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Diabetes Prevention Program Research Group.

Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension. 2002;40(5): 679-86 No author given:

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Volume with supplement:

Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. Headache. 2002;42 Suppl 2:S93-9.

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Glauser TA. Integrating clinical trial data into clinical practice. Neurology. 2002;58(12 Suppl 7):S6-12.

Article published electronically ahead of the print version: Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002 Nov 15; 100(10):3828-31. Epub 2002 Jul 5.

2. Books and Other Monograph Personal author(s):

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Original Article

Relationship of HBsAg and Kidney Biopsy Marker with HBV Related Glomerulonephropathy

*Rahman GMH[1], Alam MR[2], Rahman HMM[3], Taslima AAU[4], Ahmed F[5], Sikder GM[6]

Abstract

Hepatitis B virus infection is a major public health problem worldwide and it causes not only hepatic diseases but also extra hepatic manifestations particularly HBV-associated Glomerulonephritis (GN). HBsAg has been observed in the glomeruli of some patients with glomerulonephritis. HBV related glomerulonephritis may be found in HBV seropositive as well as seronegative patients. HBV may present in the renal tissue of such patients. In most cases detection of HBsAg in the renal tissue by renal biopsy and immunohistochemistry can establish the etiology. To find out the relationship of HBsAg and Kidney biopsy marker with HBV related glomerulonephropathy, this cross sectional study was done in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), during the period of July 2015 to June 2016. A total number of 53 cases who fulfilled the inclusion and exclusion criteria were selected as sample. Samples were selected by purposive sampling technique. HBsAg antigen in renal tissue was found in 2 patients among 7 patients who were seropositive for both HBsAg and Anti HBc(total), 2 patients among 8 patients who were HBsAg seronegative but Anti HBc (total) seropositive, 2 patients among 38 patients who were seronegative for both HBsAg and Anti HBc(total). There were no patients in this study who was HBsAg seropositive but Anti HBc (total) seronegative. Total 11.3% (6 patients) of renal biopsy specimens were found to have HBsAg deposits which included 3 cases of Membrano- proliferative GN and one of each of Membranous nephropathy, Mesangial proliferative GN and IgA nephropathy. The high rate of HBsAg deposits found in renal tissue indicates that detection of HBsAg deposition should be done for all histological varieties of GN. Antiviral therapy may be used to stop progression of HBV associated nephropathy.

Keywords: *HBsAg, Anti HBc (total), Renal Biopsy, Glomerulonephritis.*

1. *Dr. G. M. Hafizur Rahman, Assistant Professor, Department of Nephrology, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh. Email: hafiz.gazi@gmail.com, Mobile: 01712798618
2. Professor (Dr.) Muhammad Rafiqul Alam, Professor and Ex-Chairman, Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.
3. Dr. Hossain Muhammad Mustafijur Rahman, Assistant Professor, Department of Nephrology, DMCH, Dhaka, Bangladesh.
4. Dr. Al Asma Ul Taslima, Junior Consultant (Radiology and Imaging), Sheikh Hsaina National Institute of Burn and Plastic Surgery, Dhaka, Bangladesh.
5. Dr. Faruque Ahmed, Assistant Professor (Nephrology), Department of Nephrology Shaheed Surawardy Medical College, Dhaka, Bangladesh.
6. Dr.Golam Mahabub Sikder, Nephrologist, Department of Nephrology, Cumilla Medical College Hospital, Cumilla, Bangladesh.

*For correspondence

INTRODUCTION

Hepatitis B virus (HBV) infection is a worldwide epidemic, and is particularly prevalent in developing countries such as those in Southeast Asia and Africa. In addition to the liver damage, HBV infection causes manifestations in other organs, which is increasingly recognized as a major pathogenesis of HBV-related morbidity and mortality. Among the extra-hepatic manifestations related to HBV infection, HBV-related nephritis is a major manifestation by HBV infection.[1]

Different pathological types of glomerular lesions have been described in association with HBV infection, including pathological patterns such as Membrano- proliferative Glomerulonephritis (MPGN), Mesangial- proliferative glomerulonephritis (MesPGN), and Membranous glomerulonephritis (MN). However, among these histological types, MN has been reported as the commonest pathological type of HBV-GN in Hong Kong and South Africa, compared to IgA nephropathy (IgAN) followed by MN in Thailand and MN and MPGN in Japanese adults.[2]

Approximately one-third of the world's population has serological evidence of past or present infection with HBV and it is estimated that 350 million people are chronically

infected, making it one of the most common human pathogens.[3,4]

The spectrum of disease and natural history of chronic HBV infection are diverse and variable, ranging from an inactive carrier state to progressive hepatic and extrahepatic (Renal) manifestations but it is not possible to predict which patient with HBV infection are more likely to develop kidney disease.[5]

Pathogenesis of HBV related nephritis is mediated by subendothelial and mesangial deposition of immune complexes.[6]

The diagnosis of HBV-related glomerulonephritis is based on established criteria. Patients with serum and renal tissue HBV antigens with symptoms and signs of glomerulonephritis and without other secondary diseases were diagnosed as HBV-related glomerulonephritis.[7] In fact, HBV infections are sometimes occult. These patients are characterized by the presence of HBV infection with undetectable HBsAg antigen in serum, whereas the viral DNA may be present in the blood or tissues, or the tissues may be positive for viral antigens. Occult HBV infections have often been neglected. However, they can also cause immune complex deposition in tissues. Hence an occult HBV infection may cause HBV-associated glomerulonephritis as well.[8]

Hepatitis-B-associated glomerulonephritis (HBGN) is a distinct entity occurring frequently in hepatitis-B-prevalent areas of the world. The disease affects both adults and children who are chronic hepatitis-B-virus (HBV) carriers with or without a history of overt liver disease. The diagnosis is established by serologic evidence of HBV antigens/antibodies, presence of an immune complex glomerulonephritis, immunohistochemical localization of 1 or more HBV antigens, and pertinent clinical history, when available.[9]

In this study we will detect HBsAg antigen in the renal tissues (obtained by Biopsy) of both seropositive and seronegative patients with GN. The results may provide clue to the underlying aetiology and may help to formulate treatment plan in the management of GN patients.

MATERIALS AND METHODS

This was a cross sectional study carried out in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from January 2015 to September 2016. A total number of 53 cases who fulfilled the inclusion and exclusion criteria were selected as sample. Samples were selected by purposive sampling technique.

Selection of Patients:

- **Inclusion Criteria**
  - Patients diagnosed as GN (both HBV seropositive and seronegative) admitted in the department of Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
  - Age: ≥ 18 years
  - Sex: Both Sexes
  - Patients who gave informed written consent.
- **Exclusion Criteria**
  - GN patients with contracted kidneys.
  - Patients with contraindications to renal biopsy.
  - Patients aged below 18 years.
  - Patients who are unwilling to participate in the study.
  - Patients with pregnancy.

Study procedure:

Serological test both HBsAg and anti-HBc (total) were done to identify the HBV seropositive and seronegative individuals by ELISA technique and Chemiluminescense Method respectively. Then after proper counseling and consent; renal biopsy was done percutaneously through a posterior approach. One core of tissue was preserved in formalin in a test tube for light microscopic study and immunohistochemistry and one core was preserved in normal saline for direct immunofluorescence (DIF). Both test tubes were sent to find out histological features and presence of HBsAg in renal biopsy tissue in Pathology Department of Bangabandhu Sheikh Mujib Medical University, Dhaka.Tissue for light microscopic examination was fixed in 10% formalin, processed routinely for paraffin section. From paraffin embedded material 5 micron thick tissue sections were stained by hematoxylin and eosin, periodic acid Schiff's (PAS) methods.

Immunofluorescence microscopy

Tissue kept in normal saline was used for direct immunofluorescence study. Specimen were placed on block holder and rapidly frozen and embedded in O.C.T compound (Thermoshandon, Pittsburgh PA, and USA). Cryostat sections were cut at -20°C cooled chamber at 4-5

micron thickness and was then collected on glass slides. The sections were air dried and kept in deep freeze at -20°C until staining. Staining were done by incubating the sections with FITC (Fluorescain isothiocyanate) conjugated rabbit antisera against human IgG, 1gM, IgA, C3 and fibrinogen. The sections were than examined under fluorescence microscope. During microscopy photomicrographs were taken for each positive case.

Immunohistochemistry

In this study immunohistochemical stain was done to detect viral antigens in the kidney tissue. Streptavidine-Biotin system for immuno-peroxidase stain was used on deparaffinized tissue sections. Primary antibodies used were monoclonal mouse anti-hepatitis B virus surface antigen (Thermo Scientific USA). The streptavidin–peroxidase kit was used as a secondary antibody. Staining was visualized using 3,3'diamino-benzidine (DAKO, Denmark).

Data collection, processing and analysis:

Relevant data were collected by using a preformed data sheet. All other required data was collected from history sheet, clinical examination and investigation papers. Renal biopsy as well as immunohistochmeistry report was recorded in the data sheet.

Statistical analysis of the study was done by computer software device as the Statistical Package for Social Science (SPSS), version-22.0 (Chicago, IL) software. The result was presented in tables, figures and diagrams. Quantitative variables were expressed as mean±SD and significance was estimated with student's unpaired t-test while qualitative variables were expressed as frequency or percentage and their significance was assessed using Chi-square test. The result was presented as mean+SD or median, according to normality characteristics of each variable with 5% ($p<0.05$) significance level. To compare parametric variables paired t-test was used.

RESULTS

This cross sectional study was conducted among 53 study subjects with Patients diagnosed as GN (both HBV seropositive and seronegative). Data were analyzed with SPSS software using appropriate stastical method and were presented in tables in this chapter.

Table-I shows MN and FSGS patients presented with nephrotic syndrome and the rest presented with either nephrotic or nephritic syndrome.

Table-I: Clinical presentations in various histological types of GN (n=53)

Histological types of GN	Clinical presentation		P value
	Nephrotic syndrome No. (%) (n=25)	Nephritic syndrome No. (%) (n=28)	
MN	5(20.6%)	0(0.0%)	
MPGN	6(24.8%)	7(25.0%)	
MesPGN	7(28.0%)	8(28.6%)	
FSGS	4(16.0%)	0(0.0%)	0.005[s]
lgAN	2(8.0%)	3(10.7%)	
LN	1(4.0%)	10(35.7%)	
Total	25(100.0%)	28(100.0%)	

Table-II shows among 7 seropositive cases HBsAg antigen was found in renal tissue only 2(28.6%) and was absent in 5(71.4%) cases. However among 46 HBsAg seronegative cases HBsAg antigen was present in renal tissue in 4(8.7%) and absent in 42(91.3%) cases.

Table-II: Presence of HBsAg deposition in renal tissue in HBsAg seropositive and seronegative cases (n=53)

HBsAg sero-status	n	HBsAg Deposition in renal tissue		P value
		Present No. (%)	Absent No. (%)	
HBsAg seropositive	7	2(28.6%)	5(71.4%)	
HBsAg seronegative	46	4(8.7%)	42(91.3%)	0.174[ns]
Total	53	6(11.3%)	47(88.7%)	

Table-III shows that among 15 anti-HBc (total) seropositive cases HBsAg antigen was found in renal tissue in 4(26.7%) and was absent in 11(73.3%) cases. However among 38 Anti-HBc (total) seronegative cases, HBsAg antigen was present in renal tissue in 2(5.3%) and absent in 36(94.7%) cases.

Table-III: Presence of HBsAg deposition in renal tissue in Anti-HBC (total) seropositive and seronegative cases (n=53)

Anti-HBc (total) sero-status	n	HBsAg Deposition in renal tissue		P value
		Present No. (%)	Absent No. (%)	
Anti HBc (total) seropositive	15	4(26.7%)	11(73.3%)	0.026s
Anti HBc (total) seronegative	38	2(5.3%)	36(94.7%)	
Total	53	6(11.3%)	47(88.7%)	

Table-IV shows that among 6 cases with HBsAg antigen deposition in renal tissue, 1(16.7%), 3(50.0%), 1(16.7%) and 1(16.7%) were MN, MPGN, MesPGN and lgAN respectively.

Table-VI: Distribution of histological types of GN patients with HBsAg deposition in renal tissue (n=6)

Histological types of GN	HBsAg present in renal tissue	
	No	Percentage (%)
MN	1	16.7
MPGN	3	50.0
MesPGN	1	16.7
FSGS	0	0.0
lgAN	1	16.0
LN	0	0.0
Total	6	100.0

Table –VII shows that among 53 total patients in the sample, 2 cases had HBsAg in both serum and renal tissue as well as Anti-HBc (total) seropositivity. 2 cases had HBsAg deposits in renal tissue but were HBsAg seronegative and anti-HBc (total) seropositive. 5 patients had both HBsAg and Anti HBc (total) seropositivity but no HBsAg deposit in renal tissue, there were 6 patients who were HBsAg seronegative and Anti HBc seropositive but no HBsAg deposit in renal tissue were found. 2 cases had HBsAg deposits in renal tissue but both HBsAg and Anti HBc (total) were seronegative. The rest 36 patients had neither HBsAg deposit in renal tissue nor HBsAg (total) soropositivity.

Table –V: Presence of HBsAg deposition in renal tissue in HBsAg and Anti HBc (total) seropositive and seronegative cases (n=53)

Sero –status of HBV Antigen and Antibodies	No (n)	HBsAg deposition in renal tissue	
		Present No (%)	Absent No (%)
HBsAg Seropositive + Anti HBc (total) seropositive	7	2(28.6%)	5(71.4%)
HBsAg Seropositive + Anti HBc (total) seronegative	0	0(0.0%)	0(0.0%)
HBsAg seronegative + Anti HBc (total) seropositive	8	2(25%)	6(75%)
HBsAg seronegative + Anti HBc (total) seronegative	38	2(5.3%)	36(94.7%)
Total	53	6 (11.3%)	47(88.7%)

DISCUSSION

This study was conducted to estimate the frequency of HBsAg deposition in renal tissue of patients with glomerulonephritis (GN). Twenty one (39.6%) among 53 patients were in the 18-29 years of age group. Mean age was 34.5±12.33 years, minimum 18 years and maximum 60 years. 25(47.2%) patients were male and 28(52.8%) were female.

In this study among 53 study subjects, 7 (13.2%) cases were HBsAg seropositive and 46(86.8%) cases were HBsAg seronegative. Among the 7 seropositive cases, HBsAg antigen deposition in renal tissue was present in 2 (28.6%) and absent from 5(71.4%) cases. Among the 46 HBsAg seronegative cases, HBsAg antigen deposition in renal tissue was present in 4(8.7%) and absent from 42(91.3%) cases. Among 53 study subjects 15(28.3%) cases were Anti-HBc (total) seropositive and 38(71.7%) cases were anti-HBc (total) seronegative. Among the 15 Anti-HBc (total) seropositive cases, HBsAg antigen deposition in renal was present in 4(26.7% cases and absent from 11(73.3%) cases. Among the 38 Anti-HBc (total) seronegative cases, HBsAg antigen deposition in renal tissue was present in 2(5.3%) cases and absent from 36(94.7%) cases.

Kong et al. (2013) found HBsAg antigen present in immunohistochemical staining in 3(0.6%) out of 500 renal biopsy cases.[8] Among 3 patients with HBsAg antigen in renal tissue, 2 had Anti-HBc (total) positive in serum and 1 did not. However HBsAg serostatus was negative in all 500 patients in that study.

In this study among 7 HBsAg seropositive cases, histological types of GN were MN, MPGN, FSGS and LN and HBsAg antigen deposition was found in 2(28.6%) cases. Among 15 Anti-HBc (total) seropositive cases, histological types of GN were MN, MPGN, MesPGN, FSGS, IgAN, LN and HBsAg antigen deposition was found in 4(26.7%) cases. In this study 25(47.16%) patients presented with nephrotic syndrome where the most common histological types of GN were MesPGN 7(28.0%) cases and MN 5(20.6%) cases. Nephritic syndrome was found in 28(52.8%) patients out of which LN was established in 10(36%) cases, MesPGN in 8(29%) patients and MPGN in 7(25.0%) cases.

In this study, among the 7 HBsAg seropositive cases, 2 patients had HBsAg antigen present in renal tissue (1 MN, 1 MPGN). Among 46 HBsAg seronegative cases, 4 patients had HBsAg antigen present in renal tissue (2 MPGN, 1 MesPGN and 1 IgAN). Among 15 Anti-HBc (total) seropositive cases, 4 patients had HBsAg antigen present in renal tissue (1 MN, 2 MPGN, 1 IgAN). Among 38 Anti-HBc (total) seronegative cases, 2 patients had HBsAg deposition in renal tissue (1 MPGN, 1 MesPGN). Amarapurakar et al. (2015) conducted a study including 28 patients (10 HBsAg seropositive and 18 seronegative), All 10 HBsAg seropositive patients showed HBsAg deposits in renal tissue (Histology: MN in 4 patients and proliferative GN in 6 patients). Only 8 patients had HBsAg present (5 patients proliferatrive GN, 3 post-transplant rejection) in renal tissue among the other 18 seronegative patients with GN. Among the 28 patients studied by Amarapurakar 20 were Anti-HBc (total) seropositive cases and among them 14 patients were found to have HBsAg antigen deposition in renal tissue. Meanwhile among the 8 Anti-HBc (total) seronegative cases and among them 4 patients were found HBsAg antigen deposition in renal tissue.[10]

Among the 6 cases with HBsAg antigen in the renal tissue the following diagnoses were established: MPGN in 3 (50.0%) cases, MN in 1(16.7%) cases and MesPGN in 1(16.7%) cases and IgAN 1(16.7%). Amarapurakar et al. (2015) found HBsAg antigen in both glomerulus and tubular epithelium which resemble the findings of our study.[10]

CONCLUSIONS

This study showed different histological types of GN patients had deposition of HBsAg in renal tissue. All patients with seropositive for HBsAg and anti-HBc (total) did not displayed HBsAg deposition in renal tissue and patients with seronegative for both HBsAg and Anti-HBc (total) were also found the HBsAg antigen deposition in the renal tissue. Cases of GN should undergo renal biopsy and immunohistochemistry for diagnosis of HBV related GN irrespective of their HBsAg and/or anti-HBc (total) seropostivity.

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Original Article

Vitamin D Status in Patients with Proximal Muscle Weakness

Bhuiyan MMU[1], Asha AH[2], Hasan MK[3], Bhowmic R[4], Siddiki [5], *Naafi SMU[6], Chowdhury MFI[7]

Abstract

Vitamin D deficiency has emerged as a concerning public health issue, and almost 25-50% of patients with proximal muscle weakness suffer for this deficiency. It has been documented that myopathy could be a presentation of hypovitaminosis D. Most often, it remains unnoticed or undiagnosed because muscle weakness develops gradually over the years. As fewer studies are available on this topic, the study was designed to assess the vitamin D status in patients presenting with proximal muscle weakness. This hospital-based descriptive cross-sectional study was conducted at the Inpatient and outpatient Department of Medicine of Dhaka Medical College Hospital for 6 months following approval of this protocol. The Ethical Review Committee approved the protocol, and informed written consent was obtained from all the patients. The patients were selected as per inclusion and exclusion criteria with the purposive sampling method. Data were collected by a preformed semi-structured questionnaire. Total 50 patients were included in the final analysis. Collected data were analyzed by the Statistical Package for the Social Sciences version-22 (SPSS). Among 50 patients, 70% were females and mean age was 58.92 ± 12.3 years with a frequent age group> 65 years (46%), where more than two third (68%) of the respondents were from urban area. Among the study subjects, the majority of them had involvement of the lower limb muscles (54%) and one-fifth of them (20%) had both upper and lower limb involvement, whereas more than one-fourth (26%) had only upper limb involvement. The mean duration of illness was 8. 6 ± 3.4 months. The study found more than three fourth, (78%) had hypovitaminosis D the and mean value of serum 25(0H) D was 22.3 ± 7.7 ng/ml. Among them 36% had mild insufficiency, 30% had a moderate deficiency, and 12% had severe deficiency. About two-thirds of proximal myopathy patients had hypovitaminosis D. Difficulties in walking, standing from sitting, climbing, raising hands above the head, bone and joint pain were significantly associated with the severity of vitamin D deficiency (P-value < 0.05). The severity of muscle weakness was strongly associated with the severity of vitamin D deficiency (P-value <0.05). Females were comparatively more affected than males, it was not statistically significant. However, further large-scale analytical studies are needed to find the association of this hypovitaminosis with the disease process.

