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ANTIBIOTIC RESISTANCE IN BANGLADESH

Asma Kabir

Antimicrobials are the most commonly prescribed drugs in hospitals and general practices. Despite the improvement in health care delivery in Bangladesh, infectious diseases remain priority public health problem where wide spread use of different antimicrobials against bacterial, viral, fungal and parasitic infection is required. Important factors associated with resistant bacteria attributed to poor hygiene, overcrowding, lack of resources for infection control and lack of trained personnel in controlling infection in hospital.[1] Treatment of bacterial infections in the hospital has been drastically altered over the past few decades with the emergence of pathogenic organisms that are no longer susceptible to our most commonly prescribed antibiotics.

Resistance to commonly used antimicrobial drugs is remarkably high in countries where antibiotics can be bought over the counter. High rate of antibiotic resistance leaving the clinicians with limited drug options while treating cases with severe infections.[2]

The environment in Bangladesh is ideal for rapid spread for antimicrobial resistance possibly due to high population density, lack of safe drinking water, availability of inexpensive antimicrobials from over the counter suppliers.[3,4] There is growing resistance to antimicrobials in Bangladesh. Bangladesh is facing dual problems. On the one hand it failed to eradicate age old infectious diseases due to indiscriminate and irrational use of antimicrobials, on the other hand it is also facing drug resistant micro-organisms. It has been observed that pseudomonas aeruginosa is responsible for wound, ear and throat infection and in more than 50% cases resistant to commonly used antibiotics in Bangladesh including ciprofloxacin, gentamicin, ceftriaxone, cefixime and azithromicin.[5-7] Azithromicin was 100% ineffective in wound and urine infection, while ceftriaxone and cefixime was 100% ineffective in tracheal infection. *Eschericia coli* resistance was observed in 40% cases to ceftriaxone, levofloxacin, ciprofloxacin, amoxicillin and ampicillin and 95% resistance to azithromicin.[8] Study conducted in an urban hospital of Bangladesh showed that 92% of cases *Salmonella typhi* isolates were resistant to nalidixic acid and ciprofloxacin.[9] The prevalence of MDR- TB was 2.3% among new cases and 13.8% in previously treated patients in Bangladesh.[10] In Bangladesh availability of antibiotics without a prescription has possibly given rise to antibiotic resistance alarmingly. The uncontrolled use of antibiotics can be harmful because of masking of symptoms and also associated with the emergence and spread of antimicrobial resistance. These problems require appropriate measure by policy makers to develop policies and ensure its implications.

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SERUM VASPIN STATUS IN NONOBESE IMPAIRED GLUCOSE TOLERANT SUBJECTS OF BANGLADESHI ORIGIN

Shahnaj Begum[1], Muhammad Saiedullah[2], Md Omar Faruque[3], Md Masudul Hasan Khan[#4]

ABSTRACT

Background and Aim: Adipokine, vaspin is postulated to be an insulin sensitizer. However, it's role in relation to hyperglycemia still to be clearly understood and studying serum vaspin in non-obese impaired glucose tolerance subjects appeared to be interesting. The aim of this study was to evaluate serum vaspin levels in impaired glucose tolerant (IGT) subjects with normal BMI and compared with age-sex-BMI matched apparently healthy controls. **Materials and Methods**: This study included 26 subjects with IGT and, age- and sex-BMI matched 20 apparently healthy controls which was conducted between February-December 2015 in the Bangladesh University of Health Sciences (BUHS) and approved by its ethical committee. Fasting serum insulin and vaspin levels were measured by enzyme linked immunosorbent assay. Insulin secretory capacity (HOMA-%B), insulin sensitivity (HOMA- %S) and insulin resistance (HOMA-IR) were assessed from fasting glucose and insulin using HOMA2 calculator. Results were expressed as mean$\pm$SD and median (range) as appropriate. Student's unpaired 't' and Mann Whitney Tests, as appropriate, were performed using MedCalc 11.4 and a two-tailed $p<0.05$ was considered as significant. **Results:** The mean (SD) of age and BMI were 43.2$\pm$7.9, 41.8$\pm$6.3 years and 24.4$\pm$2.0, 23.7$\pm$2.3 Kg/m^2 respectively. Fasting insulin ($p<0.001$), HOMA-%B ($p=0.001$) and HOMA-IR ($p<0.001$) were significantly higher and HOMA-%S ($p=0.0003$) was significantly lower in IGT compared to control. The median (95% CI) of serum vaspin levels were 0.73 (0.56-1.26) ng/ml in IGT and 1.95 (1.13 - 2.49) ng/ml in controls ($p=0.003$). **Conclusions:** Data concluded insulin resistance in impaired glucose tolerant subjects as evidenced by low HOMA-%S and higher HOMA-IR possibly resulted from lower circulating vaspin level and needs to further investigate the possible mechanism(s) in this regard.

Key Words: Vaspin, Impaired glucose tolerance, Beta cell function, Insulin sensitivity, Insulin resistance

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Introduction

Recently identified visceral adipose tissue-derived serine protease inhibitor (vaspin) found to show profound insulin-sensitizing effects.[1,2] This adipokine improves glucose tolerance through its effects on human kallikrein 7 (hK7),[3] genes associated with insulin resistance1or by reducing food intake.[4] Expression of vaspin gene in human adipocytes and its higher circulatory levels are observed in obesity, obesity-associated diseases and type 2 diabetes mellitus (T2DM).[4-7]

A number of study have reported higher circulatory vaspin in subjects with T2DM in various population[8-10] while Feng et al[11] and Yan et al[12] in Chinese population and Tasnim et al[13] in a group of Bangladeshi population have reported lower serum vaspin levels in T2DM. Low serum vaspin concentrations in impaired glucose tolerant (IGT) has also been observed in Korean population[7] and in a group of Bangladeshi population[14] which is in agreement with corresponding diabetic groups[13] but possibly be associated with obesity. The aim of this study was to determine circulating serum vaspin concentrations in impaired glucose tolerant subjects with normal body mass index (BMI) and to compare with BMI-matched nondiabetic controls.

Materials and Methods

This cross-sectional observational study was conducted between February to December 2015 in the Dept Physiology and Molecular Biology, Bangladesh University of Health Sciences (HUHS) and approved by institutional ethical committee. The included 26 subjects with impaired glucose tolerance with BMI $\leqslant$ 27.5 kg/m^2 (18 male and 8 female) aged between 30 to 55 years and age-sex-BMI matched 20 healthy subjects with BMI $\leqslant$27.5 Kg/m^2 (14 male and 6 female) were included. IGT was defined according to WHO criteria. Subjects with diabetes mellitus (according to WHO definition), with a previous or current histories of gestational diabetes mellitus (GDM), hypertension, patients with serious comorbid diseases (infection, stroke, myocardial infarction, major surgery), subjects using drugs that significantly affect glucose metabolism (anti-hyperglycemic agents, glucocorticoids, thiazide diuretics etc.) and, pregnant and lactating mothers were excluded.

With all aseptic precautions, blood samples were collected after an overnight fast and aliquots of plasma/serum were kept at -20°C for future biochemical analysis. Glucose concentration was measured by hexokinase method using automated chemistry analyzer, Dimension RxL Max (Siemens Healthcare Diagnostics Inc., USA). Total cholesterol, triacylglycerol, high-density lipoprotein cholesterol, creatinine and alanine amino transferase were measured by spectrophotometric method using Dimension RxL Max chemistry analyzer. Low-density lipoprotein cholesterol was calculated by Friedewald formula.[15] Serum vaspin and insulin were determined using enzyme-linked immunosorbent assay.

Data were analyzed by Student's t-test and Mann Whitney Tests using Med Calc 11.4 and a two-tailed $p < 0.05$ was considered as statistically significant.

Results

In this cross-sectional observational study, 46 subjects were included according to inclusion-exclusion criteria, among them 26 subjects had impaired glucose tolerance (IGT) and the rest 20 were age-sex matched apparently healthy controls. The study was conducted to explore the status of circulating vaspin levels in subjects with impaired glucose tolerance and to compare with controls.

Clinicobiochemical characteristics of the study subjects

Characteristics of the study subjects and controls were presented in table 1. IGT group and controls were matched for age (p=0.650) and BMI (p=0.294). The age ranges for IGT and control groups were 30-55 years and 32-53 years respectively. In IGT group, 69% were male, in control, 70% were male. The waist-hip ratio (WHR) were similar in both groups (p=0.264). Blood pressures were similar in both groups (p>0.05). The IGT group had significantly higher fasting and postprandial plasma glucose levels compared to control group (Table 1). Compared to the mean of HbA_{1c} in the control group, the mean of HbA_{1c} values was significantly higher in IGT group (p<0.0001) and mean was within the range of prediabetes according to ADA diagnostic criteria based on HbA_{1c}. Among the lipid parameters studied, fasting serum total cholesterol, fasting serum triacylglycerol and low-density lipoprotein cholesterol were higher andfasting HDL-cholesterol was lower in IGT groups compared to control but not statistically significant (Table 1). Serum creatinine and ALT levels were similar in IGT and control subjects.

Serum vaspin and insulinemic status of the study subjects

Insulinemic status of IGT and control group is presented in Table 2. The median (95% CI) value of fasting serum insulin was significantly higher in IGT compared to control (p<0.001). Compared to control, insulin secretory capacity as assessed by HOMA %B was higher in IGT group and it was statistically significant (p=0.001). Insulin sensitivity as assessed by HOMA %S in IGT group was significantly reduced compared to control (p<0.0001) and insulin resistance as assessed by HOMA IR was significantly higher in IGT group compared to control (p= 0.004).

Table 1: Clinico-biochemical characteristics of the study subjects

Parameters	IGT (n=26)	Control (n=20)	p value
Age (yrs)	43.2±7.9	41.8±6.3	0.482
Sex (male/female)	18/8	14/6	-
BMI (kg/m^2)	24.4±2.0	23.7±2.3	0.294
WHR	0.99±0.05	0.97 0.07	0.264
SBP (mmHg)	116±14	110±11	0.122
DBP (mmHg)	77±11	73±10	0.210
FPG (mmol/L)	5.6±0.6	5.0±0.4	<0.001
PPG (mmol/L)	9.8±0.8	5.8±0.9	<0.0001
HbA1c (%)	6.2±0.4	5.3±0.3	<0.0001
Triacylglycerol (mg/dl)	172±77	150±68	0.318
Total Cholesterol (mg/dl)	183±71	162±55	0.280
HDL-c (mg/dl)	39.3±8	41.3±10	0.455
LDL-c (mg/dl)	110±66	91±47	0.281

Results were expressed as mean±SD and number as appropriate. Unpaired Student's t-test was performed to calculate statistical significance. P<0.05 was taken as level of significance. BMI, Body mass index; WHR, Waist hip ratio; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, fasting plasma glucose; PPG, post prandial glucose.

Serum vaspin levels in control and IGT groups

In IGT group, the median (95% CI) of serum vaspin concentration was 0.73 (0.56 - 1.26) ng/ml and it was 1.95 (1.13 - 2.49) ng/ml in control (Table 2). Difference between median value was statistically significant (p = 0.003). Serum vaspin concentrations were significantly lower in IGT only in male [0.71 (0.56 - 1.19) vs 1.53 (0.97 - 2.45) ng/ml, p = 0.009) but not female [1.05 (0.46 - 2.70) vs 2.66 (1.59 - 3.05) ng/ml, p = 0.126). Furthermore, serum vaspin showed no significant difference between male and female in IGT group (p = 0.415) or control group (p = 0.111) (Fig 1).

