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Papers should be divided into: (a) Title page (b) Summary (c) Introduction (d) Materials and methods (e) Results (f) Discussion (g) Acknowledgement (h) Reference (i) Tables (j) Figures and Captions. The summary should not exceed 250 words and should state concisely what was done, the main findings and how the work was interpreted.

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Abbreviations and symbols must be standard and SI units should be used throughout. Whenever possible drugs should be given their approved generic name. Acronyms should be used sparingly. Statistical analysis must explain the methods used. Reference should follow the Vancouver format. In the text they should appear as numbers starting at 1. At the end of the paper they should be listed (double spaced) in numerical order corresponding to the orders of citation in the text. All authors should be quoted for papers with upto six authors, for papers with more than six authors the first six only should be quoted followed by et al.

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2. Parkin DM, Clayton D, Blook RJ, Massyer E, Fried HP, Iranov E, et al. Childhood Leukaemia in Europe after Chernobyl : 5 years follow-up. Br J Cancer 1996; 73 : 1006-12.

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1. Phyllyps SJ, Whisnant JP. Hypertension and Stroke. In : Lurgh JH, Brennes BM, editors. Hypertension : Pathophysiology, diagnosis and management. 2nd ed. New York : Raven Press; 1995. p. 465-78.

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## ORIGINAL ARTICLES

# *HELICOBACTOR PYLORI* ERADICATION THERAPY WITH RABEPRAZOLE, AMOXICILLIN AND LEVOFLOXACIN IN BANGLADESHI DUODENAL ULCER PATIENTS

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**Abstract**

Helicobacter pylori *eradication is the mainstay in the treatment of* H. pylori*-associated peptic ulcer disease. Studies in Bangladesh have largely shown low eradication rates with different* H. pylori *eradication regimens. But there is no trial with levofloxacin and rabeprazole containing regimen, which has been shown to be very effective against* H. pylori *in several trials in different countries. So, the aim of this study was to assess the efficacy of 2weeks of triple therapy consisting of rabeprazole 20mg o.d, amoxicillin 1gm b.d, and levofloxacin 500mg o.d in the eradication of* H. pylori *in duodenal ulcer associated with* H. pylori*. A total of 43 consecutive patients with* H. pylori*-associated duodenal ulcer were included in the study. Healing of DU was assessed three months after the end of treatment and at the same time* H. pylori *eradication was assessed by CLO test and histology. Thirty-five of the forty-three patients completed the follow-up. On an intention to-treat (ITT) basis, the eradication rate was 41.86%, on a per-protocol (PP) basis, the eradication rate was 51.43% and ulcer healing was noted to be 74.29%. The regimen was proved to be well tolerated and comparatively cheaper. The eradication rate found parallels with the rates of the most of the studies in Bangladesh. So, we conclude that this regimen can be used when indicated until more effective regimen could be found.*

**Introduction**

Duodenal ulcer is common in Bangladesh. The prevalence of duodenal ulcer was estimated to be 11.98%. 1 Helicobacter pylori infection is now accepted as a major cause of duodenal ulcer. 2 *H. pylori* is widely prevalent in Bangladesh, with 60% of children being infected by the age of 3 months and 80% being infected by the age of 3 years. [3] In adults, about 92% have been found to be sero-positive for *H. pylori* anti body. [4]

Successful eradication of *H. pylori* markedly reduces the risk of ulcer recurrence. [2] International consensus conferences have recommended that *H. pylori* eradication should be the treatment of peptic ulcer associated with *H. pylori.* [5,6] Although eradication rates have found to be high in developed countries, studies in Bangladesh have shown low eradication rates with different standard *H. pylori* eradication regimens and a higher rate of re-infection. [7,8,9,10] In most of the studies in Bangladesh, the eradication rate was between 30-64%. [8,9,10] Bacterial resistance to drugs, bio-availability of drugs, various virulence factors of the bacterium, poor compliance and host factors may contribute to the failure of eradication. So, an effective eradication regimen, which could be recommended for our patients with H. pylori associated duodenal ulcer, has not yet been found. In this situation finding of a regimen, which would be effective, safe and cheaper, has become important.

Levofloxacin has been shown to be very effective against *H. pylori* in several trials in different countries. [11,12,13,14,15,16] The drug is comparatively cheaper and with a few adverse effects. Amoxacillin resistance was found to be low in Bangladesh. [17] Rabeprazole has been shown to have a greater suppressive effect on *H. pylori* than omeprazole and lansoprazole [18,19] and has a faster onset of anti-secretory activity than omeprazole. [20] In Bangladesh, there is no study with regimens containing levofloxacin and rabeprazole which would expected to give better results.

So, this study was designed to find out the efficacy of levofloxacin in combination with amoxicillin and rabeprazole in the eradication of *H. pylori* in duodenal ulcer patients and to find out the ulcer-healing rate.

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**Materials and Methods**

This study was a prospective open clinical trial conducted in the department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University from July 2005 to June 2006. A total of forty-three patients with endoscopically proven duodenal ulcer and with positive CLO test were included in this study. Patients were of both sexes with age range of 15 to 60 years. Pre-treatment with PPIs, H2-receptor antagonists, bismuth or antibiotics within 4 wks prior to study, history of being treated with *H. pylori* eradication regimen in the past, complicated duodenal ulcer disease (narrowing of duodenal bulb, active bleeding and perforation), patients on regular intake of NSAIDs or steroids, patients with gastric ulcer or erosive GERD, pregnant or lactating women, patients with concomitant illness and patients who previously have undergone gastric surgery were excluded from the study. A complete medical history was obtained and physical examination was performed in each patient. Informed consent was taken from each.

Pre-treatment endoscopy of upper GIT was done with Olympus forward viewing video endoscope GIF-0145 for the presence, number, size and location of duodenal ulcer and to take biopsy from antrum for CLO test for *H. pylori.* Those patients with duodenal ulcer who were found to be positive for *H. pylori* by CLO test were than treated with rabeprazole (20mg o.d), amoxicillin (1gm b.d) and levofloxacin (500mg o.d) for 14 days.

Drug compliance was monitored by daily drug intake diary maintained by the patient in which the patient was requested to mark each dose taken in the day and by counting of empty drug packages. The patients were also requested to note any adverse effect and to report.

Follow up endoscopy of upper GIT was performed in each patient 3 months after the end of therapy. Presence or absence of ulcer healing was noted and biopsies from the antrum and body of the stomach were taken. Biopsy samples were studied by CLO test (one sample from antrum) and histology (one same from antrum and one from body of stomach). Eradication was confirmed only by both negative results with CLO test and histology.

**Results and observations**

A total of 43 patients fulfilling the inclusion criteria were enrolled in this study. Baseline characteristics of the patients are shown in the *table-I*. Eight patients dropped out from the study, remaining 35 patients completed the study protocol. On an intention-to-treatment analysis (ITT) 20 of 43 patients (46.51%) were cured of *H. pylori* infection as determined by histology and considering only the CLO test the eradication rate was 51.16%, where as combining with histology the rate was 41.86%. On a per-protocol analysis (PPA) 20 out of 35 patients (57.14%) were cured of *H. pylori* infection as determined by histology and considering CLO test only the eradication rate was 62.86%, where as combining with histology the rate was 51.43%. On the other hand, 26(74.28%) patients had their ulcer healed. *Table-II, III, IV*.

Patients who completed the trial had excellent compliance. Some patients complained of nausea, taste disturbance, mild abdominal discomfort, diarrhoea and headache but did not require interruption of treatment.

**Table-I**

*Baseline characteristics of the patients*

| Parameters | N=43 |
|---|---|
| Age | |
| Mean | 34.77 |
| Minimum | 16 |
| Maximum | 60 |
| Range | 16-60 |
| Sex | |
| Male | 40 |
| Female | 3 |
| Socioeconomic status | |
| Low | 17 |
| Middle | 26 |
| Smoking | |
| Yes | 17 |
| No | 26 |

**Table II**

*Eradication of H. pylori*

| | Frequency | Percent (Intention to treat) | Percent (Per protocol) |
|---|---|---|---|
| Not Eradicated | 17 | 39.54% | 48.57% |
| Eradicated | 18 | 41.86% | 51.43% |
| Drop out | 8 | 18.60% | 0 |
| Total | 43 | 100.00% | 100.00% |

**Table III:** *Eradication failure by CLO and Histology*

| | Failed eradication by CLO n=35 | Failed eradication by Histology only n=35 | Failed eradication by both CLO & Histology N=35 | Total Failure of Eradication n=35 |
|---|---|---|---|---|
| No | 13 (37.14%) | 15 (42.86%) | 17 (48.57%) | 17 (48.57%) |

## Discussion

Although *H. pylori* is susceptible to many different antibiotics, successful treatment remains a challenge. Even the most effective regimen available today fails in 5-20% of cases. [6] The picture is more disappointing in Bangladesh with low eradication rates and higher rates of re-infection[7, 8,9,10].In most of the studies; the eradication rate was between 30-64%. [8,9,10] However, most studies in other developing countries showed also much lower eradication rates than those obtained in developed countries and the higher rates of recurrence. [21,22,23]

In this prospective study we have observed the efficacy and safety of 2 weeks of levofloxacin based triple therapy. Levofloxacin has been shown to be very effective against *H. pylori* infection in several trials in different countries. In a study from China, it was found that the resistance rates to levofloxacin, amoxicillin and clarithromycin were 1.9%, 11.5% and 25% respectively. A dual resistance to amoxicillin and clarithromycin was demonstrated in 9.6% strains, which were all susceptible to levofloxacin. [12] Rabeprazole has been shown to have greater suppressive effect on *H. pylori* than omeprazole or lansoprazole [18,19] and has faster onset of anti-secretory activity than omeprazole. [20] But in Bangladesh, there is no study with regimens containing levofloxacin and rebeprazole. On the other hand amoxicillin resistance was found to be low in Bangladesh. [17] So, this rabeprazole, amoxicillin and levofloxacin containing regimen was chosen for the study.

This study has shown eradication rate of 51.43%, which parallels with the rates of the most of other studies in Bangladesh. But the rate is much lower than those in developed countries. In a study from Italy, Commorota et al. [11] showed with a 7 day course of rabeprazole 20mg o.d plus levofloxacin 500mg o.d and either amoxicillin 1gm b.d (RLA group) or tinidazole 500mg b.d (RLT) eradication rates of 92% and 90% respectively. Zullo et al.[14] showed a eradication rate of 88.2% with levofloxacin based rescue therapy for *H. pylori* eradication.

Low eradication rate in this study may be due to factors, which were beyond the scope of this study. Since drug compliance was ensured and other medications such as NSAIDs that may influence healing and eradication were excluded drug sensitivity, bioavailability of drugs, bacterial virulence factors and host factors may be the possible causes. Pre-treatment assessment of microbial sensitivity to drug as culture and sensitivity test was not assessed in this study. Indiscriminate use of fluoroquinolones in our country may be a possible cause of selection of drug resistant strains to this group of antibiotics. Another factor for low eradication rate may be due to bacterial virulence factors. Cag A negative strains have been shown to be a risk factor for low eradication. Marais et al. [24] showed that *H. pylori* eradication was 87% of Cag A positive strains while only 69% of Cag A negative strains could be eradicated. However, the Cag A and Vac A status in this study was not known. It is also possible that other virulence factors may be involved in the bacterial response to *H. pylori* eradication therapy.

Further studies are needed to find out factor or factors responsible for the low eradication rate in Bangladeshi patients and a more effective eradication therapy. Newer drug may be available in future and therapies containing such drugs may be more effective. Till such time, a 14-day regimen consisting of rabeprazole 20mg o.d, amoxicillin 1gm b.d and levofloxacin 500mg b.d can be used in the eradication of *H. pylori* in Bangladeshi duodenal ulcer patients.

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# EPIDEMIOLOGICAL STUDY OF GASTROESOPHAGEAL REFLUX DISEASE IN AN URBAN POPULATION OF BANGLADESH

MM SHAHED, MMR BHUIYAN, M HASAN, ASMA RAIHAN, PK ROY, BF ARA.

**Abstract**

***Background:*** *Gastro-oesophageal reflux disease (GORD) is a common condition in the western population. As there had been so far no epidemiological study on GORD in Bangladesh, there is little community-based information in this aspect here.*

***Aims:*** *To determine the prevalence of the symptoms of GORD in an urban population and to identify the factors associated with it.*

***Methods:*** *It was a cross-sectional, population-based study. Subjects aged 15 years and above were interviewed, by using interviewer-administered questionnaires. Data were statistically analyzed to provide the prevalence of GORD. Factors associated with GORD were studied using logistic regression models.*

***Results:*** *Of the total population of 1692 in Sher-E-Bangla Nagar Govt. Staff Colony, 1434 responded, yielding a response rate of 84.75%. Complete data from 1417 questionnaires were analyzed, representing 711 (50.2%) men and 706 (49.2%) women. Mean age of the respondents was 32.09 ± 13.19 years. The prevalence of heartburn for at least monthly, weekly and daily episodes was 38.0%, 11.2% and 1.5% respectively. The corresponding figures for acid regurgitation were 39.0%, 11.5% and 0.4%, respectively. Heartburn and acid regurgitation, at least once a week, were significantly more frequent in women (heartburn, 13.5% vs. 8.9%, p<0.001, acid regurgitation, 14.3% vs. 8.7%, p<0.01). Heartburn was more common in subjects between 25 to 34 years (3.7%, p< 0.001).*

*Based on presence of heartburn and/or acid regurgitation once a week, the prevalence of GORD was 18.1%. GORD was more common in 25-34-year age group, and in individuals with higher body mass index (BMI) (>24.9). Atypical symptoms like dysphagia and chest pain were significantly associated with GORD.*

*Using the scoring system of the questionnaire for diagnosis of GORD, the prevalence of GORD was 40.9%; males comprised 35.3% and women, 46.5%. Advanced age (55-64 years, p<0.05, odds ratio 2.13, CI: 1.11-4.07), female gender (p<0.001, odds ratio 2.04, CI 1.41-2.96), smoking (p<0.01, odds ratio 2.18, CI 1.56-3.05), and low education level (illiterate, p<0.001, odds ratio 1.0) were risk factors for suffering from GORD.*

***Conclusion:*** *The prevalence of GORD was common in this urban population. GORD was more prevalent in 25-34-year age group, and in individuals with greater BMI.*

## Introduction

Gastro-oesophageal reflux disease (GORD) is currently one of the most prevalent gastrointestinal disorders. The Genval gastroenterologists' agreement proposed that reflux disease should be defined by the presence of reflux oesophagitis and/or when reflux symptoms impair the quality of life and/or when there exists a risk of long term complications.[1] Heartburn and acid regurgitation both are considered to be reasonably specific symptoms for the diagnosis of GORD.[2]

Heartburn in the western countries occurs in approximately 7% of the adult population on a daily basis, 14-20% on a weekly basis and 44% on a monthly basis.[3,4] In the Olmsted County, Minnesota, USA, the prevalence of at least weekly heartburn reported in 1997 was 17.8% and of acid regurgitation, 6.3%.[3] Manterola et al.[5] conducted a cross-sectional survey in an urban population in Temuco, Chile between 2002 and 2003. The prevalence of GORD was 52.8%. The prevalence is lower in Asian countries.[6,7] The annual, monthly and weekly prevalence rates of gastroesophageal reflux disease were 29.8%, 8.9% and 2.5% respectively in a Chinese population.[8] Reports from Korea revealed the prevalence of GORD at 3.5%.[9] In the recent few years, there has been an increase in the frequency of GORD in Asia.[6,7,10] Several factors have been implicated in the lower prevalence in the Asian countries; these include low dietary fat intake, genetic factors, and low body mass index.[11]

There has been so far no epidemiological study on GORD in Bangladesh before the present work; as such, there is little community-based information in this aspect here. We aimed in this study to estimate the prevalence of GORD in an urban community in Bangladesh, and to explore the risk factors of GORD.