Key words: *Hypovitaminosis D , Serum 25(OH)D, Vitamin D status, Proximal Myopathy , Muscle Weakness, MRC score*

1. Dr. Md. Minhaj Uddin Bhuiyan, Registrar, Dept. of Medicine, Dhaka Medical College Hospital (DMCH)
2. Dr. Ayesha Hoque Asha, Medical Officer, Lions Eye Institute & Hospital, Agargaon, Dhaka
3. Mohammad Kamrul Hasan, Consultant (Medicine) OSD: DGHS, Deputation: Department of Gastroenterology, DMCH.
4. Dr. Rajib Bhowmic, Assistant Registrar, Dept. of Medicine, DMCH.
5. Dr. Md. Shahriar Siddiki, Medical Officer, Dept. of Medicine, , DMCH.
6. *Dr. Shah Mubdi-Un-Naafi, Assistant Surgeon, DGHS, Mohakhali, Dhak, Attached: Upazila Health Complex, Gangachara, Rangpur. Email: smnaafi@gmail.com, Call: 01755-013344
7. Prof. Dr. Md. Faizul Islam Chowdhury, Professor of Medicine, Anwer Khan Modern Medical College

*For correspondence

INTRODUCTION

Vitamin D is an essential part of calcium and phosphate homeostasis and thus to bone health. many other tissues including skeletal muscle are home to Vitamin D receptors.[1,2] One of its metabolites, 25-hydroxycho- lecalciferol, influences the muscle's resting energy state and increases the protein turnover in muscle cells.[3] Because vitamin D affects type 2 muscle fibers, it was tempting to speculate a protective effect of vitamin D on falls, via improvement in muscle function. A high number of Randomized control trials have investigated whether vitamin D supplementation affected muscle function and the incidence of falls.[4]

It is surprising that in South Asia, 80% of the healthy population is deficient in vitamin D (<20 ng/mL) and up to 40% of the population is severely deficient (<9 ng/mL).[5]Those most at risk include older people in residential care[6], darker-skinned women[7](particularly if veiled), vegetarian diet[8] and people with medical conditions that require sun avoidance or cause malabsorption.[9] The salient features in vitamin D deficiency-related myopathy are the proximal distribution, the waddling gait, and pain and discomfort due to muscular effort..[10] Myopathy or muscle weakness, worse in the legs than the arms and cutaneous hyperalgesia have been reported [11]. New research suggests that leaked calcium is responsible for muscle cells to become fatigued and muscle lysis by a calcium driven

enzyme [12] Muscle atrophy, particularly of type-2 fibres in vitamin D deficiency has been described histopathologically.[13,14,15] Proximal myopathy has been seen in 70% of patients with severe osteomalacia. A serum 25-hydroxy vitamin D level below 30 ng/ml causes increased body sway, and below 10 ng/ml leads to symptoms like difficulties in standing from seat, inability to climb height, and muscle aches due to effort.[16] An elevation in serum alkaline phosphatase with a low-normal plasma calcium concentration is clue to the diagnosis. Serum 25(OH)D level is the only way to confirm clinically present myopathy as biochemical signs like decreased Calcium and Increased Alkaline phosphatase levels are present late. The circulating Serum 25(OH)D level is the most appropriate pointer of vitamin D status because it is easily measurable, stable, and has a half-life of 3 weeks. Muscle biopsy is not directed and if done, shows nonspecific muscle fiber atrophy and no signs of inflammatory reaction.[17] The ultimate evidence of the diagnosis rests on the response to therapy, as it is reversible and potentially treatable.[18,19]

As this myopathy is potentially reversible with adequate vitamin D treatment, proper clinical evaluation and investigations should be conducted for appropriate treatment of the patient to reduce the morbidity. Keeping this in mind, this study aimed to assess the vitamin D status in patients with proximal muscle weakness and estimate the frequency of hypovitaminosis D in patients with proximal muscle weakness.

MATERIALS AND METHODS

This cross-sectional observational study was conducted in the department of medicine, DMCH. Fifty patients of either sex, age ≥18 years, with clinical features suggestive of proximal muscle weakness for at least three weeks were taken. Those diagnosed with thyroid disorders, pre-existing neurological or rheumatological conditions with lower limb weakness, patients taking corticosteroids, patients with alcoholism, pregnant women, and critically ill patients were excluded from the study.

1) Proximal muscle weakness, also known as proximal myopathy, is defined by the presence of one or more of the following features:[20]
   a. Difficulty in standing up from squatting or sitting position
   b. Difficulty in walking
   c. Difficulty in raising hands above shoulder
   d. Difficulty in climbing up the stairs
2) Muscle power is graded according to the Medical Research Council scale:

Grade	Description
0	No visible muscle contraction
1	Flickering contraction but no actual movement
2	Joint movement when effect of gravity removed
3	Movement against gravity but not against the resistance of the examiner
4	Movement against resistance but weaker than normal
5	Normal power3) Reference value of serum vitamin D[21]: Serum 25(OH)D in ng/ml unit is measured and it is categorized as following.

25 (OH)D level (ng/ml)	Interpretation
≥30	Normal
<30	Hypovitaminosis D
21-29	Insufficient/Mild hypovitaminosis D
10-20	Deficient/Moderate Hypovitaminosis D
<10	Severe deficient

History, clinical examination & necessary investigations for the study were done. Subjects or their relatives were briefed about the study's objectives, risk and benefits, freedom for participating in the study, and confidentiality. Informed written consent was obtained accordingly. Face-to-face interviews filled up the pre-structured Case Record Form (CRF)/data collection sheet.

RESULTS

Among 50 study participants, fifteen (30%) were males, and thirty-five (70%) were females, with an overall male-to-female ratio of 1:2.33. Among the 50 patients, the mean age was 58.92 ± 12.3 years. Most of the patients studied up to SSC (46%), and 10% were illiterate.

Among the 50 studied proximal myopathy patients, involvement of lower limb muscles was more frequent (54%), 20% had both upper and lower limb involvement, and 26% had only upper limb involvement. The mean duration of illness was 8.6 ± 3.4 months.

Serum 25(OH) D level was measured in all patients, and 78% showed hypovitaminosis D. Mean value of serum 25(OH) D was 22.3 ± 7.7 ng/ml. Among them, 36% had mild insufficiency, 30% had a moderate deficiency, and 12% severe.

In this study majority of the patients showed moderate muscle weakness (52%).

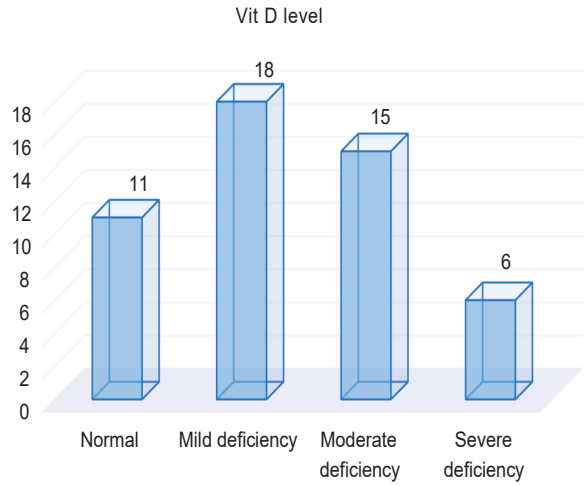

Fig.-1. Serum 25 (OH) D status in the patients (n=50)

Table I shows the MRC score of involved muscle in proximal myopathy patients.

Table 1. Muscle power assessment of the patients (n = 50)

Severity of myopathy	Score	Frequency
Severe (n=04)	00	00
	01	04
Moderate (n=26)	02	10
	03	16
Mild (n=20)	04	20

Table II shows socio-demographic profile of proximal myopathy patients showed hypovitaminosis D was significantly found among elderly patients (P-value < 0.05). Females were comparatively more affected than males, but it was not statistically significant. Females using veils outside of the home suffered from vitamin D deficiency (P-value < 0.05).

Table II. Socio-demographic characteristics and frequency of hypovitaminosis D in proximal myopathy patients (n= 50)

Variable	Normal Vit-D	Hypovitaminosis D	χ^2 value	P-value
Age groups				
18-35 years	02	02	16.88	0.001
36 - 50 years	02	06		
51 - 65 years	03	12		
> 65 years	04	19		
Sex				
Male	04	11	0.272	0.602
Female	07	28		
Residence				
Rural	02	14	1.237	0.262
Urban	09	25		
Monthly income (taka)				
< 15000	06	22	0.778	0.668
15000-40000	04	10		
> 40000	01	07		
Academic qualification				
Illiterate	01	04	1.679	0.642
Up to primary	03	11		
SSC	05	18		
HSC and above	02	06		
Use of veil (in female)				
Yes	03	21	14.258	0.004
No	04	07		

Table III shows presenting symptoms of proximal myopathy patients (n=50) were matched with the severity of vitamin D deficiency. Difficulties in walking, standing from sitting, climbing, raising hands above the head, and bone and joint pain were all significantly associated with the severity of vitamin D deficiency (P-value < 0.05).

Table III. Association of the presence of different symptoms with the severity of vitamin D deficiency in proximal myopathy patients (n= 50)

Symptom		Normal vit-D	Mild deficiency	Moderate deficiency	Severe deficiency	χ^2 value	P value
Difficulty in standing (n)							
	Yes (27)	3	18	11	5	13.711	0.003
	No (23)	8	10	4	1		
Difficulty in walking (n)							
	Yes (22)	4	4	9	5	11.892	0.008
	No (28)	7	14	6	1		
Difficulty in climbing (n)							
	Yes (31)	8	7	11	5	8.434	0.038
	No (19)	3	11	4	1		
Difficulty in raising the hand above the head (n)							
	Yes (23)	5	9	7	2	0.507	0.917
	No (27)	6	9	8	4		
Bone pain (n)							
	Yes (21)	2	5	10	4	9.302	0.026
	No (29)	9	13	5	2		
Joint pain (n)							
	Yes (16)	3	2	7	4	12.384	0.007
	No (34)	8	16	8	2		

Table IV shows the severity of vitamin D deficiency was not significantly associated with the duration of disease and involvement of the upper or lower limb of the proximal myopathy patients (n=50). The severity of muscle weakness was strongly associated with the severity of vitamin D deficiency (P-value < 0.05).

Table IV. Association of disease duration, limb involvement, and severity of muscle weakness with the severity of vitamin D deficiency in proximal myopathy patients (n= 50)

Variable		Normal vitamin-D	Mild deficiency	Moderate deficiency	Severe deficiency	χ^2 value	P-value
Duration of disease (n)							
	< 6 months (12)	5	3	3	1		
	6months–1year (22)	3	8	8	3	8.08	0.232
	> 1 year (16)	3	7	4	2		
Limb involvement (n)							
	Upper (13)	3	6	3	1		
	Lower (27)	6	9	9	3	2.827	0.830
	Both (10)	2	3	3	2		
The severity of muscle weakness (n)							
	Mild (20)	7	10	3	0		
	Moderate (26)	4	8	10	4	15.775	0.015
	Severe (04)	0	0	2	2		

DISCUSSION

Among 50 study participants, fifteen (30%) were males, and thirty-five (70%) were females, with an overall male-to-female ratio of 1:2.33. Female predominance was observed in this study which is somewhat similar to other studies like Karthik A et al. [22]

Most of the subjects were above 65 years (46%) with 22–86 years. Hossain et al.[23] reported that 80% of the study population belongs to the 31-50 years of age range. Another study by Mehta M et al.[24] reported majority 48% of cases was from 25 to 49 years of age

Among 50 patients majority were from urban areas (68%) than those from rural areas (32%). Mehta M et al.[24] reported majority of 92% of cases were from urban areas. Hossain et al.[23] found that 3/4th of the studied population with vitamin D deficiency were from urban areas. These findings support the findings of this study.

In this study majority of 56% of the patients were from a poor socio-economic background with a monthly income of fewer than 15,000 takas. The study by Micka et al.[25] Mehta M et al.[24] Jääskeläinen et al.[26] reported no such findings, whereas Hossain et al.[23] reported that among 212 patients, 85% (n=180) belonged to the middle class, which is different from this study. This could be due to the place and population of the study.

Out of 50 patients, most of the patients 46% studied up to SSC. This is analogous to the findings of Hossain et al., where those with higher education had lower levels of vitamin D.Contrary to the conclusions of this study, Jääskeläinen et al.[26] reported that those who had education >12 years had higher levels of vitamin D, than those with education 7-12 years and <7 years. Micka et al.[25] reported majority of 36% of the study population with lower levels of vitamin D had no formal education. Among the 50 studied proximal myopathy patients, involvement of lower limb muscles was more frequent (54%), 20% had both upper and lower limb involvement, and 26% had only upper limb involvement. The study by Al-said et al.[27] reported progressive proximal muscle weakness and Gait disturbances in 100% of cases, with diffuse musculo-skeletal pain(hips and lower limb) in 66% cases, back pain in 32% cases, carpopedal spasm in 13% cases and growth deficiency in 6% cases. Six patients (13%) had severe proximal muscle weakness with wheelchair-bound states. Twenty-two (42%) patients had a moderate weakness with a significant constraint of activities of daily living but with sustained independent mobility. As well, problems in rising from a siting position, inability to ascend height, and diffuse muscle pain were the main clinical symptoms in these patients. In a case study of 6 women by Hoigné et al.[28]reported that 100% of the cases clinical findings included mild proximal muscle weakness and gait abnormalities with difficulties running and climbing stairs. Another case study by Rawat et al.[29] reported patient had presented with quadriparesis. Another case study of an Indian man and a woman by Thabit et al.[30] reported that both had proximal myopathy and difficulty walking. These findings are supportive to the results of this study.

In this study of 50 patients Mean duration of illness was 8.6 ± 3.4 months. The majority, 44% were between 6 -12 months. The severity of vitamin D deficiency was not significantly associated with the duration of disease and involvement of the upper or lower limb of the proximal myopathy patients. A study by Al-said et al.27 reported that all the patients had symptoms of the disease duration ranging between 6-24 months with a mean of 14. In the case study of Rawat et al., [29] patients had proximal muscle weakness for three years. Another case study by Thabit et al.[30] reported that a male patient had a one-year history of bilateral lower limb weakness, and a female patient had pain and aches in the pelvic region for 4 years with a referral to a rheumatologist for proximal development of muscle weakness. In another case study, Chandrashekara et al.[31]presented a 42-year-old female with weakness in all four limbs, gradually deteriorating for one and half years.

Serum 25(OH) D level was measured in all patients, and out of 50 patients, 78% showed hypovitaminosis D. Mean value of serum 25(OH) D was 22.3 ± 7.7 ng/ml. Among them, 36% had mild insufficiency, 30% had a moderate deficiency, and 12% severe. In a study by Al-said et al., low Serum 25-hydroxy Vitamin D levels (<20 nmol/l) with a high level of parathyroid hormone were documented in 90% of patients. Which supports the findings of other studies.[22,24,,27,28,32,33]

Out of 50 patients, the majority of the patients showed moderate muscle weakness (52%). Muscle power was graded according to the Medical Research Council scale. A study by Karthik A et al.22 reported that 36 of the patients who had a history of falls had motor weakness and MRC grading of 4 or less with severe Vitamin D deficiency. Also, a case study by Rawat et al.34 reported that the patient had muscle power 3/5 in both upper limbs, while in lower limbs, it was 1/5 proximally and 3/5 distally. These findings are somewhat similar to the results of this study.

Among 50 patients Socio-demographic profile of proximal myopathy patients showed hypovitaminosis D was significantly found among elderly patients (P-value < 0.05). Females were comparatively more affected than males, but it was not statistically significant. Females using veils outside of the home suffered from vitamin D deficiency (P-value < 0.05). These findings are similar to the results of the study by Al-said et al.[27]

Presenting symptoms of proximal myopathy patients (n=50) were matched with the severity of vitamin D deficiency. Difficulties in walking, standing from sitting, climbing, raising hands above the head, and bone and joint pain were all significantly associated with the severity of vitamin D deficiency (P-value < 0.05). The severity of muscle weakness was strongly related to the severity of vitamin D deficiency (P-value < 0.05). Karthik A et al. 22 found a correlation between the severity of vitamin D deficiency and loss of muscle power and frequency of falls, which supports the findings of this study.

CONCLUSIONS

A significant number of patients presenting with proximal myopathy to medical facilities have a low vitamin D level, which may remain undiagnosed. This morbidity increases with increasing age and female gender. This study is a picture of patients presenting to a tertiary level hospital. Further studies are required to support the findings and to understand the real scenario of the whole country.

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Original Article

Outcome of Patients with Left Main Coronary Artery Disease Together with Left Ventricular Dysfunction Following OPCAB and Conventional CABG Surgery

*Raha SK,[1] Biswas SK,[2] Rahaman S,[3] Jahan H,[4] Hasan K[5]

Abstract:

In-hospital mortality and morbidities are significantly higher in patients who undergo coronary artery bypass graft (CABG) surgery having a depressed left ventricular function or a left main (LM) coronary artery disease. Due to the improvement in technique and clinical outcome, Off-pump Coronary Artery Bypass (OPCAB) is thought to be beneficial in patients with depressed left ventricular function by avoiding prolonged ischemic time. This study was performed with an aim to assess whether OPCAB is better than conventional on-pump CABG (CCAB) in these sub-groups of patients. We purposively selected 100 patients with left main coronary artery disease (defined as ≥50% stenosis) with reduced left ventricular ejection fraction (defined as ejection fraction 40% or less) who underwent elective CABG in National Institute of Cardiovascular Diseases (NICVD) between January 2014 and December 2020. Among them OPCAB was done in 50 patients and conventional CABG in another 50 patients. Both groups had similar pre-operative parameters. Total operative time, intubation time, blood loss, requirement for blood and blood products, intensive care unit (ICU) stay and hospital stay were all significantly lower in the OPCAB group. Post-operative complications were not statistically different among the two groups. Study finds that patients with left main coronary artery disease with left ventricular dysfunction can be safely revascularized in OPCAB technique.

