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Editorial

WHAT IS THE NEW KNOWLEDGE GAINED THROUGH *IJT* IN 2012?

[*Indian J Tuberc 2013; 60:* 1-4]

In addition to focusing on the current issues related to TB control programme, *Indian Journal of Tuberculosis (IJT)* also publishes articles on basic aspects of TB and respiratory diseases, newer diagnostic methodologies, experiences gained with treatment strategies, drug resistance (DR) issues in TB, KAP studies, TB and HIV co-infection and interesting case reports of rare clinical presentations. We have reviewed the manuscripts published during the year 2012 to gain an idea to what extent *IJT* has been able to fulfill its mission of sharing the information gained by researchers with the esteemed readers of the journal.

TB Diagnostics

Newer rapid molecular diagnostic methods and innovations in the presently used methods remained the hot topic during the period. A study to find agreement between tuberculin skin test and quantiferon TB gold assay to detect latent tuberculosis infection among household contacts found good association between the two tests among pediatric cases but poor association among adults and warranted larger studies to authenticate the findings[1]. Regarding ZN staining for acid fast bacilli, microscopists opine that acid alcohol slides may enhance smear positivity but equivalence of acid and acid-alcohol in ZN staining is not easily accessible. The study[2] used 25% sulphuric acid and compared with 3% hydrochloric acid alcohol as decolourising agent and found equal results and concluded that the common belief of acid-alcohol decolourised slides giving enhanced smear positivity stands void.

Prospective evaluation of use of cocktail of ES-31 and EST-6 antigen proved to be an adjunct test for diagnosis of pleural effusion and MPT-64 antigen estimation was found to be a rapid and reliable method to differentiate *Mycobacterium tuberculosis* complex from non-tubercular mycobacteria[3,4].

TB Therapeutics

RNTCP recommends intermittent thrice a week DOTS, both in intensive and continuation phases for a total of nine months for tubercular meningitis. However, most recent guidelines recommend daily regimen. An in-hospital study[5] comparing the two regimens however found the same mortality rate in both the groups. However, there was less incidence of hepatic dysfunction in intermittent regimen, even though it was statistically insignificant. Recent guidelines of WHO[6] recommend daily regimen, both for immuno-compromised and immuno-competent patients under the programme. In India, evidence is being gathered to implement this recommendation.

Sputum smear conversion rate [SCR] is an operational indictor for DOTS strategy of RNTCP. A prospective study[7] conducted to observe relationships between initial sputum smear grading with smear conversion and treatment outcome concluded that patients with higher grade of sputum positivity at the

beginning of treatment have significantly low SCR at the end of intensive phase and even after extending intensive phase by a month. Hence, they are likely to remain infectious for a longer duration. The SCR at two and three months is an operational indicator and should be given more importance rather than being practised only as a documentation and an academic exercise. Such patients should be investigated for possible co-morbid conditions and drug resistance which could be a cause for the persistent sputum smear positivity at two and three months and hence poor treatment outcome.

However, another study[8] recommended that smear positivity at the end of intensive phase need not reflect the continued infectiousness because a large number of them may be culture negative.

TB programme

Onsite evaluation (OSE) of activities of microscopic centres under RNTCP with standard checklist is a first step to promote effective and consistent supervision. Improvement was noted in standard operating procedure practices, disinfection practices and internal quality control practices after all the laboratories were visited as part of OSE visits[9].

Evaluation of treatment outcome is central to the assessment of tuberculosis control programme. But most of the studies have short term outcomes. Evaluation of the outcome of Category I treatment in smear positive tuberculosis after five years of treatment revealed 4.5% relapse rate and 5.4% mortality. Significant proportion of patients had radiological sequelae. Smoking was the preventable risk factor associated with sequelae, relapse and mortality[10].

TB drug resistance

The emergence of resistance of anti-tuberculosis drugs and multi drug resistance has become a significant public health problem and an obstacle to effective TB control. Baseline and adequate information on epidemiological factors and their interaction are pre-requisites for its effective control. The particular study[11] found that most of MDR cases were living in poor environmental conditions, had previous history of ATT and frequent defaulters of treatment. Motivation of private practitioners for increasing referrals, use of incentives and enablers enhancing contact tracing and increasing awareness regarding sputum disposal practices and measures to prevent the spread are necessary for effective control of tuberculosis.

Newer Initiatives

The *IJT* carries a regular feature on status report on RNTCP in which newer initiatives taken up by the programme are highlighted. During the year 2012, three important initiatives taken up by the programme were highlighted for the benefit of our readers, *viz.* notification of TB cases[12], TB and DM initiative[13] and ban on serological tests[14].

Accordingly, all health care providers/clinical establishments run or managed by Government (including local authorities), private or NGO sectors and/or individual practitioners will be required to notify TB cases to local health authorities i.e. District Health Officer/Chief Medical Officer of a district and Municipal Health Officer of a Municipal Corporation/Municipality. Health care providers can notify such cases to the authorities by sending the details of patients in hard copy or by emails.

Regarding TB and DM initiative, the number of people with diabetes are estimated to increase in the coming years and this can seriously threaten TB control in India. Available evidence shows that people

with DM have significantly increased risk of active TB which is two to three times higher than people without diabetes. In addition, evidence suggests that diabetes worsens TB treatment outcomes – increased death, failure and relapse rate. The programme has decided to test the feasibility of by-directional screening (screening of TB patients for DM and DM patients for TB) within routine health care services.

Regarding ban on serological tests, 1.5 million TB suspects in India are annually subjected to sero-diagnostic tests, cost amounting to 15 million USD[14]. Several meta analyses have shown that these tests are inaccurate and lack consistency. An updated systematic review commissioned by WHO and TDR have re-confirmed the findings. There is no role for inaccurate/inconsistent diagnostics like serology (IgM, IgG, IgA antibodies against MTB antigens), various in-house or non-validated commercial PCR tests and BCG test. There is no role of IGRAs in clinical practice for the diagnosis of TB (adult and children).

Indoor pollution and childhood TB

The association between tuberculosis and smoking was reported as early as in the year 1918. Passive smokers are also exposed to similar toxic substances as active smokers but concentration level is different in both the groups. A hospital-based case control study[15] found significant association between passive smoking and childhood TB but no association was found with biomass fuel. Further studies are needed to establish temporality of passive smoking and development of childhood TB.

During 2012, most of the articles published dealt with event issues related to almost all aspects of TB, viz. epidemiology, diagnostics, clinical presentations, treatment strategies, control programme and KAP studies. This is in line with the topics of interest of participants attending our annual conference. During 2013, we will continue to actively encourage submission of articles on lung diseases also and will endeavour to continue publishing new knowledge in the areas of interest of our readers as gained through their views during our national conference.

K. K. Chopra*

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The Editor-in-Chief and the members of the Editorial Board of the ***Indian Journal of Tuberculosis*** wish all its readers a Very Happy and Prosperous New Year 2013.

D. BEHERA
EDITOR

Original Article

TUBERCULOUS MENINGITIS: DO MODERN DIAGNOSTIC TOOLS OFFER BETTER PROGNOSIS PREDICTION?

Fernando Alarcón[1], Juan Moreira[2,3], José Rivera[1], Robert Salinas[1], Gonzalo Dueñas[4] and Jef Van den Ende[3].

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Summary

***Background*:** The British Medical Research Council (BMRC) staging has been extensively used to evaluate the disease severity and establish the approximate prognosis of tuberculous meningitis.

***Aims*:** This study aimed at analyzing the predictive accuracy for mortality and neurological sequelae of a set of clinical features, laboratory tests and imaging.

***Methods*:** We compared the British Medical Research Council (BMRC) staging with a new scoring proposal to predict the prognosis of patients with Central Nervous System Tuberculosis. Data from Ecuador was collected. A score was built using a Spiegelhalter and Knill-Jones method and compared with BMRC staging with a ROC curve.

***Results*:** A total of 213/310 patients (68.7%) were in BMRC stage II or III. Fifty-seven patients died (18.3%) and 101 (32.5%) survived with sequelae. The associated predictors were consciousness impairment (p= 0.010), motor deficit (p = 0.003), cisternal effacement (p=0.006) and infarcts (p=0.015). The new score based on these predictors yielded a larger area under the curve of 0.76 (95% CI: 0.70-0.82), but not significantly different from the BMRC (0.72: 95% CI: 0.65-0.77).

***Conclusions*:** This modern score is easy to apply and could be a sound predictor of poor prognosis. However, the availability of modern tests did not improve the ability to predict a bad outcome. **[*Indian J Tuberc 2013; 60: 5 - 14*]**

Key words: Tuberculosis, Meningitis, Prognosis, Predictors.

INTRODUCTION

Despite effective antituberculous treatment, mortality and morbidity remain high in patients with Central Nervous System Tuberculosis (CNSTB).[1,2] Clinical, laboratory and image findings are not very sensitive or specific for diagnosis.[1] Early recognition and treatment of CNSTB may improve the outcome. The British Medical Research Council (BMRC) staging has been extensively used to evaluate the disease severity and establish the approximate prognosis of tuberculous meningitis (TBM).[3] Additionally, some clinical and neuro imaging predictors have also been evaluated.[2,4-11] However, uptill now, no clear indications are given to assess the prognosis of such a devastating disease.[12]

In 1989, we started a prospective CNSTB Data Registry, collecting clinical, laboratory, radiological, therapeutical and follow-up data of all patients with CNSTB admitted to the Department of Neurology as well as other wards of the Eugenio Espejo Hospital in Quito. All patients were examined and treated by a neurologist from the Department of Neurology.

With this study, we aimed at analyzing what the predictive accuracy for mortality and neurological sequelae was of a set of clinical features, laboratory tests and imaging of patients with a definite or probable diagnosis of CNSTB. We developed a user-friendly approach to deal with several positive and negative features to predict severe disability or mortality in patients suspected of having CNSTB and to compare its discriminatory power with the BMRC staging.

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METHODS

All patients admitted between 1989 and 2004 at the Eugenio Espejo Hospital, a major public care centre located in Quito – Ecuador, in whom an antituberculous treatment was started for a clinical diagnosis of CNSTB, were included. Patients were carefully followed-up until the end of antituberculous treatment. Their clinical files, which included a description of signs and symptoms at admission, laboratory results, imaging, and therapy, as well as the outcome in terms of neurological disability and mortality, were reviewed.

DATA

In all patients, we established the length of evolution of the disease before admission to the hospital, the severity of the disease upon admission based on BMRC staging (Box 1), the time span between admission to the hospital and start-up of treatment, contact with known cases of tuberculosis, the clinical and neurological features upon admission (including degree of coma) and during the first four weeks after admission. Complementary examinations included blood leukocyte count, serum sodium, Mantoux intradermal test (purified protein derivate; PPD), bacteriological analyses of sputum, gastric aspirate, urine collection, magnetic resonance imaging (MRI) and/or computer assisted tomography (CT-scan) of the brain and/or spinal cord. In the cerebrospinal fluid, we included a differential cell count, protein and glucose levels, acid-fast bacilli (AFB) staining, culture in Lowenstein-Jensen (LJ) medium, immunobiological study by enzyme-linked immunosorbent assay (ELISA) for detecting anti-Bacille Calmette-Guerin (BCG) antibodies, and the dosage of adenosine deaminase activity (ADA). Indian ink staining was performed in order to exclude cryptococosis. Three patients had a lymph node biopsy done, and three patients had a culture performed on material obtained from a draining peri-renal abscess. Surgery was done for two patients with intracranial abscesses, four with hydrocephalus and two with spinal tuberculosis.

Diagnostic criteria

The diagnosis of definite CNSTB was based on AFB staining, mycobacterial culture and/or pathology on surgery or autopsy. In patients with probable CNSTB, the diagnosis was considered on clinical grounds based on the following criteria: 1) MRI or CT brain images compatible with cerebral abscess or tuberculoma; 2) CSF with inflammatory changes; 3) MRI spinal images compatible with tuberculomas, syringomyelitis, arachnoiditis, myelitis, spondylitis, or para-spinal abscesses; 4) positive ELISA or ADA in the CSF; 5) positive direct smears or culture isolates of *M. tuberculosis* from another tissue or body fluid. Other clinical arguments consisted of Mantoux test; chest x-ray; hydrocephalus, leptomeningitis, basal cistern effacement, or infarction on the MRI or CT;[13] or a previous history of tuberculosis or clinical response to antituberculous treatment.

Box 1: British Medical Research Council staging

Stage I: No definite neurological symptoms on admission or in the history before admission, with or without meningismus

Stage II: Signs of meningeal irritations with or without slight clouding of consciousness with focal neurological signs such as cranial nerve palsies or hemiparesis

Stage III: Severe clouding of consciousness or delirium, convulsions and serious neurological signs such as hemiplegia, paraplegia, involuntary movements.

Treatment

All patients received oral administration of isoniazid, rifampicin and pyrazinamide. Ethambutol was added in 126 patients, simultaneously with a quinolone in 18 cases. Streptomycin was added in 78 cases, simultaneously with a quinolone in five cases. In five additional cases, a quinolone alone was added to the regimen of three drugs. The anti-tuberculous drugs were started between one hour and seven days after admission. The first phase, which lasted two months, included all the drugs, and the second phase, which lasted four to 10 months or more, was restricted to isoniazid and rifampicin. Steroid therapy with prednisone was given to patients with severe impairment of consciousness, bilateral motor deficit, vasculitis, spinal tuberculosis and cerebral tuberculomas with intracranial hypertension and focal deficit. We determined that treatment was complete when all the CSF parameters were within normal limits and abnormal image findings were cleared.

Outcome

We established the outcome when treatment had ended, using the approach advocated by Smith for tuberculous meningitis which recognizes five categories:[8,14-16] 1) apparently normal patients; 2) patients with slight mental abnormality, or normal intelligence but with some degree of hemiparesis, minor behavioural problems, deafness or epilepsy, with the possibility of leading relatively normal autonomous lives without assistance; 3) patients with mild sequelae, that is mild mental abnormality and/or having a well-established physical impairment, being able to lead relatively normal lives with some assistance; 4) patients with severe sequelae, that is severe mental abnormality and/or having a severe physical impairment being totally dependent; 5) death.

Statistics and score

We used bivariate analysis for statistical comparison of age, sex, pre-admission duration of the symptoms of tuberculous meningitis, clinical manifestations upon admission and abnormal movements during the first month of treatment, blood and CSF examination, and MRI- and/or CT scan upon admission, early onset of anti-tuberculous treatment, and use of steroids related to the prognosis. For categorical predictors, contingency tables were drawn to estimate Pearson's chi-square coefficients with its related two-tailed asymptomatic p values. For continuous predictors, analysis of variance (ANOVA) was performed; the corresponding F coefficient with its related p value was computed for each predictor.

For the multivariate analysis, we selected predictors that had statistical significance on bivariate analysis. Steroid prescription was not included, since it could have been biased, due to use only in severe cases. The outcome variable at discharge was the above described five-category scale.

To develop the severity score for predicting mortality, we used the methodology advocated by Spiegelhalter and Knill-Jones.[17] Since this method requires a dichotomized outcome, we explored different models of splitting the scale of five ordinal categories into two categories. The adjusted logLRs (adjusted weights) were multiplied by 10, rounded and summed for every subject in order to obtain an individual score.

This score was plotted against the outcome in a Receiver Operator Characteristics (ROC) curve. The Area Under the Curve (AUC) with 95% confidence intervals was computed. Analysis was performed using SPSS V. 13 (SPSS Inc, Chicago, IL, USA).

RESULTS

Patient characteristics

From our prospective CNSTB Data Registry, we report 312 patients who developed definitive or probable CNSTB. Two of them were excluded for having missing values. Female to male ratio was 0.57, the mean age was 34.5 years (95% CI: 32.7-36.4). Two patients had HIV infection. One hundred and forty patients (45.1%) had a definite diagnosis, 40 with AFB staining, 28 with culture, 11 with autopsy and 61 with combined results.

Table 1: BMRC Stage at admission and functional prognosis at discharge in 310 patients with Central Nervous System Tuberculosis

		Functional prognosis at discharge					
		total recovery n=152	mild sequelae n=47	moderate sequelae n=26	severe sequelae n=28	Death N=57	Total n=310
BMRC I	Count	66	13	10	5	3	97
	Percentage	43.4	27.7	38.5	17.9	5.3	31.3
BMRC II	Count	53	23	12	9	22	119
	Percentage	34.9	48.9	46.2	32.1	38.6	38.4
BMRC III	Count	33	11	4	14	32	94
	Percentage	21.7	23.4	15.4	50.0	56.1	30.3
Total	Count	152	47	26	28	57	310
	Percentage	49.0	15.2	8.4	9.0	18.4	100

BMRC Stage = British Medical Research Council Stage
BMRC staging: Pearson´s R^2=0.12 B=0.69 p value<0.001

Table 2: Results of Bivariate Analysis of data for neurological signs at admission, steroid treatment and functional status at discharge.