## Materials and methods

*Study design and population*

This study was designed as an epidemiological, cross-sectional and population-based evaluation. It was carried

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out from March to May 2005 in a defined population at Sher-E-Bangla Nagar, Agargaon, Dhaka, having a population of about 1700. Dhaka is the capital and the largest city of Bangladesh; it has a population of about 13 million. The place of study was chosen because it was within easy traveling distance of the investigator; the accompanying interviewers had a good access to the subjects, as they were members of the local community, and the subjects were amenable to interview.

Adult subjects aged 15 years and above were included in the survey; they were interviewed using the questionnaire by the investigator and two interviewers, who had been trained by the investigator. The questions were read out to the subjects and filled up by the team of interviewers.

Subjects were excluded if they had jaundice, upper gastrointestinal haemorrhage, acute abdominal pain, pregnancy, previous gastric surgery or mental disease, if absent during the period of survey, or owing to lack of cooperation and significant illnesses that might impair their ability to complete the questionnaire.

**Questionnaire**

A structured questionnaire developed and validated by Manterola et al. was used in this epidemiological study.[12] The highest sensitivity and specificity, 91.6% and 94.9%, respectively were reported by Manterola et al.[12] Its positive and negative predictive values were 98% and 79%. This questionnaire has the advantage of briefness and simplicity. For these reasons, this questionnaire was selected for the present study.

The questionnaire was translated into Bengali by the method of forward and backward translation for application in Bengali-speaking population. The original questionnaire provided a valid, reliable scale to detect GORD symptoms, with a cut-off point of three providing correct classification of 92% of the subjects, sensitivity greater than 91%, and specificity of almost 95%. In this study a cut-off point of three (3) was used.

The following definitions are used to identify symptoms in this questionnaire: Heartburn: a burning pain or discomfort behind the breastbone in the chest; Acid regurgitation: a sour- or bitter-tasting fluid coming into the throat or mouth; Chest pain: any pain or discomfort felt inside the chest but not including heartburn or any pain that primarily in the abdomen; Dysphagia: a feeling that food sticks in the throat or chest; Hoarseness: rough and harsh voice; Asthma: a history of asthma over the past year. Symptom frequency was measured on the following scale: Never – 0, At least once per month – 1, at least once per week – 2, daily – 3, always – 2, occasional – 1, never -0, yes – 1, no – 0.

*Survey design*

All subjects were interviewed face-to-face at their home by the investigator and the interviewers. For those who were not available at the first visit, at most two follow-up visits were conducted on the next evenings. Subjects who were unwilling to face the interview were not contacted further. Twenty to twenty-five subjects were interviewed at each evening. The investigator checked the questionnaires that were filled up by the interviewers at weekly intervals. Randomly selected two or three individuals were interviewed by the investigator, and the questionnaires filled up this time were compared with their corresponding ones obtained previously.

*Statistical analysis*

The questionnaires were coded for analysis, and the data were entered in a computer and analyzed by using SPSS 11.5 software. Univariate analysis was performed by Student's t-test for continuous variables and by chi-squared test for categorical variables to determine the association between GORD and patient characteristics such as age, sex, education, BMI, occupation, smoking and marital status. Multivariate logistic regression analysis was used to identify predictors of GORD. The results are shown as odds ratios (OR) with 95% CI (Confidence Interval). The reference group was given an OR of 1.00. Following variables were included as independent variable: sex, age category, marital status, BMI category, smoking and occupation.

**Results**

*Population sampled/ demographic data*

Among the 1692 residents of Sher-E-Bangla Nagar Govt. Staff Colony, 258 could not be interviewed as 212 were absent during the survey period, forty-one refused to participate in the study and five were pregnant. A total of 1434 completed the questionnaire, yielding a response rate of 84.75%. Seventeen inadequately completed questionnaires were excluded. Data from 1417 questionnaires were entered on a computer, representing 711 (50.2%) men and 706 (49.2%) women. The age range was 15 years and above. Mean age of the respondents was 32.09 ± 13.19 years, with a male: female ratio of 1: 0.99. Service holders were the largest (32.2%) among the professional categories; there were small numbers of businessmen (5.0%) and manual workers (3.2%) in this population. Education up to secondary school certificate (SSC) was attained by 37.9%.

Prevalence of gastro-oesophageal reflux symptoms

The prevalence of heartburn for at least monthly, weekly and daily episodes was 38.0%, 11.2% and 1.5% respectively (Table I). The corresponding figures for acid regurgitation were 39.0%, 11.5% and 0.4%, respectively (Table I). Heartburn, at least once a week, was significantly more frequent in women (13.5% vs. 8.9%) ($P<0.001$) (Table I). The male: female ratio was 1: 1.51. Heartburn once weekly was more prevalent in 25-34-year age group (3.7%, $P < 0.001$) (Table II). Acid regurgitation at least once weekly was also more common in females (14.3% vs. 8.7%, $P=0.009$) (Table I).

**Table I**

*Sex-specific prevalence of heartburn and regurgitation*

| | At least once a month | | At least once a week | | Daily | |
|---|---|---|---|---|---|---|
| | Heart burn | Regurgitation | Heart burn | Regurgitation | Heart burn | Regurgitation |
| Male | 279 | 279 | 63 | 62 | 4 | 3 |
| n (%) | -39.20% | -39.20% | -8.90% | -8.70% | -0.60% | -0.40% |
| Female | 259 | 274 | 95 | 101 | 17 | 3 |
| n (%) | -36.70% | -38.80% | -13.50% | -14.30% | -2.40% | -0.40% |
| Total | 538 | 553 | 158 | 163 | 21 | 6 |
| | -38.00% | -39.00% | -11.20% | -11.50% | -1.50% | -0.40% |

Regurgitation was more prevalent in 25-34-year age group (3.6%), but it did not reach a statistical significance (p>0.05) (Table III).

Prevalence of gastro-oesophageal reflux disease (GORD)

Gastro-oesophageal reflux disease (GORD) was defined in this study as the presence of heartburn and/or regurgitation at least once weekly. The prevalence of GORD was 18.1%, with 14.5% in males and 21.8% in females.

Association with demographic factors (Table III)

**Age.** Univariate analysis shows that GORD was common in subjects in 25-34-year and 35-44-year age group. In multivariate analysis, GORD was more prevalent in age group of 25-34 years (p < 0.05, odds ratio [OR] 1.71, 95% CI, 1.05-2.77).

**Gender**. In univariate analysis, women were at increased risk of suffering from GORD (p<0.001, OR 1.64, 95% CI 1.25-2.16). In multivariate analysis, men and women were equally likely to have GORD (p>0.05, OR 1.46, 95% CI 0.92-2.30) considering heartburn and/or regurgitation.

**Body mass index (BMI)**. In both univariate and multivariate analysis, GORD was more common in subjects with higher BMI, and the odds of having GORD increased with greater BMI.

**Educational level.** In both univariate and multivariate analysis, GORD (heartburn and/or regurgitation) had no significant association with educational level.

**Working status**. In univariate analysis, GORD was more prevalent in service holders and housewives. In multivariate analysis, no occupational group had significance relationship with GORD.

**Smoking**. There was no significant relationship between and GORD, considering heartburn and regurgitation (OR 1.266, 95% CI 0.82-1.95, p>0.05), as shown in univariate and multivariate analysis.

**Table II**

*Age-specific prevalence rates of heartburn and regurgitation.*

| Age category (years) | Heartburn and regurgitation | | | | | |
|---|---|---|---|---|---|---|
| | At least once a month | | At least once a week | | Daily | |
| | Heart burn | Regurgitation | Heart burn | Regurgitation | Heart burn | Regurgitation |
| 15-24 | 158 -11.20% | 183 (12.9%) | 37 -2.60% | 46 (3.2%) | 3 -0.20% | 0 (0.0%) |
| 25-34 | 131 -9.20% | 143 (10.1%) | 52 -3.70% | 51 (3.6%) | 10 -0.70% | 3 (0.2%) |
| 35-44 | 116 -8.20% | 100 (7.1%) | 38 -2.70% | 34 (2.4%) | 3 -0.20% | 2 (0.1%) |
| 45-54 | 88 -6.20% | 86 (6.1%) | 22 -1.60% | 21 (1.5%) | 2 -0.10% | 1 (0.1%) |
| 55-64 | 27 -1.90% | 24 (1.7%) | 4 -0.30% | 8 (0.6%) | 2 -0.10% | 0 (0.0%) |
| 65-74 | 13 -0.90% | 12 (0.8%) | 4 -0.30% | 3 (0.2%) | 1 -0.10% | 0 (0.0%) |
| 75-84 | 4 -0.30% | 5 (0.4%) | 1 -0.10% | 0 (0.0%) | 0 0.00% | 0 (0.0%) |
| 85+ | 1 -0.10% | 0 (0.0%) | 0 0.00% | 0 (0.0%) | 0 0.00% | 0 (0.0%) |

**Table III**

*Variables associated with GORD (Heartburn & Regurgitation)*

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| Age | P value | OR (95% CI) | P value | OR (95% CI) |
| 15-24 | 0.08 | 1 | >0.05 | 1 |
| 25-34 | 0.001 | 1.80 (1.27-2.57) | <0.05 | 1.71 (1.05-2.77) |
| 35-44 | 0.02 | 1.57 (1.07-2.32) | >0.05 | 1.44 (0.83-2.51) |
| 45-54 | 0.29 | 1.26 (0.81-1.98) | >0.05 | 1.24 (0.67-2.27) |
| 55-64 | 0.97 | 1.01 (0.47-2.14) | >0.05 | 1.02 (0.43-2.43) |
| 65-74 | 0.41 | 1.52 (0.55-4.18) | >0.05 | 1.31 (0.41-4.24) |
| 75-84 | 0.7 | 1.52 (0.1-13.81) | >0.05 | 1.11(0.10-11.42) |
| Gender | | | | |
| Female | <0.001 | 1.64 (1.25-2.16) | >0.05 | 1.46(0.92-2.30) |
| BMI | | | | |
| Underweight | 0.03 | 1 | >0.05 | 1 |
| Normal | 0.04 | 0.65 (0.43—0.98) | 0.01 | 0.58 (0.37-0.90) |
| Overweight | 0.84 | 1.04 (0.66—1.65) | >0.05 | 0.81 (0.48-1.35) |
| Obese | 0.83 | 0.92 (0.43—1.97) | >0.05 | 0.64 (0.28-1.44) |
| Extreme obese | 0.64 | 1.76 (0.15—20.01) | >0.05 | 1.41(0.11-17.10) |
| Education | | | | |
| No education | 0.06 | 1 | >0.05 | 1 |
| Class five | 0.4 | 1.31 (0.69-2.47) | >0.05 | 1.30 (0.66-2.55) |
| SSC | 0.39 | 0.77 (0.42-1.39) | >0.05 | 0.87 (0.45-1.70) |
| HSC/Diploma | 0.32 | 0.72 (0.38-1.37) | >0.05 | 0.96 (0.46-2.00) |
| Graduate | 0.96 | 0.98 (0.52-1.86) | >0.05 | 1.31 (0.62-2.74) |
| Master | 0.31 | 0.66 (0.30-1.46) | >0.05 | 0.76 (0.31-1.85) |
| **Occupation** | | | >0.05 | |
| Service | 0.002 | 1 | >0.05 | 1 |
| Business | 0.22 | 1.47 (0.79-2.75) | >0.05 | 1.53 (0.79-2.94) |
| Student | 0.81 | 0.95 (0.64 -1.41) | >0.05 | 1.55 (0.81-2.96) |
| Housewife | 0 | 1.83 (1.30-2.58) | >0.05 | 1.31 (0.79-2.16) |
| Servant | 0.98 | 0.99 (0.42-2.30) | >0.05 | 0.90 (0.34-2.40) |
| Professional | 0.22 | 5.51 (0.34-89.15) | >0.05 | 5.00 (0.30-83.36) |
| Unemployed | 0.57 | 0.82 (0.42-1.59) | >0.05 | 1.00 (0.49-2.04) |
| Marital status | | | | |
| Married | 0.004 | 1 | >0.05 | 1 |
| Unmarried | 0.001 | 0.59 (0.43-0.81) | >0.05 | 0.66 (0.39-1.11) |
| Widow | 0.86 | 0.91 (0.34-2.46) | >0.05 | 0.84 (0.27-2.58) |
| **Smoking** | 0.54 | 0.89 (0.63-1.26) | >0.05 | 1.26 (0.82-1.95) |

**Table IV**

*The Frequency of atypical symptoms by frequency of GORD (heartburn and regurgitation)*

| Symptoms | GORD=257 N (%) | No GORD =1160 n (%) | P value (chi-square test) | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | | | | P | OR | 95% CI |
| Dysphagia | 105 (40.9%) | 210 (18.1%) | <0.001 | <0.001 | 2.13 | 1.53 - 2.97 |
| Chest pain | 153 (59.5%) | 339 (29.2%) | <0.001 | <0.001 | 2.830 | 2.07 - 3.85 |
| Cough | 52 (20.2%) | 166 (14.3%) | 0.057 | >0.05 | 0.982 | 0.66 - 1.46 |
| Hoarseness | 12 (4.7%) | 48 (4.1%) | 0.702 | >0.05 | 0.725 | 0.34 -1.53 |
| Asthma | 45 (17.5%) | 150 (12.9%) | 0.054 | >0.05 | 1.150 | 0.76 -1.72 |

**Marital status**. In univariate analysis, GORD was significantly less common in unmarried persons (p<0.001, OR 0.59, 95% CI 0.43-0.81). In multivariate analysis GORD had no significant association with marital status.