Keywords: *OPCAB, CCAB, left main coronary artery disease, left ventricular dysfunction.*

1. *Dr. Sanjay Kumar Raha, Associate Professor, Department of Cardiac Surgery, NICVD, Dhaka
E-mail: drsanjayraha77yahoo.com, Contact: 01720988629
2. Dr. Smriti Kana Biswas, Medical Officer, Department of Gynaecology and Obstetrics, 250 Bedded TB Hospital, Shyamoli, Dhaka.
3. Dr. Salahuddin Rahaman, Assistant Registrar, Department of Cardiac Surgery, NICVD
4. Dr. Hosne Jahan, MBBS, Associate Professor (CC), Department of Microbiology, NICVD.
5. Dr. Md. Kamrul Hasan, Professor, Department of Cardiac Surgery, NICVD

*For correspondence

INTRODUCTION

Coronary artery bypass (CABG) grafting remains as the most frequently performed surgery in the practice of an adult cardiac surgeon.[1]Both the early and long-term outcomes of CABG have improved with the advances in instruments, myocardial protection and surgical technique. Therefore, an increased number of high-risk patients suffering from coronary artery disease are now being treated with surgical revascularization.[2]

As a consequence of increase in the incidence of risk factors of ischemic heart diseases in most of the countries of the world, severe and diffuse coronary artery diseases are becoming more common day by day.[3] On the other hand, improvement in invasive cardiology has led to referral of patients having complex and diffuse disease with poor ventricles to surgeons.[4]

A large scale meta-analysis of patients who underwent isolated CABG found seven independent variables of post-operative morbidity and mortality. These included low left ventricular ejection fraction (LVEF) and significant stenosis of the left main coronary artery.[5]

Patients with left main coronary artery disease associated with severe left ventricular dysfunction are more prone to develop ventricular arrhythmias, heart failure and sudden death. Left ventricular dysfunction in patients with coronary artery disease might be caused by scars, repetitive ischemia, myocardial stunning and hibernation or some combination thereof; thus, this condition might be partially or completely reversible in numerous patients who undergo revascularization.[6] Comparison of medical therapy with CABG surgery for patients with symptomatic coronary artery disease and ejection fraction (EF) as low as 30% have shown a long-term survival benefit for those receiving CABG.[7]

Conventional CABG surgery has long been considered as the gold standard operation for ischemic heart disease but high risk patients specially those having low ejection fraction are extremely sensitive to cardioplegic arrest and have higher intra-operative and post-operative morbidity and mortality.[8] OPCAB surgery was initially performed on

patients having single or double vessel disease with good left ventricular function.[9,10] But with the availability of modern retractor-stabilizers, intracoronary shunts, and growing surgeon experience, similar completeness of revascularization and graft patency can be achieved with OPCAB surgery even in patients with left main disease with reduced left ventricular function.[11,12,13] The international CABG Off or On Pump Revascularization Study (CORONARY) showed no significant treatment-related differences between off-pump and on-pump CABG with regard to any 5-year outcomes.[13] But the United States–based counterpart of that trial, the ROOBY Follow-up Study (ROOBY-FS) showed that off-pump CABG led to lower rates of 5-year survival and event-free survival than on-pump CABG.[14]

The aim of this study was to determine whether Off-pump Coronary Artery Bypass (OPCAB) provides better early outcome in patients with left main coronary artery disease with left ventricular dysfunction in comparison to conventional CABG.

MATERIALS AND METHODS

This prospective non-randomized clinical study was conducted in the Department of Cardiac Surgery, National Institute of Cardiovascular Diseases (NICVD) from January 2014 and December 2020. The study was carried out on patients left main coronary artery disease together with reduced left ventricular ejection fraction (≤ 40%) who were scheduled for elective coronary artery bypass graft surgery in NICVD, during the specified period of time and fulfill the inclusion and exclusion criteria. Among them 100 patients were purposively selected and allocated into two groups on the basis of operative procedure:

Group A: 50 patients who underwent OPCAB (Study group) and

Group B: 50 patients who underwent conventional CABG (Control group).

Anesthesia and Monitoring

Patients were placed in supine position on the operating table. Non-invasive monitoring lines like ECG, non-invasive blood pressure (NIBP), and pulse oxymeter were connected. Two peripheral venous lines were established. Radial arterial cannula was introduced under local anesthesia and was connected to a polygraph monitor for continuous blood pressure monitoring. Under general anesthesia CVP cannula was introduced and was connected to a polygraph monitor for continuous CVP display. Urinary catheter was introduced to monitor hourly urine output. In patients with low left ventricular ejection fraction (<35%) femoral arterial cannula was introduced because they might intra-aortic balloon pump (IABP) support.

Anesthetic drugs were used as per institutional protocol. After premedication with opioid (morphine or fentanyl) and sedative agent (midazolam/ diazepam), induction of anesthesia was achieved with thiopental sodium or etomidate and muscle relaxation was obtained by pancuronium or vecuronium. Maintenance of anesthesia was achieved by isoflurane/halothane, and propofol along with incremental doses of analgesics and muscle relaxants in both the groups. OPCAB was performed under normothermia and CCAB under mild hypothermia.

Technique of Off-pump coronary artery bypass graft surgery:

OPCAB was done through midline sternotomy. Arterial and venous conduits were harvested following standard protocol. Then patients were heparinized (100 IU/ kg) to achieve an activated clotting time (ACT) of ≥300 seconds before grafting. Stabilizer and positioning devices were used for stable grafting. Pericardial traction sutures were applied to expose obtuse marginal arteries where appropriate. Intracoronary shunts were routinely used to maintain coronary flow during distal anastomoses. Humidified blower and normal saline spray were used for better visualization. All left anterior descending (LAD) arteries received left internal mammary artery (LIMA) graft. The sequence of grafting was individualized. Proximal anastomoses were performed on the partially clamped ascending aorta using 6-0 or 7-0 polypropylene suture. For distal anastomoses we used 7-0 or 8-0 polypropylene suture. After grafting, heparin was reversed with protamine in 1:1 ratio. All the wounds were closed in layers. Then patients were transferred to cardiac ICU.

Technique of conventional CABG

Median sternotomy was done as usual. After harvesting of conduits heparin was introduced (300 IU/kg) to achieve an activated clotting time (ACT) >450 seconds. Aortic and two stage single venous cannulation were done for cardiopulmonary bypass (CPB). The flow was maintained between 2.0 to 2.5 L/ min/ m^2. The blood pressure was kept between 60 to 70 mm Hg. Mild hypothermia was maintained during cardiopulmonary bypass. After cross clamping the aorta antegrade cold blood cardioplegia was administered for myocardial protection. Cardioplegia was

repeated every 20 minutes. Distal anastomoses were performed first. Then proximal anastomoses were performed during rewarming. Patients were weaned from cardiopulmonary bypass. Heparin was reversed with protamine as before. All the wounds were closed in layers. Then patients were transferred to cardiac ICU.

Postoperative Management in ICU

In the cardiac ICU patients were monitored and managed as per standard protocol. Hourly urine output and blood loss were measured. Inotropes and vasodilators were used as per surgeon's choice. Post-operative complications were treated accordingly. After extubation patients were encouraged to respiratory exercise and early mobilization. Inotropes were weaned, drains were removed when appropriate. Subsequently patients were shifted to general wards and discharged home.

RESULTS

Table-I showed patient characteristics. The study samples of two groups had similar mean ages (p=0.1428; >0.05). Sex distribution was homogenous but with male predominance (88% vs. 90%). Although the body mass index (BMI) of two groups were not statistically different (p=0.0728; >0.05) overweight and obese patients were more prevalent among CCAB group. Distribution of co-morbidities and risk factors were not different between the groups (p values >0.05). Coronary angiography showed that majority of the left main patients had triple vessel coronary artery disease (TVD) in each group (72% vs 72%; p=1.000). Other patients had double vessel disease (DVD) (p=0.7901) and left main only (p=0.7493). So, pre-operative characteristics were statistically similar among the two groups (p> 0.05).

Table-I : Patient Characteristics of Left Main (LM) Coronary Artery Disease and Left Ventricular Dysfunction

Variables	OPCAB group (n=50)	CCAB group (n=50)	*p* Value
Age (years)	61.2±6.74	59.2±6.8	0.1428*ns*
Male, n (%)	44(88.0)	45(90.0)	0.7493*ns*
BMI (kg/m²)	26.2±2.2	26.98±2.1	0.0728*ns*
Hypertension, n (%)	30(60.0)	29(58.0)	0.8369*ns*
Diabetes mellitus, n (%)	22(44.0)	23(46.0)	0.8407*ns*
Smoking, n (%)	27(54.0)	26(52.0)	0.8412*ns*
Dyslipidemia, n (%)	21(42.0)	19(38.0)	0.6831*ns*
Family H/O Coronary Artery Disease, n (%)	5(10.0)	6(12.0)	0.7493*ns*
Stroke or Transient Ischemic Attack, n (%)	2(4.0)	1(2.0)	1.000*ns*
COPD, n (%)	6(12.0)	5(10.0)	0.7493*ns*
History of Myocardial Infarction, n (%)	22(44.0)	21(42.0)	0.8399*ns*
Peripheral Vascular Disease, n (%)	5(10.0)	6(12.0)	0.7493*ns*
Renal dysfunction, n (%)	3(2.0)	2(4.0)	1.000*ns*
Arrhythmia, n (%)	4(8.0)	3(6.0)	1.000*ns*
Left Ventricular Ejection Fraction, (%)	38.3 ± 2.6	37.96±2.3	0.4902*ns*
NYHA class II or III, n (%)	5(10.0)	5(10.0)	1.000*ns*
CCS angina class III or IV, n (%)	23(46.0)	26(52.0)	0.5484*ns*
Left Main (LM) Disease only	5(10.0)	6(12.0)	0.7493*ns*
LM + Double Vessel Disease	9(18.0)	8(16.0)	0.7901*ns*
LM + Triple Vessel Disease	36(72.0)	36(72.0)	1.000*ns*

***ns* = Non-significant**

Table-II showed that CCAB group had higher operating time (p=0.000) because of the time required for institution and termination of cardiopulmonary bypass. All patients received left internal mammary artery (LIMA) to left anterior descending artery (LAD) graft. Long saphenous vein (p=1.000) and radial artery were used similarly (p=0.6882**).** Most of the patients of both groups had 3 grafts.

Table-II: Comparison of Intraoperative Variables between OPCAB and CCAB Groups

Variables	OPCAB group (n=50)	CCAB group (n=50)	*p* Value
Conversion to Cardiopulmonary Bypass (CPB), n (%)	1(2.0)		
CPB time (minutes)		87.3 ± 12.5	
Total operating time (minutes)	267.7 ± 24.6	309.6 ± 29.7	0.000^{s}
Conduit¥			
Left Internal Mammary Artery, n (%)	50(100.0)	50(100.0)	1.000^{ns}
Radial artery, n (%)	24(48.0)	22(44.0)	0.6882^{ns}
Saphenous Vein, n (%)	50(100.0)	50(100.0)	1.000^{ns}
Graft distribution			
Left Anterior Descending, n (%)	50(100)	50(100)	1.000^{ns}
Left Circumflex territory, n (%)	48(96.0)	49(98)	0.5577^{ns}
Right Coronary Artery, n (%)	46(92.0)	45(90.0)	0.7268^{ns}
Intra-aortic Balloon Pump	0(0)	1(2.0)	1.000^{ns}

***ns* =Non-significant; *s* = Significant**

Table-III showed post-operative variables of the study groups. In the ICU OPCAB patients were extubated earlier from mechanical ventilation than CCAB patients (p=0.000). Requirements for IABP and inotropes were similar between two groups. Post-operative bleeding and blood product requirement were less in OPCAB group (p=0.000). Postoperative stay period in ICU and ward stay were also shorter in OPCAB group (p=0.000).

One patient of CCAB group died immediate post-operatively due to cardiac temponade followed by multi-organ dysfunction from prolonged low output syndrome. None died in OPCAB group (p=1.000). Two patients of the CCAB group and one of the OPCAB group developed post-operative myocardial infarction (MI) but all of them recovered completely. Post-operative complications like re-exploration for bleeding, stroke, arrhythmia, renal dysfunction, wound infection and pulmonary complications were not statistically different.

Table III: Comparison of Post-Operative Variables between OPCAB and CCAB Groups

Variables	OPCAB group (n=50)	CCAB group (n=50)	*p* Value
Operative mortality, n (%)	0(0)	1(2.0)	1.000^{ns}
Mechanical ventilation time, hours	6.98±0.5	11.85±0.48	0.000^{s}
Low Output Syndrome or Prolonged inotropic support	3(6.0)	5(10.0)	0.715^{ns}
Intra-aortic Balloon Pump	1(2.0)	1(2.0)	1.000^{ns}
Chest tube drainage (ml)	460 ± 56	640 ± 62	0.000^{s}
Requirement for blood and blood products (ml)	750 ± 50	1120 ± 40	0.000^{s}
ICU stay (hours)	72 ± 2.8	96 ± 2.0	0.000^{s}
Post-operative hospital stay (days)	7.1 ± 0.4	9.9 ± 0.2	0.000^{s}
Re-exploration	1(2.0)	3(6.0)	0.6175^{ns}
Post-operative stroke	1(2.0)	1(2.0)	1.000^{ns}
Lung complication	5(10.0)	6(12.0)	0.7762^{ns}
New myocardial infarction	1(2.0)	2(4.0)	1.000^{ns}
Post-operative arrhythmia	7(14.0)	12(24.0)	0.2025^{ns}
Wound infection	3(6.0)	4(8.0)	1.000^{ns}
Acute Kidney Injury	6(12.0)	8(16.0)	0.5643^{ns}

***ns* =Non-significant; *s* = Significant**

DISCUSSION

OPCAB is being performed regularly in NICVD. Patients with left main coronary disease with reduced left ventricular ejection fraction (≤40%) are a high-risk group for surgical revascularization. As in other studies we found that in-hospital morbidities were less frequent in patients of OPCAB group. Long term studies showed that incomplete revascularization was more common with OPCAB approach which led to increase in cardiac mortalities and morbidities, repeat hospitalization and re-intervention.[15,3] Two studies performed by Shroyer et al. and Meharwal et al. having large sample showed that the average numbers of grafts were similar between OPCAB and CCAB groups.[16,17] Youn et al. showed that patients with CCAB had more distal anastomoses, but this was not statistically different between the groups. Complete revascularization can be performed in both techniques.[18] In all OPCAB patients we used intracoronary shunts during distal grafting as we believe them useful to maintain coronary flow and reduce bleeding. During the lateral and inferior grafting in OPCAB procedure blood pressure may fall.[19] Myocardium may further suffer if tourniquets are used around coronary arteries. However, studies have shown inconclusive results regarding their use.[20]

Some early post-operative parameters like period of mechanical ventilation, blood loss, use of blood and blood products, ICU stay and hospital stay were significantly less in OPCAB patients. Transmission related complications are less in this group of patients.[21]

Studies showed that OPCAB had lower post-operative mortality in high- risk patients having one or more co-morbidities and left ventricular dysfunction.[22] In our study, hospital mortalities for OPCAB and CCAB patients with left main disease with reduced left ventricular ejection fraction (≤40%) were comparable. Meharwal et al. showed that the operative mortality was lower in OPCAB group (0.97% vs 1.86%; p<.001).[17] Ruzzeh et al. in a meta-analysis showed similar result (1.4% vs. 2.9%).[23] However, Sajja et al. (2.8% vs.3.9%, p=0.746) showed that though mortality was lower in OPCAB group the difference was not statistically significant.[24]

CONCLUSIONS

There is an ongoing debate whether OPCAB or CCAB has better post-operative outcome. Study found that OPCAB had some favorable post-operative findings e.g. less operative time, mechanical ventilation time, blood loss, blood transfusion, intensive care unit (ICU) stay and hospital stay. However, operative mortality and morbidity were similar among them. This concludes that these patients can be safely revascularized in OPCAB technique.

Study Limitations:

The limitations of the study are as follows:

1. Purposively selected small sample size.
2. No randomization before grouping.
3. There is chance of biasness because the surgical procedure (OPCAB or CCAB) was chosen by the performing surgeon.
4. This study was of short period without any follow up information.
5. The finding of this research was drawn from NICVD only. So it may not be comparable to that of a large scale study.
6. Variations in surgeon's competence, severity of coronary artery disease and echocardiographic parameters have to be taken in account for better comparison.

Recommendations:

Our recommendations are as follows:

1. Patients with left main disease with reduced left ventricular ejection fraction (≤40%) can be safely revascularized by OPCAB procedure.
2. A well designed randomized trial is required to validate the information of our study.

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Original Article

Clinical Profile of Posterior Circulation Stroke: A Prospective Study at Dhaka Medical College Hospital

*Rahman HMM[1], Rahman GMH[2], Mony MB[3], Samsuzzaman SM[4], Taslima AAH[5], Sikder GM[6], Ahmed F[7]

Abstract

Studies regarding clinical characteristics of stroke involving the posterior circulation territory of the brain in Bangladesh are rare although large number of patients were found in hospital admission and with a high morbidity and mortality. Study for better understanding of the clinical features, risk factors and aetiologies of posterior circulation stroke (PCS) may be very healpfull for early diagnosis, treatment, and also for setting primary and secondary prevention strategies. The objective of the study was to identify clinical features and short-term outcome of PCS. Adult patients admitted in Dhaka Medical College Hospital with clinical features consistent with posterior circulation stroke involving brain stem or, cerebellum or thalamus or occipital area and confirmed by computer tomography (CT) scan of brain were the the cases as respondents. Few cases were needed MRI of brain to confirm diagnosis. This was a hospital based prospective observational study with descriptive and analytical component. Sample was selected from the study population by purposive type of non-probability sampling technique. Sample size was 30. A semi-structured questionnaire was prepared containing patients' profile as well as stroke patients' reporting form which included all the essential information regarding clinical profile of PCS as well as short term outcome. Analysis was done using Statistical Package for the Social Sciences (SPSS) software. Thirty consecutive cases of strokes involving posterior circulation territory were included in the study according to inclusion and exclusion criteria. Male female ratio was 1.7:1. Most of the patients in both sexes were affected after the age of 50 years. Hemorrhagic PCS was significantly higher than ischaemic PCS. Among hemorrhagic PCS common symptoms were decreased level of consciousness and motor disturbances. Most common clinical sign in ischemic PCS is impaired consciousness which was present in 55.6% of the total ischemic PCS cases. Whereas this sign was present in all the cases of hemorrhagic PCS (100%). Like presenting symptoms, most of the clinical signs were also more common in hemorrhagic PCS. But few clinical signs were more common in ischemic strokes, such as cranial nerve involvement and nystagmus. Commonest predisposing factors were tobacco abuse, hypertension and dyslipidemia. Mortality was higher in hemorrhagic PCS than ischemic PCS within 7 days of follow up.

Keywords: *Posterior circulation stroke, stroke subtypes, risk factors.*

1. *Dr. Hossain Muhammad Mustafijur Rahman, Assistant Professor, Department of Nephrology, Dhaka Medical College, Dhaka, Bangladesh. Email: rizvi.sky@gmail.com, Phone: 01720581583
2. Dr. G. M. Hafizur Rahman, Assistant Professor, Department of Nephrology, Dhaka Medical College, Dhaka, Bangladesh.
3. Dr. Maksuda Begum Mony, Assistant Professor, Uttara Women Medical College, Uttara, Dhaka.
4. Dr. Sheikh Mohammad Samsuzzaman, Assistant Professor, Sir Salmullah Medical College Hospital, Dhaka.
5. Dr. Al Asma Ul Taslima, Junior Consultant (Radiology and Imaging), Sheikh Hsaina National Institute of Burn and Plastic Surgery,Dhaka, Bangladesh.
6. Dr. Golam Mahabub Sikder, Nephrologist, Department of Nephrology, Cumilla Medical College Hospital, Cumilla, Bangladesh.
7. Dr. Faruque Ahmed, Assistant Professor (Nephrology), Department of Nephrology Shaheed Surawardy Medical College Dhaka, Bangladesh.