		Functional status at discharge					
		total recovery n=152	mild deficit n=47	moderate deficit n=26	severe deficit n=28	Death N=57	p value
Impaired consciousness N=310	Count	106	29	16	21	55	<0.0001
	%	69.7	61.7	61.5	75.0	96.5	
headache N=306	Count	127	31	17	24	41	0.011
	%	84.7	66.0	65.4	88.9	73.2	
irritability N=308	Count	125	32	18	26	43	0.027
	%	82.2	68.1	69.2	96.3	76.8	
papilloedema N=310	Count	19	12	3	8	22	<0.0001
	%	12.5	25.5	11.5	28.6	38.6	
motor deficit N=310	Count	52	38	18	21	41	<0.0001
	%	34.2	80.9	69.2	75.0	71.9	
involuntary movements N=310	Count	19	13	7	7	11	0.081
	%	12.5	27.7	26.9	25.0	19.3	
Cranial nerves palsy N=310	Count	27	14	4	9	25	0.002
	%	17.8	29.8	15.4	32.1	43.9	
meningeal signs N=310	Count	118	32	16	20	55	0.001
	%	77.6	68.1	61.5	71.4	96.5	
seizures N=309	Count	24	1	2	3	12	n.d.
	%	15.8	2.1	7.7	11.1	21.1	
Unconjugated gaze N=309	Count	9	5	0	2	13	
	%	5.9	10.6	0.0	7.1	23.2	n.d.
Steroid use N=	Count	20	16	10	17	17	
	%	13.2	34.0	38.5	60.7	29.8	<0.0001

n.d.: non definable, cells with too few patients.

One hundred two patients (32.9%) showed a time span from onset of symptoms to initial presentation of less than three weeks. For 92 patients (29.6%), it was three to four weeks and for 116 patients (37.4%), it was more than four weeks. Two hundred nine patients (67.5%) received early anti-tuberculous treatment the first three days after admission, and 80 patients (25.8%) were prescribed steroids. Two hundred thirteen patients (68.7%) were in BMRC stages II and III; 57 patients (18.4%) died; 101 (32.5%) survived with sequelae and a complete clinical recovery was observed in 152 (49.0%) (Table 1).

General and neurological symptoms are summarized in Table 2. Laboratory examinations and image studies are summarized in Table 3.

Multivariate analysis

The multivariate analysis model retained as features related with poor prognosis, following the five point scale by Smith, impairment of consciousness ($p<0.001$), motor deficit ($p<0.001$), papilloedema ($p=0.043$), AFB smear or positive culture ($p=0.002$), cisternal effacement ($p<0.001$) and cerebral infarcts ($p=0.029$). An early start (within the first three days after admission) of anti-

Table 3: Results of Bivariate Analysis of data in CSF examination and neuro-imaging

		Functional prognosis at discharge					p value
		total recovery n=152	mild deficit n=47	moderate deficit n=26	severe deficit n=28	Death N=57	
Findings in CSF							
Cells in CSF	Mean	300.0	183.7	95.3	194.0	177.1	0.306
	95% CI	186.0-413.9	49.9-317.5	49.7-141.0	26.6-362.3	97.9-256.3	
Glucose in CSF	Mean	35.6	35.4	32.7	33.1	32.3	0.909
	95% CI	31.2-40.0	29.0-41.9	25.4-40.1	25.3-40.8	25.4-39.3	
Proteins in CSF	Mean	172.6	168.6	395.9	262.1	282.8	0.048
	95% CI	130.5-214.6	124.7-212.5	68.7-723.1	112.2-411.3	154.3-411.3	
ELISA	Mean	0.7	0.6	0.6	0.7	0.8	0.847
	95% CI	0.4-0.9	0.4-0.8	0.3-0.9	0.5-0.9	0.7-1.0	
Adenosine Deaminase Activity	Mean	4.9	4.2	3.3	5.8	7.6	0.087
	95% CI	3.7-6.2	2.2-6.2	0.3-6.2	2.4-9.2	5.6-9.7	
Neuroimaging in CT or MRI							
Hydrocephalus 142/310	Count	54	20	8	18	42	<0.001
	%	35.5	42.6	30.8	64.3	73.7	
cisternal effacement 80/310	Count	25	10	5	12	28	<0.001
	%	16.4	21.3	19.2	42.9	49.1	
Leptomeningitis 100/310	Count	37	12	9	13	29	0.002
	%	24.3	25.5	34.6	46.4	50.9	
Infarcts 72/310	Count	21	13	3	11	24/57	<0.001
	%	13.8	27.7	11.5	39.3	42.1	
Granuloma 62/310	Count	35	10	4	4	9	0.651
	%	23.0	21.3	15.4	14.3	15.8	
Calcifications 9/309	Count	4	2	2	0/28	1	n.d.
	%	2.6	4.3	7.7	0.00	1.8	

CSF = Cerebrospinal Fluid; CT = Computed Tomography; MRI = Magnetic Resonance Image

tuberculous treatment was a predictor of good prognosis ($p < 0.001$). The model showed a Pearson R^2 of 0.35. (Table 4)

Scoring system

Table 5 shows the logistic regression model with a dichotomous outcome for severe sequelae or mortality *versus* minor or absent sequelae identified impairment of consciousness, motor deficit, cisternal effacement, and brain infarcts as significant predictors. All were considered for the construction of the scoring system for which we suggested the name of Score Quito (Table 6).

Individual scores were plotted in a ROC curve and compared with the BMRC staging. The area under the curve of Score Quito was nearly the same [AUC: 0.76 (95% CI: 0.70 – 0.82)] as the area under the curve of the BMRC staging [AUC:0.72 (95% CI: 0.65 – 0.78)]. (Figure) Separate analysis for confirmed and probable TB cases did not change the conclusions. (AUC for confirmed TB cases: Score Quito 0.75, BMRC 0.71; AUC for probable TB cases: Score Quito 0.77, BMRC 0.73).

Table 4: Significant predictors following multivariate analysis, with the Smith 5 point scale as outcome parameter.

	Unstandardized Coefficients		Standardized Coefficients		95% Confidence Interval for B	
	B	Std. Error	Beta	Sig.	Lower Bound	Upper Bound
(Constant)	0.287	0.189		0.130	-0.085	0.659
Impairment of consciousness	0.402	0.091	0.224	0.000	0.223	0.581
Motor deficit	0.481	0.077	0.307	0.000	0.331	0.631
Papiledema upon admission	0.406	0.2	0.102	0.043	0.012	0.799
Bacteriological confirmation in CSF	0.468	0.152	0.149	0.002	0.168	0.767
Cisternal effacement	0.679	0.184	0.189	0.000	0.316	1.042
Cerebral infarcts	0.416	0.190	0.113	0.029	0.042	0.790
Early treatment	-0.637	0.165	-0.189	0.000	-0.962	-0.312

Pearson´s R^2 coefficient =0.35

Table 5: Logistic regression model with dichotomous outcome: mortality or severe sequelae vs. minor or no sequelae.

	B	Sig.	Exp(B)	95,0% C.I.for EXP(B)	
				Lower	Upper
Impaired consciousness	0.792	**0.010**	2.208	1.210	4.031
Motor Deficit	0.926	**0.003**	2.525	1.381	4.620
Papilloedema	0.535	0.100	1.707	0.903	3.227
AFB staining	-0.768	0.814	0.464	.001	276.388
Culture	0.741	0.288	2.098	0.535	8.224
Brain image Hydrocephalus	0.342	0.223	1.408	0.812	2.439
Brain image cysternal effacement	0.771	**0.006**	2.161	1.250	3.736
Brain image Leptomeningitis	-0.118	0.747	0.888	0.433	1.823
Brain image infarcts	0.655	**0.015**	1.926	1.138	3.259

Bolded values are statistically significant predictors.

Table 6: Score Quito

	Present	Absent
Impaired consciousness	2	-9
Motor deficit	4	-6
Cysternal effacement	8	-3
Cerebral infarcts	6	-2
Sum of score	20	-20

Present and absent findings can be summed up to a maximum of 20 points, and a minimum of -20. This score predicts the outcome in two classes: death or serious sequelae on one side, healing or minor sequelae on the other.

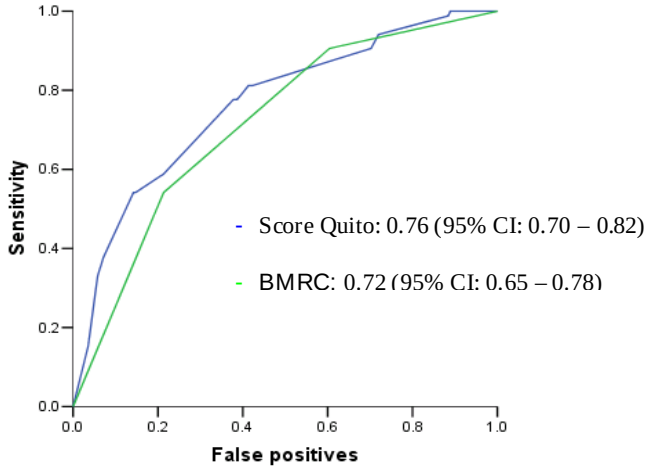

Figure: ROC curve of Score Quito compared with BMRC staging.

DISCUSSION

General

This study is one of the largest validating prognostic scores in CNSTB. Most patients presented with a BMRC Staging of the disease of II or III, which is similar to previous reports about CNSTB.[18-24] The percentage of patients in Stage III was lower than that from a study reported previously by us.[16] This can be explained by an improved capacity to establish early diagnosis and treatment in patients arriving at the emergency room of our hospital. Some patients who started treatment in Stage III had a good recovery; this could be due to early and correct management of hydro electrolytic disturbances and secondary infections.

Limitations

This study presents a retrospective analysis on an existing prospectively gathered dataset. Conception of this analysis from the beginning would have influenced the definition of certain parameters and strengthened the conclusions.

One might argue that diagnostic criteria were not strict in this cohort. The diagnosis of tuberculous meningitis is a presumptive part of the time, without definite microbiological proof. Direct stain, culture and polymerase chain reaction, if anyhow available in low to middle income countries, lack sensitivity.[1] Moreover, the inevitable fatal outcome without treatment sets the treatment threshold at a very low level.[25] As shown also through our results, prompt

treatment, not awaiting further confirmation, is a factor of good prognosis.

Scoring systems have to be validated in other cohorts. The rarity of CNSTB makes this a difficult to realize research, necessitating a multicentre setup, if one does not want to wait for 15 years, the time of case sampling for this study.

Prognosis

Previous studies have established the outcome of CNSTB as "good" or "poor", the latter usually including both mortality and morbidity.[2,10] In our study, clinical variables that predict complete recovery, survival with disability and fatal outcome have been identified separately.

A few factors have shown a significant association with prognosis. The BMRC staging which was developed to establish the degree of severity of the patients with CNSTB at the start of anti-tuberculous treatment has been used in some studies to establish its association with the outcome.[3] The weakness of BMRC is that it is a descriptive scale with overlapping features which do not include images nor CSF analysis and was not built with a multivariate procedure.[3,16,26-30]

Mortality and morbidity (sequelae) rates of CNSTB remain high, ranging from 5.1% to 63% and 8.3% to 50% respectively.[7,10] In our series, as in other, 34 % of the patients who started anti-tuberculous treatment in Stage III died.[10] In 13.8% of the patients admitted in Stage III of the BMRC, the deficit was severe at the end of treatment. This could be related with the cerebral infarcts, hydrocephalus, tuberculomas or spinal tuberculous lesions.[31-34]

Multivariate analysis

Non-significant predictors

Seizures were present in 13.7% of the cases, which is similar to other findings, not being a predictor of poor prognosis.[2,21] The damage of cranial nerves, meningeal signs, loss of weight, hyponatremia and high initial CSF protein levels were not predictors of morbidity-mortality in our patients in contrast with other studies.[2,7,20,22,28] Our results confirm other series where the MRI or CT scan findings of hydrocephalus and leptomeningitis were not significant in the multivariate analysis.[2,6,10,19,21,33,34] The tuberculomas or tuberculous abscesses were also not associated with morbidity-mortality.[2,6,20]

The use of steroids in our patients was associated with poor prognosis in contrast to a recently published paper.[35] This may be because in our study we used steroids in patients with severe tuberculosis who would have a poor prognosis anyway; furthermore, this study was not designed with the purpose of testing the effect of steroids in predicting prognosis.

As in other series, impairment of consciousness was significantly associated with mortality disability.[4,6,7,11,16,26-30,36] This association suggests that severe intra-cranial damage with or without intra-cranial hypertension, found in a high percentage of these patients, may be progressive or irreversible.

The irreversibility of neurological deficit in patients with CNSTB may be related with ischemia, edema or distortion of the adjacent structures.[24] The fact that papilloedema is associated with poor prognosis but not hydrocephalus, could be explained by other factors including venous thrombosis.[31] Positive CSF Ziehl Neelsen (ZN) stain or culture for *M. tuberculosis* represents a high concentration of mycobacteria in the CSF. In our patients, as in other series, it was associated with morbidity-mortality.[17]

Imaging by cranial MRI or CT-scan is a useful tool for diagnosis and follow-up of tuberculous meningitis cases.[2,6,20,33,34] Cisternal effacement has been shown to be associated with poor prognosis.[20] Infarction is a common complication of CNSTB.[16] Two patients who started treatment in Stage I and who had brain infarcts in the first MRI died.

Our study confirms that early anti-tuberculous treatment, before the third day after admission, exerts a protective impact on the morbidity-mortality of patients with CNSTB.[16,26]

Scoring systems

Initially, we hypothesized that correctly analyzing predictors and adding imaging findings would generate a much better score than the rather rough indicators of the BMRC prognostic score. Although the AUC of the Score Quito is somehow larger, the confidence intervals clearly overlap. In any case, the Score Quito shows superiority in its simplicity (only four independent predictors) and in its soundness: confirming and excluding powers are taken into account. It is also important to consider that BMRC staging, when it was built 50 years ago, was not aimed at predicting prognosis, but to classify patients who were submitted to a new therapy (streptomycin) in degrees of severity.[3]

Future research

As suggested in the limitations, this prediction score should be validated in a multi centre study, with a large sample size and a diagnosis as definite as possible. This brings us to the most wanted research result of all, a better diagnostic tool for tuberculous meningitis, CNSTB and tuberculosis in general.

CONCLUSION

An important challenge in CNSTB is the prediction of disability and death on the basis of different indicators exhibited by the patients at the start of treatment. The Score Quito is easy to apply and is a good predictor of poor outcome. The score tested in this study is a valuable indicator of prognosis, but does not outperform the BMRC prognostic score. On the other hand, the predictors resulting from our multivariate analysis discriminate well for a broad prognostic range.

Past decades of scientific breakthroughs, including new techniques of laboratory and imaging diagnostic aid, have contributed very little to a better prediction of prognosis in patients with CNSTB.

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Original Article

GENITO-URINARY TUBERCULOSIS REVISITED - 13 YEARS' EXPERIENCE OF A SINGLE CENTRE

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Summary

Background: Tuberculosis had been declared by the World Health Organization (WHO) as 'public health emergency' in 1993. Extra pulmonary tuberculosis (E.P.T.B.) comprises 20-25% total burden of the disease in which genitourinary tuberculosis (G.U.T.B.) is 4%. Timely diagnosis and treatment will prevent the sequelae of this disease.

***Aims*:** To know the varied clinical presentations, diagnostic modalities and management of G.U.T.B.

***Methods*:** During a 13-year-period, 117 retrospective cases of GUTB were admitted in the tertiary care centre. They were analyzed for clinical presentation, diagnostic modalities and management.