Association with atypical reflux symptoms

In both univariate and multivariate analyses, dysphagia and chest pain were each more common among those subjects with GORD than non-GORD population. The prevalence of dysphagia and chest pain in GORD population was 40.9% and 59.5%, respectively. No significant association between GORD and cough, hoarseness and asthma was detected in this study.

## Discussion

The present study is the first to report the prevalence of GORD (defined based on the presence of heartburn and/or acid regurgitation at least once a week) in Bangladesh. Heartburn and acid regurgitation, are considered to be reasonably specific symptoms for the diagnosis of GORD;[2] some atypical symptoms are also associated with it. There are reports of a number of population surveys on GORD; these surveys reported a wide range of prevalence of GORD, assessed its association with various risk factors and demonstrated differences in the findings varying with populations; there were differences in its relationship with age, gender, education, occupation, smoking, alcohol ingestion, psychosomatic ailments etc.

The present survey was conducted face to face in subjects' home with the guidance by the members of local community, and the questionnaires were administered by the interviewers instead of self-reporting; this allowed for better clarification of terms and questions and significant responder bias was avoided. This resulted in a high (84.75%) and more accurate response rate. This study sought for the prevalence of GORD and GORD-related symptoms and examined the risk factors, which were found to be associated with GORD in different studies.

Prevalence of gastro-oesophageal reflux symptoms

The prevalence of heartburn and acid regurgitation for weekly episodes in our study were 11.2%, and 11.5%. There are few reports of studies in Asia from epidemiological works on gastro-oesophageal reflux symptoms, and the studies may not be comparable because of methodologies and definitions used. However, these prevalence rates are higher than in Singapore, China, Korea, and Japan.[7, 8,9,18,19] but was lower than those of western population, such as the rate of weekly heartburn of 17.8% in Olmsted County, USA, 14% California, 27% in Belgium, and 20% in Sweden.[3, 4,20,21]

### a. Prevalence of GORD

The prevalence of GORD, defined as the occurrence of heartburn and/or acid regurgitation at least once a week, was 18.1%. The prevalence rate is higher than those in other Asian countries, such as China[8] (8.9%), Korea[9] (3.5%) and Japan[19] (6.6%). The variation in the prevalence of GORD and individual symptoms between our study and these populations may be explained by several factors. The population in the present study was from an urban community that might not represent the general population. Variation in dietary and environmental factors could contribute to the differences. There may be a problem with the interpretation of the word 'heartburn' in the present study population.

### b. Factors associated with GORD

The prevalence of GORD was similar in men and women in many studies.[3,7,8,9,18,19,22,23] in the present study, GORD was also unrelated to gender. In the Belgian study heartburn was significantly more frequent in women (31.1%) than in men (25.6%). [20] The relationship between GORD and age is controversial, in that some study has observed a direct relationship,[18, 24] while others found no

association.[3,7,8,9,25,20] The prevalence of GORD, in our study, was higher in younger (25-34-year) age group than in older subjects, which agreed with the study in Xi'an, China.[18] There was an inverse relationship, with the prevalence of GORD decreasing with age.

A number of studies demonstrate an association between GORD with BMI, [18,25,20,22,23]whereas some other studies found no relationship.[9,25] The population-based cross-sectional study by Lagergren et al.[26] revealed no association between BMI and gastro-oesophageal reflux symptoms. The present study also reveals the positive association between higher BMI and GORD.

Previous studies of the association between smoking and reflux symptoms have produced conflicting results: smoking was significantly associated with risk of GORD in three studies,[24,22,23] and not at all in two studies[27,28] Locke et al.[22] found that a past history of smoking was associated with frequent GORD defined as having heartburn and/or acid regurgitation at least once weekly, and no associations were detected for current smokers. We found no association between smoking and GORD in the present study. This may be due to diagnostic criteria of GORD, number of subjects, environmental factors, and categorization of smoking; in the present study, we did not take the duration and amount of smoking into consideration.

Few studies attempted to show any association of education, occupation, or marital status with GORD. In this study, there was no association of GORD with educational status, in contrast with the finding reported by Diaz-Rubio et al.[25] Wong et al.[8, 25] and Andersen et al.[28] found no significant correlation between occupation and GPRD; our study yielded the same result.

**c. Atypical symptoms and GORD**

The association between GORD and atypical symptoms, namely, dysphagia, chest pain, cough, hoarseness, and asthma were assessed in some studies.[3,8,9,18,29,30] Locke et al.[3] showed that heartburn and acid regurgitation were associated with chest pain, dysphagia, dyspepsia, and globus sensation. Pain behind the sternum and dysphagia were significantly related to GORD in the study by Wang et al. in China.[18] Cho et al.[9] demonstrated significant association between typical GORD symptoms and dysphagia, chest pain, hoarseness and asthma.[9] In the present study, dysphagia and chest pain were significantly associated with presence of GORD. An association of borderline significance was identified with cough and asthma, but this did not remain when the demographic factors and other atypical symptoms were included in the regression model.

In conclusion, GORD was common in this urban population surveyed, the prevalence being comparable to that in western populations. This high prevalence in this population might be due to differences in lifestyle, dietary habit, environmental factors, or occupational status. This population consisted mostly of middle class people, and of service holders, with a small number of businessmen and manual workers; thus it might not be representative of all the urban population. In addition, there was no time frame for the prevalence of any symptom described in the questionnaire, and the prevalence of chest pain might well include subjects with yet undiagnosed coronary artery disease. GORD was more prevalent in 25-34-year age group, and in individuals with greater BMI. There was no relationship of GORD with occupation or marital status by either criterion.

Further studies including all socioeconomic strata and all occupational groups of the urban population are needed to define more accurately the prevalence of GORD and its risk factors in the urban population.

GORD (heartburn and regurgitation) = gastro-oesophageal reflux disease, heartburn and/or acid regurgitation at least once a week, OR=odds ratio, CI=confidence interval

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# DIAGNOSTIC APPROACH AND OUTCOME OF MANAGEMENT OF NEW CASES OF TUBERCULOUS LYMPHADENITIS

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**Abstract**

*One hundred and fifty six consecutive cases of tuberculous lymphadenitis (TBL) were collected from medicine outpatient department (MOPD) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, during the period from May 1998 through March 2006. Data were collected using a structured questionnaire. A detailed history was taken and a thorough physical examination was done in each of the cases. Appropriate investigations including fine needle aspiration cytology (FNAC) and in selected cases biopsy from subcutaneous nodules were taken to confirm the diagnosis. Vast majority (83.98%) of the patients were below 40 years of age. Service-holders (36.54%), businesspersons (26.28%) and students (23.08%) were the major bulk (85.90%) of the patients. Majority (75.64%) of the patients came from semiurban (47.44%) and urban (28.20%) areas and majority ((75.64%)) of the patients were of lower (42.31%) and middle (33.33%) income groups. Vast majority (85.25%) of the patients presented with cervical lymphadenitis. Multiple lymph nodes were present in 84.62% of cases, where 66.67% were matted and in 90.38% of the cases lymph nodes were nontender with firm consistency in 88.46% of the cases. FNAC gave the diagnosis of tuberculous lymphadenitis in 76.92% of the patients but the rest 23.08% required biopsy for the diagnosis. The standard short course category-I antituberculosis treatment regimen (2HREZ/4HR) for six months was given to each and every patient with appropriate dose adjustment according to the body weight. Response to antituberculosis therapy was evaluated periodically at about the 15th day, at the end of the 1st, 2nd, 3rd, 5th and 6th month and any adverse reaction to the drugs were noted. With good compliance of the patient's response to therapy was satisfactory with only a few tolerable adverse reactions, which were managed symptomatically without any interruption of therapy.*

## Introduction

Tuberculosis, a global health problem, continues to be a leading cause of mortality and morbidity of the mankind throughout the world[1] and of course, the major health problem in Bangladesh as well[2]. Although tuberculosis is uncommon in developed countries, its prevalence, especially that of extrapulmonary tuberculosis, is increasing world wide[3,4]. Tuberculous lymphadenitis (TBL) is the commonest form of extrapulmonary tuberculosis[5,6,7]. Cervical lymphadenitis constitutes the predominant lymph node group involved. In United States, over the last 35 years, the proportion of tuberculous lymphatic disease has risen substantially. In patients with subacute to chronic lymphadenitis especially from Indian subcontinent, tuberculosis should be strongly considered even if tuberculin test (MT) is negative and sputum is negative for mycobacterium tuberculosis. Lymph node pathology showing characteristic caseation granuloma establishes the diagnosis tuberculous lymphadenitis even if culture is negative. Fine needle aspiration cytology (FNAC) is a highly cost effective, almost painless, safe, easy and rapid cytological method for tissue diagnosis. By this technique actual procedure takes a few minutes and result can be obtained in a day and unnecessary surgery for incisional or excisional biopsy can be avoided. As such FNAC is an effective alternative to biopsy and is very well applicable for the diagnosis of tuberculous lymphadenitis. Large scale use of this technique was developed by Scandinavian workers. More recently 90-98% accuracy rate had been reported by other workers[8,9]. In regions where tuberculosis is endemic, treatment can be instituted without the need for excisional biopsy if the FNAC results show characteristic caseation granuloma[10].

Management of tuberculosis is a difficult problem particularly in the developing countries, like ours and was not well organized until a few years back[11]. The difficulties include the need for multiple drugs, which are costly and have to be continued for a pretty long time. So, there remains the possibility of loss of compliance. Therefore, each and every patient should

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**Bangladesh J Medicine 2007; 18 : 12-19**

be instructed elaborately about the importance and significance of regular antituberculosis drug intake and probable ill effects and danger of any irregularity, inadequacy and noncompliance.

This study was designed to see the diagnostic approach including clinical profile as well as outcome of management of new cases of tuberculous lymphadenitis using the standard short course category-I antituberculosis treatment regimen (2HREZ/4HR) for six months.

**Materials and methods**

One hundred and fifty six consecutive new cases of tuberculous lymphadenitis (TBL) were collected from medicine outpatient department (MOPD) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka during the period from May, 1998 through March, 2006. Data were collected using a structured questionnaire. A detailed history was taken and a thorough physical examination was done in each of the cases. Age, sex, occupational status, living areas, all the symptoms and sign including fever, cough, expectoration, chest pain, breathlessness, loss of weight, loss of appetite, cutaneous manifestations, subcutaneous nodular swellings were recorded. Investigations like total count (TC) and differential count (DC) of leucocytes, hemoglobin percentage (Hb%), erythrocytes sedimentation rate (ESR), chest x- ray postero-anterior (PA) view, sputum for acid fast bacilli (AFB), tuberculin test (MT), fasting plasma glucose, fine needle aspiration cytology (FNAC) and in selected cases biopsy from subcutaneous nodules and ultrasonography (USG) of the whole abdomen were done. Liver and renal function tests were done when required. In clinically convinced new cases of tuberculous lymphadenitis, FNAC reports showing characteristic caseation granuloma suggestive of tuberculous lymphadenitis were considers as confirmed cases of tuberculous lymphadenitis and enrolled consecutively in the study protocol. Defaulter, relapse and treatment failure cases of tubaerculosis were excluded from the study.

**Definition of terms**

1. New case of tuberculosis: A new case of tuberculosis is defined as a patient of tuberculosis who has never received antituberculosis drugs or received antituberculosis drugs for less than one month.
2. New case of tuberculous lymphadenitis: A new case of tuberculous lymphadenitis is defined as a patient of tuberculous lymphadenitis who has never received antituberculosis drugs or received antituberculosis drugs for less than one month.
3. Dropped out case of tuberculosis: A dropped out case of tuberculosis is defined as a patient of tuberculosis who completed at least one month of antituberculosis treatment and then lost to follow up.
3. Defaulter case of tuberculosis: A defaulter case of tuberculosis is defined as a patient of tuberculosis who completed at least one month of antituberculosis treatment and returned after at least two months interruption of treatment.
4. Relapse case of tuberculosis: A relapse case of tuberculosis is defined as a patient of tuberculosis who previously completed antituberculosis treatment and was cured and has again developed either symptoms or signs of tuberculosis or developed smear positive pulmonary tuberculosis.
5. Treatment failure case of tuberculosis: A treatment failure case of tuberculosis is defined as a patient of tuberculosis who previously received antituberculosis treatment for at least two months or more with no improvement or initial improvement followed by deterioration or patient who began treatment for smear positive tuberculosis and remained or became smear positive again at five months or later during the course of treatment.

On the basis of areas where the patients are living, three living areas are defined. Villages are defined as rural areas and cities or towns are defined as urban areas and the areas in and around the cities or town are defined as semiurban or slum areas where overcrowded people live without enough sanitary or hygienic facilities.

Incomes of the study population were ascertained after interviewing the patients or their guardians about monthly income of the family from all possible sources and grouped them accordingly[12].

1. Lower income group (Lower class): The patients or their guardians having monthly income less than taka 5000.00 (five thousand) only.
2. Middle income group (Middle class): The patients or their guardians having monthly income between taka 5000.00 (five thousand) and less than taka 15000.00 (fifteen thousand) only.
3. Higher income group (Higher class): The patients or their guardians having monthly income taka 15000.00 (fifteen thousand) or more.

The standard short course category-I antituberculosis treatment regimen (2HREZ/4HR) for six months was given to each and every patient with appropriate dose

adjustment according to the body weight. Response to anti tuberculosis therapy was evaluated periodically at about the 15th day, at the end of the 1st, 2nd, 3rd, 5th and 6th month and any adverse reactions of the drugs were noted.

The obtained data were computed, tabulated and analyzed using the software SPSS version 10.

**Results**

Age range of the patients was from 18 to 62 years with a mean age of 29±9 years. Age distribution of patients is shown in table-I, where it is seen that vast majority (83.98) of the patients were below 40 years of age. Out of total 156 patients 102 were male and 54 were female with male to female ratio 5.1:2.7. Occupational status of the patients is shown in table-II, where it is seen that service-holders (36.54%), businesspersons (26.28%) and students (23.08%) were the major bulk (85.90%) of the patients. Living areas of the patients is shown in table-III, where it is seen that majority (75.64%) of the patients came from semiurban (47.44%) and urban (28.20%) areas. Income groups of patients is shown in table-IV where it is seen that majority ((75.64%)) of the patients were of lower (42.31%) and middle (33.33%) income groups.

Clinical presentations of the patients are shown in table-V, where it is seen that 68.38% of the patients had fever, loss of appetite and body weight. As shown in table-VI, vast majority (85.25%) of the patients presented with tuberculous cervical lymphadenitis. As shown in table-VII, multiple lymph nodes were present in 84.62% of cases with matted lymph nodes in 66.67%. Lymph nodes were nontender in 90.38% of the cases with firm consistency in 88.46%. The range of duration of symptoms was from one month to one year with a mean duration of 5±3 months.