*For correspondence

INTRODUCTION

The World Health Organization (WHO) defines stroke as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin.[1] The National Institute of Neurological Disorders and Stroke (NINDS) applies the term stroke to "any one or all of a group of disorders including cerebral infarction, intra-cerebral haemorrhage or subarachnoid haemorrhage.[2]

Stroke is a common medical emergency with an annual incidence of between 180 and 300 per 100 000. The incidence rises steeply with age, and in many developing countries, the incidence is rising because of the adoption of less healthy lifestyles.[3] About one-fifth of patients with an acute stroke will die within a month of the event, and at least half of those who survive will be left with physical disability.[3]

Posterior circulation strokes (PCS) account for 10 to 15%[4] of all strokes. The area includes brainstem, cerebellum, occipital lobes and thalamus and is supplied by 2 vertebral arteries, 1 basilar artery and 2 posterior cerebral arteries.[5] Posterior circulation ischemia ranges from fluctuating

brainstem symptom caused by intermittent insufficiency to many syndromes like lateral medullary, medial medullary, locked in to top of basilar syndrome.[6] Dizziness, vertigo, headache, vomiting, double vision, loss of vision, ataxia, numbness and weakness involving both sides of the body are frequent symptoms and limb weakness, gait and limb ataxia, oculomotor palsies and or pharyngeal dysfunction are most common signs of vertebra-basilar insufficiency.[7] Cerebellar, pontine and other brainstem ischemia/ hemorrhage are more common in posterior circulation strokes(PCS).[8]

There is no known study regarding clinical characteristics of stroke involving the posterior circulation territory of the brain in Bangladesh although it consists of significant number of hospital admission and having a high morbidity and mortality rate. A better understanding of the clinical features, risk factors and etiologies of PCS will be very effective for early diagnosis and treatment, and also for setting primary and secondary prevention strategies.

This study aims to identify most commonly encountered symptoms, signs, and risk factors as well as short term outcome of PCS.

MATERIAL AND METHODS

This was a hospital based prospective observational study with descriptive and analytical component. This study was done in the Department of Medicine & Neurology, Dhaka Medical College Hospital, Dhaka since 1st July, 2016 to 31st December, 2016). Total 30 consecutive cases were taken as study sample.

Inclusion criteria

1. Adult patients admitted in medicine and neurology ward.
2. Admitted within 72 hours of the onset of symptoms.
3. Posterior circulation strokes confirmed by CT scan of brain and/ or MRI of brain.

Exclusion criteria

1. CT scan of brain showing stroke involving anterior circulation.
2. Head injury.
3. Not agreed to take part in the study.

A semi-structured questionnaire was prepared after pre-testing consisting of patients' profile as well as stroke patients' reporting form which included all the essential information regarding clinical profile of posterior circulation stroke.

Detailed clinical history and physical examination data was recorded for each individual patient in a predesigned case-record form (CRF). All relevant investigation reports were also been used for data collection.

RESULTS

During the study period the total number of strokes were 1200 and percentage of posterior circulation stroke was 2.5 % of all strokes. Stroke was more common in the middle aged and elderly. Hemorrhagic posterior circulation strokes (PCS) were more common (66.7%) than ischemic PCS (33.3%). And males were three times more commonly affected than female. About 66 % cases were of more than 50 years of age.

Table I shows the frequency of clinical manifestations present at the time of admission to hospital. Most frequent manifestations were altered sensorium (55.6 %) and vertigo (55.6 %) in ischemic strokes; and in hemorrhagic strokes altered sensorium (100%), motor disturbances (76.2%) and headache (66.7 %) were commonly encountered symptoms.

Table I: Symptoms in ischemic and hemorrhagic PCS

Manifestation	Ischemic Stroke		Hemorrhagic Stroke	
	No. of Patients (N=9)	%	No. of Patients (N=21)	%
Altered sensorium	5	55.6	21	100
Vertigo	5	55.6	13	61.9
Haedache	2	22.2	14	66.7
Vomiting	2	22.2	17	81
Ataxia	1	11.1	9	42.9
Speech disturbances	2	22.2	13	61.9
Visual disturbances	…	…	2	9.6
Blurring and blindness	…	…	…	…
Diplopia	…	…	1	4.8
Motor disturbances	1	11.1	16	76.2
Sensory disturbances	2	22.2	5	23.8
Convulsion	…	…	5	23.8

Table II shows the most common neurological findings in ischemic stroke were impaired consciousness (55.6%), motor weakness (44.4%) and speech disturbances (44.4%). The next findings were cranial nerve involvement (33.3%) and nystagmus (33.3%). In hemorrhagic strokes all the patients had altered sensorium (100%); 76.2% had both speech disturbances and motor weakness and loss of orientation was present in 71.4% of cases.

Table II Clinical signs in ischemic and hemorrhagic PCS

Features	Ischemic stroke		Hemorrhagic stroke	
	No. of Patients (N=9)	%	No. of Patients (N=21)	%
Consciousness impaired	5	55.6	21	100
Orientation impairment	1	11.1	15	71.4
Speech disturbances	4	44.4	16	76.2
Memory impairment	2	22.2	419	
Cranial nerve involvement	3	33.3	29.6	
Motor weakness	4	44.4	16	76.2
Sensory disturbances	2	22.2	628.6	
Cerebellar signs	2	22.2	838.1	
Nystagmus	3	33.3	419	
Meningeal irritation	…	…	…	…
Fundal changes	2	22.2	12	57.1

Table III shows in ischemic stroke the commonest risk factors were tobacco abuse (44.4%) and dyslipidemia (44.4%).

Table III: Risk factors for Ischemic PCS

Name of factors	Frequency (%)
Tobacco abuse	44.4
Dyslipidemia	44.4
Carotid Artery Disease	44.4
IHD	33.3
Diabetes Melitus	22.2
Alcohol	11.1

Table IV shows in the hemorrhagic strokes the commonest risk factor was hypertension (57.1%) and next to hypertension is diabetes mellitus (33.3%).

Table IV: Risk factors for Hemorrhagic PCS

Name of factors	Frequency (%)
Hypertension	57.1
Diabetes Mellitus	33.3
IHD	23.8
Alcohol	19.0
IHD	23.8

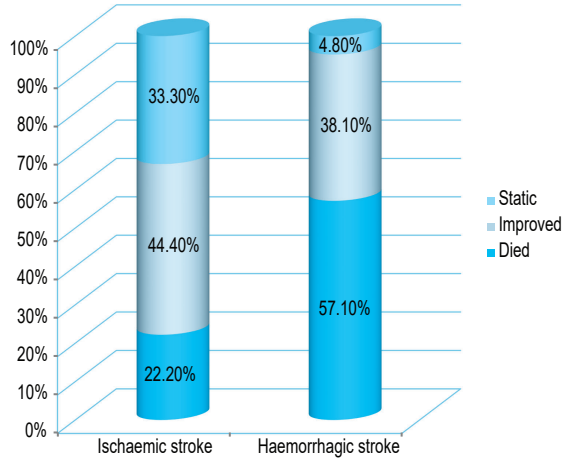

Figure 1 Graphical representation of short-term outcome of ischemic and hemorrhagic PCS.

Figure 1, Mortality in ischemic stroke was 22.2% and in hemorrhagic stroke it was 57.1%. Improvement was seen in 44.4% of ischemic and 38.1% of hemorrhagic strokes within 7 days of follow up.

DISCUSSION

Of the 30 patients studied, the age ranged from 35 to 81 years. Most of the patients' (36.67 % of total patients) age was in between 50 to 70 years. This shares the same sort of findings (61.7±14.6 years) with the research paper published in JNNP in 2011 and with the NEMC-PCR (mean age 60.5 years).[20,21]

Total 1200 stroke patients were admitted in Dhaka Medical College Hospital during the study period. Among them 30 cases were posterior circulation stroke. That means 2.5% of the admitted stroke patients were suffered from posterior circulation stroke.

Among the affected patients 19 (63.33%) were male and 11 (37.67%) were female. Ma.Cristina L et al study and R.B. Libman et al also found more males compared to females in theie study.[22,23] Male and female ratio was 1.7:1. According to NEMC-PCR 63% was male and 37 % was female.[21] This is similar to the findings of the present study. But in a study conducted in Southern India in 2011 stated that male and female ratio was 3.1:1.[24] That means in Southern India incidence of PCS is more common in males than this study conducted at Dhaka Medical College Hospital.

Approximately 57.89 % of the male patients' age was between 51 years to 70 years and 45.45 % of the affected female patients' age was between 51 years to 70 years. Incidence is less in the patients aged <51 years and >70 years in both sexes. Caplan et al., Patrick et al. and Kora S.A. et. al. found similar findings.[10,12,24] In Ratnavalli E et al most of the PCS patients' age was > 65 years of age.[26]

Specific reason was not found why hemorrhagic strokes are more common in Bangladesh than India but poorly controlled hypertension and irregular intake of anti-hypertensive medication may be the cause. As we know that the role of hypertension as a leading risk factor is well established, and its frequency has been estimated to be between 72% and 81%.[25,26,27]

The causative role of hypertension is supported by the presence of high blood pressure in 57.1 % of hemorrhagic strokes compared to 11.1 % in ischemic strokes. Among the males 31.58 % was ischemic stroke and remaining 68.42 % was hemorrhagic. And among the females 27.27 % was ischemic and 72.72 % was hemorrhagic stroke. So, it was clearly seen that in both male and female hemorrhagic strokes were significantly higher.

Among the ischemic PCS altered sensorium and vertigo were the most common symptoms. Both these symptoms were present in 55.6 % cases of the ischemic strokes. Whereas in Kora S.A. et. al. most common symptom in ischemic PCS was motor disturbances (63.2 %) and after that next most common was altered sensorium and headache (both was 57.8 %).[24]

Headache, vomiting, speech disturbances and sensory disturbances all were present in 22.2 % of ischemic strokes. 11.1 % of ischemic stroke cases complaints of motor weakness. But in the present study no patients among ischemic strokes complaints of visual disturbances or blurring of vision or blindness or diplopia or convulsion.

Similar to Kora S.A. et. al. we found that among hemorrhagic strokes 100 % patients' level of consciousness was poor.[24] And next to this the most common symptom was motor disturbance which was present in 76.2 % of cases in the present study. Compared to ischemic strokes where altered sensorium and motor disturbances were the presenting complaints in 55.6 % and 11.1 % cases sequentially, these were much more common in the hemorrhagic strokes. Whereas in Kora S.A. et. al. most common sign in hemorrhagic PCS next to impaired consciousness was headache and vertigo (both were present in 66.6 % of cases).[24]

Similarly, in the present study other presenting symptoms like vertigo, headache, vomiting, ataxia, speech disturbances, sensory disturbances all were 2-3 times more common in hemorrhagic strokes. Comparative frequency has been shown in bracket in the form of ischemic vs hemorrhagic stroke (vertigo 55.6 % vs 61.9 %; headache 22.2 % vs 66.7 %; vomiting 22.2 % vs 81 %; ataxia 11.1 % vs 42.9%; speech disturbances 22.2 % vs 61.9 %; sensory disturbances 22.2 % vs 23.8 %).

Convulsion was only present in 23.8 % of hemorrhagic stroke cases where as no ischemic stroke cases developed convulsion. It is obvious from the above data that hemorrhagic PCS presents with more symptoms than Ischemic PCS.

Overall if it is compared to the study known as Patrick et al, it is seen that all the symptoms are more common in the present study except ataxia, visual disturbances and diplopia.[12] Most common symptom is altered sensorium in both the study.

Most common clinical sign in ischemic PCS is impaired consciousness which was present in 55.6 % of the total ischemic PCS cases. Whereas this sign was present in all the cases of hemorrhagic PCS (100%). Like presenting symptoms, most of the clinical signs were also more ommon in hemorrhagic stroke. For example, disorientation is more common in hemorrhagic PCS (71.4 %) compared to 11.1 % in ischemic PCS. Similarly, speech disturbances, memory impairment, motor weakness, sensory disturbances, cerebellar signs and fundal changes like hypertensive and diabetic retinopathy were more common in hemorrhagic strokes.

Ischemic vs hemorrhagic PCS (speech disturbances 44.4% vs 76.2%; memory impairment 22.2% vs 19%; motor weakness 44.4% vs 76.2%; sensory disturbances 22.2% vs 28.6%; cerebellar signs 22.2% vs 38.1%; and fundal changes 22.2% vs 57.1%). But few clinical signs were more common in ischemic strokes, such as cranial nerve involvement (33.3%) was more common in ischemic PCS than 9.6 % in hemorrhagic PCS. Nystagmus was a more frequent finding in ischemic PCS (33.3%) than in hemorrhagic PCS (19%).

Tobacco abuse and dyslipidemia were the most common risk factors (both were present in 44.4% of cases) in ischemic PCS. Other factors that were found associated with ischemic PCS were BMI >25 (was present in 55.6 % of cases), carotid artery disease (was present in 44.4% of cases), ischemic heart disease (was present in 33.3% of cases) though these are directly related to or result of dyslipidemia.

In hemorrhagic PCS most common risk factor was hypertension. It was seen that hypertensive patients who used to take anti-hypertensives irregularly and those who did not take anti-hypertensives were commonly suffered from hemorrhagic stroke. This is also seen in hemorrhagic strokes in other vascular territories of the brain.

Next to hypertension most common risk factor was diabetes. But it is not clear why this is a less common risk factor in Ischemic PCS. Diabetes is present in 33.3% cases of hemorrhagic PCS compared to 22.2% in ischemic PCS.

Other risk factors that were present includes dyslipidemia and conditions associated with it. Dyslipidemia was present in 28.6 % cases, TIA & BMI > 25 28.6 % cases, Ischemic heart disease 23.8 % cases in hemorrhagic PCS.

Most common risk factor was hypertension in the present study which is comparable with the Caplan et. al. But in the other studies most common risk factor was tobacco abuse. In these studies, most of the cases was ischemic PCS. And this may be the reason behind this difference.[10,24,25,26] A comparative table has been given below to show how much difference was there among different studies.

In the present study also tobacco abuse was the most common risk factor for ischemic PCS as I already have mentioned above. And similarly, for the hemorrhagic PCS most common risk factor was hypertension, this has also been mentioned above. As in the present study 70% cases were hemorrhagic PCS so when most common risk factor was calculated for the total number of patients it was found to be hypertension.

Patients were followed up for 7 days to see immediate outcome of the treatment. We found that most of the patient died in hemorrhagic PCS but most of the patient was improved in ischemic PCS. 22.2 % patient was died ischemic stroke whereas 57.1 % was died in hemorrhagic stroke within 7 days.

Level of consciousness, symptoms like vertigo, headache etc. speech disturbances & motor weakness were significantly improved compared to what those were 7 days back in 44.4 % of cases of ischemic PCS and in 38.1 % of cases of hemorrhagic PCS.

Approximately 33.3 % patient was remained in the same condition after 7 days of treatment in ischemic PCS compared to 4.8 % in hemorrhagic PCS. So, most of the hemorrhagic cases were either improved or deteriorated.

Compared to other studies like Patrick et al (25.6%), Jones et al (27.5%) and Uma et al (17%) mortality ratio is higher this study (46.7%).[9,14,25] Percentage of improvement in this study was 44.4% in ischemic PCS and 38.1% in hemorrhagic PCS (average 40%) whereas it was higher in Patrick et al[9] study (46%) and Uma et al[25] study (52%) but in Jones et al[14] study it was 35% on an average. [9,25,14] Death ratio was higher may be due to lack of adequate treatment facilities here.

CONCLUSIONS

Study shows that PCS commonly affects the elderly but may occur in young. Clinical profile of PCS in this study emphasizes deep concern about elderly persons and those having risk factors like hypertension, tobacco abuse, diabetes, dyslipidemia. Knowledge of clinical characteristics of PCS is necessarily a concern of prevention and management strategy of this strokes.

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Original Article

Clinical Pattern of Thoracic Spine Pain (TSP)

*Alam MM[1], Hossain MS[2], Hojaifa MM[3], Rahman HH[4] ,Hosain M[5], Rana MS[6], Kamruzzaman M[7], Alam MA[8]

Abstract

Thoracic spine pain (TSP) is defined as pain perceived anywhere in the region bounded superiorly by a transverse line through the tip of the spinous process of T1, inferiorly by a transverse line through the tip of the spinous process of T12, and laterally by vertical lines tangential to the most lateral margins of the erector spine muscles. One year prevalence of TSP ranged from 8.3-38.1% in different Asian countries. A longitudinal observational study was conducted to observe the clinical feature, demographic profile and clinical course of patients with TSP attending at the Department of Physical Medicine and Rehabilitation (PMR) of Shaheed Suhrawardy Medical College Hospital (ShSMCH). Among the 100 study patients mean age ±SD was 34.76±13.26. Highest number of the patients (45%) belong to 16-30 years age group and male-female vatioo was 3:1. Highest frequency in the level of education 28% belonged to higher secondary or diploma. Twenty six percent (26%) patients were housewife, manual labor 20%, students 19%, sedentary worker 15%, manufacturing and industrial worker 8%, health professional 4%, driver 3% and 5% were in others group. Most of them (71%) belong to <12000 taka monthly income group and 91% patients' lived in urban area. Duration of thoracic spine pain was found acute (6 weeks) 46%, sub-acute (>6-12 weeks) 16% and chronic (>12 weeks) 38%. Upper TSP was found among 51% of the patients. Onset of pain among the patients 66% was gradual. Mild intensity of pain was reported in 54% patients, moderate 44% and severe in only 2% patients and 64% patients had no radiation. Aggravating factors were found in patients with was prolong sitting in 42%. More than one third (36%) patients relieving factor were lying, 24% rest, activity 16% and no relieving factors in 24% patients. Morning stiffness and depression was found 20% and 25% patients respectively. Associated conditions were found as diabetes mellitus (DM) 25%, sleep disturbance 16%, dyspepsia 10%, hypertension (HTN) were in 7% patients and 42% patients had no associated condition. Large number of the patients' was occupational 46%; rest of the factors were MFPS 16%, degenerative 14% (dorsal spondylosis 5%, cervical spondylosis 6% and lumbar spondylosis 3%), Ankylosing Spondylitis (AS) 7% and traumatic were 6%. Pott's disease 4% and 7% patients' cause were others. According to Numeric Rating Scale in the first visit mild causes were in 54% patients, 44% moderate and 2% severe. In the last visit 69% patients were found mild and rest had no pain (p value=0.001). Assessment of joint tenderness in first visit; 56% patients were in grade 1, 20% grade 2 and 3% in grade 3, 21% patients had no tenderness. In the last visit it was found that only 21% patients in grade 1 and rest 79% had no tenderness (p value=0.001). According to Pain Disability Index in the first visit mild disability was found in 67% patients, moderate 31% and 2% had no disability. In the last visit mild were 74% and 26% had no disability (p value=0.001). Teenager, young adults and adults were the most commonly affected patients with TSP with M:F=1.5:1. Most of the patient of upper TSP presented before 6 weeks; common presenting features were gradual onset, pain was constant in nature, mild to moderate in intensity without radiation, aggravated by prolong sitting and leaning forward, relieved by lying and rest, with no depression and significant morning stiffness. Most of the factors were occupational and MFPS. Occupations were commonly housewife and manual labor. They were improved significantly (p value=0.001) with conventional treatment.

Keywords: *Thoracic spine pain (TSP), myofascial pain syndrome (MFPS).*

1. *Dr. Md. Mahfuzul Alam, Assistant Professor, Department of Physical Medicine & Rehabilitation, Kurmitola General Hospital, Dhaka, Bangladesh. Cell: 01720839973, E-mail: mahfuzulalam80@gmail.com
2. Professor Dr. Md. Shahadat Hossain, Vice Principal and Head, Department of Physical Medicine & Rehabilitation, Shaheed Suhrawady Medical College, Dhaka.
3. Dr. Musa Muhammad Hojaifa, Assistant Professor, Department of Physical Medicine and Rehabilitation, Sheikh Hasina National Institute of Burn and Plastic Surgery (SHNIBPS), Dhaka.
4. Dr. Hasan Habibur Rahman, Assistant Professor, Department of Physical Medicine and Rehabilitation, SHNIBPS, Dhaka.
5. Dr. Mohammad Hosain, Medical Officer, Department of Physical Medicine and Rehabilitation, BSMMU, Shahbag, Dhaka.
6. Dr. Md. Sohel Rana, Medical Officer, Department of Physical Medicine and Rehabilitation, SHNIBPS, Dhaka.
7. Dr. Mohammed Kamruzzaman, Assistant Registrar (Medicine), Kurmitola General Hospital, Dhaka.
8. Dr. Md. Aminul Alam, Indoor Medical Officer, Department of Physical Medicine and Rehabilitation, Dhaka Medical College Hospital, Dhaka.