***Results*:** Young patients mainly in third decade of life were commonly affected with higher incidence in females. In our study, the most common presentation was irritative voiding symptoms (66.47%) followed by haematuria (47.60%). Although it can affect the entire organ in genito-urinary system but, in the present study, kidney was the most affected organ (64.9%) following ureter (27.35%), urinary bladder (17.09%), prostate (3.4%) and epididymis (5.19%). In this study, we had not encountered any case of testicular and penile tuberculosis. Among the different diagnostic modalities in this study, the diagnostic positivity rate was 41.6% for the urine AFB test, 55.4% for the urine *M. tuberculosis* culture test and 67.7% for PCR. Chest x-ray was positive in 25.6% (30). ESR was raised in 62.5% and Mantoux test was positive in 61.2% patients.

***Conclusion*:** A high index of suspicion and a wide range of investigations may be required to achieve a complete diagnosis of genitourinary tuberculosis. Though short course chemotherapy with four-drug-regimen for six-month-duration is the mainstay of treatment, surgical interventions were required in 60% of cases of this study. **[*Indian J Tuberc 2013; 60:* 15 - 22]**

Key words: Chemothearpy,Genito-urinary, Surgery, Tuberculosis

INTRODUCTION

Tuberculosis (TB) is one of the leading causes of infectious diseases' morbidity and mortality.[1] Tuberculosis had been declared by the World Health Organization (WHO) as 'public health emergency' in 1993. [1, 2] Extra-pulmonary tuberculosis (E.P.T.B.) comprises 20-25 % total burden of the disease in which genito-urinary tuberculosis (G.U.T.B.) is 4%. In India, the incidence of GUTB is 2.2 million/year (worldwide six million new cases), with a mortality rate of 29/100,000 population/year and prevalence of TB is 168/100,000 population/year.[1,2]

Timely diagnosis and treatment will prevent the sequelae of this disease. This study was conducted to know the varied clinical presentations, diagnostic modalities and management of G.U.T.B.

MATERIAL AND METHODS

This was a retrospective study of a total of 117 patients with GUTB, who were admitted between January 1997 to December 2009 in the Urology Department of I.P.G.M.E and R and S.S.K.M. Hospital, Kolkata. The case records of all cases diagnosed as genito-urinary tuberculosis were analyzed for clinical presentation, urine AFB smear, urine *M. tuberculosis* culture, urine PCR (polymerase chain reaction) for *M. tuberculosis*, radiological and histopathological examinations.

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RESULTS

Four thousand seven hundred thirty three patients were admitted in our department during a recent 13-year-period, of whom 117 were admitted owing to GUTB. Most patients were in their third decade of life (63.2%) and there was female sex dominance (Table 1). Irritative voiding was the commonest presentation and most of the patients had more than one presenting features.

A past history of pulmonary tuberculosis was detected in 22 (18.9%) patients and spine tuberculosis in one.

Urinalysis was non-specific, revealed sterile pyuria in 73 (62.4%), proteinuria in 68 (57.4%), and hematuria in 72 (61.5%) patients. Except for seven, all patients underwent at least one of the following tests: the urine AFB test, the urine culture test, and PCR. Of these patients, 101 (86.4%) were positive for at least one test; the positivity rate was 41.6% of the urine AFB test, 55.4% for the urine *M. tuberculosis* culture test, and 67.7% for PCR.Chest x-ray was positive in 25.6 % (30), ESR was raised in 62.5% and Mantoux was positive in 61.2% patients.

Intra venous pyelogram (I.V.P.) was done in all patients. In I.V.P, kidney was the major primary site of involvement followed by ureter and bladder (Table 2). In all films, no specific type of common deformity was seen.

Table 1: Characteristics GUTB patients in study

Total number of cases	117	
Male to female ratio	1-1.51	
Presentation	**Total no. of patients**	**Percentage (%)**
Irritative voiding symptoms	78	66.47
Haematuria	56	47.6
Flank pain	38	33.8
Constitutional symptoms	37	32.6
Recurrent urinary tract symptoms	22	18.9
Scrotal mass	6	5.1
Colocutaneous fistula	1	.8
Nephrocutaneous fistula	2	1.8
Associated renal failure	17	14.7
Infertility, haematospermia	4	3.4

Table 2: Site of involvement in IVP in GUTB patients

Organ involved	**Number of patients**	**Calyx and infundibular deformity**	**Hydro nephrosis**	**Non-functioning kidney**
Kidney*	76	39	31	6
Ureter	32	Stricture (lower ureter)	Multiple stricture	others
		16	5	11
Bladder	20			

*in 76 cases of renal involvement, 56 patients had unilateral while 20 had bilateral involvement.

Table 3: Organs involved and surgical procedure performed in GUTB patients

Organ involved	Procedure done	Number of patient under went procedure	Percentage of patient under went procedure
Kidney (76)	Nephrectomy	29	38.17 %
	Nephrouretectomy	5	6.5 %
Ureter (32)	D-J Stent Insertion	19	59.3%
	Nephrostomy Placement	10	31.25%
	Ureteric Reimplantation	7	
Bladder (20)	Augmentation Cystoplasty	6	30 %
Prostate (4)	T.U.R.P.	1(incidental)	25%
Scrotal swelling (6)	Epididymectomy	1	16.6 %

Epididymis was involved in six patients ; three of them detected on evaluation of scrotal swelling, two as stricture associated with vas difference on infertility work up and one as scrotal sinus . Seminal vesicle was involved in one patient in haematospermia work up. Prostate involvement was detected incidentally in one patient after Trans Urethral Resection of Prostate (T.U.R.P.) and in three patients, after Trans Rectal Ultrasonography (TRUS) guided prostatic biopsy.

All patients were scheduled to receive 6-month chemotherapy with isoniazid, rifampicin, and ethambutol or pyrazinamide according to the Centers for Disease Control and American Thoracic Society protocol. As for adverse reactions, abnormal liver function was observed in four, pruritus in three and skin eruption in one. At least one of the urine tests (urine AFB test, urine culture test and PCR) was positive in 101 (86.4%) patients before the start of chemotherapy, but it became negative in all patients within three months of chemotherapy. Surgical procedures were needed in 71 (60.13%) patients. (Table 3).

Follow-up period was one year to 13 years and all operated cases were on regular follow-up without any recurrence of disease.

DISCUSSION

The term GUTB was first introduced by Willbolz *et al*. It is the second most common form of extra-pulmonary tuberculosis after lymph node involvement.[4] Although GUTB was the most common sub-type of extra-pulmonary tuberculosis (EPTB), it was recently reported to account for <5% of all patients with EPTB.[1] Eight to 15% of patients with pulmonary tuberculosis are supposed to be at risk of developing GUTB.[5] In our study, 19.6% of patients had the history of pulmonary tuberculosis. Active GUTB usually presents 5-25 years after the primary infection.[6] The primary organ affected in urinary tract is kidney. Renal involvement is usually slow, progressive and destructive. It may lead to unilateral renal loss and renal failure in bilateral involvement. Other part of urinary tract is involved as extension of disease from kidney.[6] In our study, kidney was involved in 64 .9 % and 14.7% had associated renal failure.

In the genitalia, primary site of infection is epididymis in males and fallopian tube in females. Involvement of the genital tract usually occurs in the reproductive age group.[7] The epididymis are affected in 10 to 55% of men with urogenital

tuberculosis.[7] It may manifest as an acute infection, chronic infection or infertility. Acute infection may manifest as a combined epididymo-orchitis with pain, tenderness and scrotal swelling. This may be the commonest manifestation in up to 40% cases.[7] The other common presentation is a scrotal or testicular mass or abscess with or without pain.[8] Infertility may be the presenting feature in about 10% cases.[7] The sperm counts and motility may be reduced due to blockage of the vas and/or secondary atrophy.[9] Epididymal tuberculosis is bilateral in 34% of cases, presenting as a nodule or scrotal hardening in all patients, scrotal fistula in half of cases, and hydrocele in only 5%.[10] The testis is a rare site for tuberculous involvement. Testicular involvement usually occurs contiguous to the epididymal involvement.[7] In our study, of the six patients who had epididymis involvement, three presented as scrotal swelling, two as infertile patients and one with scrotal sinuse. In our country, possibility of tubercular involvement of epididymis is often forgotten and it is considered due to non-specific infection or filarial origin.

Tuberculosis occurs in the seminal vesicle in males and in the uterus and ovarian tube in females through the hematogenous or lymphatic route.[10] Only one patient in our study had seminal vesicle involvement, diagnosed after haematospermia and infertility work-up.

Prostate tuberculosis is rare.[11] Route of infection may be either hematogenous or descending.[11] Although such patients are mostly asymptomatic, but a few advanced cases may present as perineal sinus or decrease ejaculatory volume. On digital rectal examination, the gland is usually non-tender, nodular and rarely enlarged. [12]The diagnosis is most often made by pathologists after prostate biopsy or TURP.[11-13] In our study, four patients had prostate T.B.; three were diagnosed by T.R.U.S guided biopsy and one by prostatectomy indicated for other reasons.

The clinical symptoms of GUTB vary according to interactions between the host and *M. tuberculosis*.[14-16] The most common presenting symptoms in patients of GUTB are irritative voiding and hematuria in 60% and 50% cases respectively.[15,16] Other presenting features may be recurrent urinary tract symptoms, flank pain or scrotal mass, infertility and pelvic inflammatory disease or non-healing wound, sinus and fistulae. In our series, irritative voiding symptoms were seen in 78 (66.47%) cases and hematuria in 56 (46.8%) cases. 22 (18.8%) had recurrent urinary infection. The incidence of renal failure in our series was 17 (14.5%).

Autopsy studies showed that only 50% of patients with renal tuberculosis were symptomatic and only 18% of these received a clinical diagnosis.[2,10] The delayed diagnosis is due to the insidious progression, paucity or non-specificity of symptoms, lack of physicians' awareness and bizarre presentation. Therefore, diagnosis is rarely made before advanced urogenital lesions develop.

G.U.T.B. is diagnosed by demonstration of mycobacterium in urine or body fluid and granulomatous lesion on histopathology. Other features which help in diagnosis are changes in radiographic study (I.V.P, C.T. and Chest X-ray), raised ESR .[17,18] Although urine AFB test is simple, economical, and rapid, it has low sensitivity and specificity for *M. tuberculosis*. In urine examination, sterile pyuria is a classical finding, but demonstration of mycobacterium is used as primary test for diagnosis.[17] The yield of direct A.F.B. smear is low and it is positive in 30% of cases.[18] The culture in special medium takes six-eight weeks, but it is sensitive in 20- 97% of cases and has a higher specificity compared with the urine AFB test.[18,19] Urine PCR can detect the presence of *M. tuberculosis* within a few hours of D.N.A extraction from the sample, even when the urine AFB test and the urine *M. tuberculosis* culture test are negative. It has a reported sensitivity approach to 94% with specificity 88%.[20] In our study, the positivity rate was 41.6% for the urine AFB test, 55.4% for the urine *M. tuberculosis* culture test, and 67.7% for PCR. Kim *et al* have demonstrated that non-tuberculous mycobacteria (NTM) or hemoglobin in hematuria can lead to false PCR negativity.[19, 20] This was the reason of low sensitivity of PCR in our study. Jung *et al* reported that PCR sensitivity in urine was relatively low (60%) and the detection rate of NTM was also low compared with sputum specimens.[19,20]

There are several methods for decreasing false PCR negativity, such as multiple collections of urine samples, collection of high-quality samples such as the first morning urine, removal of inhibitors of PCR, and increasing urine concentration by centrifugation before the analysis.

Imaging tests are important in investigation module of GUTB. Initial tests are plain x-ray abdomen and chest x-ray. Plain X-ray abdomen may show calcification primarily in kidney (7-14%), rarely in ureter, bladder wall or seminal vesicle.[6] USG is poor modality to detect morphological change, but it is more useful in follow up than initial diagnosis.[21] I.V.U is one of the most useful tests as it provides anatomical as well as functional details of kidney, ureter and bladder. The earliest change detected in GUTB may be loss of sharpness or blunting of minor calyces .With progression, there may be moth eaten appearance of calyces or lost calyces, infundibular stenosis, renal cavitation, pseudo tumour or renal scarring and non-functioning kidney.[22] Ureter are initially dilated or irregular and later on with progression, they give beaded or pipestem or corkscrew appearance. Healing in TB, with or without chemotherapy, is often accompanied by fibrosis which leads to stricture. Strictures have been reported in 10-56% of patients with GUTB.[22] Elke *et al* found that ureteric strictures are most commonly located in distal ureter (56%). Mid ureter was involved in 13% and the proximal ureter in 17.19% has the multiple stricture.[22] Multiple stenosis of the collecting system from the infundibulum to the ureterovesical junction are the findings most suggestive of urogenital tuberculosis.[22,23] Bladder involvement is frequent. The earliest manifestations are mucosal edema and ulceration in surrounding of ureteric orfice. Bladder lumen appears irregular because of this ulceration and multiple tubercular granulomas. With advanced disease, cicatrical contraction of wall produces small bladder with multi-lobular shape and finally minute proportion bladder "the thimble bladder".[22] In patients with a contracted bladder due to tuberculosis, the most frequent and characteristic radiological finding is unilateral non-functioning kidney, contracted bladder, and vesicoureteral reflux into the functional contralateral kidney (Figure 1).[23] Now-a-days, CT Scan is imaging modality of choice for GUTB (Figure 2). Over IVU, it provides extra information about adjacent adrenal, retroperitoneal space ,prostatic and seminal vesicle abnormality.[23] MRI is preferred in patients of compromised renal function, contrast allergy and pregnancy (Figure 3).[24] In our series calyces, infundibular irregularities were predominant renal findings. In ureter, lower ureteric stricture with proximal hydrouretro nephrosis is more common. In 20 patients of bladder involvement, 12 had mucosal hyperemia, six with contracted bladder and one with colovesical fistula.

Cystoscopy with bladder biopsy is indicated when there is clinical suspicion of malignancy. The most frequent findings are local hyperemia, mucosal erosion and ulceration, tubercle formation, irregularity of the ureteral

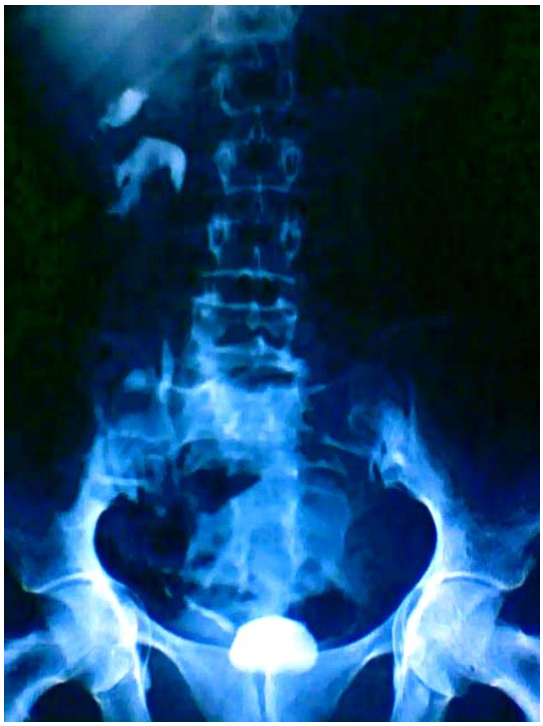

Figure 1: I.V.P of GUTB patient showing non-excretory kidney on left side, small capacity bladder

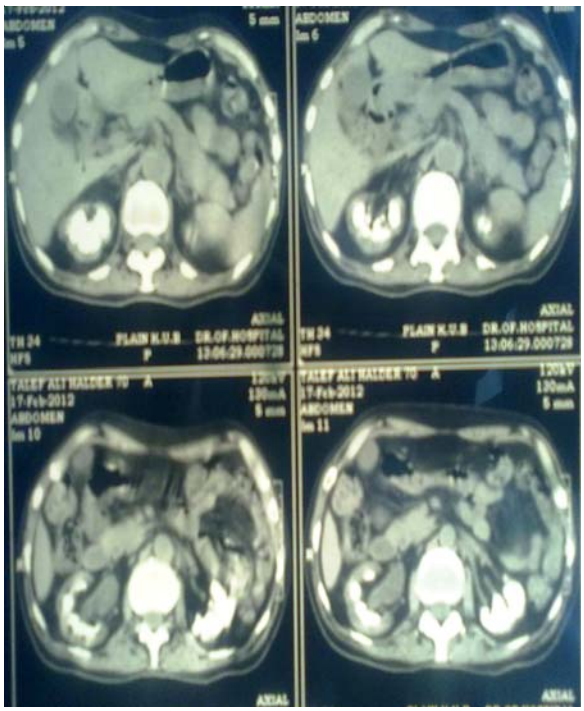

Figure 2: Non-contrasting CT scan showing extensive calcification in both the kidneys

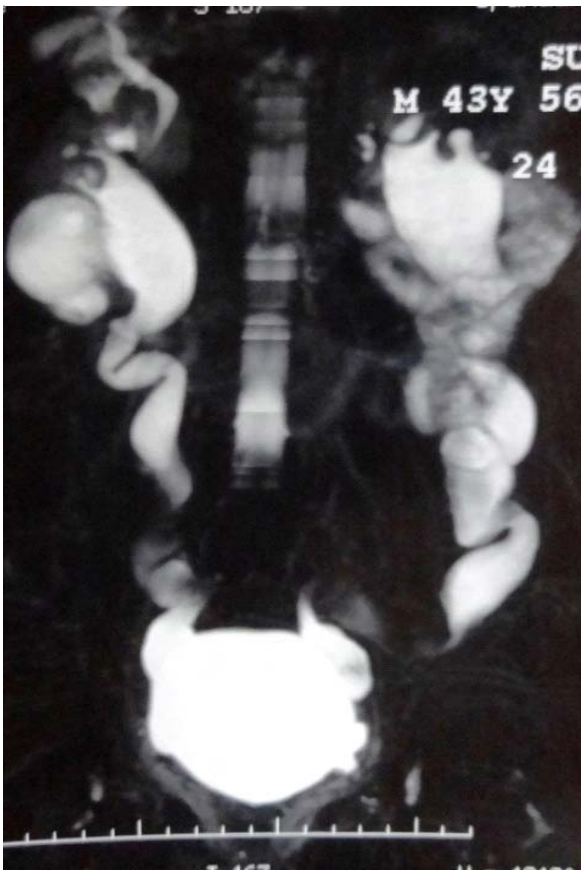

Figure 3: MR Urogram in GUTB patient with compromised renal function showing severe involvement of the kidney, severe bilateral hydrouretro nephrosis and low capacity bladder

meatus and reduced bladder capacity. It should be done after six weeks of medical therapy to prevent the dissemination of disease. Bladder biopsy is 18.5% to 52% sensitive.[25] In our study, 20 patients had involvement of bladder, all were positive for bladder biopsy.