Baseline investigation findings of the patients are shown in table-VIII, where it is seen that 36.54% of the patients had leucocytosis with neutrophilia. ESR more than 30 mm in the 1st hour was present in 77.56% of the patients and in 75.64% of the cases tuberculin test (MT) was positive. Patchy opacities suggestive of pulmonary tuberculosis were present in 30.77% of the cases with 16.03% sputum smear positive cases. FNAC report showing caseation granuloma suggestive of tuberculous lymphadenitis, confirmed the diagnosis in 76.92% of patients but the rest (23.08%) required biopsy for the diagnosis.

Management outcome of the patients after six months of antituberculosis treatment is shown in table-IX, where it is seen that 77.56% of the patients had complete cure, 18.60% had incomplete cure, 2.56% did not respond to treatment and 1.28% dropped out. Patients who were detected and treated early had early and rapid response to therapy. Total disappearance of symptoms and signs, including disappearance of subcutaneous lymph node swellings, as found at the end of 1st, 2nd, 3rd, 5th and 6th month of antituberculosis therapy, were 7.05%, 18.60%. 39.10%, 66.67% and 77.56% of the cases respectively. Pruritus (4.49%), maculopapular skin eruption (1.28%), Nausea (3.20%), Vomiting (1.92%) and arthralgia (2.56%) were the adverse effects of the drugs recorded during therapy.

**Table-I**

*Age distribution of the patient (n=156)*

| Age group in years | Number | Percentage |
|---|---|---|
| < 19 | 25 | 16.03 |
| 20-29 | 49 | 31.41 |
| 30-39 | 57 | 36.54 |
| 40-49 | 13 | 8.33 |
| 50-59 | 7 | 4.49 |
| > 60 | 5 | 3.20 |

**Table-II**

*Occupational status of the patients (n=156)*

| Occupational status | Number | Percentage |
|---|---|---|
| Service-holders | 57 | 36.54 |
| Businesspersons | 41 | 26.28 |
| Students | 36 | 23.08 |
| Housewives | 13 | 8.33 |
| Cultivators | 6 | 3.85 |
| Drivers | 3 | 1.92 |

**Table-III**

*Living areas of the patients (n=156)*

| Living areas | Number | Percentage |
|---|---|---|
| Urban area | 44 | 28.20 |
| Semi urban area | 74 | 47.44 |
| Rural area | 38 | 24.36 |

**Table-IV**

*Income groups of the patients (n=156)*

| Income groups | Number | Percentage |
|---|---|---|
| Lower class | 66 | 42.31 |
| Middle class | 52 | 33.33 |
| Upper class | 38 | 24.36 |

**Table-V**
*Clinical presentations of the patients (n=156)*

| Clinical presentations | Number | Percentage |
|---|---|---|
| Subcutaneous nodules | 156 | 100 |
| Fever | 102 | 65.38 |
| Loss of appetite | 102 | 65.38 |
| Loss of weight | 102 | 65.38 |
| Cough | 52 | 33.33 |
| Expectoration | 48 | 30.77 |
| Hemoptysis | 9 | 5.77 |

**Table-VI**
*Clinical presentations of the patients: Distribution of tuberculous lymphadenitis (n=156)*

| Region | Number | Percentage |
|---|---|---|
| Cervical | 133 | 85.25 |
| Axillary | 17 | 10.90 |
| Inguinal | 6 | 3.85 |
| Cervical & Axillary | 9 | 5.77 |
| Cervical, Axillary & Inguinal | 4 | 2.56 |

**Table-VII**
*Clinical presentations of the patients: Characteristics of tuberculous lymphadenitis (n=156)*

| Characteristics | Number | Percentage |
|---|---|---|
| Single | 24 | 15.38 |
| Multiple | 132 | 84.62 |
| Discrete | 28 | 17.95 |
| Matted | 104 | 66.67 |
| Firm | 138 | 88.46 |
| Soft | 18 | 11.54 |
| Nontender | 141 | 90.38 |
| Tender | 15 | 9.62 |
| Fixity to overlying skin / underlying structures | 22 | 14.10 |
| Abscess | 11 | 7.05 |
| Discharging sinus | 5 | 3.21 |

**Table-VIII**
*Baseline investigation findings of the patients (n=156)*

| Baseline investigation | Number | Percentage |
|---|---|---|
| Total count of WBC d" 11000/mm$^3$ | 99 | 63.46 |
| Total count of WBC >11000/mm$^3$ | 57 | 36.54 |
| Differential count of neutrophil d" 75% | 99 | 63.46 |
| Differential count of neutrophil > 75% | 57 | 36.54 |
| ESR d" 30 mm in the 1$^{st}$ hour | 35 | 22.44 |
| ESR > 30 mm in the 1$^{st}$ hour | 121 | 77.56 |
| MT d" 10 mm after 72 hours | 38 | 24.36 |
| MT >10 mm after 72 hours | 118 | 75.64 |
| X-ray chest PA view with patchy opacity | 48 | 30.77 |
| X-ray chest PA view with patchy opacity & pleural effusion | 13 | 8.33 |
| Sputum smear AFB positive | 31 | 19.87 |
| Lymph node FNAC suggestive of tuberculosis | 120 | 76.92 |
| Lymph node biopsy suggestive of tuberculosis | 36 | 23.08 |

**Table-IX**
*Management outcome of the patients (n=156)*

| Management outcome | Number | Percentage |
|---|---|---|
| Completely cured | 121 | 77.56 |
| Incompletely cured | 29 | 18.60 |
| Not cured | 4 | 2.56 |
| Dropped out | 2 | 1.28 |

**Discussion**

In the present series majority of the patients were between 18 and 40 years of age. Most of the patients were in their active years of life and they were the working force of the community. The world health organization reported highest incidence of tuberculosis in this age group[1]. Similar observations were found in many other series[,13,14,15]. In the

present series male to female ratio was 5.1:2.7. The world health organization and the government tuberculosis control programme committee[16] reported male to female ratio as 2.5:1 which is almost similar to that of the present series. In another series[6] male to female ratio was noted as 3.1:1.9 which is closely similar to the present series. In another series[15] male to female ratio was noted as 2.1:1.2, which is closely similar to the present series All these observations indicate the male preponderance of the disease. But it may not reflect the actual fact of the society because female patient might have less consultation tendency and feasibility than their male counterpart especially in a tertiary care centre like ours.

Majority (85.90%) of the patients of the present series were service holders (36.54%), businesspersons (26.28%) and students (23.08%). In one series businesspersons and students were 18.90% and 14.90% respectively[13]. In another series[17] affected students were 17.50%. These observations are closely similar to that of the present series. While students become the sufferer from such a chronic disease like tuberculosis, their academic progamme is seriously affected.

In the present series majority (75.64%) of the patients came from semiurban (47.44%) and urban (28.20%) areas. In one series 47.30% of the patients came from semiurban area[5,13] which is exactly similar to the present series. Majority ((75.64%)) of the patients of the present series were of lower (42.31%) and middle (33.33%) income groups. In one series majority (83.80%) of the patients came from lower (20.30%) and middle (63.50%) income groups[13]. which is almost similar to the present series. Similarly, in another series majority (93.80%) of the patients were of lower (66.20%) and middle (27.6%) income groups[17]. These observations indicate that tuberculosis is the disease of the poor as reported by other[18] but the rich are not exempted from the disease.

Fevers, loss of appetite and body weight are common but not invariable features of tuberculous lymphadenitis. Of course, patients may present otherwise asymptomatically with visible or palpable lump, which may remain undetected for several months due to painless very slow enlargement of lymph nodes. In our series 68.38% of the patients had fever, loss of appetite and body weight. Fever was recorded in 70% of the patients in another series[17], which is very closely similar to similar to our series.

In the present series 85.25% of the patients presented with tuberculous cervical lymphadenitis but axillary and inguinal regions were involved in only 10.90% and 3.85% of the cases respectively. In one series 86.20% of the cases presented with tuberculous cervical lymphadenitis whereas axillary and inguinal lymph nodes were involved in 10.35% and 3.45% of the cases respectively[17]. These findings were just similar to that of the present series. Similarly, in another series tuberculous cervical lymphadenitis (72%) was predominant, followed by axillary (24%) and inguinal (2%) regions[19]. All these observations indicate that tuberculous cervical lymphadenitis is the commonest form of tuberculous lymphadenitis.

Tuberculous lymphadenitis may present as a unilateral single or multiple or bilateral multiple painless lump, mostly located in the posterior cervical or supraclavicular region[20]. In our series most of the patients presented with multiple (84.62%), firm (88.46%), matted (66.67%) and nontender (90.38%) lymph nodes free from overlying skin and underlying structures and mostly located in the posterior cervical and supraclavicular regions.

In our series 36.46% of the patients had leucocytosis with neutrophilia, which indicates that neutrophilic leucocytosis is not uncommon in tuberculous lymphadenitis. We found raised ESR in 77.56% of the cases and patchy opacities on x-ray chest postero-anterior (PA) view suggestive of pulmonary tuberculosis in 30.77% of the cases. Tuberculous lymphadenitis may sometimes be associated with active pulmonary tuberculosis or tuberculous pleural effusion as was found in our series in 30.77% and 8.33% of the patients respectively.

FNAC is a satisfactory tool in the diagnosis of tuberculous lymphadenitis. The procedure is simple, safe, repeatable, and inexpensive and can be recommended on an outpatient basis. However, histopathological examination is required for definitive confirmation in patients of reactive hyperplasia and chronic nonspecific lymphadenitis diagnosed by FNAC[21] or in some of these cases repeated FNAC may further increase the diagnostic yield of caseation granuloma. In the present series FNAC report showing caseation granuloma suggestive of tuberculous lymphadenitis was found in 76.92% of the cases including 7.69% increase of the diagnostic yield of caseation granuloma after repeated FNAC. The rest 23.08% of the cases required excisional biopsy for confirmation of diagnosis, as because in these cases FNAC reports were given either as reactive hyperplasia or chronic nonspecific lymphadenitis. In some other series it has been shown that FNAC detected tuberculous lymphadenitis in 25 to 77% of the cases[22,23]. The sensitivity and

specificity of FNAC in the diagnosis of tuberculous lymphadenitis are 88% and 96% respectively[24]. Combination of FNAC with culture or Mantoux test further increases the diagnostic yield in tuberculous lymphadenitis[25]. In our series culture of the FNA specimen was not done but Mantous test was positive in 75.64% of the patients. In another series Mantoux test was found positive in 60% of the cases[19]. FNAC is a sensitive, specific and cost effective way to diagnose tuberculous lymphadenits[24].

Patients with subacute and chronic lymphadenitis especially from Indian subcontinent, where the disease is endemic, tuberculosis should be strongly considered even if Mantoux test is negative and sputum smear is negative for AFB. Lymph node FNAC showing caseation granuloma establishes the diagnosis even if the culture is negative[19].

There are treatment schedules of six and nine months duration, which have similar relapse rates of 3.3 and 2.7% respectively[26]. Six months of treatment is adequate in most of patients but some authors advocate 12 months of drug treatment for tuberculous lymphadenitis, which results in complete cure after two years of follow up in nearly all cases[20,27]. A tuberculous lymphadenitis usually responds very well to antituberculous chemotherapy[28], surgery has a limited role in the treatment. A surgical intervention in tuberculous lymphadenitis should include fine needle aspiration, drainage, incisional or limited excisional biopsy[29].

In our series, as found after six months of antituberculosis treatment, 77.56% of the patients had complete cure, 18.60% had incomplete cure, 2.56% did not respond and 1.28% dropped out. Patients who were detected and treated early had early and rapid response to therapy. Total disappearance of symptoms and signs, including disappearance of subcutaneous lymph node swellings, as found at the end of 1st, 2nd, 3rd, 5th and 6th month of antituberculosis therapy, were 7.05%, 18.60%. 39.10%, 66.67% and 77.56% of the cases respectively. Our six (3.85%) patients became worse initially on treatment before they got better over next few months, which can happen in up to 25% of patients with tuberculous lymphadenitis. Successful management outcome of our series corresponds to that of many other series using different regimens[14,30,31]. Very closely similar success rates ranging from 77 to 78% were noted in other series[32]. In our series 29 (18.60%) patients still had subcutaneous nodular swellings at the end of six months of treatment. Similar findings were seen in other series[33]. We followed up these 29 (18.60%) patients for further six months to see the behaviour of the lymph nodes after completion of six months of antituberculosis therapy. We continued to follow up these 29 (18.60%) patients because during treatment period they gradually became free from symptoms and signs except a few slowly regressing lymph nodes. During our drug free six months follow up we noticed that at the end of three months 21(13.46%) and at the end of six months further five (3.21%) patients had complete disappearance of lymph nodes. The rest three (1.92%) patients had a few negligible size lymph nodes still persisting but regressing. These findings indicate that the standard short course category-1 treatment regimen for six months is adequate for tuberculous lymphadenitis if they are really responding to treatment, and persisting lymph nodes would gradually regress in size and disappear in course of time.

Out of 16 (10.26%) patients, who had abscess (7.05%) or discharging sinus (3.21%), five (3.21%) had a slow response and three (1.92%) had no response to treatment. Those who were not cured (2.56%) were considered for excisional surgery.

Severe adverse effects of antituberculosis chemotherapy were not found in our series. Pruritus (4.49%) without any skin eruption was the commonest adverse effects of antituberculosis chemotherapy occurring within a few days after commencement of drugs. Next common findings were nausea (3.20%), arthralgia (2.56%), vomiting (1.92%) and maculopapular skin eruptions (1.28%). But all the cases improved with symptomatic therapy within a few days or weeks and antituberculosis chemotherapy could be continued without any interruption. Rifampicin commonly causes itching without a rash in the first two weeks of treatment, but in this situation treatment should not be stopped and the patient should be advised that the itch usually resolves on its own. Similar adverse effects were also recorded in other series[31].

## Conclusion

Tuberculous cervical lymphadenitis is the most common form of tuberculous lymphadenitis, which is the most common form of extrapulmonary tuberculosis. After a meticulous history, thorough physical examination and pertinent investigations like ESR & MT a clinical diagnosis of tuberculous lymphadenitis can be confirmed by FNAC, of course, if it is done in an expert hand. Amongst a variety of diagnostic modalities FNAC is a fairly reliable diagnostic procedure for the diagnosis of tuberculous lymphadenitis. It can enable us to avoid hazardous, costly and time consuming unnecessary surgery. It

is neither wise nor practical to apply all the diagnostic procedure in all the patients. This would be expensive as well as time consuming. So, the test battery should be individualized and may be guided by clinical as well as FNAC findings. Tuberculous lymphadenitis can be diagnosed and best treated on outdoor basis with antituberculosis medication without unnecessary surgery. The outcome of management of tuberculous lymphadenitis with standard short course category-I antituberculosis treatment regimen (2HREZ/4HR) for six months is satisfactory if the patient is educated, motivated and convinced to complete the full course with adequate dose and combination of the drugs.