*For correspondence

INTRODUCTION

Thoracic spine pain (TSP) is considered to be pain perceived anywhere in the region bounded superiorly by a transverse line through the tip of the spinous process of T1, inferiorly by a transverse line through the tip of the spinous process of T12, and laterally by vertical lines tangential to the most lateral margins of the erector spine muscles[1]. TSP may arise from thoracic and cervical spinal structures, thorax, gastrointestinal, cardiopulmonary and renal systems.[1,2,3] Thoracic spine is a common site for inflammatory, degenerative, metabolic, infective, neoplastic, osteoporosis, vertebral fractures,[4-7] hyperkyphosis, ankylosing spondylitis, osteoarthritis and Scheuermann' sdisease.[8-11] However, TSP is common in different countries of the world in different settings. One meta-analysis (52 studies describing65 cohorts and out of this 11 cohorts from Asia) showed that one year prevalence of TSP ranged from 3.0-55.0%, with most occupational groups having medians around 30%.[12] One year prevalence of TSP among physicians is 29% in China[13], among female hospital nurses 8.3% in Taiwan[14] and 37% in China,[15] among male rubber factory workers 38.1% in Iran[16]. TSP is common in youth and has an increasing incidence with age during adolescence.[17,18] One study[17] reported that back pain in children is most common in the middle back area, whereas in adolescence middle back pain and low back pain are equally common.

Spinal pain is a common condition associated with significant personal and community burdens. Very few research work was done on thoracic spine in comparison to lumbar and cervical spine.[19] TSP is equally disabling, imposing similar burdens on the individual, community and workforce.[12,19-21] Societal cost of spinal pain is about 1% of gross national product per annum.[22] An advanced google search has been made using key words prevalence of thoracic spine pain, upper back pain in Bangladesh and no specific data is found in any article or abstract. So detailed knowledge about the demographic profile and pattern of TSP is very important for proper management including rehabilitation.

MATERIAL AND METHODS

This Longitudinal Observational Study was carried out in the department of Physical Medicine & Rehabilitation of Shaheed Suhrawardy Medical College Hospital (ShSMCH) during July 2015 to December 2015. Patients presented with thoracic spine pain (TSP) were recruited in this study. History taking, physical examination and baseline investigations were done for every consecutive patient to reach a diagnosis. All cases were checked for eligibility criteria (inclusion & exclusion criteria) and those found eligible were approached for informed consent by the investigator.

Inclusion criteria:

a) Patients with thoracic spine pain of any duration.
b) Age group 16-75 years.

Exclusion criteria:

a) Patients with co-morbidities like IHD, COPD, bronchial asthma, pneumonia, CLD, renal failure.
b) Patients of remote area who will not be able to come for follow up visit.

One hundred ten (110) cases were enrolled for the study from ShSMCH, among them 95 cases from outpatient and 15 cases from inpatient department. The pre-designed semi-structured questionnaire was used for all cases. A face to face interview with the cases were carried out for filling up the questionnaire. The minimum time to take an interview was one (1) hour. Then they were given conventional treatment according to their diagnosis. Treatment modalities include rest for acute and traumatic pain. NSAID-local & systemic and other drugs like muscle relaxant, anti-depressant, calcium supplementation, vitamin D, bisphosphonates, anti-TB drugs according to cause of pain. Physical therapy-superficial heat, deep heat like SWD, MWD. Upper back pain rehabilitation exercises like pectoralis stretch, thoracic stretch, thoracic extension, arm slides on wall, scapular squeezes, mid-trap, rowing-all these exercises done 2-3 sets of 10 daily. Besides spinal mobilization, exercises for scoliosis, aerobic exercises were given. Spinal bracing was also given when indicated. General measures like postural correction, avoid carrying heavy loads, weight reduction, dietary modification, stop smoking/alcohol were advised. Patients were evaluated clinically and by standardized assessment tools at enrolment and followed up at 7 days interval for one visit, two weekly for three visits (total four visits). Assessments were included baseline demographics, clinical findings and disabilities. The tools used for measurement of pain intensity, tenderness and disability were Numeric Rating Scale (NRS-11).[23] Assessment of tenderness,[24] Pain Disability Index

(PDI)[25]. Information obtained from history, physical examination and assessment tools were recorded in patients' data sheet.

Collected data was sorted and screened for any discrepancy and edited for finalized result. After editing and coding, the coded data were analyzed by SPSS®16. Results on continuous measurements were presented on mean ± SD (min-max) and results on categorical measurements were presented in number (%). Descriptive statistical analysis was done where P- value (<0.05) was considered as significant. Student 't' test was done to see the level of significance.

OPERATIONAL DEFINITIONS:

Acute, sub-acute and chronic TSP: Acute TSP present for up to six weeks. Sub-acute TSP present with duration of greater than six weeks after injury but no longer than 12 weeks after onset of symptoms. Chronic TSP present for more than 12 weeks.[26]

Myofascial pain syndrome (MFPS): MFPS is a form of myalgia that is characterized by local regions of muscle hardness that are tender and that cause pain to be felt at a distance, i.e., referred pain. The central component of the syndrome is the trigger point that is composed of a tender, taut band[27].Patients with MFPS often report regional, persistent pain that usually results in a decreased range of motion of the muscle in question.[28] So according to operational definition of TSP, trigger points situated in the inter-scapular area were included in the study.

Occupational TSP: Occupational thoracic spine pain can be defined as pain experienced in the region of upper back or middle back from repetitive movement or prolong bad posture during various occupation.[29,30]

RESULTS

Of the 110 subjects enrolled in the study, 3 subjects lost at 3rd follow up visit and 7 subjects were lost at 4th follow-up visit. Finally 100 patients evaluated and analyzed according to objectives. The findings are presented through tables, graphs and organized as below:

Table-I shows that the Mean SD age among the patients was 34.76±13.26. Highest 45% patients belong to 16-30 years age group. Rest 35%, 18% and 2% were belonged to 31-45, 46-60 and 61-75 years age group respectively. The study shows 60% patients were male and 40% were female with M:F = 1.5:1.

Table-I Age distribution

Age group			
Age group	Frequency	Percent (%)	Mean SD
16-30 years	45	45	34.76±13.26
31-45 years	35	35	
46-60 years	18	18	
61-75 years	2	2	
Total	100	100	

Table-II shows that among the study patients highest frequency 28% belonged to higher secondary or diploma level. Primary 27%, secondary 25%, illiterate17%and graduate or more were 3% respectively.

Table-II Distribution of educational level

	Educational level	
Education	Frequency	Percent (%)
Illiterate	17	17
Primary	27	27
Secondary	25	25
Higher Secondary or diploma	28	28
Graduate or more	3	3
Total	100	100

Table-III shows that maximum 26% patients were house-wife. Among the rests manual labor 20%, students 19%, sedentary worker 15%, manufacturing and industrial worker 8%, health professional 4%, driver 3% and 5% were in others group.

Table-III Distribution of occupation

	Occupation	
Occupation	Frequency	Percent (%)
Housewife	26	26
Manual labor	20	20
Student	19	19
Sedentary worker	15	15
Manufacturing and industrial worker	8	8
Health professional	4	4
Driver	3	3
Others	5	5
Total	100	100

Among the patients 86.0% were married and 14.0% were unmarried. Ninety one percent (91%) patient's residences were in urban area and 9% were from rural area.

Table-IV shows that most of the patients (71.0%) belong to <12000-taka monthly income group. Others 19.0% were 12001-25000, 6.0% were 25001-40000 and 4.0% were above 40,000 taka monthly income group.

Table-IV Monthly income status of the population

	Monthly Income	
Monthly Income	Frequency	Percent (%)
<12000	71	71
12001-25000	19	19
25001-40000	6	6
Above 40000	4	4
Total	100	100

Table-V shows that among the patients the mean duration of thoracic spine pain was 1.80±0.889. Acute TSP was found 46%, sub-acute 16% and chronic in 38% patients.

Table-V Distribution of TSP duration

	Thoracic spine pain duration		
TSP Duration	Frequency	Percent (%)	Mean±SD
Acute (6 weeks)	46	46	1.80±0.889
Sub-acute (>6-12 weeks	16	16	
Chronic (>12 weeks)	38	38	
Total	100	100	

Table-VI shows that most of the patient's site of pain were (51%) upper TSP. Among the others right sided TSP 18%, left sided TSP 17%, widespread TSP 9% and lower TSP 5% respectively.

Table-VI Distribution of site of pain

	Site of pain	
Site of Pain	Frequency	Percent (%)
Upper TSP	51	51
Lower TSP	5	5
Right sided TSP	18	18
Left sided TSP	17	17
Widespread TSP	9	9
Total	100	100

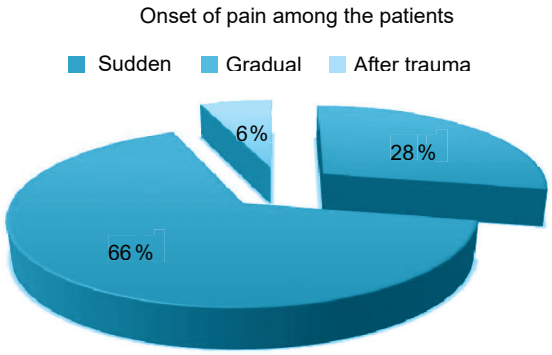

Figure-1 Onset of pain distribution

Figure-1. shows onset of pain among the patients 66% were gradual. Sudden and after trauma onset pain were 28% and 6% respectively.

Table-VII shows character of pain according to chronicity among the patients 52% were constant, intermittent 27%, recurrent 20% and episodic1% respectively.

Table-VII

Distribution of character of pain according to chronicity.

Character of pain according to chronicity		
Character of Pain	Frequency	Percent (%)
Constant	52	52
Intermittent	27	27
Recurrent	20	20
Episodic	1	1
Total	100	100

Table-VIII shows nature of pain among the patients 57% was dull, burning 27% and stabbing16% respectively.

Table-VIII Distribution of nature of pain.

Nature of Pain		
Character of Pain	Frequency	Percent (%)
Dull	57	57
Burning	27	27
Stabbing	16	16
Shooting	0	0
Total	100	100

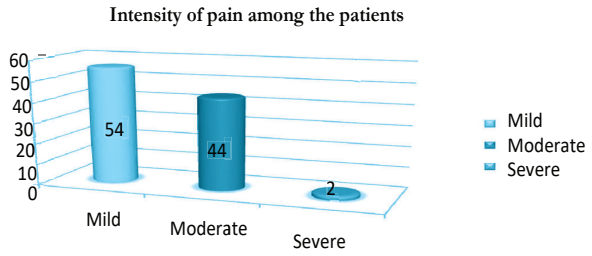

Figure-2 Distribution of intensity of pain

Figure-2 shows intensity of pain among the patients were mild 54%, moderate 44% and severe 2% respectively.

Table-IX shows 64% had no radiation. Radiation of pain on neck had 4%, low back region 18% and shoulder 14% respectively.

Table-IX Distribution of radiation of pain

Radiation of pain		
Radiation of pain	Frequency	Percent (%)
Neck	4	4
Low back region	18	18
Shoulder	14	14
None	64	64
Total	100	100

Table-X shows aggravating factors among the patients 42% were prolong sitting, 15% and 30% were prolong walking and leaning forward. Only 2% patients aggravating factors were empty stomach and rich diet each. Nine percent (9%) patients had no aggravating factor.

Table-X Distribution of aggravating factors

Aggravating Factor		
Aggravating Factor	Frequency	Percent (%)
Prolong sitting	42	42
Prolong walking	15	15
Leaning forward	30	30
Empty stomach	2	2
Rich diet	2	2
None	9	9
Total	100	100

The table-XI shows that 36% patients relieving factor were lying, 24% rest, activity 16% and no relieving factor for 24% patients.

Table-XI Distribution of relieving factors

Relieving Factor		
Relieving Factor	Frequency	Percent (%)
Rest	24	24
Lying	36	36
Activity	16	16
None	24	24
Total	100	100

Table-XII shows associated condition among the patients 42% had no associated condition. DM 25%, sleep disturbance16%, dyspepsia10% and HTN were in 7% patients respectively. This study also shows 20% patient had morning stiffness and 25% had depression among all patients respectively.

Table-XII Distribution of associated condition

Associated Condition		
Associated Condition	Frequency	Percent (%)
Sleep disturbance	16	16
DM	25	25
HTN	7	7
Dyspepsia	10	10
None	42	42
Total	100	100

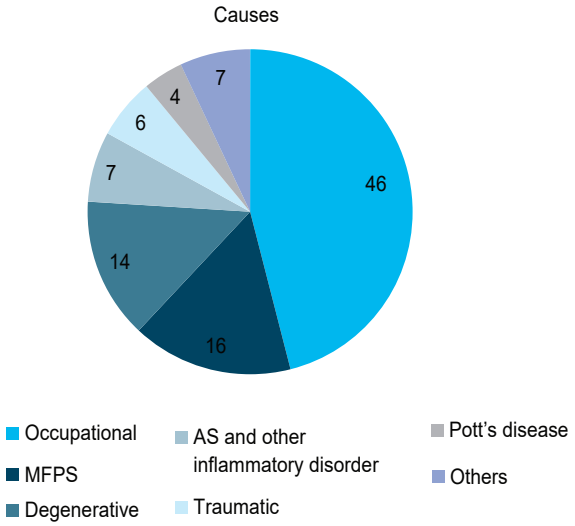

Figure-3 Distribution of causes of TSP

Figure-3 shows most of the patients' cause was occupational 46%. Rest of the causes were MFPS 16%, degenerative 14% (dorsal spondylosis 5%, cervical spondylosis 6% and lumbar spondylosis 3%), Ankylosing Spondylitis (AS) and other inflammatory disorder 7% and Traumatic were 6%. Pott's disease 4% and 7% patients' causes were others. Among others group, Dyspepsia were 3%, Kyphoscoliosis 1%, Kyphosis 1%, Odynophagia 1% and Osteoporotic fracture 1% respectively.

Table-XIII according to Numeric Rating Scale (0-10) at enrollment 54% patients were mild, 44% moderate and 2% severe. In the last visit (week-7) it was found that 69% patients were mild and rest 31% had no pain. This status was statistically significant (p=0.001).

Table-XIII TSP according to Numeric Rating Scale (0-10)

Numeric Rating Scale (0-10)			
Numeric Rating Scale	Frequency (%)		P value
	First Visit Day-1	Last Visit Week-7	
No Pain (0)	0 (0%)	31(31%)	0.001
Mild (1-3)	54(54%)	69(69%)	
Moderate (4-6)	44(44%)	0(0%)	
Severe (7-10)	2(2%)	0(0%)	
Total	100 (100%)	100(100%)	

According to Assessment of Joint Tenderness Table-XIV shows at enrollment 56% patients were in grade 1, 20% grade 2 and 3% in grade 3, 21% patients had no tenderness. In the last visit (week-7) it was found that only 21% patients in grade 1 and rest 79% had no tenderness. This status was statistically significant (p=0.001).

Table-XIV TSP according to Assessment of Tenderness

Assessment of Tenderness			
Assessment of Tenderness	Frequency (%)		P value
	First Visit Day-1	Last Visit Week-7	
No tenderness	21 (21%)	79(79%)	0.001
Grade 1	56(56%)	21(21%)	
Grade 2	20(20%)	0(0%)	
Grade 3	3(3%)	0(0%)	
Grade 4	0(0%)	0(0%)	
Total	100 (100%)	100(100%)	

Table-XV shows mild disability were found in 67% patients, moderate 31% and 2% had no disability. In the last visit (week-7) mild were 74% and 26% had no disability according to Pain Disability Index at enrollment. This status was statistically significant (p=0.001).

Table-XV TSP according to Pain Disability Index

Pain Disability Index			
Pain Disability Index	Frequency (%)		P value
	First Visit Day-1	Last Visit Week-7	
No disability (0)	2(2%)	26(26%)	0.001
Mild (1-28)	67(67%)	74(74%)	
Moderate (29-49)	31(31%)	0(0%)	
Severe (50-70)	0(0%)	0(0%)	
Total	100(100%)	100(100%)	

DISCUSSION

This study was conducted in a tertiary care hospital in Dhaka city. One hundred (n=100) patients with thoracic spine pain (TSP) attending in the Department of Physical Medicine and Rehabilitation (PMR) of Shaheed Suhrawardy Medical College Hospital (ShSMCH) were selected for the study during a period of six months from July 2015 to December 2015.

The demographic characteristic of study people found Mean±SD age among the patients was 34.76±13.26. Most of the patients 45% belong to 16-30 years age group. Rest 35%, 18% and 2% were belong to 31-45, 46-60 and 61-75 years age group respectively. One study[31] reported mean age was 47.1 (±20.2) years among 300 patients age ranged from13 years to 78 years (range 65 years). Age composition of their study population showed that 30% of patients were more than 60 years and 65% of patients were in the age-group of 40- 60 years. Only 5% of patients belonged to less than 40 years group.

In the current study among 100 patients 60% were male and 40% were female. Male and female ratio was 1.5:1. A study[32] showed male 71.09% and 28.9% were female patients.

Among the study patients highest frequency 28% belonged to higher secondary or diploma level. Primary 27%, secondary 25%, illiterate 17% and graduate or more were 3% respectively. One study[31] showed the educational level of the patients (expressed in terms of

number of completed years of formal institutional education) ranged from 0 (illiterate) to 17 years the mean being 8.3 (±5.1) years.

In current study most of the patients (26%) were housewife. Among the rests manual labor 20%, students 19%, sedentary worker 15%, manufacturing and industrial worker 8%, health professional 4%, driver 3% and 5% were in others group. In others group there were players, military personnel, performing artists and others occupation excepting the listed occupation in the study. Almost half of the male patients were agriculture worker by profession while more than two-third of the female patients were household worker found in a study[31].

Most of the patients 86% were married and 14% were unmarried found in our study. Highest 71% patients belong to <12000 taka monthly income group. Others 19% were 12001-25000, 6% were 25001-40000 and 4% were above 40000 taka monthly income group. In a study[31], per capita monthly income of the patients ranged from Rs.2000 to Rs.7200, the mean being Rs.6610 (±2842.8%) and the median being Rs.6000.

Among the studied patients 91% residences were in urban area and 9% were from rural area. One study[31] showed patients coming from urban areas were 61% whereas 39% patients belonged to rural areas.

Among the patients the mean duration of thoracic spine pain was 1.80±0.889. Acute TSP was found 46%, sub-acute 16% and chronic in 38% patients. One study[33] found eight patients with an acute presentation (3.8%) included 4 men and 4 women with a mean age of 53 years (range 38-76 years), whereas 201 patients without an acute presentation included 82 men and 119 women with a mean age of49.2 years (range 23-83 years).