Table 2: Serum vaspin and insulinemic status between IGT and control

Parameters	IGT (n=26)	Control (n=20)	p value
Vaspin (ng/ml)	0.73 (0.56 - 1.26)	1.95 (1.13 - 2.49)	0.003
Fasting Insulin (μIU/ml)	17.5 (16.6 - 23.1)	11.4 (10.3 - 13.5)	<0.001
HOMA %B	160.9 (122.4 - 176.2)	93.9(76.8 - 125.9)	0.001
HIOMA %S	36.9 (28.9 - 41.7)	55.7 (49.6 - 59.4)	<0.001
HOMA-IR	2.7 (2.4 - 3.5)	1.8(1.7 - 2.0)	0.004

Results were expressed as median (95% CI); Mann Whitney U test between case and control performed to calculate statistical significance. P<0.05 was considered as level of significance.

HOMA-%B, homeostatic model assessment percent B cell secretion (B cell insulin secretory capacity); HOMA-%S, homeostatic model assessment percent insulin sensitivity; HOMA IR, homeostatic model assessment insulin resistance

Discussion

Visceral adipose tissue-derived serine protease inhibitor (vaspin) is one of the recently identified adipocytokine in obese OLETF rats which have potential insulin-sensitizing effects[1,2] and claimed to improve glucose tolerance and affects the candidate genes for insulin resistance.[1] It also acutely reduces food intake in obese mice.[16] In human obesity-associated diseases and type 2 diabetes mellitus, vaspin gene expression in adipocytes and circulating vaspin levels are found to be positively related.[5-7] The exact mechanism by which vaspin is linked to the impairment of glucose homeostasis, insulin sensitivity, developing type 2 DM or T2DM itself are seems to be controversial and are not clearly understood. Since serum vaspin level was found to be significantly lower in type 2 diabetic subjects of Bangladeshi origin,[13] It is of scientific interest to evaluate circulating vaspin in subjects with IGT to explore its association with the progression of type 2 DM.

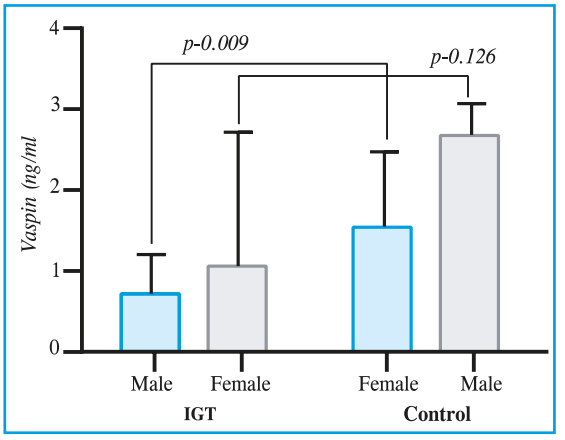

Figure I. Comparison of serum vaspin (ng/ml) between IGT and control according to gender.

In this study, the mean value of fasting serum insulin, insulin secretory capacity (HOMA %B) and insulin resistance as assessed by HOMA IR were significantly higher with reduced insulin sensitivity (HOMA %S) in IGT group compared to control that represented the characteristic feature of intermediate hyperglycemia. These results are in accordance with previous studies done on Bangladeshi population.[13,17]

In this study, mean (SD) of serum vaspin is significantly lower in subjects with impaired glucose tolerance (IGT) with normal BMI than apparently healthy control irrespective of gender. This result is consistence with the study one in Korean IGT subjects.[7] Recntly, Jian et al reported that low circulating vaspin is a risk factor for the development and progression of type 2 DM in a group of Chinese population.[18] Previous study done on newly diagnosed T2DM subjects has also reported a lower circulating vaspin in T2DM in this population.[13] Lower serum vaspin in T2DM of Yan et al[12], Feng et al[11], Choi et al[7] is in accordance with current findings. On the other hand, a number of study reported a higher levels of serum vaspin in T2DM[8-10,19] as well as in prediabetes.[20] This

inconsistency indicates a bi-directional mode of vaspin in relation to T2DM which may be greatly influenced by other confounders.

Conclusions

Data suggested that insulin resistance in impaired glucose tolerant subjects possibly triggered by lower circulating vaspin level may be occurred through yet unexplained mechanism. It would be interesting to look into the interrelationship of different adipokines in the loss of glucose homeostatic mechanisms in this population.

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LAPAROSCOPY AS A DIAGNOSTIC TOOL IN THE EVALUATION OF CHRONIC PELVIC PAIN: EXPERIENCE IN NON-GOVERNMENT MEDICAL COLLEGE HOSPITAL

Naireen Sultana[1,#], Nahid Sultana[2], Hasina Yesmin[3], Farjana Islam[4], Rawshan Ara Begum[5]

ABSTRACT

Background and Aim: Chronic pelvic pain, a common problem in gynecology practices, poses major challenge in diagnosis due to diverse etiology, complex natural history and poor response to therapy. Considering the usefulness of laparoscopy to directly delineate structures the present study was aimed to examine pelvic organs in patients with pelvic pain appeared inconclusive on ultrasonography and clinical examinations. **Materials and Methods:** A total 51 patients with chronic pelvic pain for more than six months consecutively underwent laparoscopic examination in Non-government Medical College in Dhaka. Relevant history was taken and meticulous clinical examination done. Laparoscopy was performed under general anesthesia. Data were expressed as number (percent) and analyses carried out using statistical package for social science (SPSS) for Windows Version 16.0. P value <0.05 was considered as statistically significant. **Results:** Study subjects were between 26-45 yrs of age. Of the 51 women 38 (74.5%) were between 26-35 yrs (45.1% and 29.4% in 26-30 and 31-35 yrs age group respectively, $p=0.332$). Per-speculum examination demonstrated normal cervix in 41 (80.4%) cases. Bimanual examination revealed normal uterus and fornices in 39 (76.5%) and 35 (68.6%) cases respectively. Laparoscopic examination confirmed no pathology in 13 (25.5%) compared to 41 (80.4%) on clinical examination ($z=2.197$, $p=0.028$). Pelvic pathology revealed on laparoscopy included pelvic adhesions in 14 (27.5%), endometriosis 7 (13.7%), pelvic inflammatory disease 5 (9.8%); uterine fibroid 3 (5.9%) and pelvic congestion syndrome 2 (3.9%). **Conclusions:** Data concluded that laparosccopic examination confirmed abnormalities in pelvic area of 76% cases suggesting the procedure as an excellent tool to reveal possible cause(s) of perplexing chronic pelvic pain in women. The procedure also provided additional benefit to undertake corrective measures like adhesiolysis and cyst aspiration.

Key Words: Chronic pelvic pain, laparoscopy, pelvic adhesion, endometriosis.

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Introduction

Chronic pelvic pain is the most common and perplexing complaints of patients presenting in gynecology practices.[1,2] It has been described in a variety of ways, it is most commonly defined as 'non menstrual pelvic pain of six months or more duration, that is severe enough to cause functional disability or require medical or surgical treatment'.[2] A recent systemic review reported the prevalence of chronic pelvic pain among women worldwide, with rates of 6% to 27%[3], although there was a lack of consensus on the definition of chronic pelvic pain. In primary care practices 39% of women found to complain of pelvic pain and noncyclic pelvic pain found to vary from be 4-43% and in India and Pakistan the prevalence was around 5.2% and 8.82%.[4,5]

Chronic pelvic pain attributed to number of abnormalities in pelvic organs.[6-11] Objective evaluation of pain poses a complex task as most of the times physical signs are absent and patients are treated symptomatically or referred to psychiatrist as somatoform disorder without adequate diagnostic evaluation.[12] Clinical history and clinical examinations, though meticulously done, are not sufficient and concluding for exact diagnosis of chronic pelvic pain. Since the late 1960s laparoscopy, has been used as both diagnostic and therapeutic modality in patients with chronic pelvic pain and presently being considered as the gold standard diagnostic tool for evaluation of chronic pelvic pain and by late 1980s the potential application of operative laparoscopy been recognized.[13] And chronic pelvic pain has become responsible for up to 50% of laparoscopies in women.[14]

Laparoscopy, in addition to direct visualization of pelvic and abdominal viscera diagnosis of endometriosis and adhesions, allows possible option(s) for visually directed biopsy samples and undertaking simultaneous treatment of evident cause(s) at the same sitting.[15] With appropriate patient preparation, supported by skilled anesthetists and the procedure carried out an experienced gynecologists the hazards of laparoscopy found to be virtually nil1.[16-21] The procedure is usually of short duration and additionally patient's hospital stay also minimum which ultimately make it cost effective. Laparoscopic procedure was carried out to evaluate unexplained abdominal pain and around 84% cases correct diagnosis was possible[22] and another study demonstrated cost effectiveness of the procedure.[23] Diagnostic laparoscopy is frequently done in gynecological practices in Bangladesh. However, data are lacking that evaluated the usefulness in regard to diagnosis and its impact on their treatment. The present study evaluated the usefulness of laparoscopy in dealing chronic pelvic pain presented to gynecological practices.

Materials and Methods

This cross sectional study was carried out in the Dept of Obstetrics & Gynaecology, Shaheed Monsur Ali Medical College & Hospital, Dhaka, during the period of October 2013 to March 2014. The subjects were informed about the nature and purpose of the study and written consent was obtained from the consenting cases. Institutional permission was obtained to mitigate the ethical issues regarding the study. Women suffering from chronic pelvic pain admitted in this hospital and having lower abdominal pain for more than 6 months were included in this study. Patients with haemodynamic instability, coagulopathy, uncontrolled systemic disease- diabetes, hypertention, chronic obstructive airway disease, known massive intra-abdominal adhesions, suspected malignancy were excluded from the study. Variable of interest were age, findings of clinical and laparoscopic examination were recorded in a predesigned data collection sheet.

Data were expressed as number (percent). Statistical analyses were carried out using statistical package for social science (SPSS) for Windows Version 16. P vale <0.05 was taken as level of statistical significant.

Results

Age range of the patients was 20-45 years. Of the 51 (74.5%) patients were between age 26-35 years [45.1% and 29.4% in 26-30 and 31-35 age groups respectively, p=0.332] (Table I).

Table 1: Age distribution of the study subjects (n=51)

Age (yrs)	Number	Percent (%)
<26	9	17.65
26-30	23	45.10[a]
31-35	15	29.41[b]
36-40	3	5.88
41-45	1	1.96

Results were expressed as number (percent). Proportion test was performed.

P<0.05 was taken as level of significance. a vs b p=0.332

Findings of per-vaginal examination were shown in table 2. No abnormality was observed in the external genitalia in none of the subjects. Per-speculum examination revealed normal cervix in 41 (80.39%) cases. Of the total in cases 5 (9.80%) and 3 (5.88%) had discharge and deposit respectively and 2 (3.92%) were hypertrophied (Table 2). Bulky uterus was found in 5 (9.8%) cases. Uterus was retroverted and restricted to movement in 3 (5.88%) and 4 (7.84%) cases

Laparoscopic examination of the uterus ovaries was shown in table 3 and 4 respectively. In 33 (64.7%) out of 51 cases uterus was normal. In 5 (9.8%) cases uterus was bulky. Endometriotic spot was present in 8 (15.69%) and fibroid appearance 3 (5.88%) cases. Uterus could not be visualized in 2 (3.92%) cases (Table 3).