Short-course chemotherapy (SCC) is the standard of care for the treatment of TB. [26] Six-month regimens containing rifampicin and pyrazinamide are very effective with the fastest rates of culture-conversion and the lowest rates of relapse.[1, 26] In India, DOTS implementation began in the year 1993 on a pilot basis. By March 2006, 100% coverage of the nation had been achieved. [27] The treatment success rate has remained consistently above the global benchmark of 85%, and about 1.2 million lives have been saved.[27] Standard Category I regimen is effective for the treatment of patients with GUTB. Currently, there is no evidence to recommend the use of corticosteroids in the management of patients with GUTB. Same protocol was followed in our centre and 86.4% (101) patients who were positive for at least one urine test before the start of therapy became negative in three months.

Despite availability of effective antitubercular therapy (ATT), surgery continues to play a role in management of GUTB.[28] A minimum of four weeks of ATT is recommended before any major surgical intervention because it allows stabilization of the lesion and better planning of reconstructive surgery.[29] For renal and ureteral TB, stricture of pelvicalyces system is initially treated for drainage of hydronephrosis by ureteric stenting or percutaneous

nephrostomy . The strictures should be monitored with CT or IVU. If there is deterioration or no improvement after six-week period, then surgical re-implantation or other minimally invasive procedures including balloon dilatation may be necessary.[31]Partial nephrectomy is indicated for (1) a localized polar lesion containing calcification that has failed to respond after six weeks of intensive chemotherapy; (2) an area of calcification that is slowly increasing in size and threatening to gradually destroy the entire kidney. Traditionally, nephrectomy is strongly indicated in patients with a non-functioning tuberculous kidney with calcification or extensive disease involving the whole kidney with other complications including hypertension or co-existing renal cell carcinoma. The indications for nephrectomy in a non-functional asymptomatic tuberculous kidney are still debatable, but most of the urologists are in favour of removing it.[29,30] The indication for reconstructive bladder surgery is tubercular vesical contracture with frequency of micturition, vesicoureteral reflux and progressive hydro ureteronephrosis.[32] Augmented cystoplasty should be considered in cases of non-compliant contracted bladders where non-operative management protocols have failed.[32] Surgical treatment should also be considered in tuberculosis of the testis or epididymis that shows persistent symptoms after administration of antituberculous agents.[7] In our study, 60.13% of patients underwent surgical intervention.

LIMITATIONS

The results of this study are subject to a few limitations. First, this study was retrospective and conducted only with in-patients. This might have resulted in selection bias. Reliance on urinary PCR positivity, which may have high false positive rate, is another limitation. Lastly, comparisons between overall GUTB patients in the Indian population and enrolled patients in this study were not made. Further studies are needed to confirm.

CONCLUSIONS

Taken together, our results show that G.U.T.B occurred slightly more frequently in females and mainly in subjects in their third decade of life. It has delayed and various modes of presentation. A high index of suspicion is necessary and a wide range of investigations may be required to achieve a complete diagnosis of genitourinary tuberculosis. Multidrug chemotherapy combined with judicious surgery as and when indicated is the ideal treatment. Although short-term antituberculous chemotherapy showed good treatment outcome with less adverse drug reactions but, unlike tuberculosis of other organs, ≥60% of the patients with G.U.T.B needed surgical treatment.

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Original Article

TB/ HIV COORDINATION THROUGH PUBLIC PRIVATE PARTNERSHIP: LESSONS FROM THE FIELD

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Summary

***Background*:** Co-infection with tuberculosis adversely affects the quality of life of HIV infected individuals and additionally, HIV testing among TB patients gives an opportunity for prevention and treatment of HIV infection. TB-HIV coordination activities are therefore a good public health intervention.

***Methods*:** It was a three-year Public Private Partnership Project, implemented in four districts of Maharashtra, to improve access to public health facilities through community awareness and motivating referrals. Outreach workers were engaged to motivate patients attending Integrated Counselling and Testing Centres (ICTCs) and Designated Microscopy Centres (DMCs) for cross referrals and adherence to services. Community leaders and private health providers were sensitized to issues around TB and HIV/AIDS.

Observations: 357 outreach workers referred 17,200 individuals for HIV testing and 32,549 TB suspects were referred for testing. An average of 18% TB cases (13% to 26%) and 7% (4% to 13%) HIV infected cases were identified. Involvement of PLHA and cured TB patients can better motivate symptomatics to avail of diagnostic services. Erratic funding affects smooth implementation of programmes.

Conclusion: Public Private Partnerships improve access to care. Constant dialogue between all stake holders is essential for successful implementation of such partnerships. **[*Indian J Tuberc 2013; 60:* 23 - 27]**

***Key words*:** Access to care, Public Private Partnership, TB/HIV Coordination.

INTRODUCTION

Infection with Human Immunodeficiency Virus (HIV) increases an individual's risk of being infected with TB and early progression to TB disease. TB accelerates HIV disease progression. It becomes a public health priority to diagnose both TB and HIV infections and take effective measures to prevent their spread and improve the quality of life of the infected individuals. World Health Organization (WHO) has formulated guidelines[1, 2] to improve coordination and cross-referrals, and optimal, comprehensive use of the community reach between the TB and HIV control Programme. Indian Revised National Tuberculosis Control Programme (RNTCP) and the National AIDS Control Organization (NACO) have jointly prepared an action plan for TB – HIV coordination.

Both TB and HIV programmes in India have focused on Public Private Partnerships (PPP) to improve their reach and success. TB – HIV coordination is also implemented through PPP in different settings. The Global Fund for AIDS, Tuberculosis and Malaria (GFATM) in its round 3, awarded a component to strengthen TB-HIV Coordination by involving NGOs through the PPP. This was implemented in five States across the country between November 2006 and March 2009.

We present our experiences as a Nodal NGO in the implementation of the Programme in four districts of Maharashtra State.

METHODS

GFATM round 3 awarded the project to strengthen TB-HIV coordination in five states in the country in 2006. The NGO component of this project was to be implemented through a PPP. Action plans were developed by the principal recipient of the grant i.e NACO.

Identification of Nodal NGOs at the state

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level was carried out through stakeholder meetings.

Four Nodal NGOs were selected for the state of Maharashtra. Our organization was responsible for the project implemented in four districts, *viz*. Dhule, Jalgaon, Nagpur and Nashik. Details of demography and public health infrastructure involved in TB and HIV/AIDS activity are given in table 1. For each district, a field NGO was identified with help from local public health authorities. Human resources included a district level supervisor and outreach workers (ORWs) who were locally residing people living with HIV/AIDS (PLHIV) or cured TB patients. One outreach worker was enlisted for around 40,000 population. Monitoring and evaluation were the functions of the nodal NGO with no financial support for field monitoring.

All staff were given intensive training in project implementation at the beginning of the project and periodically.

The district supervisors carried out advocacy, sensitization on issues related to TB and HIV/AIDS through meetings with community leaders, decision-makers and private health care providers. Out–reach workers were primarily involved in interacting with the community through group sessions, one-to-one interaction, home visits and follow-up visits. This activity was directed to bringing about awareness of both the diseases and the available facilities in the public health system. ORWs were also involved in motivating patients attending DMCs/DOTS centres and ICTCs to get tested for HIV and TB respectively.

Data and analysis

The data capture and analysis tools were developed centrally by the State AIDS Control Society.

Process related data was compiled at the district level by the Supervisor through weekly district level meetings. Data of cross referrals was obtained from both ORW documents and from the DMC and ICTC in the district. Monthly technical reports were compiled in pre-designed formats and sent to the nodal NGO. This data was compiled quarterly and submitted to the State AIDS Control Society (SACS).

The project was implemented between November 2006 and March 2009.

OBSERVATIONS

During the first year of the project, many proposed ICTCs were not functional, some were introduced after the project was started, and some either had no manpower or irregular supply of testing kits. Issues of cooperation between the RNTCP, HIV/AIDS Programme and TB/HIV coordination project staff led to poor documentation of the referrals. These were managed at the monthly review meetings at the district headquarters.

After the initial grant for the first two months' activities, funding by the SACS was erratic. Funds were received after the activities were

Table 1: District Demography

Particulars	Dhule	Jalgaon	Nagpur	Nashik	Total
Population	**17,08,993**	**36,79,936**	**40,51,444**	**49,87,923**	**144,28,296**
ICTC	11	24	23	28	**86**
DMC	18	44	37	65	**164**
Supervisors	1	1	1	1	**4**
ORWs	42	92	100	123	**357**

ICTC – Integrated Counseling and Testing Centers
DMC – Designated Microscopy Centers
ORWs – Outreach Workers.

completed for at least three to four quarters. This led to suspension of activities during the third quarter of 2007 as the field NGOs could not sustain the staff due to inordinate delay in receipt of funds from the MSACS. Final settlement was made six months after the project was over. In spite of this, the NGO at Nashik continued activities through its own funds during the period.

After the first two quarters of the project, the post of Supervisor at the NGO was discontinued for more than five quarters and the responsibility was given to the District Supervisor of the public health. Poor coordination at the field level led to the reappointment of NGO Supervisor for the remaining three quarters of the project. Apart from these major challenges, frequent changes in the action plans and delay in communication of the changes from the central agency led to confusion at the field level.

Table 2 shows the data on the process of advocacy, sensitization and community contacts and also the referrals and their outcomes.

Supervisors conducted an average of 174 meetings per quarter with the community, eight with

Table 2: Data on Processes and Referrals#

Particulars	**2006**	**2007**				**2008**				**2009**
	Q4	**Q1**	**Q2**	**Q3***	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**
Supervisor Activity										
Meetings with community	**153**	48	43	50	158	106	141	148	720	1084
Meeting with decision makers	**27**	11	0	0	2	6	3	9	18	364
Meeting with private health care providers	**29**	17	204	0	5	6	5	5	28	1390
ORW Activity										
One to One sessions	**18600**	80652	38337	14337	74733	91530	82888	92847	98466	154284
Group sessions	**3807**	20497	6894	3937	13026	13390	9408	9463	7891	7263
Home visits	**10774**	74171	48489	23626	115054	130429	98989	98239	116753	190153
Follow up visits	**3134**	13697	6537	2935	11804	10722	8167	7540	8804	7345
Total contacts	**36315**	**189017**	**100257**	**44835**	**214617**	**246071**	**199452**	**208089**	**231914**	**359045**
Referrals										
Referred for HIV test (a)	**1101**	6433	2655	1315	6593	6046	5036	8415	8866	8958
Tested for HIV (b)	**412**	1854	970	595	3786	3856	3200	4888	5569	4852
Detected Positive (c)	**32**	246	72	30	236	160	284	237	450	252
HIV detection rate from investigated (c/b)%	**8**	**13**	**7**	**5**	**6**	**4**	**9**	**5**	**8**	**5**
Referred for TB (d)	**1954**	7255	3083	1491	6387	5844	5193	5578	6152	7224
Tested for TB (e)	**1028**	3573	1465	705	4111	3670	3880	4183	4090	3497
Diagnosed as TB (f)	**173**	572	380	132	543	601	701	646	566	748
Put on DOTS (g)	**163**	511	288	103	474	411	602	568	553	547
Case detection rate from investigated (f/e)%	17	16	26	19	13	16	18	15	14	21

#Unless otherwise indicated, figures indicate actual numbers.
*One NGO continued activity through its own funds

decision-makers and 33 with private health care providers.

ORW could make an average of eight contacts per day during the project period (range 2 to 17 – increasing with the duration of the project). An average of 15 and 17 suspects were referred for TB and HIV diagnosis respectively every quarter (range 4 -22 and 3 – 27 respectively). Of these referrals, an average of two and nine were diagnosed as TB and HIV infected respectively. Referrals yielded an average of 18% TB cases (13% to 26%) and 7% (4% to 13%) HIV infected cases. Of the cases detected as TB, 84% were put on DOTS. The number of HIV infected individuals referred for further management could not be determined due to issues of confidentiality.

DISCUSSION

Scientific modeling[3] has shown that improving access to quality care and implementing preventive measures can reduce morbidity and mortality related to TB/HIV co-infection. To meet this end, coordination between TB and HIV/AIDS Programme is essential. This project is unique as it enlists support from affected persons to improve the access to care for both TB and HIV infected individuals. The motivation and dedication of PLHIV and cured TB patients to improve the quality of life of their peers improved coordination between the two programmes, increased cross referrals and case detection. ORWs, in spite of their medical condition, could make eight contacts in a day.

Our TB case detection rate of 16 to 26% compares well with 23% reported in a similar intervention in 83 districts from six Indian states[4]. A study from Tamil Nadu[5] reported 12% (range 8–25) sputum smear-positive cases of the TB suspects referred to DMCs. HIV case detection in our intervention varied from 4 to 13% of all tested individuals and is similar to 4.1% in the different districts in Tamil Nadu[5].

One limitation of this analysis is the inability to assess the number of TB / HIV co-infected individuals. This was not possible as there was no desegregation of HIV infected and non-infected individuals among the TB referrals due to issues of confidentiality.

Although our results are comparable to similar interventions reported, the outcomes could have been better had the funding been regular and timely. Erratic funding[6] led to suspension of activities for over a quarter resulting in loss of staff morale, loss of trained staff to other projects and delays due to retraining of new staff.

For any PPP to be fruitful, public health infrastructure should be in place and fully functional before sensitization and advocacy is initiated[7-9]. Lack of functional public facilities in the initial stages at some places could have resulted in a poor image of the system and led to reluctance on the part of the beneficiaries to utilize services.

Ongoing supportive supervision is essential for effective programme implementation and to ensure quality of care[10]. Absence of a district supervisor, led to poor coordination and improper implementation of the project for over a year. Activities of ORWs were unregulated and no guidance available during the period resulted in lower than expected results.

PPPs are collaborative programmes and all stakeholders should have equal voice irrespective of the donor recipient relations. Poor communication between the donor and the recipient was a major barrier to programme success.

CONCLUSIONS

Coordination between TB and HIV/AIDS Programme is essential to help improve access and quality of life of patients. PPPs with NGOs further enhance access, PLHIV and TB patients are committed to help improve quality of life of the peers. Public health facilities need to be fully operational; policies and guidelines need to be formulated before partnerships are formed. Constant dialogue between all stakeholders and timely, sustainable funding is essential for successful implementation of such partnerships.

Regular monitoring and evaluation with appropriate budget allocation should be inbuilt in the project.