Most of the patient's site of pain were (51%) upper TSP. Among the others rights sided TSP 18%, left sided TSP 17%, widespread TSP 9% and lower TSP 5% respectively. One article reported some causes of right upper back pain and left upper back pain[34] but these causes are not included in the current study. Onset of pain among the patients 66% was gradual. Sudden and after trauma onset pain were 28% and 6% respectively. Character of pain according to chronicity among the patients 52% were constant, intermittent 27%, recurrent 20% and episodic 1% respectively. Fifty seven percent (57%) patients' nature of pain was dull, 27% burning and stabbing 16%. According to history of patient mild intensity of pain among the patients was 54%, moderate 44% and severe 2%. No radiation was found in 64% patients. Radiation of pain on neck had 4%, low back region 18% and shoulder 14%.Aggravating factors like prolong sitting were 42%, prolong walking 15% and 30% were leaning forward. Only 2% patients aggravating factors were empty stomach and rich diet. Nine percent (9%) patients had no aggravating factors. Thirty six percent (36%) patients' relieving factor were lying, 24% rest, activity 16% and no relieving factors were found in 24% patients. Morning stiffness and depression was found 20% and 25% patients respectively.

Most of the patients (42%) had no associated condition. Among the others DM 25%, sleep disturbance 16%, dyspepsia 10% and HTN were in 7% patients respectively. One study[35] found hypertension 30%, diabetes 24.7% and rheumatoid arthritis 13.3%, the three most commonly associated disease conditions.

Most of the patients' cause was occupational 46%. One meta-analysis[12] showed one year prevalence of TSP ranged from 3.0-55.0%, with most occupational groups having medians around 30% which did not differ much with this study. This implies that occupational TSP is prevalent in both developed and developing countries.

Second most common cause was MFPS 16%. One study[36] reported 0.45% prevalence of MFPS in the rural community of Bangladesh. The difference may be due to the sample taken in the current study is not representative of the rural community as 91% patients' residences were in urban area.

In the present study degenerative causes were 14% (dorsal spondylosis 5%, cervical spondylosis 6% and lumbar spondylosis 3%). One study[37] reported the prevalence of disc degeneration (DD) over the entire spine was 71% in men and 77% in women aged <50 years and >90% in both men and women aged >50 years. The prevalence of an intervertebral space with DD was highest at C5/6 (men 51.5%, women 46%), T6/7 (men 32.4%, women 37.7%) and L4/5 (men 69.1%, women 75.8%)[37]. The high prevalence possibly due to sample taken from the population irrespective of symptoms and definite spinal pathology on MRI in the thoracic spine in asymptomatic individuals is also prevalent[38].

The current study showed the prevalence of Ankylosing Spondylitis (AS) and other inflammatory disorder was 7%. Another study[39] reported11.03% were inflammatory

arthritis and out of this AS was 28.89%, studied in the department of Physical Medicine & Rehabilitation, Chittagong Medical College Hospital (CMCH), Bangladesh. Globally the mean prevalence[40] of AS per 10,000 in Asia was 16.7, in Europe 23.8, in North America 31.9, in Latin America 10.2 and 7.4 in Africa.

This study showed traumatic cause was 6% and Pott's disease 4%. One retrospective cross-sectional study of the spinal injury patients in the Spine Unit of Bangabandhu Sheikh Mujib Medical University (BSMMU) Hospital reported that traumatic spinal injury affected the thoracic spine in 13.54%, thoraco-lumbar 06.25% and cervico-thoracic region 03.13% cases[35]. Majority of the tuberculous spondylitis involved the thoracic spine (30.3%)[41].

Among others group (7%), Dyspepsia were 3%, Kyphoscoliosis 1%, Kyphosis 1%, Odynophagia 1% and Osteoporotic fracture 1% respectively. One study[39] reported the prevalence of osteoporosis about 1.63% in CMCH, Bangladesh. Approximately 25% of all postmenopausal women in the USA get a compression fracture during their lifetime. The prevalence of this condition increases with age, reaching 40% by age 80[42].There is no widely-accepted definition of hyperkyphosis, and therefore the prevalence of hyperkyphosis in older persons is not precisely known. However, the current estimates range between 20 and 40 percent among community-dwelling individuals aged ≥60 years[43].

According to Numeric Rating Scale (0-10) in the first visit 54% patients were mild, 44% moderate and 2% severe. Three percent (3%) patients had no pain. In the last visit it was found that 69% patients were mild and rest had no pain. One study[30] showed that the baseline pain score mean (SD) was 5.6(2.0) and in the last visit3.4(2.4) indicating moderate intensity in both settings according to Visual Analogue Scale (VAS). Both of the studies show significant improvement in pain intensity ($p<0.05$).

Assessment of Joint Tenderness in first visit 56% patients were in grade 1, 20% grade 2 and 3% in grade 3, 21% patients had no tenderness. In the last visit it was found that only 21% patients in grade 1 and rest 79% had no tenderness. These results show significant improvement in joint tenderness ($p=0.001$).

In the first visit rating of Pain Disability Index were found mild 67%, moderate 31% and 2% had no disability. In the last visit mild were 74% and 26% had no disability. Baseline disability score mean (SD) was 28.5(10.4) indicating moderate disability and in the last visit 17.8(15.2) indicating mild disability according to Oswestry Disability Index (0-100 ODI) modified for thoracic spine pain. Both the study results show significant improvement in their disability ($p<0.05$) found in a article[30].

CONCLUSIONS

This study revealed that maximum 45% patients belonged to 16-30 years age group and mean±SD age was 34.76±13.26. Teenager, young adults and adults were the most commonly affected patients with M:F=1.5:1. Most of the patient of upper TSP presented before 6 weeks; common presenting features were gradual onset, constant, mild to moderate, without radiation, aggravated by prolong sitting and leaning forward, relieved by lying and rest. Frequent associated conditions were none, dyspepsia, DM with no depression and significant morning stiffness. Common causes were occupational and MFPS. Most of the patients were married, completed primary and secondary level of education, monthly income <12000 taka and inhabitants of urban area. Occupations were commonly housewife and manual labor. Patients' pain, tenderness and disability were mild at enrollment and significantly improved ($p=0.001$) after seven weeks of conventional treatment in most of the cases.

RECOMMENDATION

Further multicenter descriptive and analytical studies with larger sample size that may be representative of total population are warranted to establish the clinical pattern of thoracic spine pain.

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Review Article

Skeletal and Extra-Ekeletal Effects of Vitamin D Deficiency in Children

*Begum S[1], Biswash DC[2]

Abstract

Vitamin D is essential for the maintenance of calcium and phosphorus homeostasis. It has skeletal growth and extra-skeletal effects in our body. Objective of this article is to update the information on skeletal and extra-skeletal effects of vitamin D deficiency in paediatric clinical disorders. In the paediatric population, vitamin D deficiency is associated with different clinical diseases such as rickets, insulin resistance, metabolic syndrome, respiratory tract infections, asthma, and autoimmune diseases. It is associated with prematurity, obesity, malabsorption, anticonvulsant agents, extreme latitudes, low consumption, and little sun exposure. The recommendation is to prevent vitamin D deficiency and to maintain 25(OH) D serum levels >30ng/mL (>75 nmol/L).

Keywords: *Vitamin D, Vitamin-D deficiency, Extra-skeletal manifestation.*

INTRODUCTION

Vitamin D (VD) is a pro-hormone that is essential for absorption of calcium and phosphorus. Vitamin D deficiency (VDD) is associated with rickets in growing children and osteomalacia in adolescent. VD has role in skeletal health, apart from this it causes inhibition of cellular proliferation, angiogenesis and renin production, stimulating insulin production, and macrophage cathelicidin production.[1] There is high prevalence of VDD among children which is about 85% to 98%.[2]

CLASSIFICATION OF VITAMIN D DEFICIENCY

Optimum level of 25(OH) D is >30ng/ml (>75nmol/L) and hypercalcaemia is associated if the level is >150ng/mL (> 374nmol/L).[3]

Table I: Classification of VDD [3]

Vitamin D status	ng/mL	nmol/L
Severe deficient	<5	<12.5
Deficient	<20	<50
Insufficient	20-30	50-75
Sufficient	>30	>75
Risk of Toxicity	100	250
Intoxication	>150	>374

Table II: Etiology of vitamin D Deficiency[4]

Decreased VD synthesis	Skin pigmentation, physical agents blocking ultraviolet ray exposure, clothing, latitude, season, air pollution, cloud cover, altitude, sedentary lifestyle and winter season
Decreased intake of VD	Strict vegetarian, high phytates diet
Age and physiology related	Prematurity, elderly, obese
Decreased maternal VD stores	Exclusive breast feeding
Mal-absorption	Celiac disease, pancreatic insufficiency, biliary obstruction
Decreased synthesis	Chronic liver disease
Increased degradation of 25 (OH) D	Drugs: rifampicin, isoniazid, anticonvulsants, glucocorticoids.

1. *Prof. Dr. Suraiya Begum, Professor and Chairman, Department of Paediatrics, Head of the Paediatric Endocrinology Division, Bangabandhu Sheikh Mujib Medical University (BSMMU), E-mail: suraiyadr07@yahoo.com, Phone: 01715131535
2. Dr. Dhiraj Chandra Biswash, Assistant Registrar, 300 bed hospital, Kanpur, Narayanganj

*For Correcpondence

VD levels are low in breast milk which is 22IU/L (15 -80IU/L) in vitamin D sufficient mother.[5] VDD is associated with cardiovascular disease, hypertension, autoimmune diseases, and cancer.[6,7,8,9] The reasons of VDD in this subcontinent could be low dietary VD intake, high fiber and phytate intake, reduced exposure of skin to sun light because of cultural and traditional habits or pollution.[10,11,12] Individuals with darker skin require a

longer time in the sunlight than those with lighter skin to produce the same amount of VD.[13] Sunscreens reduces the ability of the skin to produce vitamin D by over 95% to 98%.[14] Vitamin contents of food vary depending on cooking methods, fried fish loses 50% of VD.[4]

VD has effect related to: 1) Nuclear and cytosolic characteristics of VD receptor (VDR) and the enzyme that metabolizes VD in multiple tissues e.g., adipose tissue, muscle, and pancreas. 2) Regulation of more than 200 genes. 3) The risk associated with VDD, and the presence of multiple diseases.[15,16,17] Over 30 different types of tissues have been identified as having cells with a VDR.[18] Neonate has 60--70% of maternal VD levels. In case of maternal deficiency, the neonate's low reserves of VD can cause hypo-calcemic symptoms in the first six months of infant.[19]

In countries where foods are not fortified, available option is to intake of fatty fish, which provides 5-13μg of VD/three ounces of fish, egg yolk contains 0.5 μg of VD and three ounces of beef liver contains 0.3μg of VD. It would be difficult to obtain the necessary 25μg of VD through these sources.[20] When fortified foods are not available and exposure to sunlight is limited, supplementation is the only measure for attaining adequate VD status.[21]

MANIFESTATIONS OF VITAMIN D DEFICIENCY

Musculo-skeletal manifestation: VDD is associated with nutritional rickets and osteomalacia which is characterized by bone deformations, hypocalcemic seizures, tetany, severe bone pain, muscle weakness and short stature.[22] At infancy and adolescent there are increased growth velocity, the increased demand for calcium, and the children may present with hypocalcemia even before radiologic signs of rickets are observed.[23] Severe vitamin VDD is associated with cardiomyopathy related to hypocalcemia.[24]

Obesity: VD sequestration occurs in adipose tissue because of its lipid-soluble nature.[25] The active form of VD regulates gene transcription in adipogenesis, inflammation, and insulin resistance in the adipose tissue.[26] In muscle and pancreas, 1,25(OH)2D may improve insulin sensitivity, controlling insulin secretion in pancreatic beta cells and increasing insulin receptor expression in peripheral tissues.[4] Higher circulating 25(OH)D3 level was associated with low body fat, and lower number of metabolic disturbances.[27]

Insulin Resistance: There is reverse association between vitamin D and insulin resistance and VD supplementation reduces the risk for type 1 diabetes.[28]

Metabolic syndrome: Low VD levels in adolescents were strongly associated with metabolic syndrome, regardless of adiposity.[29] There is reduction in low density lipoproteins cholesterol (LDL-C) following VD supplementation.[30] There is increased risk of hypertension with VDD.[31]

Intestinal malabsorption syndromes: VDD in malabsorption syndromes due to reduced absorption of lipid soluble vitamins, and hyperparathyroidism secondary to hypocalcemia. This leads to a greater 25(OH) D conversion into 1,25 (OH)2D and lower 25(OH)D levels.[32] The prevalence of VDD in Cystic fibrosis is 95%.[33]

Anticonvulsant agents: Prevalence of VDD is 50% in children with epilepsy receiving anticonvulsant agents such as phenytoin, phenobarbital, and carbamazepine. These drugs inducing the activity of cytochrome- P450-hydroxylase enzymes, thus leading to an accelerated VD catabolism.[34]

Respiratory tract infections: There is increased risk for wheezing in children of women who had VDD during pregnancy.[35] Cord blood VDD is associated with respiratory syncytial virus bronchiolitis.[36] VD reduces the risk for influenza and achieve an adequate vaccine response because it activates T cells.[37] There is an association between VDD and asthma severity and significant reduction of asthma exacerbation with VD supplementation.[38]

Cardiovascular diseases: Low VD are associated with secondary elevation of parathyroid hormone, increased arterial resistance, and endothelial dysfunction leading to hypertension.[39] VD acts as a cardiovascular and renal protective factor by suppressing the renin-angiotensin-aldosterone system, which inhibits vascular calcification and plaque formation, and has anti-inflammatory and immunomodulatory actions.[40]

Diabetes mellitus: VD supplementation was associated with significant reduction in the progression of diabetes and higher reversal to normoglycemia. It acts on

pancreatic β-cells by binding VDR to produce insulin synthesis and on the muscle and fat cells to reduce insulin resistance.[41]

Muscle Strength: VDD causes muscle weakness and repeated fall. Infants and children with severe VDD and rickets may present with delayed motor development, muscle hypotonia, and weakness.[42]

Immune Effects: VD binds to VDR on various cells and modulate activation and deactivation of the innate and adaptive responses. VD modulates B-lymphocyte and T-lymphocyte function.[43] VDD is associated with autoimmune diseases such as type 1 diabetes and multiple sclerosis.[44,45] Protective effects of VD supplementation have been demonstrated against rheumatoid arthritis and inflammatory bowel disease.[46,47] VD supplementation showed a positive impact on autoimmunity by significantly reducing the fall in thyroid peroxidase antibody in autoimmune thyroiditis.[48]

Infectious Disorders: VD supplementation modulates T-cell function in human immunodeficiency virus (HIV) infected patients, and a useful adjunct to antiretroviral therapy.[49] VDD was associated with increased susceptibility of sepsis.[50] Systematic review was indicated that low vitamin D status might be associated with an increased risk of COVID-19 infection.[51]

Cancer: The biologically active form of VD can modulate gene expression, inhibit the cellular proliferation, induction of differentiation, and apoptosis ultimately inhibiting the cell growth of cancer. An increased incidence of VDD was observed in children suffering from cancer as compared to the control.[52] VD supplementations reduced total cancer mortality.[53]

Sleep and Pain: VD plays an important role in sleep and pain. Supplementation of VD with chronic pain improved the pain score, sleep latency, sleep duration and body pain.[54]

Skin: Keratinocytes express the VDR, and when these cells are exposed to VD, their growth is inhibited and they are stimulated to differentiate. This has led to the use of topical VD analog to treat psoriasis.[55]

Psychiatric Conditions: VDD has been linked to an increased incidence of schizophrenia, bipolar disorder and depression.[56,57] Maintaining VD sufficiency in utero and during early life is important for VD receptor transcriptional activity in the brain, brain development and maintenance of mental function later in life.[58]

Other effects: In VDD, menarche is started 9 months earlier.[59] It was found that the BMI, body fat, and testosterone were higher in polycystic ovarian syndrome with VDD. VD supplementation has provided improvement of hyperinsulinism, fertility and hyperandrogenism in PCOS.[60]

Table III: Screening of vitamin D deficiency [3]

i.	Dark skinned infants who live at higher altitude and infants born to VDD mothers
ii.	Nonspecific symptoms like poor growth, gross motor developmental delay
iii.	Suspected rickets, osteoporosis
iv.	Chronic kidney disease
v.	Hepatic failure
vi.	Malabsorption syndromes: Cystic fibrosis, Inflammatory bowel disease
vii.	Hyperparathyroidism
viii.	Medications: Anticonvulsants, Glucocorticoids, AIDS medications, Ketoconazole
ix.	Obese children and adults
x.	Granuloma forming disorders: Sarcoidosis, Tuberculosis, Histoplasmosis
xi.	Children with non-traumatic fall

TREATMENT

As per the Endocrine Society Clinical Practice Guideline, infants require 400IU/d, children ≥1 year require 600IU/d, adults between 19–70 years require 600IU/d, and elders ≥70 years of age require at least 800IU/d of VD to maximize bone health and muscle function.[4]

VD therapy is necessary for infants and children who manifest clinical features of hypocalcemia due to VDD or rickets and when VD levels are in the deficient range even if asymptomatic. [4]

Table IV: Prevention and treatment of VDD Indian Academy of Pediatrics guideline.[61]

Age	Prevention	Treatment	Treatment with large dose (oral route preferred)
Premature baby	400IU/day	1000IU/day	NA
Neonates	400IU/day	2000IU/day	NA
1-12 months	400IU/day	2000IU/day	60,000IU weekly (> 3 months of age)
1-18 years	600IU/Day	3000-6000 IU/day	60000IU weekly
At risk groups	400-1000IU/day	As per age group	As per age group

Treatment should be continued for a minimum of 3 months, after that daily maintenance doses to be given.

Table V: Recommendations for VD supplementation in different diseases in the pediatric age group

Diseases	Recommendation
Obesity	1200-2000IU/day[62]
Insulin resistance	4000IU/day for 6 months to obese children and adolescents with VDD[63]
Type 1 diabetes	2000IU/day[64]
Cystic fibrosis	Children <1 year old: 400-800IU/day; if VDD: 800IU to 2000IU/day Children 1-10 years old: 800-1000IU/day; if VDD up to 4000IU/day[65]
Celiac disease	400-600IU/day[66]
Asthma	500-1200IU/day[67]
Neurological diseases	800-1000IU/day[68]

Lactating women given 4000IU of vitamin D3 per day were able to transfer enough vitamin D3 into their milk to satisfy an infant's requirement.[69]

The following recommendations have been made to prevent VDD in the pediatric population:[70]

- Adequate sun exposure to the face, hands or legs (at least 3 times a week for 15 minutes).In extreme latitudes and during the winter, ensure an adequate consumption of food sources.
- For infants, administer VD3 at 400 IU/day until 1 year old –due to the low VD content in breast milk.
- Prevent overweight and obesity.
- Assess VD status who are at risk for deficiency and administer according to recommendations.

Calcium supplementation: In VDD, 50-75mg/kg calcium supplementation are important for avoiding subsequent hypocalcaemia from an increase bone mineralization as PTH levels normalize due to hungry bone syndrome. The maximal dose of elemental calcium that should be taken at a time is 500mg.[71]

CONCLUSIONS

VDD is associated with different clinical diseases such as bone alterations, insulin resistance, metabolic syndrome, respiratory tract infections, asthma, and autoimmune diseases. It is associated with prematurity, obesity, malabsorption, use of anticonvulsant agents, and lifestyle characteristics, such as clothing, extreme latitudes, low consumption, and little sun exposure. Inadequate vitamin D levels may be responsible for the progression of cardiovascular disorders, diabetes mellitus, autoimmune disorders, sleep disturbance and pain to a considerable extent. Therefore, awareness is needed to combat the increasing prevalence of VDD through all age groups. Screening and treatment strategies are required for VDD. Adequate intake of VD through supplementation is essential for daily requirement as VDD has impact on various comorbidities.