Ovary was normal in 32 (62.47%) of cases in right and 36 (70.59%) left side. Adhesion was present in 8 (15.69%) and 7 (13.72%) in the right and left

Table 2: Findings of the per-vaginal examination of the study subjects (n=51)

Variables	Per-vaginal examination	
	Number	Percent (%)
External genital		
Normal	51	100
Perspeculum examination of the cervix		
Normal	41	80.39
Hypertrophied	2	3.92
Deposit present	3	5.88
Discharge present	5	9.80
Bimanual examination of uterus		
Normal	39	76.47
Bulky	5	9.80
Retroverted	3	5.88
Restricted movement	4	7.84
Fornices		
Normal	35	68.63
Tender	13	25.49
Nodule in posterior fornix	3	5.88

Results were expressed as number (percent).

ovary respectively. Other findings present were: simple cyst 5 [3 (5.68%) and 2 (3.92%) in right and left respectively], Endometriosis 7 [4 (7.84%) and 3 (5.88%) respectively. Luteal cyst was found in 4 [2 (3.92%) on both sides]. In one (1.96%) case polycystic ovary (right) cases observed (Table 4). Deposit was noticed in 2 (3.92%) cases both in round and broad and, 4 (7.84%) uterosacral ligaments (Table 5).

Table 3: Laparoscopic findings of uterus of the study subjects (n=51)

Findings	Laparoscopic examination of the uterus	
	Number	Percent (%)
Normal size	31	60.8
Bulky uterus	5	9.80
Endometriotic spot	8	15.69
Fibroid	3	5.88
Non visualization of uterus	2	3.92

Results were expressed as number (percent).

Table 4: Laproscopic findings of ovaries of the study subjects (n=51)

Findings	Laparoscopic examination of the uterus	
	Right ovary N (%)	Left ovary N (%)
Normal ovary	32 (62.74)	36 (70.59)
Corpus luteum	2 (3.92)	2 (3.92)
Simple cyst	3 (5.68)	2 (3.92)
Polycystic ovary	1 (1.96)	0
Endometriosis	4 (7.84)	3 (5.88)
*Adhesion	8 (15.69)	7 (13.72)
Failure to visualize	1 (1.96)	1 (1.96)

Results were expressed as number (percent).
**Adhesion observed in both ovaries in one case*

Table 6 summarized abnormal findings revealed on laparoscopic examination. In 13 (25.5%) cases no abnormalities was observed on laparoscopic examination. The most common pelvic pathology seen in the study was pelvic adhesion 14 (27.4%) followed by endometriosis 10 (19.6%), PID 5 (9.8%) cases and ovarian cysts 4 (7.8%) cases. Fibroid uterus and pelvic congestion syndrome was found in 3 (5.9%) and 2 (3.9%) cases respectively.

Table 5: Laparoscopic findings of the utero-ovarian ligaments of the study subjects (n=51)

Findings	Laparoscopic examinations of the round, broad and uterosacral ligaments					
	Round ligaments		Broad ligaments		Broad Uterosacral ligaments	
	No	%	No	%	No	%
Normal	49	96.08	49	96.08	47	92.16
Deposit	2	3.92	2	3.92	4	7.84

Results were expressed as number (percent).

Table 6: Final laparoscopic findings of the study subjects (n=51)

Diagnosis	Laparoscopic findings	
	Number	Percent (%)
Pelvic adhesion	14	27.4
Endometriosis	7	13.73
Pelvic congestion syndrome	2	3.9
Pelvic inflammatory disease	5	9.8
Ovarian Cyst	4	7.8
Uterine fibroid	3	5.9
Normal findings		

Results were expressed as number (percent).

Discussion

Laparoscopy has been attributed to be a useful diagnostic procedure while other modalities provide inadequate information. The procedure confers benefit for the practitioners to observe the internal structures, reduce exploratory laparotomy and interpret with the presentations and in necessary cases take appropriate measures. In case of chronic pelvic pain due to pelvic congestion and endometriosis radiological and imaging tools are of little use. It has been postulated that entity of chronic pelvic pain is best investigated laparoscopically before any treatment is planned.[24]*Results were expressed as number (percent).*

The present study evaluated 51 cases of which 74.5% were in age group 26-35 years. This age of incidence of chronic pelvic pain in the present study is consistent with other studies.[25] Age range of the subjects was between 19-48 yrs (mean 28 yrs). In the present study clinical examination demonstrated 40 patients with normal finding against 13 by laparoscopic examination (p=0.028) which highlighted the usefulness of laparoscopy in evaluating chronic pelvic pain. The important aspect of

laparoscopic examination is direct visualization of internal organs. Endometriotic deposit was observed 7 (13.7%) occasions and pelvic adhesion 14 (27.4%). This confirmed diagnosis definitely is superior to other modalities like sinology and imaging which were unable to detect the pathology. Endometriosis in the ligament was also detected in the present study. Interestingly the rate of endometriosis found to be lower than that observed in the report from Slovakia.[26] but higher one other study.[27] The other important feature in the present study was detection of pelvic adhesion in 27.5% cases which could have not be possible to diagnose by other modalities. The present study, however, involved with small number of subjects compared to other reports which analyzed large number of samples over a longer period.[28-32] Rate of abnormalities reported in those studies were much higher and given a clear characterization of the procedure in the evaluation of chronic pelvic pain in women. In one study the most frequent findings were adhesions 22.3%, endometriosis 20.4%, pelvic inflammatory disease 17.7%.[28] in other study, however, pelvic adhesion and endometriosis were present in 55% and 29% cases respectively.[29] Adhesion and endometriosis were also demonstrated of very high frequency in different studies.[29-32]

Though, unlike other studies, the present study was involved with small number of stubjects yet it has clearly demonstrated the importance of the laparoscopic procedure to identify specific causes like endometriosis and pelvic adhesion in substantial number of cases and attributed to useful diagnostic procedure.

Apart from hazards of anesthesia the operative risk is the minimum. In the present study hemorrhage occurred in one (1.96%) case. This showed relatively high percentage (1.96%) of complications compared to the 0.15%[32] This, however, may be explained only by the fact of only 51 cases in the study. Other complications, though infrequent, following laparoscopic procedure included bowel injury in two cases and one hemorrhage due to vessel injury.[33] The present study again demonstrated that if procedure is carried out with utmost care operation induced complications remain very minimum.

Conclusions

Laparoscopic procedure is an important tool to examine internal structures and identify specific cause(s) of chronic pelvic pain. With appropriate selection of the patient and with adaptations of careful procedure in experienced hands, its operative hazards can be minimized.

Laparoscopy is a useful diagnostic tool evaluate chronic pelvic pain in women and can be used judicially for individualized treatment.

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DIAGNOSTIC VALUE OF SERUM ADENOSINE DEAMINASE (ADA) OF SPUTUM SMEAR NEGATIVE PULMONARY TUBERCULOSIS

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ABSTRACT

Background and Aim: Pulmonary tuberculosis (PTB) is still one of the major worldwide public health problems and in particular affecting the developing countries including Bangladesh. Sputum negative PTB poses stark challenge for clinicians in its diagnosis and subsequent treatment. Hence the study was aimed to estimate serum adenosine deaminase (ADA) of smear negative PTB cases as a tool in the diagnosis of these cases. **Materials & Methods:** This case control study was conducted between January to December 2011 in the Dept of Medicine, SSMC & Mitford Hospital, Dhaka which included a total 105 subjects and stratified as sputum smear negative PTB cases (Group A, n=35), non tubercular common respiratory diseases [chronic obstructive pulmonary disease (COPD), Bronchial asthma, suppurative lung disease and, Bronchial carcinoma cases] (Group B, n=35) and healthy controls (Group C, n=35). Serum ADA was measured by colorimetric method. Data analyses were carried out using SPPS and statistical tools (Chi-square test and ANOVA) were performed as appropriate. $P<0.05$ was taken as level of significance. **Result:** Serum ADA (mean±SD, U/L) level in sputum smear negative PTB group, Group A (40.39±21.48) ($p<0.001$) was significantly higher compared to those with non tubercular pulmonary diseases, Group B (12.73±3.23) and controls, Group C (6.63±2.09). A cut-off value for serum ADA of 24 U/L demonstrated a `sensitivity to be 81.25, specificity 66.67% and accuracy 80%. **Conclusions:** Data concluded that measurement of adenosine deaminase in sputum smear negative tuberculosis cases may be an additional tool in its diagnosis but still needs to be careful in interpretation of the laboratory value.

Key Words: Serum ADA, Pulmonary Tuberculosis, Non tubercular pulmonary diseases.

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Introduction

Tuberculosis remains to be the single largest infectious disease world wide causing 3 million deaths annually which accounts about 5 deaths every minute. Annually more than 8 million people develop pulmonary tuberculosis and approximately 1.8 million cases result in death.[1,2] Out of the total cases 40% originate in the South East Asia[1]. Diagnosis of tuberculosis is usually based on clinical presentation, radiologic findings, and positive tuberculin test with or without sputum acid fast bacillus positivity.[3,4] However, clinical and radiological features often show mark variability and it becomes more confusing when tuberculin test comes out negative.[4] In this situation antituberculer therapy is given empirically.[4] Acid fast bacilli (AFB) positive sputum smear and culture of mycobacterium is the gold standard for the diagnosis of pulmonary tuberculosis.[1] Problem arises when sputum for AFB repeatedly appears negative and the reason, however, is attributed to the fact that to detect the bacilli microscopically there should be at least 50,000 bacilli per milliliter of sputum.[1] Culture for tubercle bacilli is resource demanding and time consuming.[1,5] Chest radiograph provides only a probable diagnosis since it is often difficult to differentiate the focus of pulmonary tuberculosis from other obscure lungs shadows of pneumonitis and malignancies.[1] Researchers are working tirelessly for a sensitive and specific biomarker which might help solve the dilemma in the diagnosis of tuberculosis. Adenosine deaminase (ADA) an enzyme of purine catabolism has been shown promising results.[5] ADA level was found to be ten times higher in lymphocytes of those suffering from tuberculosis.[6] The level of ADA activity was found to be higher in those suffering from tuberculosis than other inflammatory diseases.[7] In pulmonary tuberculosis the increase in serum ADA levels and its cut-off level in the diagnosis has been demonstrated in number of studies and in addition its level shown to decline with the initiation of treatment.[8,9] Determination ADA is simple and rapid and more importantly the laboratory set up is not resource demanding.[10] Considering the above mentioned facts the present study was undertaken to determine ADA level in patients suffering from pulmonary tuberculosis and those with nonpulmonary disease to test usefulness of the marker molecule in the diagnosis of pulmonary tuberculosis.

Materials and Methods

Study subjects

A total 105 subjects were recruited in the study between January to December 2011 which was conducted in the department of Medicine, Sir Salimullah Medical College (SSMC) & Mitford Hospital. Subjects were selected purposively. Inclusion criteria included persistent cough for more than three weeks or more accompanied by one or more of the symptoms of prolonged fever, evening rise of low grade fever or high grade intermittent fever, coughing out of sputum with blood or hemoptysis, weight loss, unusual tiredness and easy fatigability, night sweating, chest pain, shortness of breath and anorexia/loss of appetite.

Three sputum samples, consists of 1st morning spot sample, 2nd overnight collection and 3rd morning on spot sample, of suspected pulmonary tuberculosis patients. Those had smear negativity in all three sputum samples were termed as negative pulmonary tuberculosis (PTB) cases (n=35) labeled as Group-A, according to WHO and National TB Guideline.

Subjects suffering from pulmonary diseases other than pulmonary tuberculosis such as bronchial asthma, chronic obstructive pulmonary disease (COPD), suppurative lung disease 'bronchiectasis' and lung abscess and bronchial carcinoma served as disease control 'Group B' (n=35). Finally 35 normal healthy, age- and sex-matched individuals served as healthy control 'Group C' (n=35).