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# SOCIODEMOGRAPHIC CHARACTERISTICS OF THE SEXUALLY TRANSMITTED DISEASE PATIENTS WITH PSYCHIATRIC DISORDERS ATTENDING TERTIARY CARE HOSPITAL IN BANGLADESH

MC MANDAL[1], MSI MULLICK [2]

**Summary**

*Objectives: Global distribution and determinants of sexually transmitted diseases and its presence with psychiatric disorders depict it as a menace. This study aims to scrutinize the socio-demographic characteristics of the sexually transmitted disease (STD) patients with prevalence of psychiatric disorders. Study Design: This cross-sectional descriptive study conducted on STD patients was carried out in two teaching institutes and their tertiary hospitals. These subjects constitute a special group of population for psychiatric diagnosis by using Structured Clinical Interview for DSM-III- R (SCID). Setting: The study was done on 250 STD patients attending the outpatient department of Dermatology and Venereology in Dhaka Medical College Hospital and Bangabandhu Sheikh Mujib Medical University, Dhaka, between January 1998 and January 1999. Results: The point prevalence of psychiatric morbidity among the STD patient was 34%. The age ranges of the patients were 18 to 55 years with mean age of 26.18 (±6.2) years. The majority of the STD cases were found between 21 and 30 years. The groups among STD cases were found more among male, Muslim, SSC & below, service holder (employed and self-employed), unmarried, urban and among low income group. Psychiatric disorders were found more in the groups of 21-30 years age, Muslim, unmarried, service holder, SSC & below. Conclusions: The results of this small-scale study can yield a guideline for further intensive research in this field in future. However, a large-scale multi-centered prospective study can provide more representative and inferential reflection of the results.*

***Key words:*** *psychiatric ailments; sexually transmitted disease (STD)*

## Introduction

Sexually transmitted diseases are one of the most common causes of illness in the world and have far-reaching health, social and economic consequences. Altered sex behavior, poverty, promiscuity, overcrowding, progression of industrialization, high rates of natural increases, recognized brothel, floating and residential commercial sex workers and amateur society girls are responsible for rising trends of STD.[1] Lack of education, social customs and lack of trained personnel are another important factor for rising STD.[2] Although social and demographic factors were of etiological importance, there are some possible contributions of psychiatric disorders such as personality disorders, abnormal personality traits and abnormal sexual attitudes.[3] The use of substance abuse and sexually promiscuous behaviors are also an important risk factor for the spread of STDS.[4,5] Several studies have shown that psychiatric disorder is common among patients attending in genitourinary medicine clinics. Empirical research findings has revealed that among patients attending the clinics for sexually transmitted diseases, 20-30% have psychiatric disorders.[4,5,6,7] The present study aimed to explore the socio-demographic characteristics among STD patients with the prevalence of psychiatric morbidity.

## Materials and Methods

A descriptive type of cross sectional study was done in the department of Dermatology and Venereology in Bangabandhu Sheikh Mujib Medical University (BSMMU) and Dhaka Medical College Hospital (DMCH) from January 1998 to January 1999. Two hundred and fifty diagnosed cases of STD were selected from dermatology and Venereology

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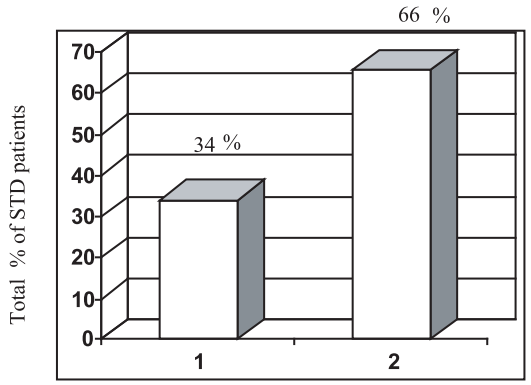
department of the two institutions in tertiary hospitals in a consecutive manner. The interview was conducted in one stage procedure. The semi-structured questionnaire containing socio-demographic data and STD related questionnaire were asked in each patient. The diagnosis was assigned according to DSM-III-R criteria. The sample size was determined by the formula $z^2pq/d^2$ [z=1.96 (for confidence 95%), p=prevalence of psychiatric morbidity (20%), [3, 4, 5] d=desired accuracy (0.05)] and it comes to a figure of 246. The socio-demographic data was collected from questionnaire database.

**Statistical analysis**

All statistical analyses were done with the help of a computer program using SPSS (Statistical Package for the Social Sciences) for windows. Statistical significance of difference between two groups was evaluated by using the't' test and chi-square ($x^2$) test where necessary. The demographic variables were age, sex, religion, education, occupation, and marital status, and sexual orientation, habited and income. All the tests were done at the level of 95% confidence. The results are presented in the following order.




1 = % with psychiatric morbidity, 2 = % without psychiatric morbidity

**Fig.-1:** *Prevalence of psychiatric morbidity among STD patients*

**Results**

Table-I shows socio-demographic characteristics of the patients.

Most of the subjects (54.4%), among total patients were in the age range 21 years to 30 years followed by 31 years to 40 years (21.2%) and 41 to 50 years age group (5.2%). Out of 250 cases 23 was female where 34.8% suffered from psychiatric disorder. Out of 227 male cases 33.9 % suffered from psychiatric illness. Most of the subjects from without psychiatric morbidity (87.3%) and from with psychiatric morbidity (89.4%) groups were Muslim. In relations of STD cases; psychiatric morbidity was more common among secondary level of education (29.4%). This was followed by both illiterate group and S.S.C. group (20.0%). The majority of STD patients were from service group suffered from psychiatric illness (48.2%). This was followed by businessman (25.9%), unemployed (11.8%), student (10.6%), and housewife (2.4%). Among service group, employed were 22.4% and 25.9 % were self-employed. In the marital status of the STD patient it was evident that 40% were married in morbid group and 60% were unmarried. On the other hand among the without morbid group the rate were 41.8% and 57% respectively. Psychiatric morbidity was found more in low income group 52.9%, followed by 29.4% in middle and 17.7% belonged to high income group STD patients. On the other hand, 57.5%, 26.1% and 16.4% were from low, middle and high income group among non-psychiatric STD patients. There were no statistical significant difference between psychiatric disorder groups and non-disorder groups in relation to their age, sex, religion, education, occupation, marital status, income and habit group. In habited group appeared that 70.4% were from urban area where as 29.4% from rural area of the country. Statistical significant difference was observed between psychiatric disorder group and non-disorder group according to their habit (social background) ($p<0.05$). Table-II shows that majority cases, the age of first sexual intercourse was observed between 18 and 24 years (58.8%) among all the STD cases. This was followed by 33.2% in less than 18 years and only 8% between 25 and 31 years .There was no statistical significant difference among their age groups ($p>0.05$) . Table-III clearly demonstrates that the use of condom among STD patients show 49.4% condom users and 50.6% were nonusers in psychiatric illness group and 48.5% and 51.5% respectively in without illness group.

**Table - I**

*Socio-demographic characteristics of the cases*

| Characteristics | With psychiatric morbidity n = 85 % | | Without psychiatric morbidity n = 165% | | Total n=250% | | Test |
|---|---|---|---|---|---|---|---|
| Age Group: | | | | | | | |
| < 20 years | 15 | 17.6 | 32 | 19.4 | 47 | 18.8 | t = 0.43 |
| 21 -30 years | 49 | 57.6 | 86 | 52.1 | 136 | 54.4 | P>0.05 |
| 31- 40 years | 16 | 18.6 | 37 | 22.4 | 53 | 21.2 | $x^2$= 2.56 |
| 41-50 years | 4 | 4.7 | 9 | 5.5 | 13 | 5.2 | P>0.05 |
| >51 years | 1 | 1.2 | 1 | 0.6 | 1 | 0.4 | |
| Sex: | | | | | | | |
| Male | 77 | 33.9 | 150 | 66.1 | 227 | 100 | $x^2$= 0.04 |
| Female | 8 | 34.8 | 1 5 | 65.2 | 23 | 100 | P>0.05 |
| Religion: | | | | | | | |
| Islam | 76 | 89.4 | 144 | 87.3 | 220 | 88.0 | $x^2$ = 1.6 |
| Hinduism | 9 | 10.6 | 18 | 10.9 | 27 | 10.8 | P>0.05 |
| Christianity | 0 | 0 | 2 | 1.2 | 2 | 0.8 | |
| Buddhism | 0 | 0 | 1 | 0.6 | 1 | 0.4 | |
| Education: | | | | | | | |
| Illiterate | 17 | 20.0 | 37 | 22.4 | 54 | 21.6 | $x^2$= 6.21 |
| S.S.C &below | 50 | 58.8 | 89 | 54.0 | 139 | 55.6 | P>0.05 |
| H.S.C &above | 18 | 21.2 | 39 | 23.6 | 57 | 2.8 | |
| Occupation: | | | | | | | |
| Unemployed | 10 | 11.8 | 15 | 9.1 | 25 | 10 | $x^2$= 11.4 |
| Service | 41 | 48.2 | 70 | 42.5 | 111 | 44.4 | P>0.5 |
| Business | 22 | 25.9 | 39 | 23.6 | 61 | 24.4 | |
| Student | 9 | 10.6 | 28 | 17.0 | 37 | 14.8 | |
| Housewife | 2 | 2.4 | 11 | 6.7 | 13 | 5.2 | |
| CSW | 1 | 1.2 | 0 | 0 | 1 | .4 | |
| Farmer | 0 | 0 | 2 | 1.2 | 2 | 0.8 | |
| Marital status: | | | | | | | |
| Unmarried | 51 | 60 | 94 | 57 | 145 | 58 | $x^2$ = 5.3 |
| Married | 34 | 40 | 69 | 41.8 | 103 | 41.2 | P>0.05 |
| Separated | 0 | 0 | 2 | 1.2 | 2 | 0.8 | |
| Income:* | | | | | | | |
| Low | 45 | 52.9 | 95 | 57.5 | 140 | 56 | $x^2$= 0.45 |
| Middle | 25 | 29.4 | 43 | 26.1 | 68 | 27.2 | P>0.05 |
| High | 15 | 17.7 | 27 | 16.4 | 42 | 16.8 | |
| Habit: | | | | | | | |
| Urban | 52 | 61.2 | 124 | 75.2 | 176 | 70.4 | $x^2$ = 5.3 |
| Rural | 33 | 38.8 | 41 | 24.8 | 74 | 29.4 | P<0.05 |

* Low income-<5000/- per month, Middle-5000-10000/- per month,
High- >10000/- per month

**Table – II**

*Distribution of age of first sexual intercourse among STD patients*

| Age of first Sexual intercourse | With psychiatric morbidity | | Without psychiatric morbidity | | Total | | Test Statistics |
|---|---|---|---|---|---|---|---|
| | n=85 | % | n = 165 | % | n = 250 | % | |
| <18 yr. | 25 | 29.4 | 58 | 35.1 | 83 | 33.2 | $x^2$ =0.84 |
| 18-24 yr. | 53 | 62.4 | 94 | 57.0 | 147 | 58.8 | p>0.05 |
| 25-31 yr. | 7 | 8.2 | 13 | 7.9 | 20 | 8.0 | |

| Age of first Sexual intercourse | With psychiatric morbidity | | Without psychiatric morbidity | | Total | | Test Statistics |
|---|---|---|---|---|---|---|---|
| | n=85 | % | n = 165 | % | n = 250 | % | |

**Table – III**

*Distribution of use of condom among STD patients*

| Use of | With psychiatric morbidity | | Without psychiatric morbidity | | Total | | Test Statistics |
|---|---|---|---|---|---|---|---|
| | n=85 | % | n = 165 | % | n = 250 | % | |
| Yes | 42 | 49.4 | 80 | 48.5 | 122 | 48.8 | $x^2$ =0.03 |
| No | 43 | 50.6 | 85 | 51.5 | 128 | 51.2 | p>0.05 |

**Discussion**

This study was conducted in out patient department of dermatology and venereology consultation centers in teaching institute and their tertiary hospital. Two hundred and fifty STD patients were included in this study. The point prevalence of psychiatric disorder was found 34% cases and it was found that this figure was consistent to other similar studies.[7, 8, 9]

In the present study, the age ranges of the STD patients were from 18 years to 55 years having the mean age 26.18 ( ± 6.2 ) years. Most of the cases 57.6% were in the age range of 21 to 30 years with psychiatric morbidity, followed by 18.6% of the 31 to 40 age group, 17.6% up to 20 years age group. Pedder and Goldberg (1970) found majorities of subject were from 20 to 29 years age group in similar types of study in London.[7] Similar age distribution has also been reported in other studies. [10,11,12] In this study 23 STD female patients were examined of which 34.8% presented with psychiatric illness that of 227 male STD cases, 33.9% had psychiatric disorders. Females were more affected than men. This appeared to be due to higher prevalence of depressive disorder in women compared with men. Hence the sex distribution is consistent with findings of study done by Pedder and Goldberg (1970)[7] a survey by questionnaire of psychiatric disturbance in patients attending a venereal disease clinic and by Fitzpatrick, Frost and Ikkos (1986)[13] survey of psychological disturbance in patients attending a sexually transmitted diseases clinic. The distributions of different education of STD patients of psychiatric morbidity were nearly homogeneous. The largest group was found in high school educational level (29.4%), followed by illiterate and SSC group of patients (20% in each group). This might be due to sample biasness as the study was conducted in special group of population and site of sample collection i.e. urban area. The distributions of different educational level of STD patients were nearly homogenous . But there was no statistically significant difference in psychiatric morbidity among the various educational groups . The largest group was found in high school educational level (29.4%) ,followed by secondary educational level and illiterate group of patients ,(20% in each group). This might be due to sample biasness as the study was conducted in special group of population and site of sample collection i.e urban In this research, among 111 STD patients 41 cases were service holder (employed and self-employed) of which was the highest that is 48.2% presented with psychiatric morbidity. It may be due to available free money in hand. Another cause may be husbands posted to distant outpost where they do not want to take their wives .Out of 61 businessmen, 25.9% cases had psychiatric illness. This was followed by 10.6% cases of students, 11.8% unemployed cases, 2.4% housewives and 1.2% commercial sex worker. In

marital status, among the STD patients with psychiatric morbidity, 60% were found unmarried and 40% was married. Barczak et al. (1988) observed similar finding, majority were single (67%), study done on patterns of psychiatric morbidity in a genitourinary clinic, London. He reported that single subjects had higher psychiatric problems than married group. This may be due to lack of family support and spouse. [12] A married couple living together the psychiatric problem and protects from STD. Regarding the prevalence of psychiatric disorders among STD patients between urban (61.2%) and rural (38.8%) population. It might be due to location of the hospital in the urban area and represents the pattern of patients' attendance in this type of hospital. Age of first sexual intercourse probably varies in different societies. A few studies in Africa revealed that nearly half the boys had their first sexual intercourse by the age of 15 and almost 80% by the age of 20.[2] In the present study age of first sexual intercourse detected a relatively greater prevalence (62.4%) of psychiatric morbidity among STD patients of age group between 18 to 24 years. It might be due to lack of specific health education such as sex education and cultural variation. Earlier age of first sexual intercourse increases the prevalence of STD infection as well as psychiatric problems. About half of the STD cases had the history of use of condom irregularly during sexual intercourse that enhances the number of psychiatric problems.

