fit and proper person to be admitted as Associate Life Member/Member/Fellow of the 'Association'.*

A.D.D. No. .... Dated ..... drawn on .....

..... for Rs. .... is enclosed herewith.

Signature ..... (Proposer)

Name: .....

Fellowship/Membership No.: .....

Signature ..... (Seconder)

Name: .....

Fellowship/Membership No.: .....

Subject to approval of the Governing Body, I agree to become Associate Life Member/Member/Fellow, and if admitted, to abide by the Rules and Regulations of the 'Association'.

.....  
(Signature of the Candidate)

### Note by the Hony. General Secretary

- Fellowship Subscription: Rs. 9,000/-  
(Minimum 10 Years Standing after Post-graduate Qualification or 5 years after membership).
- Life Membership Subscription: Rs. 3,000/-  
(Minimum Qualification: Post-graduate Qualification as specified in the Constitution of IACM).
- Associate-Life Membership Subscription: Rs. 3,000/-  
(Diploma, or Post-graduate Qualification not covered as per Constitution of IACM).
- Please attach attested photocopy of Post-graduate Degree/Diploma.
- Cheques shall not be accepted. Demand Draft should be in favour of "Indian Association of Clinical Medicine" payable at Agra.

### Correspondence Address:

Dr. TP Singh, Hony. Gen. Secretary, IACM, P.G. Department of Medicine, Sarojini Naidu Medical College, Mahatma Gandhi Road, Agra-282 002, U.P.

# MAGNEX

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