Blood Sample Collection and Processing

Blood sample (5 ml) was collected taking all aseptic precaution, centrifuged and separated serum preserved for estimation of ADA. Serum ADA was estimated by enzymatic colorimetric method in the Microbiology & Immunology Department, BSMMU.

Ethical Consideration

The study protocol was approved by the Institutional Ethics Committee (IEC). Purpose and nature of the study was brief to the patients and written consent was taken from all the respondents. All the subjects were assured of the strict maintenance of confidentiality of data and purpose of its use.

Statistical Methods

Data were expressed as mean±SD, median, minimum-maximum as appropriate. One way ANOVA was carried out to calculate statistical difference among groups. The usefulness of the ADA was evaluated using a receiver-operating characteristics (ROC) curve analysis. For the validity of the study outcome; Sensitivity, Specificity, Positive predictive value (PPV) and Negative predictive value (NPV) were calculated. Data were managed by computer base program statistical package for social science (SPSS) for Windows Version.[16] P<0.05 was taken as level of significance.

Results

Male female distribution of the study subjects was shown in figure 1. The distribution was did not show any statistical difference. The mean (±SD) serum ADA (U/L) activity was shown in table 1. In Group A ADA activity was significantly higher (40.39±21.48) compared to the disease controls 'Group B' (12.73±3.23) and healthy controls 'Group C' (6.63±2.09) p<0.001).

Table 1: Serum ADA level of the study subjects

Variable	Group A (n=35)	Group B (n=35)	Group C (n=35)
Serum ADA (U/L)	40.39±21.48[a]	12.73±3.23[b]	6.63±2.09[b]
	21.10 99.40	6.70 20.30	3.20 13.40

Results were expressed as mean±SD and range (minimum-mxximum).

Group A, Sputum smear negative pulmonary tuberculosis cases; Group B, Non tuberculous respiratory disease cases; Group C, Healthy controls One way ANOVA (Bonferroni) was carried out to calculate statistical difference. Group B and C vs Group A p<0.001; Group B vs Group C, p=0.137 Different superscript in the row indicates statistical significant difference at p<0.001.

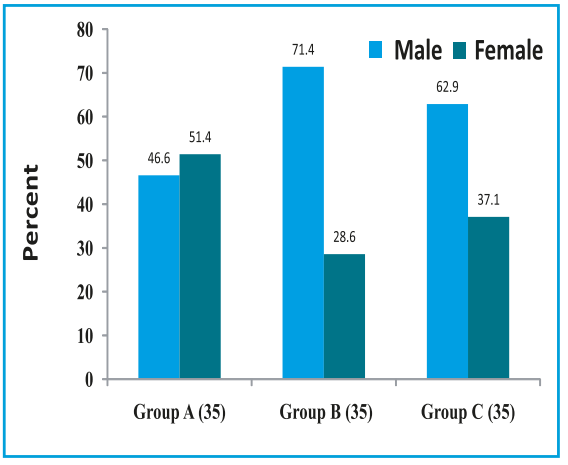

Figure I: Male and female distribution (%) of the subjects in each group.

Sensitivity for ADA activity level at cut-off 24 U/L was the highest. Positive predictive value was around 95 in all three cut-off value. Specificity and negative predictive value showed similar trend in all three cut-off levels (Table 2).

Receiver operative curve demonstrated separation of subjects suffering from pulmonary tuberculosis or other diseases (Figure II).

Table 2: Validity of serum ADA estimation of smear negative pulmonary tuberculosis (Group A) subjects

	ADA cut off value		
	24 U/L	30 U/L	33 U/L
Sensitivity	81.25	62.50	43.75
Specificity	66.67	66.67	66.67
Positive predictive value	96.30	95.24	93.33
Negative predictive value	25.00	14.29	10.00
Accuracy	80.00	62.86	45.71
Area under curve	0.740	0.646	0.552

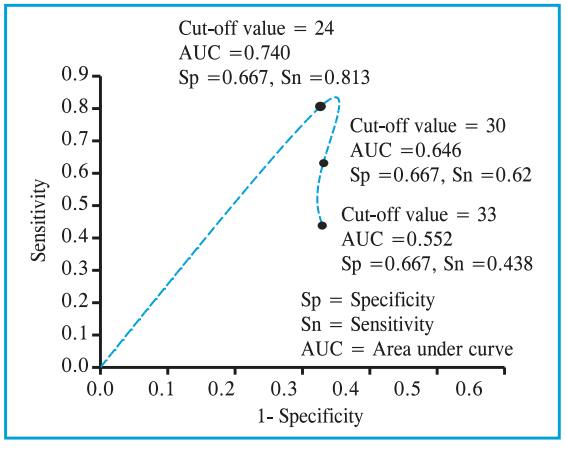

Figure II: ROC curve at different cut-off value of ADA in relation to standard criteria for sputum negative tuberculosis in Group A subjects.

Discussion

Considering the reemergence of tuberculosis and its high prevalence of multidrug resistance cases[16] its timely diagnosis is of paramount importance to reduce the morbidity and mortality. Diagnosis of tuberculosis is straight forward when acid fast bacilli are identified in the sputum and/ or M. tuberculosis culture become positive. In the event of sputum negativity and inconclusive radiological and other supportive laboratory investigations decision making hang in the balance.[4]

Table 2 Researchers are relentlessly trying to solve this dilemma of diagnosis of tuberculosis and targeted for a serological markers. The most promising breakthrough appeared to be the high activity of ADA in subjects with tuberculosis.[5,11] In the present study mean ADA was significantly higher ($p<0.001$) compared to disease control and healthy controls which is consistent with other studies.[4-6] Jhamaria et al (1988) demonstrated that, sputum negative patients with minimal, moderately advanced and far advanced disease the mean serum ADA levels were 42.09 ± 1.46, 40.02 ± 2.58 and 39.52 U/L respectively. They used 33 U/L as the cut-off and which had shown 100% specificity and 98% sensitivity.[6] A study involving 51 children with confirmed tuberculosis and 20 healthy controls showed significantly high serum ADA level compared to the controls.[13]

ADA was also determined in pleural fluid of highly endemic of tuberculosis and used as a reliable basis to start anti-tubercular drug preceding the availability of culture and biopsy report.[9] This study highlighted the usefulness of ADA assay not only in serum but also in other body fluid to decide about the suspected cases of smear negative pulmonary tuberculosis case. In addition ADA assay was also found to be useful in assessing the response of antitubercular treatment1.[11] Serum ADA activity in effusion due to pleural, pericardial, meningeal and peritoneal tuberculosis was also demonstrated in countries with high tuberculosis prevalence.[12]

At follow up after one month out of 35 sputum smear negative cases 28 (80%) showed signs of remission clinically. The rest seven (20%) did not report in scheduled follow up visit. However, one of the major limitations of the study was failure of measurement of serum ADA of those cases. In that cases serum ADA activity status would have explained the usefulness of it prognostic value in addition of the diagnostic plausibility.

Measurement of serum ADA activity was carried out for extrapulmonary tuberculosis. The marker was found significantly higher compared to the controls and in the study the authors took a cut-off value of 33 U/L which demonstrated a sensitivity of 94.29%, specificity 92.16%, PPV 89.00% and NPV 95.92%.[14]

A cut off level of 24 U/l for serum ADA among smear negative pulmonary tuberculosis in the present study found to separate them clearly from the nontuberculer causes (Figure 1). Sensitivity of the ADA cut-off level for 24 U/l found to be 82% which is consistent with study of Lamsal et al.[10] and support its importance in using the test as a diagnostic tool. In this study cut-off value of 25 U/laws taken which also demonstrated almost similar level of sensitivity. For the present study when cut-off value for ADA 33 U/L was taken sensitivity, specificity, negative and positive predictive value and accuracy shown to be 43.75%, 66.67%, 93.33%, 10%, 45.75% and 0.552 respectively. When considered with other studies a cut-off of 24 U/L appeared to be consistent and possibly useful. However, its usefulness appeared relatively weak in particular for negative predictive value which was 25% to the contrary of Mathur and his group who had shown its to be 100% but positive predictive value was almost similar 96.3% vs 95.5% repectively.[15]

In the present study ADA activity was measured by colorimetric method. A standard curve was run for each batch of measurement and values for unknown samples determined extrapolating the standard curve. Inter- and intraassay quality checks, however, missing. In addition assay of ADA activity by enzyme linked immunosorbant assay, since it is presumed to be superior to the colorimetric method, would have been given more weight in the study. The data originated in the present study, however, strongly indicated the usefulness of measurement of ADA activity in the diagnosis of sputum smear negative pulmonary tuberculosis and estimation of the marker molecule in the follow up of those cases would have evaluated its prognostic validity for ADA activity.

Conclusions

The present study demonstrated that the determination of serum ADA is adequately sensitive and specific for the diagnosis of tuberculosis using a cut off value of ADA 24 U/L. Considering the cost of determination of ADA and user friendly laboratory methods the test may be done routinely; in particular when diagnosis of tuberculosis is in doubt, ie. sputum AFB negative pulmonary cases and also to differentiate pulmonary tuberculosis from non tubercular pulmonary diseases.

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We express heartfelt gratitude to the patients who consented for the test and use the results for the academic purpose and also the healthy controls to volunteer otherwise the study would have not been possible. The authors were also grateful to the hospital authority for their kind permission to conduct the study and staff for their cooperation during the study.

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RE-EMERGENCE OF SUSCEPTIBILITY OF SALMONELLA TYPHI TO OLDER ANTIMICROBIALS IN BANGLADESH -EXPERIENCE IN A TERTIARY CARE PEDIATRIC HOSPITAL

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ABSTRACT

Background: Typhoid fever 'enteric fever' is a common endemic disease in Bangladesh. It may cause fatal multi-system illness caused primarily by *Salmonella* enterica serovar typhi. It is also a major public-health problem in many developing countries, including Bangladesh. The manifestation-pattern of typhoid fever makes this disease a true diagnostic challenge. **Objective:** the aim of the current study was to detect the antimicrobial susceptibility pattern as well as changes in susceptibility profile of *Salmonella enterica serovar typhi (S. typhi)* blood isolates at Dhaka Shishu (Children) hospital during the period of 12 months from June 2015 to July 2016. **Materials and Methods:** A descriptive study analysed the patient's records for the period between June 2015 to July 2016. Blood culture of those samples was carried out by BACTEC-PEDFPLUF (Becton Dickinson) method and *Salmonella* was confirmed by serotyping using group and type specific antisera. Antibiotic susceptibility test was performed by disk- diffusion method. **Result:** A total 23 *S.typhi* culture positive isolates were obtained. A re-emergence of susceptibility to first-line-antibiotics like amoxicillin/ampicillin and chloramphenicol was observed in 18 (78.26%) cases ($p=0.018$) and notable decline in multidrug-resistant (MDR) strains was noticeable. All the isolates were resistant to nalidixic acid (100%). Susceptibility to third generation cephalosporin ranged from 95.65% to 100% ($p=0.0012$). About 78.26% and 39.13% of isolates and decreasing susceptibility to ciprofloxacin ($p=0.024$) and azithromycin ($p=0.697$) respectively. **Conclusion:** Data concluded the re-emergence of the susceptibility to first-line antibiotics and a notable decline in MDR strains of *S. typhi*. The third generation cephalosporins seemed to be effective therapeutic options and judicious use of these antibiotics is mandatory to prevent emergence of resistant strains.

Key Words: Typhoid fever, antibiotic resistance, re-emergence.