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Original Article

AN OVERVIEW AND MAPPING OF CHILDHOOD TUBERCULOSIS: PREVALENCE, SCIENTIFIC PRODUCTION AND CITATION ANALYSIS

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Summary

Aim: The study aimed to analyze publications in the field of "pediatric tuberculosis" and associate them with regional Tuberculosis (TB) profile.

Methods: A schematic analysis of scientific production in the field of pediatric tuberculosis between 1990 and 2010 using ISI web of science was carried out. Terms used for searches were each as a combination of "*Mycobacterium Tuberculosis*", or "Tuberculos*" and "Child", or "Infant", or "New born", or "Neonatal", or "Adolescent", or "Pediatric". Features including year of publication, citation per year, country of origin, funding state, contributing university, language, leading journals and authors, and highly cited articles, main journal publishing these articles were taken into account.

Results: The search retrieved 3417 articles (of 4559 total) with an almost gradual annually progressive pattern from 20 (in 1990) to 302 (in 2009) which have been cited totally 48459 times and 14.18 times per article. The greatest contribution originated from United States of America (25.11%) followed by South Africa (12.17%), and England (11.18%). Interestingly, 82.4% of all South African articles were from Stellenbosch University and Cape Town University on contrary.

Conclusions: International Journal of Tuberculosis and Lung Disease ranked as the first with regard to the number of articles and Lancet with regard to the number of highly cited articles. Developing countries excluding South Africa despite their high prevalence scarcely contribute to the field and USA is the leading country in the field. **[*Indian J Tuberc 2013; 60:* 28 - 36]**

***Key words*:** Citation, Tuberculosis, Pediatric, Bibliometric.

INTRODUCTION

Tuberculosis (TB) is primarily a pulmonary disease transmitted *via* respiratory route which has caused human suffering and death for centuries.[1,2] Although it was identified by Robert Koch in 1882, it is still a global health challenge.[3,4] Based on published reports, over eight million people annually become infected by TB [5,6] and more than 50 million people will die of TB between 1998 and 2020.[2] The global epidemiology of TB is poorly documented,[7,8] though approximately 95% of all cases take place in developing countries[1,9] where HIV infection presents as a challenge to TB control.[10]

The extent of childhood tuberculosis is unknown which may be due to the difficult accurate diagnosis, inadequate health information systems in developing countries, and the negligence by tuberculosis control authorities.[11-14] However, the overall prevalence of infection in the 0-14 year age group is estimated to be 8.6–10%.[15] The risk of developing disease has been estimated to be 24% in children 1–5 years of age, and unfortunately as high as 43-50% in infants less than a year of age.[7,16]

An urgent step towards better diagnosis and epidemiological data acquisition in this regard seems to be a global obligation; otherwise, childhood tuberculosis remains an 'invisible' entity. Since resurgence of tuberculosis after decades of consistently declining incidence in 1990, case notifications in children have been increasing steadily.[16,17] Much efforts have also been made on tuberculosis therapeutic and diagnostic[18,19] methods.

As the diagnosis and control of childhood tuberculosis is fundamentally different from adult one,[20] and infected children are reservoirs for adult cases,[21] addressing different aspects of TB in children

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is an important health care related issue which deserves the global attention. Nevertheless, this attention has not yet been viewed by a scientometric scale to reveal meticulous details regarding its contributors. Our study aimed to analyze the 1990-to-2010-interval publications in the field of "pediatric tuberculosis" and correlate them with corresponding regional TB prevalence.

MATERIAL AND METHODS

The current descriptive study targeted a schematic view of scientific map in the field of pediatric tuberculosis. We used ISI web of science (http://www.isiknowledge.com) as our database to carry out our analysis in January 2010. Terms used for the searches were chosen in accordance with Medical Subject Heading (Mesh) which is used to index PubMed© contents. Twelve terms were used for our searches. Each term composed of a combination from "*Mycobacterium Tuberculosis*", or "Tuberculos*" and "Child", or "Infant", or "New born", or "Neonatal", or "Adolescent", or "Pediatric". The query was done with all 12 mentioned terms for the intended period of 1990 to 2010. The study merely includes articles among all other retrieved documents such as reviews, proceeding papers, letters, editorial material, meeting abstracts, notes, reprints, corrections, news items, book reviews, and additions.

Overall number of related publications besides further aspects like annual publications, annual citations per paper, language, leading countries, first authors, most contributing journals, highly cited per paper, institutional affiliations, and collaboration were retrieved from ISI Web of Sciences. The collaboration of two countries defined as the total number of articles which composed of at least one author originates from each country regardless of their order and presence of other countries. We also took *h* index into account. The *h*-index reported is defined if at least *h* papers each have been cited at least *h* times.[22,23] Other bibliometric measures to assess individual scientific achievements were total number of published articles and total number citations. The Journal's impact factor reflects journals' scientific merits and standing in a specific field.[24]

Data regarding regional TB profile including total number of new TB cases in Children less than 15 years' old and total number of new TB cases in 2009 were extracted from WHO country- based report available at http://www.who.int/tb/country/data/profiles.

RESULTS

Our query returned 3417 articles (of 4559 total items including reviews, proceeding papers, letters, editorial material, meeting abstracts, notes, reprints, corrections, news items, book reviews, and additions).

These 3417 articles were examined thoroughly from versatile view point, as stated in subsequent sub-headings.

Annual published articles

The distribution of annual publications over time span is depicted in figure 1 which is roughly reflective of an almost gradual annually progressive pattern (excluding 1996-7, 1999-2000, 2000-1, and 2009-10 intervals) with sharpest upsurges being 2005-6 interval followed by 1990-1 and 1991-2. Although the most productive year is 2009 with published 302 articles, there would be possibility of change in the number of 2010-published articles if the study was carried out later.

Citation over time

These articles have been totally cited 48,459 times where the average citation per article for the past 20 years has been 14.18.

Countries' production distribution

These 3417 articles originated from 129 countries among which United States of America with over one fourth of articles followed by South Africa with 416 articles and England with 382 articles have been the most productive ones.

Countries with over 100 articles in the time span are analyzed from different standpoints as

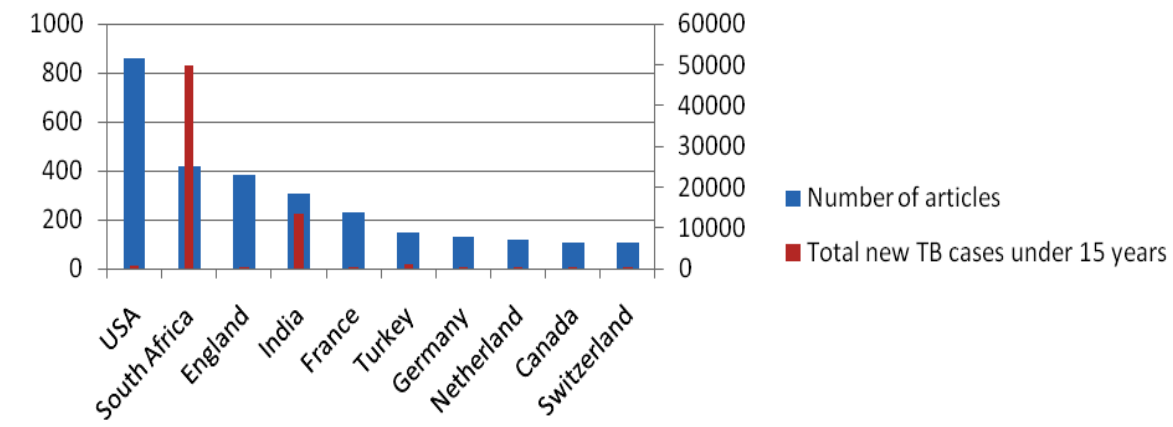

Figure 1: Published articles related to pediatric tuberculosis: Total number in ISI Web of Sciences between 1990-2010.

outlined in table 1. Looking from the perspective of citation per article, Switzerland has preceded others including USA (the most productive country) by a total citation per article of at least over two times of the rest; however, from the perspectives of *h* index and total citation per year, USA has still preserved its first rank (Table 1).

Since there is no unanimous country specific epidemiological data regarding pediatric TB prevalence, to examine the possible association between amount of regional pediatric tuberculosis cases and the extent of scientific production in the field, we used total number of new TB cases in children less than 15 years, reported to WHO in 2009,

Table 1: Countries' pediatric tuberculosis related articles production: Total number of articles, total citations per article, citations per year, and *h* index in ISI Web of Sciences between 1990-2010 in association with countries' total number of new TB cases (total, and under 15 years' old)

Country	Total article (% total)	Total Citations	Citations per Article	Citations per Year	*h* Index	Total < 15 y*	Total New*	Ratio < 15/T
USA	858 (25.11%)	21289	24.81	967.68	62	639	11545	5.53%
South Africa	416 (12.17%)	5404	12.99	245.64	36	49825	340066	14.65
England	382 (11.18%)	9021	23.62	429.57	45	339	7008	4.83%
India	308 (9.01%)	2285	7.42	103.86	23	13577	1243552	1.09%
France	232 (6.79%)	3126	13.47	142.09	25	107	2890	3.7%
Turkey	147 (4.30%)	954	6.49	50.21	13	940	15943	5.89%
Germany	130 (3.80%)	1496	11.51	74.8	21	114	3545	3.21%
Netherland	116 (3.39%)	2196	18.93	104.57	22	57	1094	5.2%
Canada	106 (3.10%)	1876	17.7	89.33	23	86	1447	5.94%
Switzerland	106 (3.10%)	5502	51.91	250.09	26	16	333	4.8%

* According to WHO country- based report available at http://www.who.int/tb/country/data/profiles in 2009.

and its ratio to total number of new TB cases in 2009 (figure 2). However, a discrepancy is evident between the extent of publication and the expense of pediatric tuberculosis cases. Although, the wealth of new pediatric TB cases might have been involved in scientific productions of South Africa, it seems USA's productions are much more independent of TB cases.

Funding state

In the time period of our study, a few articles had stated their funding state; however, among indexed funding agents, National Institute of Health has contributed the most to the field by supporting 35 articles. The utmost indexed funding agents mostly originate from USA where also most articles in the field arose from. However, if we reassessed the total funded USA's articles along the high volume of produced articles, then it would no longer seem significant.

Contributing universities' distribution

The query returned 501 universities where at least three authors/co-authors of the published articles in the time span affiliate to. However, Stellenbosch University followed by Cape Town University, both in South Africa, has got the first rank in this respect and they cumulatively have been involved in 82.4% (343 out of 416) of all South African publications. On contrary, published articles from USA should have been distributed more uniformly within the country, as evidenced by the few number USA universities in the list of major productive universities.

Applied languages

Most articles (91.31%) of the field in the time span were published in English; however, other ISI Web of Sciences indexed languages were respectively French (4.54%), German (1.49%), Spanish (1.49%), Portuguese (0.47%), Italian (0.18%), Russian (0.15%), Turkish (0.15%), and finally Croatian (0.09%).

Leading journals

Looking at the analysis from the aspect of publishing journals revealed 385 journals with at least two articles in the time span. However, majority of the articles have been published in *International Journal of tuberculosis and Lung Disease* (235 articles), *Pediatric Infectious Disease Journal* (165 articles), and *pediatrics* (78 articles). *International*

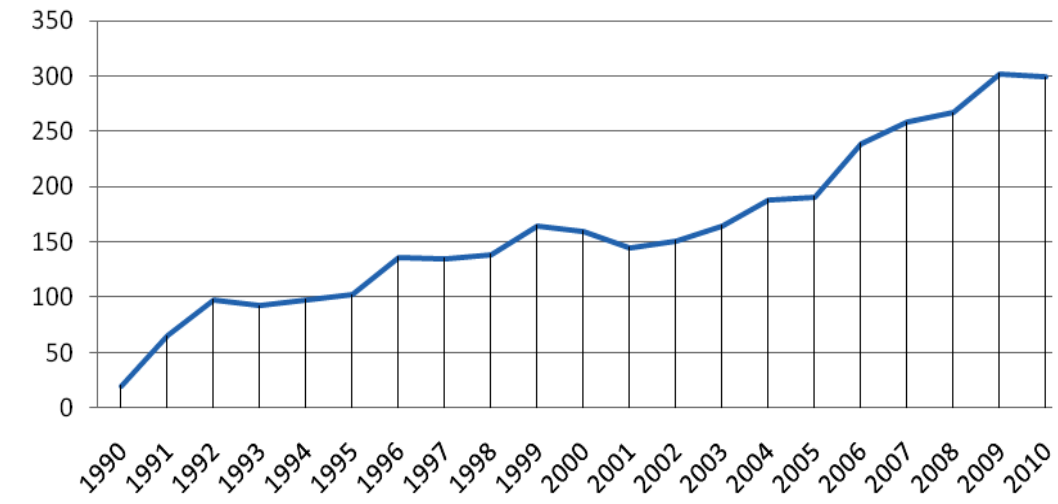

Figure 2: Association of most productive countries' articles and their new pediatric TB cases.

Journal of tuberculosis and Lung Disease in spite of being more scope specific than pediatric specific, has got the first rank in the time span (Table 2).

Leading authors

We found that 501 people co-authored at least three articles between 1990 and 2010. However, most top composing authors/co-authors are from South Africa and mostly affiliated to Stellenbosch University. Simon Hendrick Schaaf and Nulda Beyers both affiliated to Stellenbosch University have got the most top H index of 24, though Nulda Beyers' total articles' count is relatively lower (Table 3).

Highly cited articles

Our analysis regarding highly cited articles between 1990 and 2010 returned 50 articles which have been cited over 100 times in the ISI Web of

Table 2: Journals with most pediatric tuberculosis related articles: Total number as index in ISI Web of Sciences between 1990-2010 in association with journal impact factor (IF)

Journal	Articles Count (% total)	IF
International Journal of tuberculosis and Lung Disease	235 (6.88%)	2.548
Pediatric Infectious Disease Journal	165 (4.83%)	2.854
Pediatrics	78 (2.28%)	4.687
Clinical Infectious Diseases	63 (1.84%)	8.195
Archives of Disease in Childhood	54 (1.58%)	2.657
Journal of Tropical Pediatrics	53 (1.55%)	1.224
Tubercle and Lung Disease	51 (1.49%)	
Pediatric Radiology	47 (1.38%)	1.186
Annals of Tropical Pediatrics	44 (1.29%)	0.895
Archives De Pediatrie	42 (1.23%)	0.406
Lancet	34 (1.00%)	30.758

Table 3: Authors with most pediatric tuberculosis related articles: Total number as index in ISI Web of Sciences between 1990-2010 along their affiliation and topic related H index

Authors	Record Count	H Index	Affiliation	Country
Simon HendrickSchaaf	89 (2.60%)	24	Stellenbosch University	South Africa
NuldaBeyers	64 (1.87%)	24	Stellenbosch University	South Africa
Peter Roderick Donald	61 (1.79%)	22	Stellenbosch University	South Africa
Robert P. Gie	59 (1.73%)	23	Stellenbosch University	South Africa
Ben J Marais	55 (1.61%)	18	Stellenbosch University	South Africa
Anneke C. Hesseling	39 (1.14%)	17	Stellenbosch University	South Africa
SavvasAndronikou	30 (0.88%)	8	University of Cape Town	South Africa
Jeffrey R. Starke	30 (0.88%)	15	University of Texas	USA
Mark Fredric Cotton	22 (0.64%)	11	Stellenbosch University	South Africa
Jean Laurent Casanova	21 (0.61%)	12	St. Giles Laboratory	France
Gregory Hussey	21 (0.61%)	9	Stellenbosch University	South Africa
Klaus Magdorf	20 (0.59%)	4	CharitéUniversitätsmedizin	Germany

Sciences. The *Lancet* with 11 highly cited articles, 4743 citations over time and 431.18 citations per paper has got the first rank. We also calculated H/ T ratio to find out what was the proportion of published articles in each journal which have been highly cited over the time span. Nevertheless, table 4 outlines journals with at least two highly cited papers in the field of pediatric TB during the time span.

Analysis of these highly cited papers in respect of published years disclosed that excluding 2008-2010 intervals which have got lesser chances of being cited over 100 times, one highly cited article each year is at least published every year. However, 1997 with seven highly cited articles and subsequently 2002 with six highly cited articles headed the rest. To retrieve the share of collaboration upon accomplishment of these highly cited articles, we extracted them from ISI Web of Science. The countries' collaboration ranged from two to 13 and totally 23 highly cited articles were cooperative ones. Since 2000, a greater proportion of each year highly cited articles have been cooperative ones.