Undiagnosed VDD is not uncommon. It is very difficult to obtain that much vitamin D3 on a daily basis from dietary sources. Thus, sensible sun exposure and the use of supplements are needed to fulfill the body's VD requirement.

CONFLICT OF INTEREST: The authors declare that there is no conflict of interest.

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Review Article

Children and COVID-19 Vaccine: A Public Health Ethics Perspective

*Nurunnabi ASM[1], Ashique SS[2], Jahan A[3], Sweety AA[4], Sharmin S[5]

Abstract

As COVID-19 cases were in rise all over the world and the World Health Organization declared a pandemic, there was an increasing focus on availability of new vaccines and drugs against the virus. Meanwhile, we already have several vaccines in COVID-19 vaccination programmes across the globe. During the process of development and clinical trials of the vaccines, several questions were popped up by multiple stakeholders about child vaccination against COVID-19. Most of the queries focused on safety of COVID-19 vaccines, the clinical trial process, priority criteria of getting a vaccine, why and why not children be included in the vaccination programme. In adult population of the country, COVID-19 vaccination programme is being carried out in an unequalled state; the focus is now on paeditric population, as some countries have already started to vaccinate children. At the time of writing this paper when Government of Bangladesh has not yet decided to vaccinate children in the country but initiatives has been taken by health department for above 12 years children vaccination. However, this paper aims to discuss potential ethical dilemmas related to COVID-19 vaccination in children especially in low-resource settings and dig into effective strategies to implement COVID-19 vaccination programme properly in the field of public health.

Keywords: *COVID-19 vaccine, children, clinical trial, ethical issues, public health*

1. *Dr. Abu Sadat Mohammad Nurunnabi, Graduate Student, Dalla Lana School of Public Health, University of Toronto, ON, Canada; Email: abu.nurunnabi@mail.utoronto.ca
2. Dr. Shamsi Sumaiya Ashique, Assistant Professor, Department of Paediatrics, National Center for Control of Rheumatic Fever & Heart Disease, Sher-E-Bangla Nagar, Dhaka-1207, Bangladesh
3. Lt. Col. (Dr.) Asmay Jahan, Associate Professor, Department of Paediatrics, Army Medical College Bogura, Bogura Cantonment, Bogura-5801, Bangladesh
4. Dr. Afroza Akbar Sweety, Assistant Professor, Department of Virology, Dhaka Medical College, Dhaka-1000, Bangladesh
5. Dr. Saida Sharmin, Associate Professor, Department of Community Medicine, International Medical College, Tongi, Gazipur-1711, Bangladesh

* For correspondence

INTRODUCTION

During the global coronavirus disease 2019 (COVID-19) pandemic, which has resulted in considerable illness and death around the world,[1] the incidence among adolescents between 12 and 17 years of age was very less in the beginning.[2,3] However, the rate of infected children and their absolute numbers seem to be increasing day by day.[4] Since illness was found generally milder in children than adults, children can have severe disease leading to hospitalization.[5,6] Approximately one third of adolescents hospitalized because of COVID-19 needed an intensive care unit (ICU) support; among them, mechanical ventilation was ensued to 4.9% cases.[6] Moreover, it is evident that long-term complications, such as multisystem inflammatory syndrome in children (MIS-C) may follow primary infection as occurred in many cases.[7,8] School-age children represent a high proportion of COVID-19 cases in recent times in many countries, and played an important role in the transmission of infection including spread of the highly transmissible variants.[9-12] Meanwhile, in Bangladesh, people of the country are experiencing the third COVID-19 wave, as fueled by the delta variant first detected in neighbouring country, India.[13] It has hit fast on the heels of a springtime second wave, and during a shortage in vaccine doses. In some of the low-income countries with low vaccination rates, e.g., Bangladesh, coronavirus cases are surging. As COVID-19 cases were in rise around the world, there was availability of new vaccines and drugs against the virus. Meanwhile, we have got several vaccines in our vaccination program against COVID-19 around the world and so many are still in the pipelines.[14] During the process of development and clinical trials of the vaccines, several questions were popped up by multiple stakeholders about child vaccination. Most of the queries focused on safety of COVID-19 vaccines, the clinical trial process, priority criteria of getting a vaccine, why and why not children be included in the vaccination. This paper aims to discuss potential ethical dilemmas related to COVID-19 vaccination in children especially in low-resource settings and dig into effective strategies to implement COVID-19 vaccination programme properly in the field of public health.

ETHICAL ISSUES

The very first issue came up is that the approval procedure for COVID-19 vaccine is quite different in comparison to any typical vaccine. Because of severity of this pandemic situation, the FDA adopted an Emergency Use Authorization (EUA) for this vaccine, which bypasses the standard protocol or steps to vaccine licensing and termed as "Biologics License Application (BLA) process". Interestingly, this rigorous process also requires "comprehensive data on the vaccine's safety and efficacy" but not as comprehensive as needed in the standard process; however, it is authorized after multiple review by the advisory committees.[15] Thus, BLA promotes trust and confidence among clinicians and public as well. However, EUA focuses on a reasonable balance between availability of a vaccine in a short time and vaccine's safety and effectivity.[15,16]

The second issue is that usually children do not take part in any clinical research until phase-3 trial, where a vaccine is tested for its efficacy and safety by administering it to thousands of people. Typically, this was done in adults COVID-19 vaccines, which are already approved and in the waitlist.[17] However, scientists demanded more compelling safety data of those vaccines before any paediatric trial.[17-20] As children are vulnerable and heterogeneous population, we hardly calculate paediatric doses by simply measuring body weight in all cases, and some drugs may affect children badly despite their proven safety in adult population. Hence, it is important to weigh the risks and benefits while designing any vaccine research in paediatric population.[20-24]

Nevertheless, in terms of public health measures, to ensure safety, control the spread of infection, and maximize benefit for overall population, children should be vaccinated. Hence, scientists argued in favour of gathering safety and efficacy related data of all ongoing COVID-19 vaccine trials in different countries. Looking at those data that are available to date, they supported enrollment of children in vaccine trials. However, they urged that teenagers would be enrolled at first, and after proper observation of adverse effects, outcome and follow-up, inclusion of younger children and infants would be justifiable.[17,22,25]

At the time of writing this paper, in different countries, only approved vaccine for children (i.e.,12-18-year old), is the "Pfizer-BioNTech BNT612b2 vaccine".[26] To set priority, based on proportion of severity of infection with SARS-CoV-2 and further complications, children with comorbidities and physically/mentally challenged are allowed to get vaccines first comparing with normal healthy children.[27] Moreover, it is crucial to allow more time to gather safety and efficacy data of any vaccine that will ultimately show grounds for approval to use in children.[17,22]

The American Academy of Pediatrics has also advocated for the inclusion of children in paediatric COVID-19 vaccine testing.[28] However, we know that enrollment of children in biomedical research involves weighing risks and benefits, i.e. a balance between access (to experimental but potentially life-saving therapeutics) and protection (from unsafe or ineffective therapeutics).[21.22,24] As noted, children under the age of 12 years have yet to be enrolled in COVID-19 vaccine trials.[17,29] This omission can be justified ethically by the need to ensure adequate safety data are obtained in adults who can give a voluntary and informed consent to participate in such trials, particularly since adults bear the major burden of disease.[22,24] To date, multiple real-world effectiveness studies from the United States and other countries demonstrate that recommended two-dose mRNA COVID-19 vaccine is estimated 64-99% effective against infection, and able to reduce 87-97% risk of hospitalization.[29] Another reason for child vaccination is to consider protection of the wider population, as we do in case of any preventable infectious disease. When any child or adult is infected with the coronavirus, it may get a chance to mutate and create a variant in the host body that might come up being more virulent and resistant to all available therapies. Hence, the more we can reduce infections and re-infections in the population, the more we will bar to emergence of new variants and ultimately reduction of costs in healthcare during this pandemic.[30-32] However, the paediatric trial participants must be protected from unnecessary harms and must be provided with medical attention during or after the study, either because they suffer either for participation in the study or aggravating pre-existing illness.[20-24]

VACCINATION STRATEGIES

The World Health Organization (WHO) assesses the quality, safety, and efficacy of COVID-19 vaccines. The U.S. Food and Drug Administration (FDA) and the U.S. Centers for Disease Control (CDC) have granted emergency use authorization (EUA) for several COVID-19 vaccines. Some national regulators have also assessed other COVID-19 vaccine products for use in their countries. However, when we are writing this article, for children aged 12 years and above, the only recommended is the Pfizer COVID-19 vaccine.[33] However, in Bangladesh, paediatric vaccination has not been approved

at the time, which may be due to shortage of vaccine. Based on projections, it is inevitable that number of cases will increase substantially in the settings of low vaccination rates and high variant transmissibility.[32] Moreover, we support fair access to healthcare for every child like every adult citizen of the society by ensuring efficient use of our limited resources.[19,31,34] Hence, we recommend a fair, equitable policy to vaccinate children ages 12 and up. For Bangladesh, any vaccination programme tends to be successful as it has a long-standing history, infrastructure, manpower and community support for EPI programme, even in hard-to-reach areas.[35] However, monitoring and surveillance are needed to maintain the priority list and prevent vaccine misuse.[36,37] The number of available doses likely will initially be constrained and will increase over time, necessitating phased implementation.[19] Safe and efficacious vaccines are needed for all. Health departments and regulatory bodies within a government have ethical responsibilities to monitor vaccines for safety after they are licensed, which is an important means of fostering public trust.[17,28,38] Moreover, the vaccine must be widely available and easily accessible to all.[31,34,37]

Despite WHO guidance many low-income and middle-income countries (LMICs) like Bangladesh have not yet introduced COVID-19 vaccination for children. WHO guidance from July 14, 2021, states that "… children and adolescents tend to have milder disease compared to adults, so unless they are part of a group at higher risk of severe COVID-19, it is less urgent to vaccinate them than older people, those with chronic health conditions and health workers".[33] In another recent declaration of WHO's Strategic Advisory Group of Experts (SAGE) has confirmed the suitability of the Pfizer–BioNTech vaccine for children aged 12 years and above. They also suggested that children aged between 12 and 15 years screened as high risk may get priority in vaccination programme. WHO also assured of instant update of any change in policy recommendation based on evidence (results of ongoing trials on children in some countries) or epidemiological surveillance and situation as well as emergence of new variant.[33]

Meanwhile, with progression of COVID-19 vaccination programme in adult population, the Ministry of Health and Family Welfare of Government of the People's Republic of Bangladesh with consultation of the COVID-19 Task Force is preparing for an extension of this programme to school children. We assumed that this consideration is based on evidence that showed reductions in transmissibility of the virus, incidence of hospitalization, and risks of complications and deaths following vaccination in different population.[32] Another important consideration might be preventing outbreaks in educational institutions, as we have already experienced that disruption of educational activities for months ultimately causes several "medium to long term impacts on public health" alongside this pandemic's effects.[39] We assume that policy makers will also consider all other potential benefits against the risks of vaccination in children.

CONCLUSIONS

Closure of educational institutions in our country was one of the biggest challenges during this pandemic situation. However, now reopening of schools has become necessary for our children, as "schools are integral part of social-emotional learning, formative relationships with peers and adults, opportunities for play, and other developmental progression".[39] A mass vaccination among eligible children will facilitate reopening schools and help reduce devastating toll that it has taken on children. To create and uphold public trust and confidence in COVID-19 vaccination in children, a uniform, transparent, proactive, and culturally sensitive communication strategy is needed,[17,38] through which government public health agencies along with their private collaborators will inform public on a regular basis about the status of the vaccination process in children all over the country.

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Case Report

Recurrent Hypokalaemia Due to Gittleman Syndrome: A Case Report

Islam MS[1], Ahmed QMU[2], Afroze D[3], Talukder D[4], *Hasan MN[5]

Abstract

Gittleman syndrome (GS) is autosomal recessive renal tubulopathy caused by mutation of genes encoding protein for sodium chloride cotransporter and magnesium channel in the distal convoluted tubule.[1] We present the case of a-20-years old female patient admitted in our Internal Medicine Department for recurrent hypokalaemia. She presented with recurrent quadriparesis. There was no history of taking inhaled salbutamol, insulin, steroid, diuretics and vomiting or diarrhoea. Investigations revealed hypokalaemia. Hypomagnesaemia, normal urinary excretion of sodium and potassium and hypercalcaemia. Her Serum albumin was within normal limit and renal function was normal. Diagnosis of Gittleman syndrome was established and was given potassium chloride and magnesium sulphate. Subsequently, the patient improved clinically and biochemically.

Keywords: *Gittleman syndrome, autosomal recessive, recurrent hypokalaemia, hypomagnesimia.*

1. Dr. Mohammad Syedul Islam, Research Assistant, Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka-1000.
2. Dr. Quazi Mamtaz Uddin Ahmed, Associate Professor, Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka-1000
3. Dr. Dilshad Afroze, Phase B resident (Internal Medicine), Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka-1000.
4. Dr. Debashish Talukder, Phase A resident (Cardiology), Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka-1000.
5. *Dr. Md. Nazmul Hasan, Assistant Professor, Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka-1000. E-mail- nazmul_31st@bsmmu.edu.bd

*For correspondence

INTRODUCTION

Hypokalaemia is a common electrolyte imbalance encountered in hospitalized patients. Chronic hypokalaemia commonly results from gastrointestinal or urinary loss. Gitleman syndrome is an autosomal recessive disorder causing channelopathy that leads to hypokalaemia and metabolic alkalosis.[2] In comparison to barter syndrome, it is milder form of renal tubular channelopathy. It is sometimes complicated by hypomagnesemia. Hypocalciuria is also common.Although mortality is very rare from this but decrease quality of life significantly. Genetic mutation in Sodium Chloride co-transporter results in improper function in thiazide sensitive channel in distal renal convoluted tubule which secondarily leads to potassium, magnesium and calcium concentration.

CASE REPORT

A-20-years old woman presented to the hospital with recurrent episodes of weakness of both upper and lower limbs for 2 years. It involved both proximal and distal parts of limbs all at once and onset was sudden. It made her unable to walk during that period. For which, she was admitted in hospital for few occasions and diagnosed as a case of hypokalaemic periodic paralysis for which she was treated with oral potassium supplement with improvement of symptom. Her bowel and bladder habits were normal. She didn't have any history of breathing difficulty, nasal regurgitation, difficulty on swallowing, fever, dirrhoea, vomiting. She didn't take any drug except oral potassium chloride. There is no family history of such illness. On examination, her pulse was 78 beats per minute and regular, BP-120/80 mmHg. There was no neurological deficit at the time of presentation. Investigation revealed hypokalaemia (Potassium- 2.2 mmol/L), hyponatraemia (Sodium- 134 mmol/L), decreased bicarbonate level (21 mEq/L) with normal chloride level (Chloride-102 mmol/L). Her serum magnesium was low (1.5 mg/dl) with normal renal function (Serum creatinine- 0.48mg/dl) associated with alkalosis (pH-7.473). Her urinary calcium excretion was low (11.4 mg/24Hrs) with normal sodium (110mmol/24 Hrs) and

potassium (40 mmol/24 HRs) urinary excretion. Her thyroid function tests were within normal limit. Laboratory investigation have been shown in the table-1. Renal ultrasound shows both kidneys are swollen and measuring about left kidney (128mm*71mm) and right kidney (127mm * 56mm). Cortical echogenicity is raised. Normotensive patient with hypokalaemia, hypomagnesemia, alkalosis, hypocalciuria was suspected to have diagnosis of Gittleman syndrome which was also correlated with clinical findings.The patient was treated with oral supplement of potassium chloride 500mg twice daily and magnesium sulphate 4% infusion once daily and was given high sodium and potassium containing diet. She had significant improvement of her symptoms after treatment.

Table-I: Laboratory investigation profile of the patient

Investigation	Result	Reference range
Complete blood count		
	Hb:9.6 g/dl	Adult female:11.5-15g/dl
	RBC: 5.5 * 10^{12}/L	Femlae:4.5-5.5*10^{12} /l
Seum electrolytes		
	Na^+--134 mmol/L	Na^+--135-145 mmol/L
	K^+--2.2mmol/L	K^+--3.5-5.5 mmol/L
	TCO_2—25.7mmol/L	TCO_2—20-31 mmol/L
Serum creatinine	0.48mg/dl	0.5-1.3 mg/dl
Free T_4	1.42 ng/dL	0.80-1.80 ng/dL
TSH	4.17 micro IU/ml	0.35-5.50 micro IU/ml
Serum Iron	3.7 micro mol/L	9-30.4 micro mol/L
TIBC	103 micro mol/L	44.8-80.6 micro mol/L
Transferrin Saturation	3.59%	15-50 %$
Serum Ferritin	12 ng/ml	8-252 ng/ml
Serum Albumin	53 gm/L	32-48 gm/L
Serum Calcium	11.4 mg/dl	8.3-10.6 mg/dl
Serum Magnesium	1.5 mg/dl	1.6-2.6 mg/dl
Arterial blood gas analysis		
	pH-7.473	7.35-7.45
	pCO_2-28.8 mmHg	35-45 mmHg
	HCO_3^---21 mEq/L	22-28 mEq/L
24 hrs Urinary Sodium	110 mmol/24hrs	40-220 mmol/24hrs
24 hrs Urinary Potassium	40 mmol/24hrs	25-125 mmol/24hrs
24 hrs Urinary Calcium	11.4 mg/24hrs	100-300 mg/24hrs
CRP	2.1 mg/L	<5 mg/L

DISCUSSION

Gitelman syndrome is usually caused by mutations in the SLC12A33 gene. Less often, the condition results from mutations in the CLCNKBB gene. The proteins produced from these genes are involved in the kidneys' reabsorption of salt (sodium chloride or NaCl) from urine back into the bloodstream. Mutations in either gene impair the kidneys' ability to reabsorb salt, leading to the loss of excess salt in the urine (salt wasting).[3]

Gitleman syndrome (GS) also known as familial hypokalaemia-hypomagnesemia,is combined picture of hypokalaemia, hypomagnesemia, metabolic alkalosis and low urinary calcium excretion. Prevalence of this disease is 1:40000 and heterozygotes prevalence is around 1% in Caucasian population, making it one of the most common inherited renal tubular disorders. It is uncommon before the age of six years and most of the cases diagnosed during adolescence or adulthood. Most uncommon manifestation are muscle weakness, tetany, abdominal pain, vomiting, fever. Facial paraesthesia is not uncommon. Many patients may remain asymptomatic till adulthood. Blood pressure often remain lower in comparison to age matched control. Growth retardation is uncommon unless severe hypokalaemia and hypomagnesaemia is persistent.[5]

Our patient 20 years old female presented with recurrent weakness of all four limbs for 2 years with hypokalaemia, hypomagnesemia, metabolic alkalosis with low urinary calcium excretion. There was no growth retardation. There was no family history of such disease.

Management of GS is focused on the basis of patient's conditions and symptoms. Monitoring of potential complications and progression of disease is necessary. Symptoms may progress inspite of keeping potassium level in check. Patient along with his or her parents should be counselled thoroughly about the nature of disease, symptoms and available treatment options as well as their side effect as potassium and magnesium supplement can often result in gastrointestinal upsets and thus may deteriorate quality of life. Effective counseling can motivate the patient and parent's and thus improve adherence to treatment, maintain normal social life and smooth transition into adulthood.[4]

Although Prognosis is excellent but severe fatigue and recurrent weakness can hamper patient's quality of life. Progression to renal impairment is uncommon. [5]

CONCLUSIONS

Although Gittleman syndrome is generally a mild form of renal tubular channelopathy but sometimes can cause debilitative impairment of normal functioning of daily activities. So, early detection and correction of electrolyte and metabolic derangement can improve patients quality of life.