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Introduction

Typhoid fever is endemic in many developing countries particularly in the Indian sub-continent including Bangladesh.[1,2] In India, it is endemic with a morbidity ranging from 102 to 2219 per 100,000 population.[3] There is an estimated 13 million cases of typhoid fever per year in Asia.[4] The estimated mean incidence of typhoid fever is 150 to 900 per 100,000 people per annum in South America and Asia.[5] According to a recently-revised global estimate, typhoid causes 21.6 million illnesses every year, resulting in 216,500 deaths.[5] This obligatory human-pathogen is transmitted by faeco-oral route in the regions of low-standard of hygiene and sanitation. Antibiotic therapy constitutes the mainstay of management of enteric fever; mortality being as high as 30% in untreated cases, which falls to <1% with appropriate antibiotic therapy.[6] Failure to treat an infection properly leads to prolonged illness, thus increasing the chance of developing a carrier state in which persons are contagious and able to spread the resistant strains to others.[6]

Today due to its changing modes of presentation, as well as the development of multidrug resistance, typhoid fever has become difficult to diagnose and treat. Improved standards of public health have resulted in a marked decline in the incidence of typhoid fever in developed countries.[7] The emergence of resistant strains of Salmonella typhi poses a serious problem. The first major epidemic of multidrug resistant S. typhi was reported in 1972 in Mexico.[8] Since then, an increasing frequency of antibiotic resistance has been reported from all parts of the world, but significantly more from the developing countries.[9] A more useful definition of MDRST is reserved for strains resistant to all three first-line antityphoidal antimicrobial agents, namely ampicillin, chloramphenicol and trimethoprim-sulphamethoxazole.[10]

The use of chloramphenicol, ampicillin and cotrimoxazole in treating typhoid have become infrequent and quinolones took over as the first line of treatment. Fluoroquinolones have gained importance for the treatment of enteric fever in recent years. However, over the last few years there has been increase in the defervescence period in patients treated with quinolones. In our recent observation we have seen that ceftriaxone and cefixime (third generation cephalosporins) have become increasingly popular among physicians in treating typhoid and paratyphoid.[11] Hence, this study was undertaken to evaluate the current changes in antibiotic-response of typhoid fever. A considerable variation has been noted in the antimicrobial susceptibility patterns among isolates of *S. typhi* suggested in various studies conducted in different geographical locations. It was concluded that antibiotic susceptibility test has an important role in the treatment of typhoid fever.[12]

In recent years, both changes in the epidemiology and drug resistance profile of enteric fever have been noted by various workers. Firstly, many of the researchers have reported an increasing trend of *S. paratyphi* A over the last decade in India.[13] Considering, the changing trends in the susceptibility patterns of *S. typhi* along with high endemicity in the Indian subcontinent, continual monitoring of drug resistance has become imperative.

Materials and Methods

The study was involved in evaluation of data on Salmonella isolates originated following blood culture and sensitivity test carried out in the Dept of Microbiology, Dhaka Shishu (Children) Hospital between June 2015 and July 2016. Blood culture and sensitivity results were considered as cases which had serological test

(Widal test, TO 160) suggestive of typhoid fever. A total 23 samples from patients, age range upto 18 years, found to yield growth of *S. typhi*. The blood culture was processed by the Automated Blood Culture System-BACTEC PEDFPLUF (Becton Dickinson). Only one isolate per patient was included. Antibiotic susceptibility was performed using the Kirby-Bauer disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI) guidelines for the corresponding years.[14] The antibiotic discs used in antibiogram included ampicillin, amoxicillin, chloramphenical, cotrimoxazole, cefixime, ceftazidime, ceftriaxone, levofloxacin, azithromycin, ciprofloxacin and nalidixic acid. Results were expressed as number and percent. Proportion test was used to calculate statistical difference of percent value using Graph Pad Prism 5. $P<0.05$ was taken as level of significance.

Results

Among 23 *S. typhi* isolates 18 (78.26%) were found susceptible to ampicillin /amoxycillin and chloramphenical (z=2.374, p=0.018), 16 (69.56%) to cotrimoxazole (z=1.751, p=0.080), 23 (100%) to cefixime , 22 (95.65%) to ceftazidime, ceftriaxone and levofloxacin (p=3.222, p=0.0012), 11 (47.82%) to azithromycin, 3 (13.05%) to ciprofloxacin and 0 to nalidixic acid; pattern of reduced or intermediate susceptibility was 18 (78.26%) to ciprofloxacin (z=2.260/, p=0.024), 9 (39.13%) to azithromycin (z=0.396, p=0.697). Sensitivity to ceftriaxone, ceftazidime and cefepime was observed 22 (95.65%) (z=3.232, p=0.0012). Resistant pattern was 23 (100%) to nalidixic acid, 7 (30.43%) to cotrimoxazole, 5 (21.74%) to amoxycillin, ampicillin, chloramphenicol, 3 (13.03%) to azithromycin and 2 (8.7%) to ciprofloxacin.

Table 1: Anti-microbial Susceptibility of 23 S typhi isolates

Antimicrobial agent	Total tested (N)	Sensitive N (%)	Intermediate sensitive N (%)	Resistant N (%)
Amoxycillin/Ampicillin	23	18 (78.26)[a]	-	5 (21.74)[b]
Chloramphenicol	23	18 (78.26)[a]	-	5 (21.74)[b]
Cotrimoxazole	23	16 (69.56)[c]	-	7 (30.43)[d]
Cefixime	23	23 (100)	-	-
Ceftazidime	23	22 (95.65)	1 (4.35)	-
Ceftriaxone	23	22 (95.65)[e]	1 (4.35)[f]	-
Cefepime	23	22 (95.65)[e]	1 (4.35)[f]	-
Levofoxacin	23	22 (95.65)[e]	1 (4.35)[f]	-
Ciprofloxacin	23	3 (13.05)[g]	18 (78.26)[h]	2 (8.7)
Azithromycin	23	11 (47.82)[s]	9 (39.13)[t]	3 (13.05)
Nalidixic Acid	23	-	-	23 (100)

Results were expressed as number (percent).

Proportion test carried out to calculate statistical significance of percent sensitivity or resistance/ intermediate sensitivity. Different superscript in the columns indicated statistical significance; P values - a vs b, p=0.0018 c vs d, p=0.080; e vs f, p=0.0124; g vs h, p=0.024; s vs t, p=697.

Discussion

This descriptive study was carried out with an aim to evaluate the current antimicrobial susceptibility pattern of *S.typhi*. The re-emergence of susceptibility of S. typhi to the older first-line-antibiotics is a interesting information for its so far known multi-drug resistance nature. Typhoid has been a difficult-to-treat disease due to its changing pattern of susceptibility to antimicrobials and emergence of multi-drug resistance. As it is an obligatory human pathogen, there is difficulty in conducting clinical trials in regard to ethical issue. Besides this, carrier state of typhoid is another big

problem for its prevention and eradication. In this study, we found 78.26% *S. typhi* were susceptible to ampicillin and chloramphenicol, 69.56% co-trimoxazole which is similler to the study of Singhal et al (2014).[6] Raveendran et al (2008)[15] and Gupta et al (2005)[13] have also reported re-emergence of susceptibility to conventional first-line antibiotics (ampicillin, co-trimoxazole and chloramphenicol) and emergence of reduced susceptibility to ciprofloxacin among Salmonella species in different parts of India.[15,16] Singhal et al (2014) also showed that 84.5% of isolates had decreasing ciprofloxacin susceptibility. Aswini et al (2013) showed that 13.66% were resistant to ciprofloxacin but Bashudha et al (2007) found all isolates of their study were susceptible to ciprofloxacin. Madhulika et al (2003) found that 82% of their isolates were sensitive to ciprofloxacin.[17] Hasan et al (2011)[20] showed that 18.75% were resistant to ciprofloxacin and 62.5% to azithromycin respectively. In the present study we found that the pattern of reduced or intermediate susceptibility (I) to ciprofloxacin was 78.26% and to azithromycin was 39.13 % respectively whereas 13.03% isolates were resistant to azithromycin and 8.7%to ciprofloxacin.

In this study, we also found that ceftriaxone and cefixime are 95% and 100% susceptible to *S. typhi* respectively, which is similar to recent ICDDRB-Kamlapur Urban surveillance updates June 2016. Singhal et al (2014) showed all recent isolates of *S. typhi* susceptible to third generation cephalosporins. Both Khanal et al (2007)[18] and Choudhary et al (2013)[19] demonstrated similar susceptibility to third generation cephalosporins. Hasan et al (2011)[20] showed 100 cent percent susceptibility of *S. typhi* to ceftriaxone and ceftazidime but only Capoor et al (2006) reported that S. typhi was resistant to third-generation cephalosporins (though low,1%) in India.[21] This inference is encouraging that still ceftriaxone and cefixime are responding well.

Conclusion

The public health burden of typhoid fever can be substantially reduced by rapid diagnosis and appropriate antibiotic therapy. The susceptibility patterns of Salmonella species are changing frequently and are also varying according to variation of sites and population. There is a notable decline in MDR strains of *S. typhi*. The present study revealed that ceftriaxone and cefixime are the most effective drugs against S. typhi. The re-emergence of susceptibility to amoxycillin, ampicillin, chloramphenicol and cotrimoxazole seems to be increasing significantly, which may be due to long time avoidance by the physicians. Although the role of ciprofloxacin and azithromycin in the treatment of typhoid fever has recently been shown controversial. In our study, we found Salmonella highly resistant to nalidixic acid although it is less frequently used for the treatment of typhoid. Therefore we can conclude that older anti-typhoidals can be considered for the emerging multi-drug resistance of Salmonella.

Now a days, in many hospitals ceftriaxone is routinely used for any minor infection or fever which can lead to decrease in susceptibility of Salmonella to ceftriaxone. We suggest that the practicing physicians as well as the paediatricians should be rational in choosing antibiotics for treating any infection, not only typhoid. Judicious use of antibiotics is mandatory to prevent emergence of resistant strains.

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COMMUNITY ACQUIRED PNEUMONIA (CAP) IN CHILDREN IN DEVELOPING COUNTRIES - A REVIEW

Md Abbas Uddin Khan

ABSTRACT

Community-acquired pneumonia (CAP) is a potentially serious infection and is the single commonest and leading cause of death in under five children in developing countries. Severe pneumonia is an important diagnostic syndrome within WHO/UNICEF system for triage and clinical management in developing countries, the Integrated Management of Childhood Illness (IMCI). But the crucial first step in tackling childhood pneumonia is being able to diagnose it accurately, particularly after introduction of two effective vaccines against two major pathogens responsible for childhood bacterial pneumonia. Radiology and determination of hypoxia by pulse oximetry have been considered the optimal methods for diagnosing pneumonia. This review article has updated the important aspects of childhood pneumonia in developing countries. Early recognition and prompt, appropriate and adequate management can reduce the case fatality as well as morbidity associated with pneumonia.

Key Words: Pneumonia, integrated management, case fatality, effective vaccine.