Out of 129 countries involved in production of the pediatric tuberculosis related articles, only 31

Table 4: Journals with at least two pediatric tuberculosis related highly cited articles: Total number as index in ISI Web of Sciences between 1990 and 2010 along journal IF

Journal	Highly cited	Total articles	H/ T* Ratio	Total citations	Citation per article	IF
Lancet	11	34	0.323	4743	431.18	30.758
New England Journal of Medicine	6	12	0.5	2154	359	47.05
JAMA	3	10	0.3	500	166.66	28.889
Pediatrics	3	78	0.038	597	199	4.687
Science	2	2	1	1907	953.5	29.747
Radiation Research	2	5	0.4	485	242.5	2.948
Journal of Clinical Investigation	2	6	0.33	453	177	15.357
Journal of Immunology	2	5	0.4	298	149	5.646
Thorax	2	21	0.095	290	145	7.041
British Medical Journal	2	12	0.166	225	112.5	13.66

* Highly cited over total articles ratio

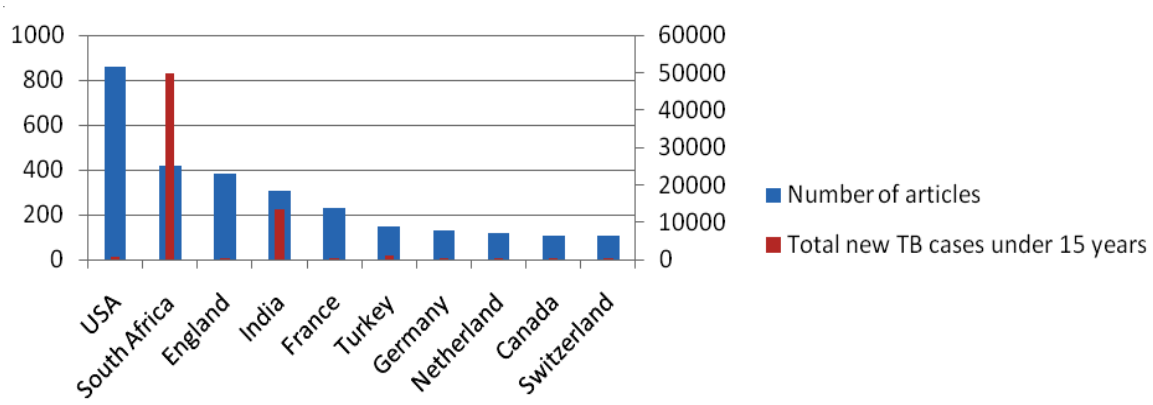

Figure 3: Countries' highly cited pediatric tuberculosis related articles along their cooperative highly cited articles: Total number in ISI Web of Sciences between 1990-2010

had taken part in collaboration resulting in publication of a highly cited article. However, these countries' total highly cited articles along cooperative highly cited articles are depicted in figure 3.

During the time span, a few countries like Egypt, Italy, and Netherlands have not yet been involved in collaboration resulting in publication of a highly cited article; On contrary, most of the England highly cited articles are cooperative, the most prevalent method among other countries. However, most of the American highly cited articles are non-cooperative (15 out of 24).

DISCUSSION

Current study aimed to review the scientific production in the field of pediatric tuberculosis between 1990 and 2010. Different foci are explained in prior section; however, it seems that generally scientific production has been progressing since 1990 when a global concern arose regarding resurgence of tuberculosis after decades of consistently declining incidence. After World Health Organization Tuberculosis Unit special study to determine the nature and magnitude of global tuberculosis in 1989/ 1990, a study which yielded to WHO call on an urgent need to develop control and elimination strategies,[5] we have witnessed two sharp rises of published articles in subsequent two intervals of 1990-1 and 1991-2. Since the WHO declaration of a "global tuberculosis emergency" in 1993, wealth of publications have been addressing different aspects of tuberculosis like its burden, management, and control but adult disease has got the most attention, nevertheless; pediatric tuberculosis share is also steadily progressive as evident yearly growth in published articles. In 2006, world attention was captured by an extremely lethal outbreak in Tugela Ferry, a rural settlement of KwaZulu Natal, South Africa following which World Health Organization Global Task Force on Extensively Drug Resistant TB (XDR-TB) altered XDR-TB definition in October 2006.[25] This event coincided with the most significant upsurge of published articles in the past 20 years in 2005-6.

Between 1990 and 2010, over one fourth of the production in the field took place in USA despite its relatively low yearly new cases in children less than 15 years. Remarkably, during the mentioned period, the contribution of USA, South Africa, and UK have been nearly equivalent to the rest of the World. On the other hand, Switzerland articles, despite having a low frequency of 3.1%, have been cited over two times of the rest during the time period. However, USA, South Africa, and UK, irrespective of order, also preserve the pattern of their precedence over the others in the aspects of state funders and contributing universities but in the aspect of total highly cited articles Switzerland has substituted South Africa.

Among 501 involved indexed institutions in the field, South African universities, especially Stellenbosch University, have had significantly high amount of publications per university during the time span of 1990 to 2010. The motivation for this great volume of research in this region may not follow similar lines of other areas, since high prevalence of HIV in this region not only exacerbates the TB disasters but also emerged to new manifestations of TB such as congenital and neonatal TB which are increasing as a result of the rising prevalence of TB in young women and mothers.[10]

Almost all articles, despite their versatile originalities, were published in English language. Journals with paramount productions have a broad range of IF from 0.406 to 30.758; however, over one of fourth of articles in the field during 1990-2010 were published by only 11 journals among which two have totally had 13 highly cited articles, i.e. cited over 100 times.

It seems that those articles published in "*Science*" (IF: 29.747) and "*The New England Journal of Medicine*" (IF: 47.05) have been credited the most since 100% of "*Science*" published articles and 50% "*The New England Journal of Medicine*" published articles have become highly cited between 1990 and 2010; however, two factors at least should be taken into account: Firstly, a few articles were published in both journals. Secondly, these journals have got high impact factors which might be to some extent explanatory of our findings.

It is worthwhile to emphasise on this point that only 40% of highly cited articles were published between 2000 and 2010, but it seems that the real frequency is much higher; lack of any highly cited papers since 2008 might be a clue to this assumption. Furthermore, a general trend of more cooperative highly cited articles since 2000 is noted in this analysis, though USA with almost half of highly cited papers during the period, has been less cooperative with other countries.

Authors with utmost articles in the field of pediatric tuberculosis are mostly affiliates of Stellenbosch University in South Africa. However, we found two following effective factors: First and foremost, the prevalence of tuberculosis in the region is significantly high. Last but not the least, most of the South African articles (343 out of total 416) during 1990-2010 were produced by Stellenbosch and Cape Town Universities in South Africa. Nevertheless, any of their articles have not yet been highly cited and the only South African highly cited article co-author is not among these leading ones. Most South African leading authors in the field of pediatric TB have got a topic specific H index which is relatively much higher than a few non-South African leading authors.

In conclusion, we have found that although pediatric tuberculosis is of discrepant geographic range and most cases take place in developing countries, it draws a wide research interest in 129 countries. However, the central publishing country is USA. Unfortunately, excluding South Africa, developing countries scarcely contribute to the field despite their high prevalence. Finally, although the number of publications and the scientific interest in pediatric tuberclusis have increased rapidly in recent years, it deserves to remind that TB in children is an important health care related issue which mandates the global attention.

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Original Article

DELAY IN DIAGNOSIS AND TREATMENT AMONG TB PATIENTS REGISTERED UNDER RNTCP MANDI, HIMACHAL PRADESH, INDIA, 2010.

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(Received on 19.7.2012; Accepted after revision on 17.10.2012)

Summary

***Background*:** Delay in TB diagnosis and treatment is associated with increased transmission, morbidity and mortality. Patient and provider factors are responsible for such delays. We conducted a study to estimate these delays and identify associated factors among new sputum positive (NSP) TB patients in Mandi district, Himachal Pradesh.

Methods: We interviewed 234 NSP patients to collect information on their health seeking behaviour. We conducted univariate and multivariate analysis to identify factors associated with longer delays.

Results: Median patient, health system and total delay were 15, 13 and 36 days respectively. Significant factors associated with total delay included patients' knowledge about TB, seeking care from non-specialized individuals as the first action, consulting >2 health facilities before diagnosis and consulting private health facilities. Patients with low family income and those who had high expenditure on consultations before initial diagnosis were associated with patient and health system delay respectively.

***Conclusion*:** It is necessary to increase community awareness about TB symptoms and availability of free treatment at public health facilities. Educating private physicians about the need for maintaining a high index of suspicion of tuberculosis and sensitizing drug-store owners to refer the chest symptomatics to government health facilities would also help in reducing these delays. **[*Indian J Tuberc 2013; 60:* 37 - 45]**

Key words: Tuberculosis, Delays, RNTCP, India

INTRODUCTION

India is the highest tuberculosis (TB) burden country in the world accounting for one fifth of the global incidence.[1] The Revised National TB Control Programme (RNTCP) which was launched in the country in 1997, achieved a nationwide coverage in 2006. In 2007, the programme for the first time achieved the target of 70% case detection while maintaining the cure rate of more than 85%. As a result of the successful implementation of the programme, TB mortality in the country has reduced from over 42/100,000 in 1990 to 24/100,000 in 2008 while the disease prevalence has reduced from 568/100,000 to 185/100,000 during the same period.[2]

RNTCP emphasizes on achieving a target of 70% case detection as well as 85% cure of TB patients. Delay in diagnosing the patient or initiation of treatment, however, is not taken into account in any of the programme evaluation indicators. Early detection followed by effective therapy is extremely important in controlling TB. Delay in diagnosis results in increased infectivity in the community.[3] Smear-positive cases are more likely to infect other individuals and it is estimated that an untreated smear-positive patient on an average can infect about 10 contacts annually and over 20 during the natural history of the disease until death. Delay in tuberculosis diagnosis may also lead to a more advanced disease state at presentation, which contributes to adverse sequelae and overall mortality.[4] In high prevalence countries, delays in diagnosis in treatment are often prolonged.[5] These delays occur at the level of patients as well as health system. Patient delays occur when patients consult the health

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care provider late after the onset of TB symptoms while the health system delay is on account of time taken for diagnosis and initiation of anti-tuberculosis treatment.[5]

Information about the magnitude of different kinds of delays as well as risk factors associated with those delays is often helpful for the programme managers to improve the case-finding and thereby reducing the transmission of the disease. In view of this, we conducted a study among the new sputum smear positive (NSP) tuberculosis patients registered under RNTCP in Mandi district, Himachal Pradesh to (1) estimate the magnitude of various delays (2) know the health seeking behaviour and (3) identify the factors associated with such delays.

METHODS

Study area and population: We conducted a cross-sectional analytical study among the new sputum positive (NSP) TB patients registered under the district TB programme in Mandi district during the last quarter of 2009 and the first quarter of 2010.

Operational definitions: We defined the 'total delay' as the time interval from the onset of symptoms of TB until the initiation of anti-tuberculosis drugs.[5] It is the sum of two time intervals: 'patient delay' defined as time interval between onset of symptoms and presentation to a health care provider and 'health system delay' defined as time interval between the consultation at a health facility and the initiation of anti-tuberculosis treatment. The total delay was also considered as the sum of diagnostic delay and treatment delay. Diagnostic delay was defined as the time interval between the onset of symptoms and labelling of the patient as a tuberculosis patient (tuberculosis diagnosis) while treatment delay was defined as the time interval between tuberculosis diagnosis and initiation of anti-tuberculosis drugs. Health facility was defined as all government and private health facilities manned by a qualified health care provider (HCP).

Sample size and sampling procedure: In Mandi district, during 2009-2010, about 475 NSP cases were registered under RNTCP in any two quarters. Assuming longer delay in 50% of patients, maximum allowed error of 5%, 95% confidence interval and 10% non-response, the required sample size for the study was 234.

Data collection: We used the questionnaire used in the WHO multi-country study to estimate the diagnostic and treatment delay in TB.[5] The questionnaire was pilot-tested on 10 TB patients and then based on results of pilot testing it was suitably modified for local use. Using this questionnaire, the trained health workers interviewed the TB patients to collect information on socio-demographic characteristics, risk factors of tuberculosis and their health seeking behaviour. We also collected information about the factors that might influence patients' health-seeking behaviour including their knowledge about the disease, fear of what would be found on diagnosis, fear of social isolation and stigma. Variables measuring knowledge and stigma were recorded on a three (0 best, 2 worst) and five point (0 the highest and 4 the lowest degree of stigma) Likert scale respectively. Variables measuring patients' knowledge included knowledge about its causes, curability, existence of vaccine, duration of treatment and type of drugs used for treatment. Stigma was measured using variables such as feeling ashamed of having TB, had to hide TB diagnosis from others, social isolation due to TB and the extent to which tuberculosis affected the following: relations with others, work performance, family responsibilities, marital relations, work performance, chance of marriage, etc.

To calculate different delays, we asked the respondents to recall the time of first clinical manifestation (cough or other symptoms) and date of first action. For ascertaining time of first contact with health facility and subsequent

health encounters, we reviewed the records available with the patients. Where records were missing or not available, patients were asked to recall the dates. We confirmed these dates with first degree relatives. Local religious festivals and agricultural events were used as a calendar to collect information for those patients who were unable to recollect the exact date of onset of first presenting symptoms and health care consultations. We also abstracted information about the dates of diagnosis and initiation of anti-TB treatment from RNTCP records.

Data analysis: We analyzed the data using Epi-Info (CDC, Atlanta, 3.5.1) and open Epi softwares**.** We calculated the mean and median delays along with their ranges. We conducted univariate analysis to identify risk factors associated with patient, health system and total delays. For the outcome variable, we used the median delay as a cut-off to dichotomize the TB patients into two groups (≥ median *versus* < median). We added the scores for different variables used to measure the knowledge about TB and stigma associated with TB and used the median score to dichotomize these variables. Median was also used to dichotomize expenses incurred during consultations before diagnosis. Variables with p-value <0.2 in univariate analysis were included in multiple logistic regression.

Human subject protection: The ethics committee of National Institute of Epidemiology, Chennai approved the study protocol. We obtained written informed consent from participants. We also obtained the permission from the Chief Medical Officer and the District Tuberculosis Officer of Mandi district, Himachal Pradesh.

Results

We interviewed 234 new sputum positive patients registered in the district during the last quarter of 2009 and first quarter of 2010.

Profile of TB patients (Table 1)

About half of patients were more than 35 years' old, two-thirds were males and one-fourth was illiterate. Most of the patients were living in rural areas and had monthly income of less than Rs. 3000. Smoking, either current or ex-smoking, was reported by more than half of the patients. Current smokers smoked a median of 10 cigarettes per day. About 30% of patients reported consumption of alcohol daily.