It is evident from the aforementioned findings that socio-demographic backgrounds of the STD patients with psychiatric co-morbidity are of great importance to multidisciplinary and comprehensive understanding, especially in a tertiary care center. Here the majority of the STD patients were found within 21 and 30 years and more among male, unmarried, Muslim, service holder (employed and self-employed), high school education level, urban and lower income group. However, a broad-based study would give the informative and representation the whole population in this issue may be conducted.

## Acknowledgement

We are very thankful to the out patient department (OPD) staffs of Dermatology and Venereology of BSMMU and DMCH, Dhaka for their assistance and cordial help.

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## *REVIEW ARTICLE*

# MEASUREMENT OF CARDIAC NATRIURETIC PEPTIDES FOR DIAGNOSTIC ACCURACY AND PROGNOSTIC RELEVANCE

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**Introduction**

Cardiomyocytes produce and secrete a family of related peptide hormones, named cardiac natriuretic hormones (CNHs), [1] that have potent diuretic, natriuretic, and vascular smooth muscle-relaxing effects and also carry out complex interactions with the neurohormonal system[2-4].

Although the role of CNHs in the identification and management of individuals with asymptomatic ventricular dysfunction remains to be fully clarified [5], the potential clinical usefulness of assays for CNHs [especially B-type natriuretic peptide (BNP) or the $NH_2$-terminal fragment of proBNP (NT-proBNP)] for screening of heart disease [6], for stratification of patients with congestive heart failure [7], for detection of left ventricular systolic and/or diastolic dysfunction [8], and for differential diagnosis of dyspnea [9] has been confirmed more recently. Furthermore, the Task Force of the European Society of Cardiology for the Diagnosis and Treatment of Chronic HF recommended that a CNH assay should be included in the first step of the algorithm for the diagnosis of HF along with electrocardiography (ECG) and chest x-rays[10].

The diagnostic accuracy and prognostic relevance of assays of different CNHs in the entire spectrum of cardiovascular disease will be evaluated. It will be evaluated the clinical relevance and cost-effectiveness of different CNH assays in all clinical settings, including their use as screening methods in asymptomatic individuals as well as their use as diagnostic tests in primary care, emergency department, coronary care unit, and cardiologic ambulatory and hospital care settings.

**Pathophysiologic Relevance of the CNH System**

The CNHs include atrial natriuretic peptide (ANP), BNP, and their related peptides, whereas C-type natriuretic peptide and urodilatin, structurally related to the ANP/BNP peptide family, are predominantly secreted by noncardiac tissues (endothelium and kidney, respectively)[1-4]. Recently, another peptide, called dendroaspis natriuretic peptide, with a structure and biological activities similar to those of the CNH family, was identified, but it is still uncertain whether dendroaspis natriuretic peptide is an endogenous entity in humans [11].

CNHs have several physiologic actions, the most important being *(a)* vasodilation and a hypotensive effect; *(b)* promotion of natriuresis and diuresis; *(c)* inhibition of the sympathetic nervous system and of the activities of several hormone systems, including the renin-angiotensin-aldosterone system, endothelins, cytokines, and vasopressin; *(d)* inhibition of the pathophysiologic mechanisms responsible for ventricular and vascular hypertrophy and remodeling; and *(e)* beneficial effects on endothelial dysfunction secondary to the atherosclerotic process, including blunting of shear stress and regulation of coagulation and fibrinolysis, as well as inhibition of platelet activation [1-4].

CNHs are greatly increased in diseases characterized by an expanded fluid volume, including renal failure, liver cirrhosis, and HF [1]. An important pathophysiologic mechanism in cardiovascular disease is the imbalance between the vasoconstrictive/antinatriuretic action of some neuroendocrine factors, including the renin-angiotensin-aldosterone system, vasopressin, endothelins, and sympathetic nervous system, and the counterregulatory vasodilatory/natriuretic response, mainly represented by CNHs . As cardiac performance decreases, all neurohormonal systems are progressively stimulated in an attempt to sustain cardiac output and circulatory homeostasis. However, the activation of neurohumoral mechanisms may worsen the hemodynamics, have direct adverse

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**Bangladesh J Medicine 2007; 18 : 25-33**

effects on myocardial function, and stimulate the CNH system [12]. According to this hypothesis, the large increases in circulating concentrations of CNHs in HF could even be related to activation of the neuroendocrine system and thus be considered an adaptive and potentially protective response mechanism in cardiovascular disease.

**Physiologic Considerations and Clinical Interpretation**

**Influence of age and gender**

The circulating concentrations of CNHs are regulated or modified by several physiologic factors, such as circadian variations, age, gender, exercise, body posture, and water immersion; eating habits, especially sodium intake; some clinical conditions and drugs, including corticosteroids, sex steroid hormones, thyroid hormones, diuretics, angiotensin-converting enzyme (ACE) inhibitors, and adrenergic agonists and antagonists [1]. The wide variations in circulating concentrations of CNHs in healthy adults in relation to aging and gender could have particular clinical relevance[13]. Indeed, Vasan et al.[5] recently demonstrated that the diagnostic accuracy of CNH assays for community screening is gender dependent.

To explain these variations, the possible influence of sex steroid hormones on the CNH system, as well as the modification of the cardiovascular system with aging, should be taken into account [14]. According to these mechanisms, the higher CNH values in women during the fertile adult period could be explained by the physiologic stimulation of female sex steroid hormones. In particular, the BNP concentration is, on average, 36% higher in women than in men at age <50 years . The increases in CNHs with aging may be attributable to the paraphysiologic decrease in myocardial function and other organs, including the kidney, that is typical of senescence . Indeed, an age modulation of maximum binding capacity of clearance (C-type) receptors for CNHs was reported in platelets of elderly persons.[15]

**Comparison between CNH assays and assays for CNH-related prohormone peptides**

All CNHs derive from preprohormones (i.e., preproANP and preproBNP) containing a signal peptide sequence at the $NH_2$-terminal end. The prohormones (i.e., proANP and proBNP) are produced by cleavage of signal peptide and then are further split into inactive longer $NH_2$-terminal fragments (i.e., NT-proANP or NT-proBNP) and a biologically active shorter COOH-terminal peptide (i.e., ANP or BNP), which are secreted in the blood in equimolar amounts. However, ANP and BNP have shorter plasma half-lives and, consequently, lower plasma concentrations than NT-proANP and NT-proBNP [1].

Studies on structure–activity relationships have shown the importance of the central ring structure of CNHs, formed by a disulfide bridge between the two cysteine residues, for the binding to the specific receptors. For this reason, only ANP and BNP, which present the disulfide bridge in the peptide chain, share the typical hormonal activity of CNHs, whereas NT-proANP and NT-proBNP do not [2].

The different analytical performances might affect the diagnostic accuracy of the assays for differentiating between individuals with or without cardiac disease [16].

The inactive propeptides better fit the definition of a disease marker than do circulating concentrations of ANP or BNP, which on the other hand may be considered a more reliable index of the activation (hormone) status of the CNH system.

Taking into account the biochemical and physiologic characteristics of the different peptides, it is conceivable that ANP is a better marker of acute overload and/or rapid cardiovascular hemodynamic changes than BNP or, especially, than NT-proANP or NT-proBNP [1,15]. ANP increases more than NT-proANP during rapid ventricular pacing [17].

Clinical Relevance of CNH Assays

The pathophysiologic and clinical relevance of CNH assays has undergone a great deal of experimental and clinical study, as reviewed recently [2,18]. In particular, it has been suggested that CNH assays may be clinically useful [1,2,19]for the screening and classification of patients with HF, as prognostic markers in cardiac disease, for the follow-up of patients with HF, and to avoid or reduce the need for expensive and/or unnecessary investigations.

Use of CNH assays in the screening and classification of patients with cardiac dysfunction

The diagnosis of HF can often be difficult, mainly in primary care settings, where patients may present with nonspecific symptoms and signs, such as dyspnea, fatigue, and ankle swelling . In several population-based studies, <40% of patients with a suspected diagnosis of HF in primary care had this diagnosis confirmed by more specific and accurate clinical investigations, which are often expensive, time-consuming, and demanding for the patient [21,22]. As a result, a relatively simple and inexpensive biochemical test (such as a CNH assay) may be very useful to confirm the clinical suspicion of HF in this clinical setting.

**Diagnostic accuracy of CNH assays in asymptomatic, mild ventricular systolic dysfunction**

Patients with asymptomatic left ventricular systolic dysfunction are likely to have lower plasma BNP than patients with overt HF [23].Two recent studies evaluated the diagnostic accuracy of the CNH assay as a screening method in a general population. The first study analyzed the Framingham Heart Study cohort (3177 individuals), using BNP and NT-proANP in the evaluation of left ventricular hypertrophy and systolic dysfunction in a community population . Disease presence was evaluated by echocardiographic findings (the prevalence of left ventricular systolic dysfunction was 9.3% in the 1470 men and 2.5% in 1707 women tested, respectively). The area under the ROC curve (AUC) for the ability of the CNH assay to identify both left ventricular hypertrophy and systolic dysfunction was, on average, ~0.75, with a good specificity (i.e., mean of 95% both in men and women) and negative predictive value (NPV; mean of 92% and 93% in men; 91% and 98% in women), but a poor sensitivity (mean of 27% and 28% in men; 13% and 14% in women) and positive predictive value (PPV; mean of 38% in men; 32% and 30% in women), based on use of gender-related BNP cutoff values .

The aim of the second study was to examine the validity of plasma BNP measurements (with the same IRMA method as the other study) for detection of various cardiac abnormalities in a rural Japanese population (1098 individuals; 693 men and 405 women) with a low prevalence of coronary heart disease and left ventricular systolic dysfunction [i.e., only 37 participants (3.0%), showed an ejection fraction (EF) <30%] . The diagnosis was made by two independent cardiologists based on a medical questionnaire, chest radiogram, ECG, and echocardiographic report. The optimal threshold for identification of disease was a BNP of 50 ng/L (14.4 pmol/L), [2] with an AUC for the ROC curve of 0.970, a sensitivity of 89.7%, a specificity of 95.7%, a PPV of 44.3%, and a NPV of 99.6%.

These two studies, taken as a whole, indicate that CNH assays may have only limited usefulness as screening methods for HF in a general population because of the poor sensitivity and PPV. However, both studies also found good specificity and NPV, thus suggesting that CNH assays may be used to rule out HF in an asymptomatic individual.

**Diagnostic accuracy of CNH assays in patients with suspected heart failure.**

Some recent studies [19,24] reported that CNH assays could be useful as screening methods and/or for the differential diagnosis of patients suspected of HF in the following clinical settings: *(a)* randomly selected general (low-risk) and/or high-risk community populations ; *(b)* patients with a primary care new diagnosis of HF; *(c)* patients with acute dyspnea in the emergency department ; *(d)* consecutive unselected hospital inpatients ; and *(e)* patients admitted to the intensive care unit [24].

Abnormalities of diastolic function may play a major role in determining signs and symptoms of congestive HF [25]. Although Doppler echocardiography is currently used to examine left ventricular diastolic filling dynamics, the limitations of this technique suggest the need for other objective measures . Some studies suggest that CNH assays, in particular a BNP assay, may be useful for the diagnosis of left ventricular diastolic dysfunction [26], although the authors of a small study (34 patients) found no significant correlation between a CNH assay and decreased diastolic function attributable to doxorubicin-induced cardiotoxicity in children with cancer [27].

**Diagnostic accuracy of CNH assays in patients with acute myocardial infarction**

Circulating concentrations of CNHs increase after acute myocardial infarction (AMI); the extent of the increase is related to the size of the infarct . Patients with smaller infarcts tend to have a monophasic increase in plasma BNP, peaking at 20 h after the onset of symptoms; on the other hand, those with larger infarcts, lower EF, and clinical signs of HF may present an additional peak at 5 days after admission [28].

Some studies are less convincing regarding the ability of CNH assays to identify patients with significant ventricular damage after AMI . These conflicting results could be attributable to the differences in sample collection time, type of CNH (ANP, BNP, or NT-proBNP) measured, type of assay (competitive vs noncompetitive), and inclusion criteria adopted. In summary, CNH assays seem to be only moderately useful in assessing left ventricular dysfunction after AMI. However, persisting increases in CNHs at 1 or 2 months after AMI would suggest a high risk of adverse remodeling and subsequent HF, although this finding should be confirmed by additional well-designed studies[29].

**Diagnostic accuracy of CNH assays in the elderly**

HF is primarily a disease of old age. The authors of some recent studies have reported that BNP assays could be clinically useful in elderly people suspected to have HF . In particular, a prospective cohort study specifically evaluated the diagnostic accuracy for HF of BNP assays in 299 consecutive patients (mean age,

79 years; 65% women) attending a day-hospital over a period of 13 months. This study suggested that both BNP assays and ECG were sensitive in detecting left ventricular systolic dysfunction but lacked specificity (the combination of the two tests improved diagnostic accuracy) and that BNP concentrations increased progressively as the number of different cardiac abnormalities increased.

**Diagnostic accuracy of CNH assays in other clinical conditions**

CNH assays could be clinically useful in other clinical conditions. For example, a very recent study reported that NT-proBNP [measured by an electrochemiluminescent assay (ECLIA)] was the most sensitive index of myocardial dysfunction and the most powerful prognostic determinant in primary systemic amyloidosis. Furthermore, this assay can add prognostic information for newly diagnosed patients more effectively than echocardiography and can be useful in designing therapeutic strategies and monitoring response [30]. Another example is the possibility, mainly by BNP assay, of identifying HF related to anthracycline cardiotoxicity [31].