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Introduction

Pneumonia continues to be the biggest killer worldwide in children under five years of age. Community acquired pneumonia (CAP) can be defined clinically as the presence of signs and symptoms of pneumonia in a previously healthy child due to an acute infection (of less than 14 days' duration) of the lower respiratory tract (usually occurs below terminal bronchioles) leading to cough or difficult breathing, tachypnea, or lower chest wall indrawing, which has been acquired in the community outside the hospital.[1]

Over the last 20-30 years, enormous reductions have occurred in the absolute and relative burden of pneumonia mortality in young children around the world when the population of young children was approximately 625 million. The recent advances in social conditions and economic development has

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resulted in remarkable improvement in child survival and health, as a result of which the population of young children rose to > 670 million in 2015. With 48% of pneumonia deaths occurring in 5 countries in Asia and Africa (India, Nigeria, Pakistan, Democratic Republic of Congo and China), which together account for only 41% of the world's population under 5 yrs of age. So, an understanding of geographic and etiological variability in pneumonia is also important.[2]

Epidemiology: morbidity and mortality burden, and risk factors

Pneumonia remains the leading infectious cause of death among children under five years of age, killing approximately 2500 children in a day, globally. Pneumonia accounted for approximately 16% of the 5.6 million under five deaths, killing around 88,000 children in 2016. Most of it's victims were less than 2 years old.

Pneumonia is responsible for around 28% of the deaths of children under five years of age in Bangladesh and around 50,000 children die of pneumonia every year. An estimated 80,000 children under five yrs of age are admitted to hospital with virus associated acute respiratory illness each year. The total number of infections is likely to be higher. Proportion of under 5 children with suspected pneumonia taken to health care provider is only ~47%.[3]

Incidence of total paediatric ARI is three to eight episodes per child per year in urban communities and one to three episodes in rural communities with most of these being self limiting viral upper respiratory infection. The incidence of pneumonia in the high income countries (Europe and North America) has been estimated to be approximately 36/1000/ year, while pneumonia related mortality in a high-income- country (HIC) remains relatively low.

Globally pneumonia accounted for approximately one-fifth (19%) of the 2 million deaths with 90% of these occurring in a low-middle-income-country (LMIC) and 50% of these death occur in Africa.[4]

In a study conducted at Dhaka Hospital of ICDDRB among 401 under5 children with diarrhea and ALRI (acute lower respiratory infection- it is a practical term in resource poor setting of the developing countries where difficulties in obtaining chest radiograph is present, especially in rural areas),[5] the most common manifestation was pneumonia and respiratory pathogen (both bacterial and viral) were identified in 30% cases and the case fatality rates were 14% in bacterial pneumonia and 3% in viral pneumonia.[6]

Table 1: Risk factors for CAP

Medical
Age < 1 year
Prematurity
Immunosuppression
Social/Environmental
Overcrowding
Inadequate housing
Passive tobacco smoke exposure
Presence of coughing siblings at home
Indoor fuel combustion
Exposure to environmental pollutants (combustive pollutants of domestic biomass burring)
Winter season
Lack of breast feeding
Poor parental income/ literacy

The disproportionately higher share of the global mortality burden in low-middle-income-countries (LMIC) may be associated with multiple pathogens and inadequate health education (of care givers) regarding early home recognition of signs of severe disease. Prevalence of several risk factors of severe

ALRI/ pneumonia is higher in poor-resource tropical countries and the predominant host factors are, infancy (age <1 yr), prematurity, LBW (including low weight for age), immunosuppression/ underlying malnutrition,[7] exposure to environmental pollutants especially the combustive products of domestic biomass burning, particularly from domestic cooking with firewood or parental smoking,[8] poor immunization coverage, adverse socioeconomic variables like poor parental income/ literacy, overcrowding, inadequate housing, lack of breast feeding, attendance at day-care centres, presence of coughing sibling(s) at home, winter season and man-made or natural disasters with consequent living in squatter/refugee conditions.[9]

Aetiological Agents

Pneumonia, inflammation of the lungs, is caused by a wide range of bacteria and viruses (and occasionally fungal and parasitic infection). Lung aspirate studies from several countries have shown that bacterial agents account for over 60% of pneumonias in the developing world, with *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus* constituting the top three.[10-12]

The spectrum of possible pathogens of acute pneumonia varies widely. Blood culture-generated bacteriological data showed that *Staphylococcus aureus* and *Klebsiella species* are the dominant pathogens of CAP in Nigerian children.[13] *Klebsiella, Escherichia coli, Proteus* and *Pseudomonas* species were reportedly common in neonate and children with measles, malnutrition and other immunocompromised states.[14] Fungal agents like *Candida, Aspergillus, Cryptococcus, Histoplasma, Nocardia species and Pneumocystis jiroveci* also accounts for a significant proportion of non-bacterial pneumonia in immunocomprised host. *Mycobacterium tuberculosis* usually causes pneumonia of a chronic nature. Viral pathogens like Respiratory Syncytial Virus (RSV) and Parainfuenza virus (PIV) constituting the top two in causing childhood pneumonia in Asia and Sub Saharan Africa.[15] A child with pneumonia who is wheezing is likely to have a viral or atypical pneumonia caused by Mycoplasma pneumonia or Chlamydia pneumonia.[16]

Table 2: Common cause of CAP in children

Bacterial
Staphylococcus pneumoniae
Moraxella catarrhalis
Hemophilus influenzae type B
Staphylococcus aureus
Mycobacterium tuberculosis
Atypical bacteria
Mycoplasma pneumoniae
Chlamydia pneumoniae
Chlamydia trachomatis
Pneumocystis jiovecii
Virus
Cytomegalo virus
Respiratory syncytial virus
Rhinovirus
Adenovirus
Human metapneumovirus
Parainfluenza virus types 1 and 3
Bocavirus
Influenza A or B
Measles virus

Induced sputum Gram stain smears and cultures from hospitalized children aged 1-59 months were evaluated and enrolled in a large study of community acquired -pneumonia. The presence of low numbers of squamous epithelial cells (SECs) (<10 per LPF) and high numbers of polymorphonuclear (PMN) (>25 per LPF) cell

are regarded as indicative of standard lower respiratory tract specimen. Induced sputum culture results were analysed from 3772 of 4232 (89.1%) children enrolled in PERCH study of which 2695 (71.4%) had severe pneumonia and 1077 (28.6%) very severe pneumonia: 518 from Bangladesh, 596 from Gambia, 592 fron Kenya, 544 from Mali, 824 from South Africa, 191 from Thailand and 507 from Zambia. Detection of 4 major potential pathogens (*Streptococcus pneumoniae, Haemophilus infuenzae, Moraxella catarrhalis, Staphylococcus aureus*) was greater in specimens from children without evidence of prior antibiotic use. Gram negative rods like *Acenatobacter* and *Pseudomonas* species were also detected.[17]Molecular diagnostic methods have the potential to improve our ability to detect small numbers of organisms in tissue and body fluids for diagnosis of childhood pneumonia. Nucleic acid amplification tests, polymerase chain reaction (PCR), assumed to be used to detect nucleic acid from potentially all respiratory pathogens, are not dependent on viable organism or fastidious culture conditions, and are not as affected by prior exposure to antibiotics as conventional culture methods. PCR pathogen detection in paired NP/OP (nasopharyngeal/ oropharyngeal) swab and IS (induced sputum) from 1114 hospitalized children (aged 1-59 months) with radiographic pneumonia, the common predominant organisms were *Streptococcus pneumoniae, Moraxella catrrhalis, Haemophilus influenza, Staphylococcus aureus, Pneumocystis jiroveci, Cytomegalo virus, Respiratory syncytial virus, Rhinovirus, Adenovirus, HMPV (human metapneumovirus), Bocavirus, Parainfluenza* 1 & 3.[18]

Pneumocystis jiroveci detection rate was higher in HIV positive radiographic pneumonia but also higher in severe malnutrion with radiographic pneumonia who were HIV negative.[19]

Haemophilus infuenzae type b (Hib) vaccine was shown to reduce radiologically confirmed pneumoniaby approximately 20% among children in trails in The Gambia and Chile.[19,20] A 9-valent PCV prevented 37% of cases of radiologically confirmed pneumonia among children in The Gambia who were already receiving Hib vaccine.[21] Following introduction of conjugate vaccines against these organisms could reduce the global burden of severe pneumonia by about half.[22]

Clinical Features

The clinical presentation of childhood pneumonia varies with the age of the child and the causative agent; the younger the infant, the less specific is the presentation. Young infant below 3 monthswith pneumonia may present with poor feeding, vomiting or irritability, minimum systemic disturbance and cough may be absent despite tachypnea.

Most infants and the majority of school-aged children with *chlamydial* and *mycoplasmal* aetiology are afebrile with minimal systemic toxicity at presentation. In severely malnourished children with pneumona, WHO defined fast breathing and chest indrawing may not be as evident as in other children with pneumonia.[23]

Viral pneumonias usually have a subacute course and may begin with coryzalsymptom. Concurrent or antecedent respiratory illness in other dwellers in the household are common. Measles may be complicated by superimposed severe bacterial pneumoniausually by necrotizing agents like *Staphylococcus aureus* or *Klebsiella pneumonia*.

Investigations

The crucial first step in tackling childhood pneumonia is being able to diagnose it

accurately. Analysis of 1,848 chest radiographs of children in Pakistan hospital outpatients settings who had had non severe pneumonia diagnosed clinically according to WHO guidelines showed that only 14% of the children had radiological evidence of pneumonia.[24] Other community studies in Pakistan also had found to have very low specificity of chest radiograph for pneumonia in young children.[25]

Radiological, microbiological and hematological investigations are done where facilities exist, to sort out confusing clinical presentations, identify the extent and severity of the disease, the presence of complications(eg. pleural effusion, air -leak syndromes), exclude other diagnostic consideration (like foreign body aspiration, pulmonary tuberculosis and congenital heart diseases) and frequently to follow the appropriateness of therapeutic interventions. Relatively invasive investigations (including lung biopsies) may be necessary in the immunocompromised subjects, in whom the spectrum of potential pathogens is wider and the presentation frequently atypical.

Non microbiologic laboratory tests have also been widely used in an attempt to differentiate bacterial from non bacterial pneumonia. However, they are not much better than chest radiographs. Several analyses show that the C-reactive protein (CRP) level and absolute neutrophil count are the most helpful.[26] Elevated CRP was positively associated with confirmed bacterial pneumonia and negatively associated with RSV pneumonia. CRP may be useful for distinguishing bacterial from RSV-associated pneumonia.[27]

In bacterial pneumonia, CBC with differential count usually shows leukocytosis in addition to raised ESR. A mild leukocytosis or leukopenia with lymphocytosis is expected in viral pneumonia,while chlamydia trachomatis causes pneumonia associated with eosinophilia in early infancy. Open lung biopsy or broncho-alveolar lavage specimens for histopathology and identification of fungal, bacterial and non-bacterial pathogens.[4]

Treatment

The management of pneumonia may be divided into two concurrently accomplishable components, namely specific and supportive therapy.

Specific Therapy

When treating CAP, the clinical, laboratory and radiographic findings should be considered, specially when the child is hospitalised. As it is difficult to distinguish bacterial from viral pneumonia and because of the frequency of mixed bacterial-viral infections (~30-40%)[1], all children with CAP require an antibiotic. The age of the child, nutritional status of the host, local epidemiology of respiratory pathogens, and sensitivity of these pathogens to particular antimicrobial agents and the emergence of antimicrobial resistance usually determine the choice of antibiotic therapy.[28]

Table 3: Indications for admission to hospital

All young children < 2 moths **Children older than 2 months**
Impaired level of consciousness
Inability to drink or eat
Cyanosis
Stridon in calm cold
Grunting
Severe chest indrawing
Room air SaO2 at sea level or <90% at higher altitude
Severe malnutrition
Family unable to provide appropriate care
Failure to respond to ambulatory care or clinical determination of treatment

The development of revised WHO classification and WHO-approved recommendations for treatment of childhood pneumonia at health facilities, specially for the first-level/ primary care level constitutes the current most effective strategy for stemming the mortality burden of pneumonia in LMICs.