Table 1: Socio-demographic characters, risk factors and symptom profile of tuberculosis patients Mandi, Himachal Pradesh, India, 2010

Characteristics	N =234	(%)
Socio-demographic characteristics		
Age (years)		
<35	115	49.1
≥35	119	50.9
Female Sex	78	33.3
Community		
General	123	52.6
Scheduled caste/Tribe	111	47.4
Education		
College /University	20	8.6
Primary/secondary	154	65.8
Illiterate	60	25.6
Occupation		
Employed	93	39.7
Unemployed	141	60.3
Residence		
Urban	18	7.7
Suburban	2	0.9
Rural	214	91.4
Marital status		
Married	177	75.6
Single	57	24.4
Income		
<3000	193	82.5
≥3000	41	17.5

Health Seeking Behaviour (Table 2)

As a first action to the symptoms of TB, 54% of the patients contacted health facility, 39% purchased the medications over the counter while a small proportion of patients resorted to self-medication or went to traditional healer. Health care facility first consulted by the majority of the patients included health sub-centre, Primary, Ayurvedic and Community Health Centre (42%), Civil and District hospitals (31%) and private clinic/hospital (22%). The commonest reasons for consulting these health facilities included proximity to patients' residence (73%) and patients' belief in these facilities (20%). The reason cited by 51 (21%) patients who visited private health facility for not consulting a government health facility initially included long waiting time at government clinics (73%) and distance from their residence (24%). When asked about the perceived causes of delay in health seeking, 63% felt that there was no delay in reaching a health facility while 23% felt that their symptoms would subside on their own. Other cited reasons for delay included fear of what

Table 2: Health seeking behaviour of tuberculosis patients in Mandi, Himachal, India, 2010

Health-seeking Behavior	N=234	(%)
First action		
Health facility*	127	54.3
Self medication	13	5.5
Traditional healer	3	1.3
Purchased medicine from Drug stores	91	38.9
Health Facility* of health care provider from whom patients first sought consultation		
Health sub-center	5	2.1
Primary health center	28	12.0
Ayurvedic health center	32	13.7
Community health center	32	13.7
Civil hospital	43	18.4
District hospital	29	12.4
Private clinic/hospital	51	21.8
Other (medical college)	14	6.0

*Any health facility, private or government, manned by qualified health care provider

Table 3: Correctness of patient's knowledge about tuberculosis and stigma experience in Mandi, Himachal, India, 2010

Items	Males (n=156)	(%)	Female (n=78)	(%)	Total	(%)
Knowledge						
Is TB Hereditary?	99	63.5	40	51.3	139	59
Is TB Contagious?	102	65.4	45	57.7	147	63
Is TB Curable?	139	89.1	63	80.8	202	86
Is there a Vaccine for TB?	22	14.1	11	14.1	33	14
Do you know Duration of treatment?	116	74.4	54	69.2	170	73
Stigma						
Feel ashamed?	63	40.4	61	78.2	124	53
Have to hide?	82	52.6	65	83.3	147	63
Affect relations with other?	64	41.0	49	62.8	113	48
Prefer to live isolated after diagnosis?	85	54.5	60	76.9	145	62
Work performance?	113	72.4	69	88.5	182	78
Marital relations?	67	42.9	55	70.5	122	52
Does TB affect family responsibilities?	96	61.5	60	76.9	156	67
Is there less chance of marriage due to TB diagnosis?	107	68.6	75	96.2	182	78
Does TB affect your family relations?	61	39.1	50	64.1	111	47

would be found on diagnosis (6%) and fear of social isolation (5%).

Knowledge and perceived stigma related to tuberculosis (Table 3)

Majority of the TB patients knew that TB was curable (86%) and the duration of anti-TB treatment (73%). Nearly 60% of the patients knew that TB was not a hereditary disease. Knowledge about the disease was not different among males and females; median knowledge score was six among both males and females. 37% of the males had poor knowledge as compared to 45% females ($\div^2$=0.98, p=0.32). TB related stigma was highly prevalent among the patients. More than three fourth of the patients felt that TB affected their work and TB diagnosis would reduce the chances of getting married. More than 60% of the patients reported that they had to hide their diagnosis of disease from others, preferred to live isolated and affected their family responsibilities. The median stigma score among females and males was 15.5 and 22 respectively. 78% of the females had high stigma as compared to 40% males ($\div^2$ =28.36, p-value = 0.000000).

Table 4: Different types of delay for tuberculosis patients in Mandi, Himachal Pradesh, India, 2010

Type of delay	N
Patient delay (days)	
Mean (SD)	24.5 (28.42)
Median(range)	15(0-180)
Health system delay (days)	
Mean (SD)	23.54(28.39)
Median(range)	13(1-204)
Diagnostic delay (days)	
Mean (SD)	46.3 (36.9)
Median(range)	33.5(6-210)
Treatment delay (days)	
Mean(SD)	1.74 (2.87)
Median(range)	1(0-20)
Total delay (days)	
Mean (SD)	48 (37.16)
Median(range)	36(7-210)

Delays (Table 4)

After the onset of symptoms, patients consulted the health care provider (patient delay) after a median duration of 15 days (range: 0-180 days). The median duration between the first consultation and initiation of treatment (health system delay) was 13 days (range 1-204 days). The median duration between the onset of symptoms and initiation of anti-TB drugs (total delay) was 36 days (range: 7-210 days). This included a median diagnostic delay of 33.5 days (range: 6-210 days) and treatment delay of one day (0-20 days). Among 79 (34%) TB patients, the total delay ranged between one - two months while in 67 (29%), the delay was more than two months; in rest of 88 (37%) it was less than one month. Median total delay in males and females was 36 and 37 respectively (p >0.5).

Factors associated with delays

On univariate analysis, TB patients who were illiterate (OR=1.94, 95% CI=1.06-3.54), smokers (OR=1.86, 95% CI 1.09-3.14), had poor knowledge about TB (OR=1.96, 95% CI=1.15-3.14), who sought care from non-specialized individuals (traditional healers, purchased the medicines over the counter or received self-medication) as the first action for their symptoms (OR=2.34, 95% CI=1.38-3.96), who consulted more than two health care facilities before diagnosis (OR=2.53, 95% CI=1.46-4.39) and consulted private health facilities (OR=2.52, 95% CI=1.30-4.87) were more likely to have the longer total delay (Table-5). Patients who had family income below 3000 (OR=2.40, 95% CI=1.18-4.86) and whose first action for their symptoms included seeking care from non-qualified providers (OR=6.21, 95% CI=3.50-11.03) were more likely to have the longer patient delay. Significant factors associated with health system delay included high expenditure (>than median i.e. 200 rupees) on consultations before initial diagnosis (OR=3.37, 95% CI=1.96-5.77), consulting

Table 5: Risk factors for delay in diagnosis and treatment of pulmonary TB on univariate analysis Mandi, Himachal, India, 2010

Risk factors	Patient delay			Health System delay			Total delay		
	≥Median (n=121)	<Median (n=113)	OR (95%CI)	≥Median (n=121)	<Median (n=113)	OR (95%CI)	≥Median (n=120)	<Median (n=114)	C (95%C
Age >35 years	62	57	1.03 (0.62-1.72)	66	53	1.36 (0.86-2.27)	67	52	1. (0.90-2.5
Female Sex	43	35	1.23 (0.71-2.12)	46	53	1.55 (0.89-2.69)	40	38	1. (0.58-1.7
Scheduled Caste/tribe	57	54	0.97 (0.58-1.63)	63	48	1.47 (0.88-2.46)	63	48	1. (0.90-2.5
Education (Illiterate)	32	28	1.09 (0.60-1.96)	36	24	1.57 (0.86-2.85)	38	22	1. (1.06-3.5
Family Income (<3000)	107	86	2.40 (1.18-4.86)	97	96	0.71 (0.36-1.42)	99	94	1. (0.51-1.9
Residence (Rural)	112	103	1.20 (0.47-3.09)	111	104	0.96 (0.37-2.46)	110	105	0. (0.37-2.4
Marital status (single)	27	30	0.79 (0.44-1.44)	24	33	0.60 (0.33-1.09)	23	34	0. (0.30-1.0
Smokers	73	62	1.25 (0.74-2.10)	69	66	0.94 (0.56-1.58)	78	57	1. (1.09-3.1
Alcohol consumption	60	56	1.00 (0.60-1.67)	60	56	1.00 (0.60-1.67)	66	50	1. (0.93-2.6
First action, sought care from non qualified people	80	27	6.21 (3.50-11.03)	NA	NA	NA	68	41	2. (1.38-3.9
Health facility first consulted(Private)	20	31	0.52 (0.28-0.99)	42	9	6.14 (2.82-13.36)	35	16	2. (1.30-4.8
Consulting >2 health facilities	NA	NA	NA	70	17	7.75 (4.13-14.54)	57	30	2. (1.46-4.3
Expenses incurred before diagnosis*	NA	NA	NA	74	36	3.37 (1.96-5.77)	61	59	1. (0.82-2.3
Stigma (High)	71	53	1.61 (0.96-2.70)	61	63	0.81 (0.48-1.35)	62	62	0. (0.54-1.5
Knowledge(poor)	55	38	1.64 (0.97-2.79)	49	44	1.06 (0.63-1.80)	57	36	1. (1.15-3.3

*> median

Table 6: Risk factors for delay in diagnosis and treatment of pulmonary TB on multivariate analysis Mandi, Himachal, India, 2010

Delay	AOR*	95% CI
Patient delay		
Income of family<3000	2.75	1.23-6.15
First action Drug stores/self medication	7.80	4.17-14.58
Stigma (High)	1.81	0.99-3.32
Knowledge(Poor)	2.04	1.10-3.79
Health system delay		
Sex (Female)	1.54	0.78-3.05
Caste (scheduled caste/Tribe)	1.70	0.89-3.55
Education (Illiterate)	1.67	0.79-3.55
Expenses incurred before initial diagnosis (>median)	2.58	1.34-4.95
Multiple Health seeking encounters with HCP	8.03	4.00-16.17
Health facility first consulted (Private)	6.68	2.75-16.23
Total Delay		
Age >35 yrs (median)	0.89	0.44-1.81
Caste (scheduled caste/tribe)	1.53	0.84-2.78
Education (Illiterate)	1.51	0.70-3.28
Smokers	1.41	0.61-3.23
Alcohol consumption	1.42	0.62-3.24
First action (non qualified persons)	2.79	1.53-5.10
Health facility first consulted (Private)	2.42	1.14-5.17
Multiple Health seeking encounters with HCP	3.21	1.71-6.03
Knowledge (poor)	2.27	1.21-4.25

(* adjusted odds ratio)

private health facilities (OR=6.14, 95% CI=2.82-13.36) or consulting two or more health facilities before diagnosis (OR=7.75, 95% CI=4.13-14.54).

On multivariate analysis, the significant risk factors associated with total delay included poor knowledge about the disease (Adjusted odds ratio, AOR=2.27, 95% CI=1.2-4.25), seeking care from non-qualified persons as the first action (AOR= 2.79, 95% CI=1.53-5.10), consulting more than two health facilities before diagnosis (AOR= 3.21, 95% CI=1.71-6.03) and consulting private health facilities (AOR= 2.42, 95%, CI=1.14-5.17). Besides these variables, patients with lower income and those who had high expenditure on consultations before initial diagnosis were associated with patient and health system delay respectively (Table-6).

DISCUSSION

RNTCP in Mandi district has been achieving high case detection as well as cure rates since 2000 (Annual reports District RNTCP Programme, District Mandi, unpublished document). One of the major policy decisions taken by RNTCP in the year 2010 was to change the focus of the NSP case detection objective of at least 70% to the concept of universal access to good quality care for TB patients. There is now global consensus that the twin objectives of 70/85 alone are not enough to achieve adequate reduction of TB transmission and reduction in disease burden. Some studies also suggest that mortality remains higher than expected, including post TB treatment mortality. One of the major reasons for death in TB patients is late diagnosis.[6] The present study was conducted to estimate the magnitude of the delay in diagnosis and treatment. TB patients,

after the onset of their symptoms, were put on anti-TB drugs after a median duration of 36 days. A major component of this delay was on account of the time spent on diagnosing the disease. We identified several factors associated with these delays including patient's income, their knowledge about the disease, first consultation from non-specialized health providers and consulting private health facilities. The findings of our study have implications on improving the case finding among the TB patients and thereby improving the performance of the programme in the district.

Several studies have estimated the magnitude of total, patient and health system delays among the TB patients in India. These delays ranged between 60-62 days, 6-23 days and 9-34 days respectively.[7-10] The total delay observed among the TB patients in our study was lower as compared to most of the earlier studies conducted in India. Shorter delay reported in our study could be on account of several reasons. First, the district is one of the well-performing districts in Himachal Pradesh with respect to indicators of RNTCP. Second, the earlier studies were conducted during 1998-2005 while RNTCP has decentralized diagnostic, treatment and monitoring services considerably in the last five years.

First action taken by a chest symptomatic is an important determinant of the patient delay. Studies conducted in India have shown that chest symptomatics in the community shop around, seeking relief at various health facilities, including private practitioners, before they are actually diagnosed as tuberculosis cases and put on appropriate treatment.[11] About half of the patients in our study either purchased the medications over the counter, resorted to self-medication or went to traditional healers and such patients were found to have significantly longer patient delays. Besides the first action, patients who had family income below 3000 and who had poor knowledge about TB were more likely to have longer patient delays. Similar findings were reported in other studies conducted in India and elsewhere.[7,12-14]

In our study, there was a longer health system delay when the patients first consulted private providers compared with a government provider, a finding similar to the earlier studies.[7,12,13] Uplekar *et al*. found that many private practitioners ultimately refer patients to the government sector, but generally do so late in the course of the patient's illness and often after partial treatment with a non-standard regimen.[15] To reduce this delay, efforts to involve private providers in the RNTCP need to be intensified, stressing the importance of timely diagnosis and treatment. In Mandi, half of the patients had to visit more than two health care facilities before the diagnosis of tuberculosis was made. Significant association was also seen between high expenses incurred during seeking care for the symptoms and health system delay. These findings point to the need to train the private providers to suspect TB, recommend appropriate investigations and reduce shopping around by patients for diagnosis/treatment.

Our study has one main limitation. TB patients registered in the last quarter of 2009 were diagnosed two to four months before the start of study and might not have recalled the exact dates of onset of symptoms and first consultation. This could have affected the median delays. To address this issue, we checked these dates with the first degree relatives of patients and used local religious festivals and agricultural events as a calendar to collect information about dates of onset of symptoms and subsequent consultations. The median total delays among the patients diagnosed in the last quarter of 2009 and first quarter of 2010 was 34 and 38 days respectively (p value>0.5), indicating that recall was comparable in these patients.

To summarize, the delay in diagnosis and treatment of TB patients in Mandi district was attributed to both patients as well as and health system. Patient delay was more among individuals with low income and was related to their first action as well as their knowledge about the disease. Patients who consulted private health facilities were more likely to have longer health system delays.

Based on these findings, we propose a number of recommendations to reduce the delays in diagnosis and treatment of TB patients. First,

efforts need to be made to increase public awareness about the symptoms of tuberculosis and to educate them about the importance of seeking early care and the availability and location of free diagnostic services in government health facilities. Such efforts could be focused among the people who are below poverty line. Second, the private physicians in the area need to be educated about the need to maintain a high index of suspicion of tuberculosis and rapidly performing appropriate tests including sputum examination. This could be achieved by increasing the involvement of private practitioners in RNTCP under various schemes. Third, the district programme officials need to sensitize the traditional healers and drug store owners to refer the chest symptomatics to government health facilities for sputum examination. Finally, various delay durations and the significant determinants of delay identified in the present study could be incorporated into routine surveillance reports. This would allow monitoring of the effectiveness of programme in reducing the duration of delay and thereby reducing the transmission and burden of tuberculosis in the district.

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Case Series

CERVICAL TUBERCULOSIS MASQUERADING AS CANCER CERVIX: A REPORT OF THREE CASES

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Summary: Tuberculosis is still frequently observed in third world countries like Africa and Asia. Here we report three cases of genital tuberculosis with variable presentations. First case was a lady of reproductive age group who presented with polymenorrhea and post-coital bleeding with unhealthy cervix. Histopathology of cervical tissue revealed tubercular cervicitis. Second and third cases presented with different complaints like discharge per vaginum, post-coital bleeding and pain in lower abdomen with growth over the cervix. Cervical biopsy was inconclusive of tuberculosis but endometrial tissue sampling for TB PCR was positive. This shows that newer diagnostic marker test can help us to detect secondary genital tuberculosis.
[*Indian J Tuberc 2013; 60:* 46 -49]

***Key words*:** Cervical, Cancer, Tuberculosis, Female genital

INTRODUCTION

Female genital tuberculosis is a prevalent infectious disease in developing countries where pulmonary tuberculosis is wide-spread. Genital tuberculosis most frequently affects fallopian tubes (95-100%), endometrium (50-60%) and ovaries (20-30%)[1,2]. Tuberculosis of cervix includes 5-24% of genital tract tuberculosis and 0.1%- 0.65% of all tuberculosis cases[3]. Tuberculosis can have varied presentations and can frequently mimic malignancy. We hereby discuss a series of three cases of genital tuberculosis which simulated malignancy of cervix but ultimately turned out to be tuberculosis and responded to anti-tubercular treatment.

CASE RECORDS

CASE-1

A 26-year-old lady P_{0+0} presented to our OPD with chief complaints of polymenorrhea, post-coital bleeding and discharge per vaginum for the past six months.