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Case Report

Pachydermoperiostosis with Chronic Diarrhoea: A Case Report

Khan MSA[1], Shazzad MN[2], Ahmed S[3], Haq SA[4]

Abstract

Pachydermoperiostosis (PDP) is a rare autosomal disorder characterized by periostosis, clubbing, thickening of the skin (pachyderma) of the face and scalp, seborrhea and hyperhydrosis. It is the primary form of hypertrophic osteoarthropathy (HOA), the other name of which is Touraine-Solente-Golé syndrome. PDP has various organ involvements and there are some rare associations of PDP with other disorders. Here we describe a 16-year-old boy who presented with skin and skeletal manifestations typical of PDP who also had chronic diarrhea, abdominal pain and weight loss. After giving treatment with risedronate sodium and mesalazine he got significant improvement in his skeletal and abdominal complaints.

Keywords: *Pachydermoperiostosis, chronic diarrhea, Crohn's disease,*

INTRODUCTION

Pachydermoperiostosis (PDP) is a rare disorder inherited as autosomal dominant trait with variable expression. In 1935, Touraine, Solente and Golé first described the PDP as the primary form of hypertrophic osteoarthropathy (HOA) and thus it has been referred to as "Touraine-Solente-Golé syndrome".[1] The disease is characterized clinically by periostosis, digital clubbing and hypertrophic skin changes (pachydermia) that includes coarse facial features and cutis verticis gyrata. Arthralgia, seborrhea, hyperhidrosis, gastrointestinal (GI) and endocrine abnormalities are also reported. Among the GI abnormalities diarrhea, gastric and duodenal ulcers, chronic gastritis, hypertrophic gastropathy, abdominal ache, multiple polyps in duodenum are found. Association of PDP with other disorders like Crohn's disease is also reported.[2,3,4,5] No treatment is curative, symptomatic treatment with NSAIDs, steroids, colchicine are used. Bisphosphonates are found to be effective in the treatment skeletal abnormalities of PDP.[6]

1. *Dr. Muhammad Shaista Ali Khan, Assistant Professor (Medicine), Sheikh Hasina National Institute of Burn and Plastic Surgery, Dhaka. Email: nomanbajit@yahoo.com, Cell: +8801712733995
2. Dr. Md Nahiduzzamane Shazzad, Medical Officer, Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University, Dhaka (BSMMU), Dhaka.
3. Shamim Ahmed, Associate Professor, Department of Rheumatology, BSMMU, Dhaka.
4. Dr. Syed Atiqul Haq, Professor, Department of Rheumatology, BSMMU, Dhaka.

*For Correspondence

CASE PRESENTATION

A 16-year-old boy presented with painful swelling of distal end of long bones for 5 years which increased in severity for 3 months. The pain and swelling used to increase during activity and partially relieved by taking rest and NSAIDs. The patient had the complaints of progressive acral enlargement from the beginning of his illness. He also had gradual coarsening of skin of face and scalp which became more prominent for one year. The skin change in the scalp became progressively furrowed and convoluted. There was no history of other skin lesions suggestive of psoriasis and no history of urethral discharge, painful red eye or low back pain.

The patient also had the complaints of frequent passage of loose stool for one and half years. He had the propensity to defecate in the morning and sometimes at night. Stool was of various forms and consistency- sometimes watery and voluminous, foul smelling, floated on water and sometimes became sticky to pan which was difficult to flush away. The patient also had abdominal cramps which used to subside following defecation. He lost 7 kg of his body weight over the period of 1½ years.

General physical examination revealed characteristics of leonine face and there was cutis verticis gyrate (Figure 1). Clubbing was present involving fingers of both hands. Musculoskeletal system examination findings included broadening of distal end of both forearms and all fingers of both hands (Figure 2) with grade II tenderness. Both the elbows, knees and ankles were also found swollen symmetrically with grade II tenderness.

(a) (b)

Fig.-1: Cutis verticis gyrate

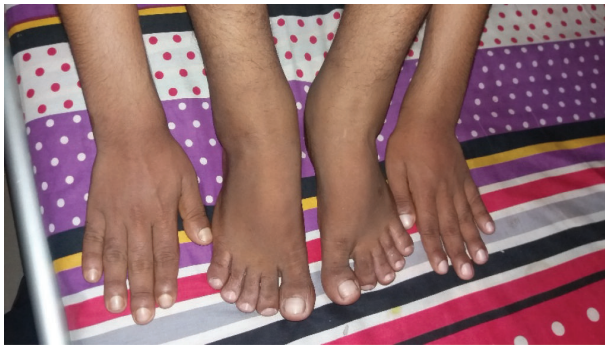

Fig.-2: Broadening of distal end of both forearms and all fingers of both hands

Laboratory reports showing Hb%-122 g/L, WBC-9.6 × 10^9/L, Platelet count-240×10^9/L, ESR- 30 mm in 1st hr, CRP-12 mg/L, Serum creatinine-1.13 mg/dl, RA factor, anti-CCP antibody-negative, S. TSH- 3.05 mIU/L, insulin hypoglycemic test showing: GH 1 hour after 100 gm glucose- 0.05 µg/L (0.05-5.0 µg/L), chest X-ray and X-ray skull (both view)–normal, X-ray both sacroiliac joints-normal. X-ray both hands anteroposterior view showed marked sclerosis, cortical thickening with obliteration of the medullary cavity involving the distal radius and ulna causing loss of normal cavity of bones on both sides. Sclerosis and minimal obliteration of medullary cavity was also seen involving the mid-shaft of proximal phalanges of both hands: findings suggestive of pachydermoperiostosis (Figure 3).

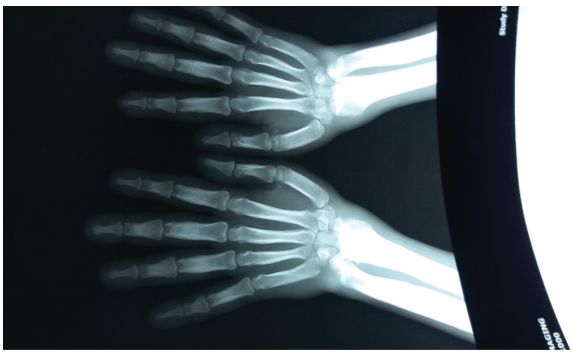

Fig.-2: Sclerosis and minimal obliteration of medullary cavity of radius and ulna

Fecal calprotectin was raised; the value was 322.63 µgm/gm (normal <50 µgm/gm). Ileoscopy revealed few superficial ulcers in the terminal ileum. Biopsy was taken and the report showed infiltration of chronic inflammatory cells in lamina propria. No granuloma or malignancy was found.

Initially, the patient was treated with risedronic acid 150 mg monthly along with calcium 1000 mg daily for skeletal involvement of PDP. Subsequently, he was prescribed with anti-tubercular four-drug regimen for a therapeutic trial, as he was suspected to have intestinal tuberculosis considering the ulceration in the terminal ileum with chronic diarrhea and weight loss. The anti-TB drugs were stopped at the end of three weeks because of a lack of clinical response.

After the failure of anti-TB therapeutic trial, we considered other entities as our differentials that mimic PDP associated gastrointestinal (GI) lesions. These included Crohn's disease (CD), chronic enteropathy associated with *SLCO2A1* gene (CEAS) and cryptogenic multifocal ulcerous stenosing enteritis (CMUSE). Due to the financial constrain we could not proceed for genetic study to see the mutations of *HPGD* and *SLCO2A1* genes of our patients that might be related to PDP. However, clinical presentation, morphological characteristics of the GI lesions guided us to differentiate PDP associated GI lesions from other entities,

Since there is no consensus for the treatment of PDP associated GI lesions, we treated the patient with mesalazine (3 gm/day) and discharged him with the advice for follow up. In the follow-up visits at one and three months, the patient was found to have Grade I tenderness on both knee joints only and he got almost normal bowel habit along with weight gain of two kg.

DISCUSSION

Our patient presented with progressive painful enlargement of the acral parts, coarsening of the skin of face and scalp giving the appearance of cutis verticis gyrata and digital clubbing which are classic symptoms of primary hypertrophic osteoarthropathy; the other name of which is pachydermoperiostosis (PDP). For the exclusion of secondary HOA, we performed physical examination and did relevant laboratory tests and imaging; none of which revealed any abnormality. Though recent genetic studies pointing towards the relation of mutations of *HPGD* and *SLCO2A1* genes to PDP, the diagnosis is still clinical.

Pachydermoperiostosis (PDP) is a rare syndrome and its precise incidence is unknown. One study has shown the prevalence to be 0.16%.[8] It usually manifests in adolescence and occurs predominantly in male with a male: female ratio of 9:1.[9] A mutation linked to X chromosome in association with testosterone-dependent proliferation may be involved in the disease distribution by gender.[10] Three forms of pachydermoperiostosis have been described, the complete form, the fruste forme and the incomplete form. The complete form comprises pachyderma, clubbing and periostosis; the fruste forme includes prominent pachyderma and minimal-to-absent skeletal changes and the incomplete form with evidence of bone abnormalities but lacking pachyderma.[10] Our patient appeared to be a case of complete form of PDP since he has had pachyderma, clubbing and periostosis altogether. As other family members were not involved, it might be due to incomplete penetrance and variable expressivity in other family members.

The pathogenesis of PDP has not been fully elucidated. There are evidences that increased level of prostaglandin E2 (PGE2) and impaired metabolism of PGE2 plays an important role in PDP. Inflammation and malignancies may lead to an increase in the PGE2 levels. Mutation in the human gene that encodes the 15-hydroxyprostaglandin dehydrogenase, a key enzyme responsible for the degradation of prostaglandins, leads to high level of prostaglandins especially PGE2 and thereafter excessive formation of collagen through fibroblast hyper-activation.[11] Circulating factors like platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) may have some role in the pathogenesis of secondary hypertrophic osteoarthropathy. Bisphosphonates have been shown to decrease the level of plasma VEGF that has the function in angiogenesis and osteoblastic differentiation.[5]

The PDP should be distinguished from secondary hypertrophic osteoarthropathy. Secondary form of HOA occurs predominantly in men aged 30-70 years and the bony changes develop rapidly and are painful. The secondary form of HOA results from several conditions including cardiopulmonary diseases (bronchiectasis, cystic fibrosis, congenital heart diseases), gastrointestinal (GI) diseases (inflammatory bowel disease and polyposis), hepatic diseases (portal and biliary cirrhosis), malignancies (e.g., bronchial carcinoma, Hodgkin's disease, nasopharyngeal carcinoma, chronic myeloid leukemia).[12]

Our patient had GI manifestations that included chronic diarrhea, abdominal cramp and weight loss. His fecal calprotectin was raised and he had superficial ulcers in terminal ileum with infiltration of cells in lamina propria (part of intestinal mucosa). Literature review reveals there are few case reports of PDP which were found to be associated with inflammatory bowel disease in particular with Crohn's disease[2,13] The GI symptoms of our patient appeared long after the appearance of cutaneous and skeletal abnormalities and IBD-associated arthritis could not explain the skin changes. Moreover, In CD, the ulcers are typically longitudinal, commonly present on the

mesenteric site and the lesions are usually transmural. We also considered other differentials like chronic enteropathy associated with *SLCO2A1* gene (CEAS) and cryptogenic multifocal ulcerous stenosing enteritis (CMUSE). In CEAS, females are predominantly affected and the lesions spares the terminal ileum.[14] In CMUSE, the CRP level is usually normal and there is skipping ulceration and stenosis restricted to mucosa and submucosa. CMUSE responds well to steroid therapy.[15] Our patients had the history of treatment with NSAID and prednisolone for few months before presenting to us without substantial improvement of his GI symptoms. Intestinal tuberculosis was also excluded by the therapeutic trial of anti-tubercular drugs.

Due to rarity of this condition, it is difficult to make standard therapeutic modalities for PDP. The proposed treatment is multi-prong with NSAIDs, colchicine for articular symptoms; bisphosphonates for rheumatological symptoms; isotreninoin for seborrhea, acne, folliculitis and pachyderma. Our patient was treated with risedronic acid 150 mg monthly along with calcium 1000 mg daily for PDP. As colchicine could lead to diarrhea, it was not the preferred drug for our patient. Due to lack of consensus for the treatment of PHO associated GI lesions, we treated the patient with mesalazine (3 gm/day) and he got substantial improvement of his GI symptoms. As mesalazine does not have proven value in Crohn's disease, this drug might be effective in PDP associated GI lesions in the small gut.

CONCLUSIONS

Secondary hypertrophic osteoarthropathy (HOA) is relatively more frequently addressed in clinical practice. However, it is important to identify the primary hypertrophic osteoarthropathy (pachydermoperiostosis) and its various associations. Mesalazine may be effective in treating pachydermoperiostosis associated GI manifestations involving the small gut.

Conflict of interest:

The authors have no conflict of interest to declare.

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Obituary news September-2021

BMA would like to express deep condolence on deaths of the following notable physicians in recent past:

Sl. No.	Name	Date of Death
1	Dr. Md. Mahmudur Rahman Nilu Associate Professor, Department of Physical Medicine & Rehabilitation, Bangabandhu Sheikh Mujib Medical University, BSMMU Ex Student of Sylhet MAG Osmani Medical College (20 Batch)	07/05/2021
2	Dr. Golam Mortuja Harun Managing Director Chevron Clinic and Laboratory (Pvt.) Ltd., Chattogram Life Member, BMA, Ex. President BMA, Chattogram Branch Ex Student of Chattogram Medical College (15th Batch)	29/05/2021
3	Professor Dr. K M Saiful Islam David Professor and Head, Department of Forensic Medicine and Toxicology, TMSS Medical College, Bogura and Ex. Head, Forensic Medicine Shahid Ziaur Rahman Medical College, Bogura. Ex Student of Rajshahi Medical College (19th Batch)	21/06/2021
4	Dr. Dinar Jebin Lacturer, Department of Community Medicine Chattogram Medical College Ex Student of Holy Family Red Crescent Medical College, Dhaka (MBBS 2011)	25/06/2021
5	Dr. Md. Mustafizur Rahman Ex. Upazila Health and Family Planning Officer Mirsharai Upazila Health Complex, Chattogram Ex Student of Chattogram Medical College (18th Batch)	30/06/2021
6	Dr. Alli Ashraf Ex. Medicl Officer of Satkhira Purasova. Ex. Medicfal Officer, Family Planning Department, Satkhira Ex Student of Dhaka Medical College (K 30th Batch)	05/07/2021
7	Dr. ANM Abdur Razzak Ex. Assistant Director Shahid Ziaur Rahman Medical College Hospital , Bogura Life Member, BMA Ex Student of Rajshahi Medical College (14th Batch)	08/07/2021
8	Dr. Jesmin Sultana Shanta Ex Student of Gazipur City Medical College (2nd Batch)	09/07/2021
9	Dr. Majed Alli Medical Officer, MCHFP Family Planning Department, Madhupur Upazila, Tangail Ex Student of Barisal Sher-e-bangla Medical College (13th Batch)	09/07/2021

Sl. No.	Name	Date of Death
10	Dr. Muhammad Hafiz Uddin Managing Director, Barisal Clinic Ex Student of Barisal Sher-e-bangla Medical College (5th Batch)	09/07/2021
11	Professor Dr. Md. Nazrul Islam Head, Department of Ophthalmology Dhaka National Medical College Ex Student of Rajshahi Medical College (23th Batch)	11/07/2021
12	Dr. Md. Shahidul Islam (Ratul) Deputy Chief (Medical Officer) Pabna Biggan O Projukti University, Pabna Ex Student of Rajshahi Medical college (36th Batch)	13/07/2021
13	Dr. Syed Md. Mostafa Kamal Professor and Head, Department of Cardiology IAHS Medical College, University of Science and Technology, Chattogram, Ex. Associate Professor Cardiology Department Chattogram Medical College Life Member, BMA Ex Student, of Chattogram Medical College (- Batch) (MBBS 1979)	13/07/2021
14	Dr. Halima Akandha MS Rasident, Phase A, Student Obstetrics and Gynaecology, Mymensingh Medical College Ex. Student of Ibn Sina Medical College (7th Batch)	20/07/2021
15	Dr. Sardar Badar Uddin Rtd. Civil surgeon Life Member, BMA, Khulna Branch Ex. Student of Rajshahi Medical College (1973)	22/07/2021
16	Dr. Jarin Tasnim Rimi Ex. Student of Shahid Suhrawardy Medical College (9th Batch)	22/07/2021
17	Dr. Md. Emdadul Haque Ex. Deputy Director, Department of Health Ex. Secretary General, BMA, Jessore Branch Ex. Student of Rangpur Medical College (7th Batch)	23/07/2021
18	Dr. A.J.M Shamsuddin Chowdhury Ex. Deputy Director, Chattogram Medical College Hospital Ex Student of Chattogram Medical College (2nd Batch)	25/07/2021
19	Dr. Shahnewaz Begum Obstetrics and Gynaecology Specialist Life Member, BMA Bogura Branch Ex. Student of Rangpur Medical College (11th Batch)	28/07/2021
20	Dr. Aliza Ayesha Ex. Student of Holy Family Red Crescent Medical College (16th Batch)	31/07/2021

Sl. No.	Name	Date of Death
21	Professor Dr. Najib Mohammad Head, ICU Department Gonoshasthaya Nagar Hospital and Gonoshasthaya Dialysis Center, Dhaka. Ex. Student of Sir Salimullah Medical College (2nd Batch)	02/08/2021
22	Dr. Zakia Rashid (Shafi) Consultant, Obstetrics and Gynaecology Sheikh Hasina Medical College, Tangail Ex. Student of Dhaka Medical College (K-50th Batch)	02/08/2021
23	Dr. AFM Shafiuddin (Pata) Ex. Civil surgeon, Department of Health Secretary General, BMA, Rajbari Branch Ex Student of Rajshahi Medical College (20th Batch)	03/08/2021
24	Dr. Shamim Ahmed Associate Professor, Department of Radiology and Imaging Dhaka Medical College Hospital Life Member, BMA Ex Student of Chattogram Medical College (32th Batch)	03/08/2021
25	Dr. Farida Yesmin Associate Professor Ex. Head, Department of Ophthalmology Community Based Medical College Bangladesh Life Member, BMA Ex Student of Barisal Sher-e-bangla Medical College (10th Batch)	05/08/2021
26	Professor Dr. Sirajul Islam Rtd. Professor, Department of Anatomy Barisal Sher-e-bangla Medical College Life Member, BMA Ex Student of Dhaka Medical College (1964)	05/08/2021
27	Dr. Atiqulla Lanin Senior Medical Officer, Department of Dermatology BIRDEM General Hospital, Dhaka Ex Student of Barisal Sher-e-bangla Medical College (25th Batch)	08/08/2021
28	Dr. Saleh Ahmed Ex. Civil surgeon, Satkhira District Ex. Deputy Director, National Institute of Kidney Diseases & Urology Ex Student of Rangpur Medical College (6th Batch)	15/08/2021
29	Dr. Mohammad Moniruzzaman Associate Professor and Head, Department of Anesthesiology President Abdul Hamid Medical Collage, Kishoreganj Ex Student of Mymensingh Medical College (8th Batch)	19/08/2021

Sl. No.	Name	Date of Death
30	Dr. Md. Mozammal Haque Ex. Ophthalmology Physician Binodini Smrity Hospital, Khulna Life Member, BMA Ex Student of Dhaka Medical College (1953-54)	20/08/2021
31	Dr. Rukan Jaman Ex Student of Satkhira Medical College (2nd Batch)	29/08/2021

May Allah bless the departed souls.
Our heartiest commiseration to the deceased's family, our prayers are with them during this difficult moment of their life.

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