Recommendation-1: Children with fast breathing pneumonia with no chest indrawing or general danger sign should be treated with oral amoxicillin: at least 40 mg/kg/dose twice daily for five days. In areas with low HIV prevalence, give amoxicillin for three days. Children with fast breathing pneumonia who fail on first- line treatment with amoxicillin should have the option of referral to a facility where there is appropriate second-line treatment.

Recommendation-2: Children aged 2-59 months with chest indrwing pneumonia should be treated with oral amoxicillin: at least 40 mg/kg/dose twice daily for five days.

Recommendation-3: Children aged 2-59 months with severe pneumonia should be treated with parenteral ampicillin (or penicillin) and gentamicin as a first -line treatment. (Ampicillin: 50mg/kg, or benzyl penicillin: 50,000 units/kg IM/IV every 6 hours for at least five days, Gentamicin: 7.5 mg per kg IM/IV once a day for at least five days). Ceftriaxone should be used as a second-line treatment in children with severe pneumonia having failed on the first-line treatment.

Recommendation-4: Ampicillin (or penicillin when ampicillin is not available)plus gentamycin or ceftriaxone are recommended as a first- line antibiotic regimen for HIV-infected and-exposed infants and for children under 5 years of age with chest indrwing pneumonia or severe pneumonia and those who do not respond to treatment with ampicillin or penicillin plus gentamycin ,ceftriaxone alone is recommended for use as second-line treatment.

Recommendation-5: empiric cotrimoxazole treatment for suspected pneumocystis jiroveci (previously Pneumocystis carinii) pneumonia (PCP) is recommended as an additional treatment for HIV-infected and -exposed infants aged from 2 months upto 1 year only with chest indrwing or severe pneumonia but not recommended over 1 year of age.[28]

Staphylococcus aureus and Klebsiella species are currently emerging as the top two important pathogens of childhood pneumonia in some urban third world communities such as Nigeria, Colombia,and India.Consequently[8], there may be a need to modify the WHO antimicrobial recommendations.

Alternative antimicrobial agents for out-patient cases include oral cephalosporin or clindamycin. The antimicrobial spectrum covered by the new generation macrolides like azithromycin is also good enough to earn a recommendation as an alternative oral medication in the ambulatory treatment of moderately severe cases.

Despite an increasing availability of specific antiviral agents which are of potential value for treating viral pneumonias especially in infants with RSV, the current recommendation is that of 'watchful waiting' while pursuing supportive care.But if facilities are available,infants with RSV disease with concomitant symptom-complex of bronchiolitis and in whom there are risk factors of mortality (ie. preterm delivary, age <2 months, chronic lung disease/ BPD (bronchopulmonary dysplasia) and congenital cardiac lesions), specific antiviral agents like aerosolized ribavirin may be offered.[4]

Supportive Care

This is a crucial aspect of the management for both ambulatory and hospitalised cases of

pneumonia.The essential elements of supportive treatment for both categories of patients comprise addressing fever and providing appropriate thermal environment, fluid and nutritional management as well as clearing nostrils. Hypoxaemia is an important risk factor for death as hypoxaemic patients are five times more likely to die than non-hypxaemic patients.[29] Oxygen was never mentioned in the recent publication by the WHO and UNICEF efforts to control pneumonia.[30] Hypoxaemia has been overlooked in world wide strategies for pneumonia control and reducing child mortality.[31]

So provision of oxygen, as well as instituting appropriate medical interventions for complications like congestive heart failure, severe anemia and appropriate surgical intervention for intrapleural complications like pleural effusion including empyema, pneumothorax and air-leak syndromes, constitute important elements of the supportive care of the hospitalised child.

Conclusion

Despite dominating the childhood mortality tables throughout the developing world,severe pneumonia has received little scientific or public health attention for decades.In developing countries, Pneumococcus and H infuenzae type b are the dominant cause of severe pneumonia in children and introduction of conjugate vaccines against these diseases could reduce the global burden of severe pneumonia by about half. The residual cases of pneumonia will have a wide variety of aetiological causes and this broad aetiological diversity will make the diagnosis,classification and management of pneumonia much more complex and expensive in future. The formation of a Global Action Plan for Pneumonia at WHO and the interest of public health foundations in supporting pneumonia research in developing countries are both welcome reversals of this longstanding neglect. The focus has extended to reducing the underlying condition recently that put the children at risk of pneumonia mortality including reducing HIV infections through preventing MTCT (maternal to child transmission), preventing and treating malnutrition and undernutrition, reducing household and outdoor air pollution exposure and ensuringthat prevention and treatment services are accessible when and where they are needed.

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PRIMARY OPEN ANGLE GLAUCOMA (POAG) - A CASE REPORT

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ABSTRACT

Primary open angle glaucoma (POAG) is commonly bilateral disease of adults commonly affects after 40 years which varies widely in different populations and usually affects both genders equally. The affected person becomes partially or completely blind before they could hardly reach a consultant ophthalmologist for diagnosis and proper treatment. The present case reported to an ophthalmologist for the first time with vision problem. On fundal examination cup-disc ratio in right and left eye found to be 0.64 and 0.93 respectively of the subject. Gonioscopic examination revealed open grade 4 (40^{o}) angles in both eyes. Visual field analysis demonstrated defect above and below the horizontal line. OCT examination demonstrated retinal nerve fiber layer damage in both fundi, more in left eye than right eye. IOP was higher than normal in both eyes. Diurnal variation of IOP was observed in both eyes. She was diagnosed as a case of POAG. Considering her age and vision remaining in only one eye she was advised conservative treatment. Treatment initiated consisted of topical brinzolamide and tafluprost in both eye. She was advised to have intraocular pressure check up twice monthly, fundoscopic examimation every 6 month and visual field analysis once a year. Development of glaucoma often insidious and individuals need to aware of the minor clinical condition to prevent or at least delay the disease process and preserving the required vision. The present case is the rude awakening and highlights the necessity of screening examination of eye and evaluation of vision to save many eyes of poor and unware peoples.

Key Words: glaucoma, vision correction, fundoscopy.

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Introduction

Glaucoma blindness constitutes the second most common form after cataract.[1] Taking in consideration the limitations of medical and surgical management glaucoma poses significant challenge in prevention of blindness.[2] It covers primary open angle glaucoma and primer angle closure glaucoma (POAG and PACG respectively). Prevalence of glaucoma varies widely in different populations of the world. It has been estimated that there were 60.5 million people with POAG and PACG in 2010 postulated to rise to 79.6 million by 2020 and of them 74% will have POAG. Women comprised 55% of POAG, 70% of PACG, and 59% of all glaucoma in 2010. Asians estimated to represent 47% of those with glaucoma and 87% of those with PACG. Bilateral blindness estimated to present 4.5 million people with POAG and 3.9 million people with PACG in 2010 and increased to 5.9 and 5.3 million people in 2020, respectively.[3] A recent meta-analysis demonstrated the highest prevalence of POAG in Africa (4.3%) and highest PACG in Asia (1.09%). In the same review authors opined that people with glaucoma worldwide will increase o 111.8 million in 2040, disproportionately affecting people living in Africa and Asia.[4]

Little earlier prevalence of glaucoma in Bangladeshi people was found to be 2.1%. The prevalence of definite and probable glaucoma was 3.1% (95% CI: 2.4 to 4.0; 58 people) in subjects of the same age. Primary open angle glaucoma was the most common form of glaucoma, accounting for 75% of the total. Among cases of blindness not attributable to refractive error, 5% were caused by glaucoma.[5]

Glaucoma is characterized by the progressive death of retinal ganglion cells, leading to optic nerve atrophy and loss of vision. Increased intraocular pressure (IOP) still remains an important primary and prognostic risk factor for POAG[6-9] but other IOP independent risk factors may be involved in the pathogenesis and progression of POAG.[6,10,11] It is assumed to be a complex inherited disorder for which an increasing number of genetic associations have been described, each contributing, however, modestly to disease burden.[12-14]

The lack of symptoms in POAG is imperative in delaying its detection and diagnosis. Typically POAG is slowly progressive and remain asymptomatic until late. By the time POAG becomes symptomatic, severe and irreversible damage has usually occurred to the visual field in one or both eyes. The rate of progression of the visual field defect varies in patients, and treatment of the glaucoma may not completely halt the visual field loss.[15] Some patients progress, however, despite aggressive therapy.[16]

Early glaucoma can create mild, diffuse depression in the visual field which could be the only detectable abnormality. Early treatment program found to recommend improvement in delaying the progression. After 4 years follow-up, 49% of the individuals without treatment progressed, compared to 30% with treatment and after 6 years follow-up, 68% of the untreated patients showed definite visual field defect progression, with an overall median time to progression of 42.8 months.[17,18] Large variation in the progression to cause damages also has been noticed among the subjects.

Case Report

A 61 years old woman presents to me with the complaints of difficulty in vision of both eyes for the last few yrs. She complained of inability to see by left eye and only partially by right eye. She did not complained of redness, pain, irritation, intolerance to light, watering in any eye. She even did not provided history of inflammatory eye disease in the past. She did not provide any history of systemic disease like diabetes and hypertension. She had no history of severe illness like malignancy and chronic drug intake.

Table 1: Findings of indirect gonioscopy of the subjects

Observations	Findings
Anterior chamber	No abnormality detected
Angle status	Open angle grade 4 (40^{o}) in both eyes
Fundi: Cup Disk ratio of right vs left eye	0.64 vs 0.93
Macula and background of both eye	No abnormality detected

Her best corrected visual acuity in the right eye was 6/12 and left eye was no perception of light (NPL) in three quardrant except temporal. The patient came from lower middle class background. She had undergone some investigations and diagnosed as a case of primary open angle glaucoma. The patient was treated with brinzolamide (0.5%) eye drop twice daily and tafluprost (0.0015%) eye drop in both eyes at 8 pm. She was advised to have intraocular pressure check twice in a month, fundoscopic exam every 6 month and visual field analysis once a year.