**Comparison of CNH assays with other markers of heart failure**

Signs and symptoms correlate poorly with the presence of HF . Davie et al.[32] found that left ventricular systolic dysfunction was virtually never present if the ECG was normal (sensitivity, 94%; NPV, 98%), and a screening ECG reduced the need of echocardiograms by 50%.

However, CNH measurements may exclude a normal heart with high probability, reducing the echocardiographic diagnostic burden . Choy et al. [33] showed that in post-AMI patients, plasma BNP is superior to all clinical indices of left ventricular systolic dysfunction (EF <40%), including signs and symptoms and a clinical score (Peel Index). Talwar et al.[34] examined the value of NT-proBNP (measured by a competitive immunoluminometric assay), abnormal ECG, and other baseline clinical and laboratory variables in identifying patients with left ventricular systolic dysfunction in a high-risk population (243 patients; 129 men; median age, 73 years; range, 20–94 years). NT-proBNP alone was a better predictor of left ventricular dysfunction than any other single or combination of factors, whereas the ECG had a poor predictive value for left ventricular systolic dysfunction . Cowie et al. reported that ROC curves for BNP (AUC, 0.96), ANP (0.93), and NT-proANP (0.89) were better than that of cardiothoracic ratio on chest radiogram (0.79) in screening for patients likely to have HF and requiring further clinical assessment. It may well be that a combination of tests is the optimal approach for screening patients with suspected HF . Indeed, Richards et al. [24] showed that a combination of NT-proBNP RIA and echocardiographic evaluation of left ventricular function better defined the risk of mortality and/or HF in patients with AMI than either test alone. In particular, for prediction of death over 24 months of follow-up, an early postinfarction NT-proBNP concentration > 160 pmol/L (1353 ng/L) had a prognostic accuracy superior to any other neurohormone measured and to assessment of left ventricular EF by echocardiography . By multivariate analysis, NT-proBNP provided predictive information for left ventricular failure and death, independently from age, gender, left ventricular EF, concentrations of other hormones, previous history of HF, myocardial infarction, hypertension, or diabetes .

**Use of CNHs as Prognostic Markers**

The authors of several well-designed and conducted studies suggested that CNHs may be useful as prognostic markers mainly in two clinical conditions: HF and acute coronary artery syndromes (ACS), as reviewed recently [1-4,35].

**Prognosis in heart failure**

The main protocol characteristics and results of some studies [36] that evaluated the prognostic value of CNH assays in patients with HF are reported in some studies, BNP and NT-proBNP (but not ANP and NT-proANP) were always found to be independent risk markers for morbidity and/or mortality .

Two studies specifically investigated whether CNH assays can predict mortality in elderly persons . Wallen et al. [37] studied the relationship of BNP concentrations with aging and whether BNP could reflect current disease states in the general elderly population (545 individuals >85 years of age). In multivariate analysis, BNP concentrations were predictive of ischemic heart disease, atrial fibrillation, renal dysfunction, congestive HF, and treatment with ß-adrenergic blockers .

**Prognosis in ACS**

ACS encompasses a continuum of cardiac ischemic events ranging from unstable angina pectoris with no biochemical evidence of myocardial necrosis to ST-elevation AMI . The prognosis for patients with ACS varies widely, and several clinical, ECG, and biochemical markers have been used to identify high-risk individuals in need of aggressive intervention [38].

Recently, CNH assays (in particular for BNP and NT-proBNP) have been shown to provide valuable prognostic information for patients with ACS [39].

**Prognostic relevance of CNH assays in the general population**

Some studies have evaluated the prognostic relevance of CNH assays in the general population, especially the elderly [41].

Davis et al. [40] studied 331 elderly volunteers free of acute illness at study entry [mean (SD) age, 88 (7) years; 23% men] in a 1-year prospective blinded cohort study. The risk of overt HF increased progressively with increasing ANP. It can be hypothesized that hypertension-prone individuals may have increased CNH concentrations as a result of increased ventricular wall stress or vascular stiffness early in the course of the disease. If this hypothesis is true, CNH assays could serve as markers of future hypertension risk in the general population. Freitag et al. [41] evaluated the relationship of plasma BNP (measured by IRMA) with longitudinal blood pressure tracking and incidence of hypertension in 1801 nonhypertensive Framingham Heart Study participants (mean age, 56 years; 57% women). In multivariate models adjusting for known risk factors, increased plasma BNP was associated with increased risk of blood pressure progression in men (odds ratio of 1.15 for trend across categories; $P = 0.046$) but not in women ($P = 0.82$).

**Prognostic relevance of CNH assays in pulmonary diseases**

The prognostic relevance of CNHs has been evaluated in acute and/or chronic pulmonary diseases because it is well known that circulating concentrations of CNHs increase in these clinical conditions with the degree of hypoxia and right heart overload [42].

Nagaya et al. sought to assess the prognostic significance of plasma BNP (measured by IRMA) in 60 patients with primary pulmonary hypertension at diagnostic catheterization. Measurements were repeated in 53 patients after a mean follow-up period of 3 months. During a mean follow-up period of 24 months, 18 patients died of cardiopulmonary causes. According to multivariate analysis, baseline plasma BNP was an independent predictor of mortality.

Another study , in which 110 consecutive patients were evaluated, examined whether plasma BNP (measured by IRMA) is a predictor of fatal pulmonary embolism. The relationship between BNP concentration measured at presentation and clinical outcome was assessed by comparing the proportion of outcome events among tertiles. The risk of death related to pulmonary embolism if BNP was >21.7 pmol/L (75 ng/L) was 17% (95% CI, 6–33%). The NPV for uneventful outcome in individuals with a BNP value <21.7 pmol/L (75 ng/L) was 99% (95% CI, 93–100%) .

Kucher et al. measured plasma BNP with a point-of-care testing (POCT) method to determine its prognostic value in 73 consecutive patients with acute pulmonary embolism. A BNP cutoff of 90 ng/L (26 pmol/L) was used for the prediction of a major adverse cardiovascular event. The sensitivity, specificity, NPV, and PPV were 85% (95% CI, 64–95%), 75% (62–85%), 93% (81–98%), and 57% (39–73%), respectively. Moreover, low BNP [<50 ng/L (14.4 pmol/L)] identified 95% of patients with a benign clinical course of acute pulmonary embolism [42].

**Diagnostic accuracy and prognostic relevance of CNH assays in kidney diseases**

It is well known that cardiovascular events are the major prognostic determinants in patients with chronic hemodialysis (cardiovascular deaths representing >50% of total mortality). In these patients, creatinine concentrations are associated with increased risk of mortality, cardiovascular disease, and chronic HF. Circulating concentrations of CNHs are greatly increased in renal failure, and several studies tested their diagnostic accuracy and prognostic relevance .

Naganuma et al. monitored cardiac mortality for 36 months in 164 hemodialysis patients and 14 healthy volunteers. By stepwise multivariate Cox proportional hazards analysis, they found that BNP (relative risk ratios, 1.002; 95% CI, 1.001–1.002), left ventricular mass index (1.027; 95% CI, 1.013–1.042) and C-reactive protein (2.192; 95% CI, 1.532–3.135) were independent predictors of cardiac death compared with other biochemical and clinical markers [43].

The clinical relevance of CNH assay in the stratification risk for cardiac or total mortality in patients with renal failure is uncertain, as suggested by the conflicting results reported above [43]. The usefulness of CNH assays as diagnostic markers of cardiac function in patients with end-stage renal disease is also doubtful, especially when taking into account the different behavior of CNHs and their N-terminal propeptides and when comparing it with other biomarkers and/or hemodynamic indices . Whereas only few data are available on NT-proBNP assays, BNP assays seem to show better diagnostic accuracy and clinical performance as prognostic markers than ANP assays.

CNH Assays in the Follow-Up of Patients with HF

Medical therapy for HF is based on improving the symptoms and signs of fluid retention (change in dyspnea, edemas, and body weight are the usual markers of response to treatment) and titrating the dosage of drugs (such as diuretics, ACE inhibitors, ß-blockers, and spironolactone), according to the evidence from randomized clinical trials . Currently, there is no specific surrogate endpoint for treating patients with HF that can be used to fine tune therapy [21].

Several authors have suggested that CNH assays may be useful in monitoring and tailoring the medical therapy in patients with HF [44]. To provide a practical objective indicator of optimal anti-HF therapy, CNHs should respond to drug treatment. Indeed, ACE inhibitors, valsartan, diuretics, and nitrates have been shown to reduce plasma CNH concentrations in parallel with hemodynamic and clinical improvement [45]. At present, only two published studies were designed to specifically evaluate the clinical use of CNH assays in monitoring and tailoring the medical therapy in patients with HF.

**Can CNH Assays Reduce the Need for Cardiac Investigations?**

It has been suggested that CNH assays could reduce the need for cardiac investigations . Indeed, ruling out HF by use of CNH assays would make unnecessary other investigations, which are often time-consuming, expensive, invasive, and sometimes, potentially harmful for the patient . Nielsen et al. sought to assess the cost-effectiveness of using plasma BNP (measured by RIA) as a pre-echocardiographic screening test for left ventricular systolic dysfunction in the general population . Plasma BNP together with simple clinical indices would reduce the number of echocardiograms and, therefore, the cost of population screening for left ventricular systolic dysfunction in the general population. Screening high-risk individuals by BNP before echocardiography could reduce the cost per detected case of left ventricular systolic dysfunction by 26%, for a cost ratio of 1:20 (BNP/ echocardiogram). More reduced costs (up to 50%) can be predicted for the group of low-risk individuals.

The results of a cost-effectiveness analysis, however, strongly depend on the relative cost of the CNH test compared with that of echocardiograms, as well as on the prevalence of HF in the population screened. Unfortunately, these factors can vary considerably among departments, countries, and healthcare systems; it therefore is probably necessary that each laboratory/clinical department analyzes the cost-effectiveness in its own economic framework. Furthermore, cost-effectiveness analysis is also dependent on the sensitivity of the CNH assay for detecting HF. Cost-effectiveness will improve if more specific assays are used: this would decrease the number of individuals with false-positive (FP) results and, consequently, the number of additional useless investigations.

**General Discussion**

CNH assays may be clinically useful for the screening and classification of patients with HF, as prognostic markers in cardiac disease, for follow-up of patients with HF, and to avoid unnecessary diagnostic procedures.

There is a general lack of good, primary studies of test evaluations for CNH assays. In particular, even some high-quality studies were not designed with the primary goal of evaluating the diagnostic accuracy of CNH assays. Indeed, this aim was considered only at a post hoc analysis and was assessed retrospectively in blood samples collected for different original purposes, even some years before the actual evaluation of diagnostic accuracy. This may introduce a significant bias, although its true clinical relevance is difficult to assess.

A simple and objective definition of chronic HF is currently impossible because there are no defined cutoffs for valvular or myocardial dysfunction or for changes in cardiac output or cardiovascular pressures, dimensions, or volumes that can be used to reliably identify patients with HF. Instead, HF is a clinical syndrome characterized by specific symptoms (dyspnea and fatigue) and signs (edemas) . Furthermore, it should be emphasized that HF is not equivalent to cardiomyopathy or to left ventricular dysfunction; these latter terms describe possible structural reasons for the development of HF .

Because there is no a objective rule to identify and/ or clinically stratify patients suspected to have HF, the different groups of investigators used different gold standards to evaluate the diagnostic accuracy of CNH assays, including clinical scores. In this case, the patients studied were stratified and grouped according to clinical severity, as described by functional classification (usually NYHA classification). In other studies, only echocardiographic measurements were used as the gold standard to determine the accuracy of CNH assays for the diagnosis of left ventricular dysfunction (and not for the clinical diagnosis of HF).

It is important to underscore that both mechanical and neuroendocrine functions contribute to overall cardiovascular function and that, although separate,

they represent interdependent functions mutually affected by many and complex feed-back mechanisms . A corollary of this assumption is that assays of the neuroendocrine system and clinical investigations of cardiac pump function offer different, but complementary, information about cardiac function . Both mechanical and neuroendocrine functions should always be tested separately by suitable methods to achieve more complete knowledge of the role played by the heart in all physiologic and clinical conditions. Therefore, we believe that echocardiographic results should not be used as the only gold standard for the evaluation of diagnostic accuracy of CNH assays in patients with HF.

Comparison of the studies concerning the diagnostic accuracy of CNH assay was also difficult because different populations were enrolled and different immunoassays were used. Indeed, diagnostic accuracy (especially predictive values) is strictly dependent on disease prevalence (pretest probability), which evidently varies greatly according to the clinical setting considered (i.e., screening for general population, outpatients seen by a general practitioner, or in primary care, emergency department, coronary care unit, and other settings). Moreover, some data reported in the literature suggested that diagnostic accuracy may significantly vary in relation to the specific cardiac peptide measured and/or immunoassay used. At present, the different CNH immunoassays also show greatly different imprecision. Consequently, it is not clear whether the observed significant variation in diagnostic accuracy is attributable to a difference in the pathophysiologic behavior of measured peptides and/or in assay performance .

Conclusions and Future Perspectives

Much work is still needed to carefully assess the diagnostic accuracies and prognostic values of CNH assays in cardiac disease. It is important to highlight that these future studies should be designed to determine what each CNH assay can provide according to its analytical characteristics. CNH assays cannot replace cardiac imaging, but both provide independent and complementary information for the evaluation of cardiac function and clinical patient status.

However, taking into account the limitations discussed above, several well-designed studies have indicated that CNH assays could be clinically useful for the diagnosis and characterization of patients with suspected HF. In particular, increased CNH concentrations in patients with suspicion of HF are highly suggestive of a correct diagnosis. On the other hand, in patients with low CNH concentrations this diagnosis is unlikely.

Furthermore, over recent years, several well-designed studies demonstrated the prognostic relevance of CNH assays in patients with both HF and ACS . Currently, use as prognostic markers seems to be the main indication for CNH assays. However, additional evidence regarding the optimal decision limits and their use in combination with other prognostic and/or risk markers is needed before they can be accepted in clinical use. Additional work is also needed to identify therapies that may reduce the risk associated with increased CNH concentrations.

Generally speaking, BNP and NT-proBNP assays show better diagnostic accuracy and clinical performance as prognostic markers than ANP and NT-proANP assays; this finding is probably attributable to the prevalent ventricular production of BNP.

It is important to highlight that the use of CNH assays as both prognostic markers and guides for tailoring pharmacologic therapy is in accordance with the pathophysiologic role played by the CNH system in HF. Increased CNH concentrations indicate that the neuroendocrine system is activated. Several studies have indicated that activation of the neuroendocrine system is the most important pathophysiologic mechanism for the progression of HF. CNH assays could be used as a faster, less expensive, and easier way to monitor activation of the neuroendocrine system than assays for catecholamines, angiotensin II, endothelins, and cytokines.