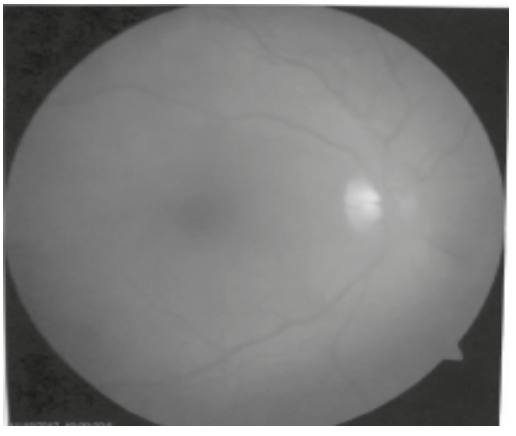
Table 2: Intraocular pressure measured by Applanation tonometry of the two eyes in the morning and evening of the subject for five consecutive days

Tonometry	Intra-ocular pressure (mmHg)					
	Right eye			Right eye		
	Morning	Evening	P value	Morning	Evening	P value
Day 1	26	23		30	27	
Day 2	25	22		28	26	
Day 3	26	25		30	28	
Day 4	27	24		32	29	
Day 5	26	23		29	27	
Mean±SD	26.0±0.7	23.4±1.4	0.003	28.9±1.5	26.8±2.8	0.022

Table 3: Optical coherence tomography findings of the subjects

Variables	OD	OS
Disk area (mm^2)	2.43	2.29
Cup volume (mm^3)	0.183	1.444
Rim area (mm^2)	1.40	0.21
Average CD ratio	0.63	0.93
Vertical CD ratio	0.63	0.93
Average RNFL thickness (μm)	103	62

Color OD 45" 11/18/2016



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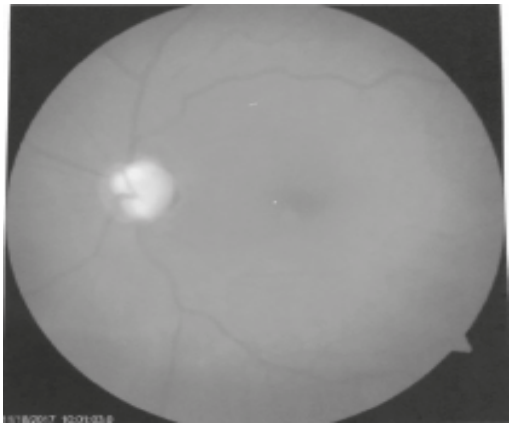
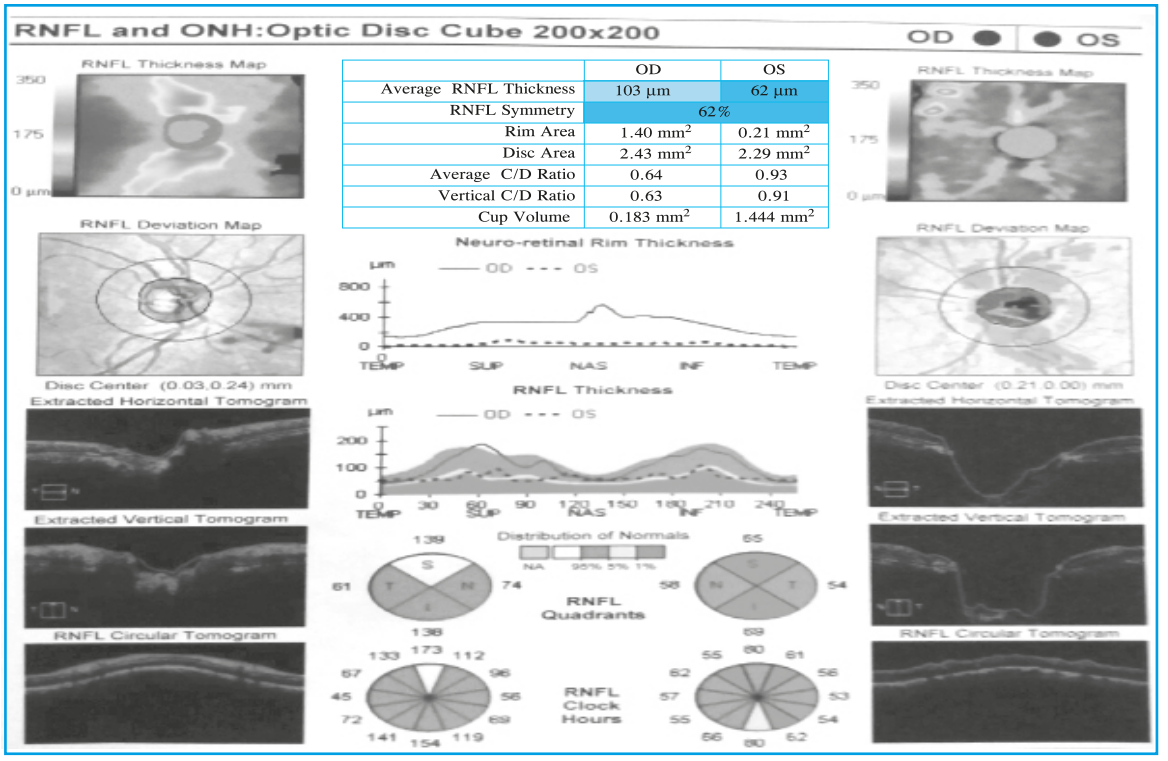


Figure 1: Fundus photograph of the both eyes of the study subject.

Discussion

Primary open angle glaucoma is a chronic, progressive disease that mostly presents with characteristic optic nerve damage, retinal nerve fiber layer defects and subsequent visual field loss. It occurs mainly in adults and is generally bilateral, however, not always symmetrical, in presentation. Generally patients with primary open angle glaucoma have elevated intraocular pressure (IOP) which is called ocular hyper tension and those present with IOP <21 mmHg (normal tension glaucoma). Treatment strategies, whatever the modalities which include incisional surgery, laser surgery or medication, are aimed to reduce the intraocular pressure.[19-21] There is an array of medications in reduction of intraocular pressure which are divided into five major classes: prostaglandin analogs, beta blockers, diuretics, cholinergic agonists, and alpha agonists and its various mechanisms of action, efficacies, and side effect profiles of these medications differ among patients.[21] The outcome of intervention however, depends on the time of diagnosis and, awareness of the patients about the disease and their adherence to the treatment plan. Awareness about glaucoma has been found very low in different populations. Studies involving rural population and urban dwellers of south Indian and central India respectively demonstrated awareness about glaucoma and their lack of education and lower socioeconomic conditions implicated in it late presentation.[22,23] Situation found to be similar also in Pakistan. About 50% of participating subjects in one study did not hear about glaucoma. Many of them mentioned it as blindness.[24] Regarding awareness, about 80% of subjects in rural Punjab believed that glaucoma is a curable disease.[25] In Sub-Saharan Africa awareness and knowledge about glaucoma is also found to be low.[26,27]



	OD	OS
Average RNFL Thickness	103 µm	62 µm
RNFL Symmetry	62%	
Rim Area	1.40 mm²	0.21 mm²
Disc Area	2.43 mm²	2.29 mm²
Average C/D Ratio	0.64	0.93
Vertical C/D Ratio	0.63	0.91
Cup Volume	0.183 mm²	1.444 mm²

Figure II: Optical coherence tomography (OCT) finding of the two eyes of the subject.

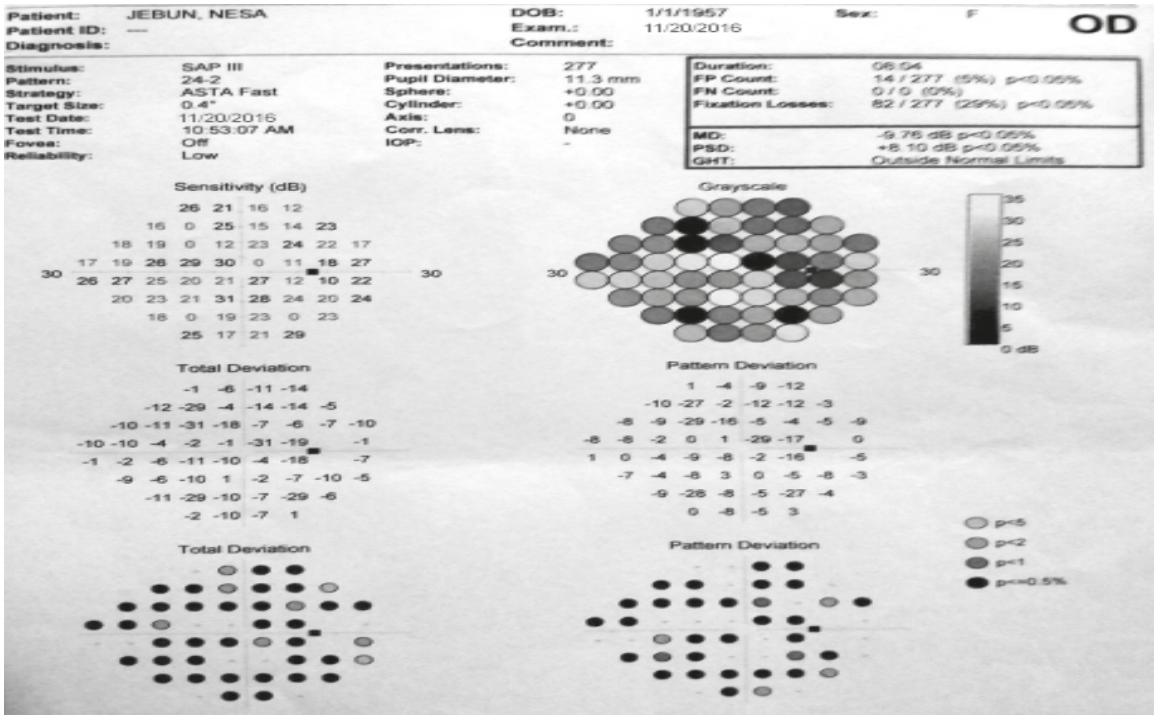


Figure III: Visual field analysis of the right eye of the subject.

In a study in remote district of Bangladesh 50% of subjects said that they knew about glaucoma but only 30% found to have knowledge about it.[28]

The present case for the first time visited an ophthalmologist for her difficulty in vision. She did not even realize that might be due to glaucoma which she also did hear about before. On examination intraocular pressure was found high, >21 mmHg, suggestive of glaucoma.[29] Measurement IOP for consecutive five days showed significant diurnal variation in both eyes ($p=0.030$ and 0.022 respectively) which is also suggestive of glaucoma.

Disk area in the two eyes was relatively larger (2.43 mm^2) than the average healthy subjects (2.14 mm^2).[30] Optic disk rim 'neuroretinal rim (NRR)' was 1.4 mm^2 for right eye and 0.2 mm^2 for left eye which is substantially smaller than the mean value of 1.6 mm^2 reported in a study.

Measurement of optic cup/disk ratio is a good indicator of its condition. Normally it is said to be 0.2-0.5 and closer the value to 1 indicates worse the damage.[31] Measurement of vertical cup/disk ratio rather than horizontal measure is a better indicator of optic disk damage. In the present case cup/disk ratio for right and left eye was 0.64 and 0.93 respectively. Interestingly the vertical measurement was similar to that of average cup/disk ratio. The value was close to 1 indicating extensive damage in the left eye and supported by total loss of vision. Optical coherence test measures retinal nerve fiber layer (RNFL) thickness. Optic disk cup volume normally measures 0.01-0.49 mm^3.[32] The value for the patient was 0.183 and 1.444 mm^3 in the right and left eye respectively which indicates the loss of nerve fiber. Thinning of the layer indicates retinal damage. Normally RNFL thickness varies between 180-310 μm. The value for the present case is 103 and 62 μm respectively and suggested the severe damage of ganglion cells and nerve fiber. All the relevant parameters clearly showed damaged in both eyes

which correlated with her clinical condition- total loss of vision in the left eye and severe loss in the right eye.

The present case simply reported to the ophthalmologist for her difficulty in vision. On examination total loss vision was observed in the left eye and severe in right eye. Subsequent investigations confirmed it to be case of primary open angle glaucoma and investigation out of academic interest revealed damage in the both retina. It is understood diagnosis of primary open angle glaucoma, if diagnosed early and institution of treatment- either medical or surgery has been reported to able delay its progression substantially, although there are different thought of schools about treatment modalities. There is noticeable lack in national guidelines regarding ocular examination for any pathology and as such loss of vision. It is exclusively patient's initiatives to sought treat once they have any problem in the vision or other symptoms. Visual field analysis and ocular examination only routinely carried out in specific situations. Considering the economic developments and improvement in the people's standard of living, time has come to think about of national program for screening of population and reduce the preventable blindness.

Conclusion

Routine eye check up in elderly using tonometry and fundoscopy should be recommended for adults in late decades of life. As it is silent killer of vision, so routine check and follow up must be continued yearly for presbiotic patients especially for late diagnosed and noncompliant patients to save the remaining vision.

Acknowledgement

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