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## CASE REPORTS

# LEIOMYOMA OF THE SMALL INTESTINE- A RARE CAUSE OF MASSIVE & RECURRENT GASTROINTESTINAL BLEEDING- A CASE REPORT AND LITERATURE REVIEW

**H Masud, SK Saha, MA Kabir, PK Roy**

### Introduction

Benign tumours are the commonest cause of massive bleeding from the small intestine. Although rare, leiomyoma is the commonest of small bowel benign tumuor cause diagnostic difficulty in routime evaluation of the source of bleeding[1]. Massive small bowel bleeding remains a diagnostic challenge. Various diagnostic modalities singly or in combination yield variable results.

Despite advances in the diagnostic methodology, a large percentage of cases are undiagnosed. Small bowel enteroscopy, a newly introduced diagnostic tool, can diagnose only about 50% cases of small bowl tumours[2]. Even video capsule endoscopy of small bowel cannot diagnose small bowel leiomyoma. With improved technique and equipment the diagnostic rate has gone upto 64%[3]. This still leaves a large population of patients without any preoperative diagnosis. In this report, a case of leiomyoma of small intestine presenting with massive and recurrent gastrointestinal bleeding who needs ultimately operative procedure for diagnosis is discussed.

### Case history

A 55 years old female complained of abdominal pain & recurrent melena for 7years. She consulted many internal medicine specialist and gastroenterologist for severe anaemia. She was admitted several times in many private hospital and given several units of blood transfusions. Upper and lower G.I endoscopies were normal. So she was referred to Apollo Hospital, Kolkata for evaluations of small bowel by double balloon enteroscopy. But there patient was undergone video capsule endoscopy. Few tiny ulcers were seen in the proximal small intestine. Rest of the visualized mucosa of the intestine appeared normal. No blood was seen in the intestinal lumen. Hb% done there showed 8.88 gm %, stool for OBT was negative. One unit of PCV was transfused. Repeat Hb% showed 11.4 gm %.

After return from kolkata at one month, this patient was admitted with abdominal pain & melena in Central hospital, Dhaka. Investigations done showed : Hb%-11.0 g/dl, TLC of WBC- 8,000/ cmm, DLC of WBC- N-76%, L-16% E-6%, M-02%. Serum electrolytes, urea & creatinine were normal. Diagnostic laparotomy was done. There is a growth (6.5×4) cm in the antimesentric border of the proximal jejunum. Six cm of the proximal jejunum with the growth was resected. End to end of the jejunum was anastomosed. Appendisectomy was done. Histology of the resected tumour showed features of leiomyoma. Patient was discharged from the hospital after one week. Now the patient is well.

### Discussion

Liomyoma is the commonest symptomatic benign lesion of the small intestine. It is usually diagnosed in the fifth decade of life, although it may occur at any age. There is no sex predilection[4]. The distribution of leiomyoma in the alinentary tract, in the study from Taiwan in 1995 in decreasing order of frequency were found in the stomach (40%), jejunum (20%), ileum & rectum (14.3% each), duodenum (8.57%) and oesophagus (2.86%)[5].

Leiomyoma usually present with massive bleeding per rectum. Preoperative diagnosis is difficult to make owing to the absence of specific clinical symptoms and difficulties in radiologic evaluation of small bowel[1]. In a large review of 5,190 patients with significant gastrointestinal haemorrhage, tumour of small intestine was the cause in only 14 cases [6].

Klinvimol et al.[7] reviewed 1489 patients of gastrointestinal haemorrhage and found only one leiomyoma out of 10 cases where the bleeding had originated in the small bowel. The diagnostic work up includes upper and lower gastrointestinal contrast series, even enteroclysis, upper gastrointestinal endoscopy & colonoscopy. This diagnostic yield has

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been claimed to be 10% in patients with obscure gastrointestinal bleeding[8]. Six such studies performed in 4 out of 13 patients failed to show any lesion in the hands of other authors[9]. Ultrasonography & CT scan with or without contrast are of little help since the features are nonspecific[1]. Invasive procedures such as selective mesentric angiography can reveal the bleeding source in 57% of cases[10] but are best reserved for cases which are actively bleeding. Demirbas A, Kaynaroglu ZV, Daphan C, Sayek I [11] diagnosed three cases of leiomyoma of the small bowel presenting with recurrent gastro intestinal bleeding by angiography in the pre operative period.

Recently 'push enteroscopy' of small bowel in gaining popularity as a diagnostic tool for detecting small bowel pathology as a source of bleeding. These procedures are time consuming[9] and the yield rate in only 25% in lesions of the distal small bowel [10]. Explorative laparotomy may be essential for removing any doubts regarding diagnosis [12]. Zak and Galtsev [13] have gone on record that in some cases only laparotomy can succeed in localizing the tumour. In our case all possible modalities of investigations failed to diagnose the case. Diagnostic laparotomy solved the dilema of diagnosis in this case.

It is concluded that leiomyoma of small bowel is a very rare cause of gastrointestinal bleeding and its preoperative diagnosis can be difficult. Explorative laparotomy as tool of diagnosis for leiomyoma of small bowel is a challenging problem.

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# PEUTZ - JEGHERS SYNDROME: A CASE REPORT

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**Summary**

*Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited disorder characterized by intestinal hamartomatous polyps in association with mucocutaneous melanocytic macules. A 24 year old lady who presented with features of intestinal obstruction is reported here. Her colonoscopy showed multiple polyps and histologically it was hyperplastic.*

*Usually most of the cases of PJS show hamartomatous polyps in the intestines. Some patients presents with intestinal obstruction or intussusception or per rectal bleeding. In addition, these patients have risk to develop intestinal or extra-intestinal malignancy. Screening by Upper and Lower GI endoscopy should be performed to detect early cancers every 2 years from age of 10 and breast or testicular examinations done once yearly from 2nd decade of life (1).*

## Introduction

PJS is characterized by the combination of pigmented perioral macules, pigmented lesions in the buccal mucosa and gastrointestinal polyps. The number, as well as the size and the location, of polyps may vary from patient to patient; size varying from few mm to 6 or 7 cm, occasionally polyps can be absent. Males and females are equally affected. Although the intestinal lesions are hamartomas, patients with Peutz-Jeghers syndrome have a 15-fold increased risk of developing intestinal cancer compared to that of the general population.[1] Cancer location includes gastrointestinal and extraintestinal sites like reproductive organs, breast, lung, pancreas etc. The cause of Peutz-Jeghers syndrome appears to be a germline mutation of the *STK11/LKB1* (serine/ threonine kinase 11) gene in most cases, located on band 19p34-p36 which controls growth regulation.[3]

## Case Report

A 24 year old lady appeared with features of subacute intestinal obstruction and severe anaemia. On examination she was severely anaemic with some signs of dehydration and per abdominal exam revealed gaseous distension and hepatosplenomegaly She was managed conservatively and past history revealed 4 times hospital admissions with severe anaemia and different previous diagnosis were Haemolytic anaemia, HbE trait, Iron deficiency anaemia, etc. Her mother first noted pigmented spots around lips when she was 8 years old (Figure 1). When we examined her, we noticed further pigmentation on the buccal mucosa (Figure 2). An investigation of the entire gastrointestinal tract was performed. Several polyps of the stomach and duodenum were found endoscopically and largest polyps were biopsied. Histologically, most of gastric polyps were of hyperplastic type.

While performing colonoscopy she expelled a cord like structure with diverticular like masses of different sizes, its histopathology report says necrosed tissue of intestinal origin (Figure5). Finally she undergone barium follow through that showed some narrowing near ileo-caecal junction. She was discharged from hospital in good condition. She will be closely and regularly monitored. We examined her mother and other family members except her father who was unavailable. Her younger sister has lower lip pigmentation and younger brother has mucocutaneous pigmentation over lips and buccal mucosa and had a laparotomy for intestinal intussusception.

**Fig 1 :** *Pigmented lips*

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**Bangladesh J Medicine 2007; 18 : 36-38**

**Fig 2:** Pigmented macules over buccal mucosa

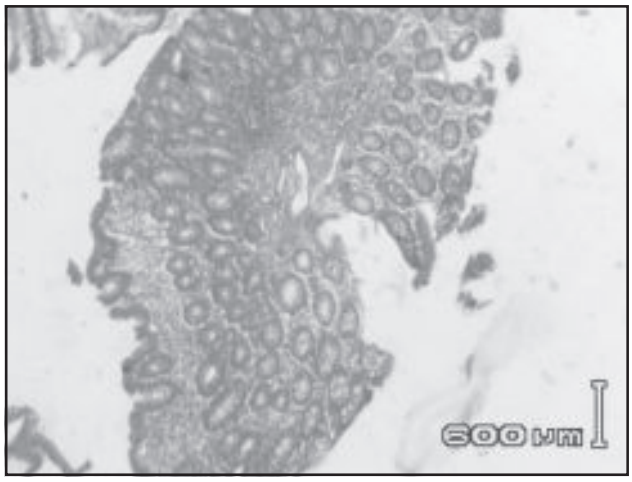


**Fig 3 :** *Colonic polyp*

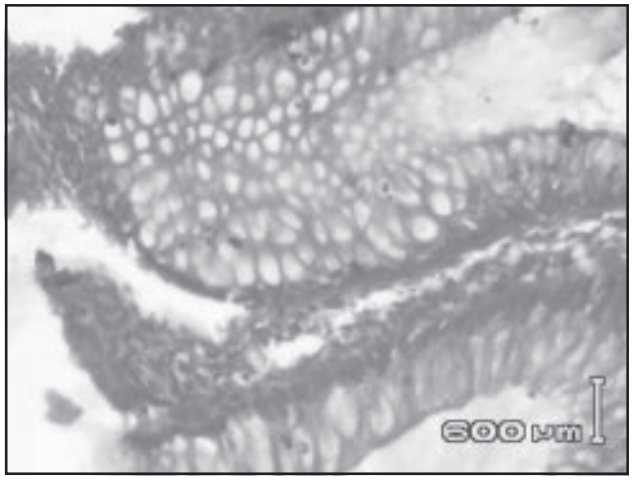


**Fig 4 :** *Hyperplastic colonic polyp*

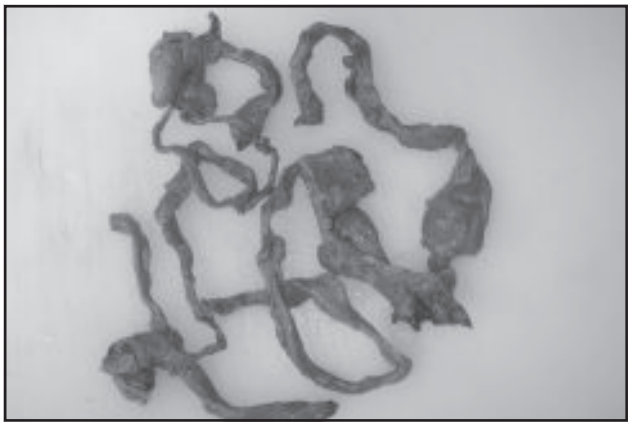

**Fig 5 :** *Expelled intestinal structure*

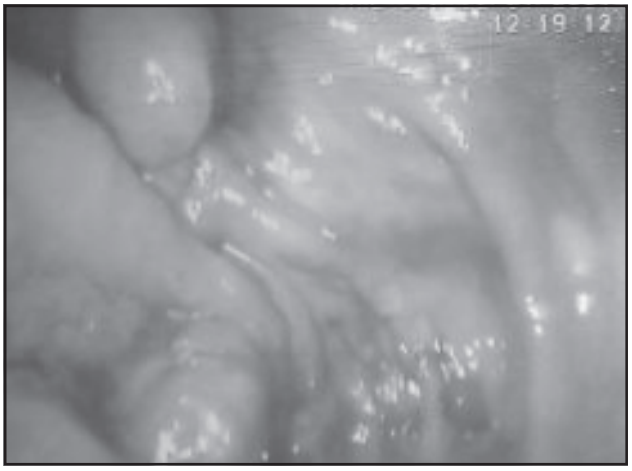


**Fig 6 :** *Colonoscopy shows multiple polyps*

**Discussion**

Peutz-Jeghers syndrome is rare, with a frequency of encounter from polyposis registries one tenth that of familial adenomatous polyposis. The incidence is 1 in 30000 to 120000 live births.[4] It is inherited GI hamartomatous polyposis syndrome that is associated with mucocutaneous pigmentation. The most distinctive clinical features are melanin pigmentations – brown to black spots in the lips and buccal mucosa. Pigmentations can also be present in other parts of the body, such as fingers, toes, hands, feet and the mucosa of the nose, conjunctiva and rectum. Some patients do not present the full spectrum of the disease. Giardello et al. proposed diagnostic criteria for PJS.[5] The definition requires histopathological confirmation of hamartomatous gastrointestinal polyps and two of the following features: small bowel polyposis, positive family history and pigmented skin or mucosal brown macules. Multiple hamartomatous polyps in the gastrointestinal tract are the hallmark of PJS though

in this case we found hyperplastic polyps in stomach, duodenum and colon.

Mostly gastrointestinal polyps are found in the small intestine. They can also be found in the stomach and large intestine. Complications induced by polyps include colicky abdominal pain, bleeding, and bowel obstruction due to intussuception. The time when abdominal symptoms commence can vary. They may present as early as the first year of life or at the age of 40 years.[6] By the age of ten years, 30% of patients with PJS already required a laparotomy.[7] Individuals with certain type of mutation (missense mutations) of STK 11 had a later onset of PJS symptoms.[8] If the polyps are symptomatic or are of significant size (greater than 1,5 cm in diameter) a laparotomy with enteroscopy is recommended. Almost half the patients underwent two or more laparotomies, which resulted in a sizable percentage of patients suffering from short bowel syndrome as a consequence of the repeated bowel resections. Recently, intraoperative endoscopy and endoscopic polypectomy, rather than segmental resection of the bowel, have been recommended. Periodic endoscopic screenings are advocated every 2 years.[7] The new mouthto anus (M2A) capsule endoscopy will probably become the most useful screening tool in the near future.

**Conclusion**

Although hamartomatous type is frequent in PJS, hyperplastic type may occur sometimes. Peutz-Jeghers syndrome should be promptly diagnosed in patients as early as possible. Genetic counseling should also be provided. Regular and close monitoring is needed because of the increased risk of cancer and this can reduce the number of laparotomies. Annual physical examination includes evaluation of the breasts, abdomen, pelvis, and testes and annual complete blood count should be done. Recent advances in genetic testing and capsule endoscopy should result in improved management of patients with PJS.

**References:**

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