On general examination, patient was thin built with mild pallor. On abdominal examination, a suprapubic lump of 16-18 weeks' size of gravid uterus, firm in consistency and non-tender on palpation was present. Per speculum examination revealed a hypertrophic, congested angry looking cervix with a nodular growth present on its anterior lip. Moderate amount of white foul smelling discharge was present (Fig. 1). On bimanual examination, the same

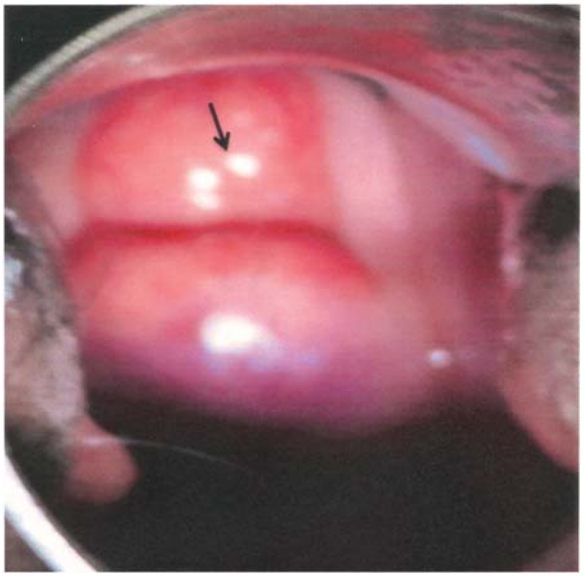

Figure 1: Congested angry looking cervix with nodular growth

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suprapubic mass was felt which could not be felt separately from the uterus with restricted mobility and the fornices were found to be thickened and tender. A strong suspicion of a cervical malignancy with pyometra was raised on the basis of above findings. Ultra sound examination revealed a normal cervix with grossly enlarged uterus with large uterine fibroid and small left ovarian cyst. Patient was re-evaluated after two weeks of antibiotic treatment and subjected to colposcopy guided cervical biopsy and endometrial tissue sampling for TB PCR. Chest X-ray was found to be normal. ESR was raised (34 mm), mantoux test was borderline positive and anti-tuberculosis IgM antibody was in equivocal range and on endometrial TB PCR, no *Mycobacterium tuberculosis* DNA was detected. Histopathology revealed well-formed caseating granulomas comprising Langhans' type of giant cells, suggestive of tubercular cervicitis. Patient was started on ATT and was reevaluated after six months of therapy when it was found that growth had regressed (Fig. 2). There was marked relief in all the symptoms of the patient, except menorrhagia. Patient was admitted and myomectomy was done and ATT was continued further for six more months. After completion of therapy, cervix was found healthy with no cervical lesion.

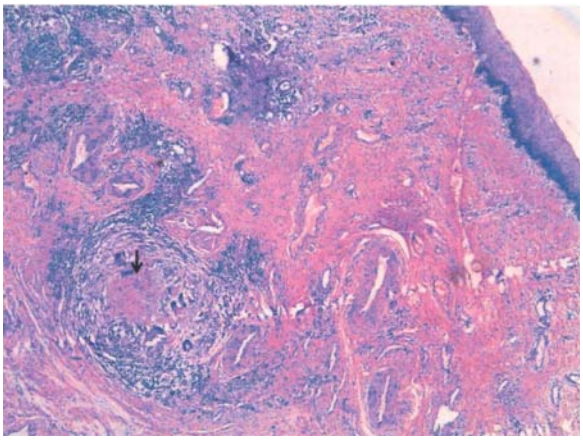

Figure 2: Chronic cervicitis with epithelioid granuloma (Tubercular) Cervix 100X

CASE-2

A 28-year-old lady P4+0 presented to our side with the chief complaints of watery discharge per vaginum for the past five years and pain in lower abdomen for the past three months. General and abdominal examinations were within normal limits. Per speculum examination revealed that a growth of around 4×4cm in size arising from both the lips of cervix was present. On per vaginum examination, the same growth was felt, uterus was retroverted with normal size and restricted mobility with thickening of right fornix and posterior vaginal wall. A strong suspicion of cancer cervix was raised on the basis of above findings. Punch cervical biopsy was taken and histopathology revealed lymphoplasmacytic infiltrate along with dilated endocervical glands and endometrial histopathology revealed proliferative endometrium, polymerase chain reaction of endometrial curettage tissue was positive for *M. Tuberculosis* on AFB culture, growth of *M. Tuberculosis* was present. Patient was taken over on antitubercular therapy and continued for nine months after which patient was completely relieved of her symptoms and cervix was free of growth.

CASE-3

A 38-year-old P1+0 lady presented to our hospital with secondary infertility, pain in lower abdomen and menorrhagia for the past seven years. Abdominal examination was within normal limits. Per speculum examination revealed a small nodule (1×1cm) on the anterior lip of the cervix, though posterior lip of cervix was also unhealthy. Uterus was bulky in size with thickened and tender adnexa. Pap smear and colposcopy were negative for malignancy. Ultrasound revealed an anteverted bulky uterus with mildly enlarged left ovary with small cyst. ESR was normal (30 mm and 20 mm for first and second hours, respectively), PPD and antitubercular IgM antibody were negative. Histopathological examination of cervical biopsy and endometrial curettage revealed features suggestive of chronic cervicitis with proliferative endometrium. Endometrial tissue sampling for TB PCR was positive. Since the patient was having secondary infertility, menorrhagia and it left sided tubo-ovarian

mass, a strong suspicion of genital tuberculosis was raised inspite of negative endometrial histopathology, antitubercular therapy was started and patient conceived spontaneously after four months and total duration of treatment was six months. In all the above cases, there was no past history or family history suggestive of tuberculosis.

DISCUSSION

Tuberculosis of cervix is rare. It is almost always secondary to tubercular salpingitis and endometritis. In rare cases, cervical tuberculosis may be primary to infection introduced from a partner with tubercular epididymitis or other genito-urinary disease[4]. Case-1 appeared to be a primary case of tubercular cervicitis which is rare as endometrial TB PCR was negative. In cases 2 and 3, cervical biopsy was inconclusive, but endometrial TB PCR was positive, which suggested that tubercular endometritis was the primary lesion.

The most common presenting symptoms of genital tuberculosis are infertility, menstrual irregularities and pelvic pain[5] which is present in one or the other case reported by us. The gross appearance of tuberculous cervix is also variable. It may present as papillary, ulcerative, interstitial, endocervical or polypoidal forms[6-8]. In cases 1 and 3, cervix was unhealthy and nodular and in case 2, cervix had a polypoidal growth of 4x4 cm. Furthermore, cases 2 and 3 ultimately turned out to be endometrial tuberculosis. All the above findings support the various clinical presentations of genital tuberculosis.

An important point of discussion in case 1 is that if cervical biopsy was suggestive of tuberculosis, then other causes of granulomatous inflammation of cervix such as Chamydia trachomatis, Neisseria Gonorrhoea, etc., should be excluded by performing other ancillary investigations (PPD, IgM TB) which point in favour of tuberculosis[9]. On the other hand, if cervical biopsy is unequivocal for TB (cases 2 and 3), then one must still be vigilant and proceed with rapid new diagnostic marker tests like TB PCR for detection of *Mycobacterium tuberculosis* DNA, with the help of which it is now possible to pick up even latent endometrial/endocervical tuberculosis[10]. Although isolation of *Mycobacterium tuberculosis* is the gold standard for diagnosis but approximately one third of cases are culture negative, hence diagnosis can be missed. But if tubercular granuloma is present, it is sufficient for diagnosis (as in case one)[11]. In case 3, AFB culture was not done and anti-tubercular treatment was started on the basis of positive PCR in endometrial tissue. Similar conclusion was made by Kulshrestha *et al*[12] in which a quarter of women received ATT solely on the basis of PCR and 31% of these women conceived. In spite of the presence of growth on cervix, in all the above cases, histopathology was variable and final diagnosis turned out to be genital tuberculosis and they responded well to anti-tubercular treatment. Though DOTS recommends antitubercular therapy for six months in genital tuberculosis[13], but as clinicians we gave extended treatment for 12 months and nine months in cases 1 and 2 respectively[14,15], as the patient did not respond completely (presence of cervical growth and symptoms) after completion of six months of therapy.

It is thus emphasized that tuberculosis should form an important differential diagnosis for malignant appearing lesions of cervix and high index of suspicion for tuberculosis is justified in dealing with cervical lesions in females of the reproductive age group, especially in endemic areas.

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BAN ON SEROLOGICAL TESTS

Despite not recommended by any international guidelines, the commercial serological tests (which detect antibodies in the blood developed in response to *Mycobacterium tuberculosis* infection) continue to be used extensively, especially in the private health sector, which claims about accuracy often based on poor quality and grossly insufficient data. It is estimated that about 1.5 million TB suspects are subjected to serological tests every year in India at an estimated cost of 15 million USD. Results of several studies have found that none of the assays are good enough to replace conventional microbiological tests or as an add-on test to rule out tuberculosis. A wrong diagnosis may mean that those with tuberculosis will not get needed therapy and may result in continued spread of the disease, or that those without tuberculosis may be subjected to possible side-effects from unnecessary treatment leading to wastage of resources for the patient and consequent impact on livelihood. This has huge epidemiological and socio-economic implications.

The WHO Expert Group concluded that currently available commercial serological tests provide inconsistent and imprecise estimates of sensitivity and specificity and strongly recommended that these tests should not be used for the diagnosis of pulmonary and extra-pulmonary TB (adults and children), irrespective of HIV status.

The National Laboratory Committee of RNTCP endorsed the WHO expert group recommendations and advised to disseminate the message to all stakeholders involved in TB control in India .

Case Report

TUBERCULOSIS OF ODONTOGENIC CYST

Preeti Sharma[1], Susmita Saxena[2], Pooja Aggarwal[1] and Vandana Reddy[1]

(Received on 24.1.2012; Accepted after revision on 19.7.2012)

***Summary*:** Tuberculous infection of the oral tissues is a rare finding. An interesting case of primary tuberculosis of mouth is described, presenting as persistent discharge of pus from the lower wisdom tooth region. Incisional biopsy revealed features of an infected dentigerous cyst while histopathological examination of the excised lesion showed keratinizing cyst with secondary infection. Non-healing of the bony defect prompted curettage of the area and the submitted sample microscopically showed granuloma with characteristic Langhans' giant cells, raising the suspicion of underlying systemic tuberculosis. The importance to the dental surgeon in the recognition, especially by use of pathological examination, is emphasized and also the value of diagnosis for the patients and the community. **[*Indian J Tuberc 2013; 60:* 50 - 54]**

Key words: Dentigerous cyst, Keratinizing cyst, Non-healing lesion, Tuberculosis.

INTRODUCTION

As the phrase goes, "The more things change, the more they stay the same." This expression continues to apply to tuberculosis (TB), a widespread infectious granulomatous type of chronic disease. On the international scene, TB still remains a leading killer of young adults, with some two billion people infected, one third of the world' s population. It can affect any part of the body; the oral cavity is no exception.[1,2] The oral lesions of tuberculosis, though not common, are seen in various forms. They may be either primary or secondary in occurrence. They may appear as ulcers, fissures, nodules or granulomas and are more commonly caused by pulmonary disease, whereas primary involvement is considered to be rare[3] and is generally seen in younger patients.[4] The mechanism of primary inoculation is not definite, but it is believed that organisms enter the mucosa through a small surface break[1].

The purpose of this report is to point out that, in the absence of any apparent systemic manifestation, the tuberculous lesions in the mouth may be the very first discovery of primary tuberculosis; and that histopathological examination of a persistent oral ulcerative/ non-healing lesion is an important aid in suspecting the presence of some underlying condition. We describe here an interesting case of odontogenic cyst which, even after excision and thorough curettage, was not healing with formation of unhealthy necrotic granulation tissue in the bony defect. Histopathological diagnosis of tuberculosis was done subsequently and institution of anti-tubercular therapy resulted in favourable response of the patient. Primary tuberculosis of the mouth in the absence of active pulmonary disease is exceptional which has prompted us to report the case.

CASE REPORT

A 25-year-old male patient was referred to the Department of Oral Surgery, Subharti Dental College and Hospital, Meerut, by his dentist for the diagnosis and treatment of a persistent pus discharge from the left side wisdom tooth region of lower jaw since two months. A swelling was observed in the same area extraorally. On intraoral examination, obliteration of the left buccal vestibule and expansion of buccal cortical plate on palpation was observed (Fig.1). Radiographic

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examination showed a well-defined radiolucency. Provisional diagnosis was given as dentigerous cyst which was confirmed by histopathological examination of the incisional biopsy specimen. Marsupialization of the cyst was done and iodoform pack was inserted which was replaced every 21 days. However, patient reported again to the Oral Surgery Department with the complaint of persistent pus discharge from the same area. When examined intraorally, there was no evidence of new bone formation and the dimensions of the cystic cavity were the same as previously noted with necrotic and unhealthy tissue debris in the defect. Histopathological examination of the curetted tissue revealed severe chronic inflammation and scattered multinucleated giant cells. After a gap of about four months, patient once again reported with the complaint of persistent pus discharge from the same area. Finally, the cyst was enucleated along with extraction of lower wisdom tooth. Histopathological examination of the excisional biopsy sample showed the features of odontogenic keratocyst with secondary infection and inflammation (Fig. 2). However, nearly after a week, patient reported to us with non-healing extraction socket showing yellowish coloured pus discharge yet again. We suspected osteomyelitic changes in the mandible. However, histopathological examination of the curetted necrotic granulation tissue revealed granuloma formation with lymphocytes, plasma cells, macrophages, epithelioid cells and characteristic Langhans' type of giant cells with sparse caseous necrotic areas (Fig. 3). The overall impression was of granulation tissue with

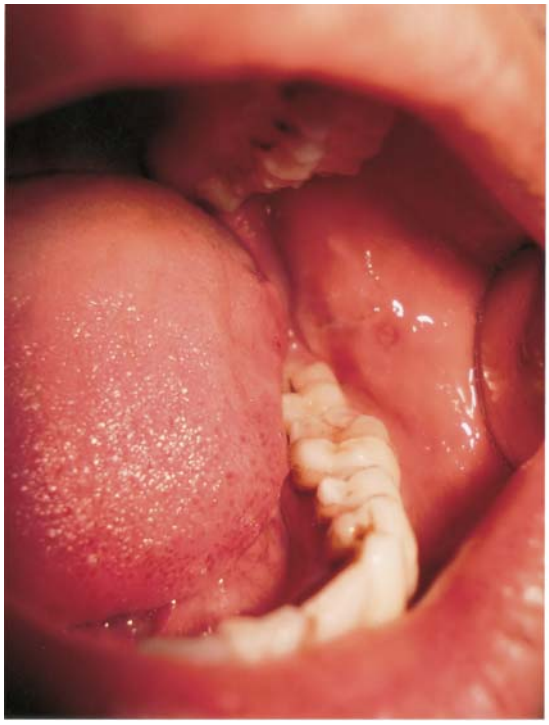

Figure 1: Obliteration of the left buccal vestibule and expansion of buccal cortical plate

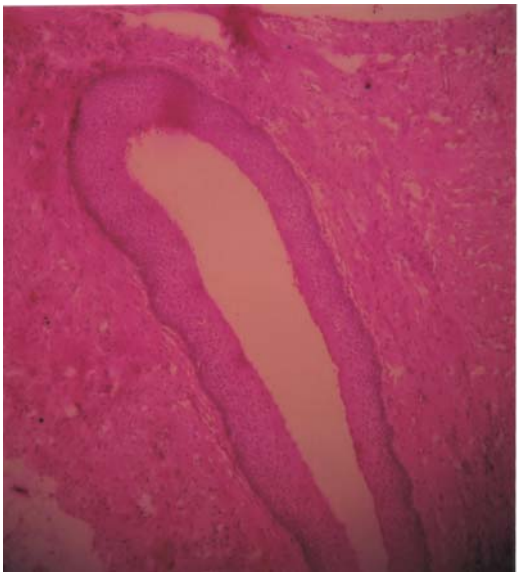

Figure 2: Excisional biopsy showing odontogenic keratocyst.

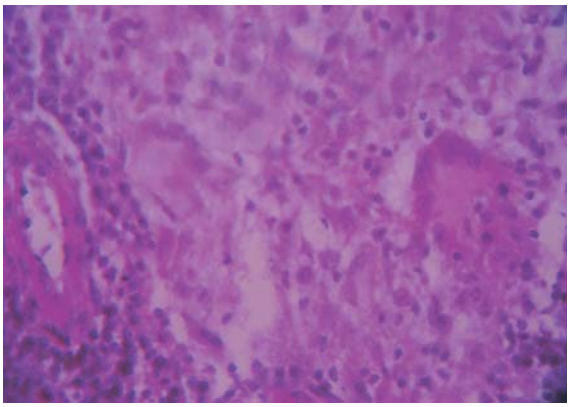

Figure 3: Tuberculous granuloma showing Langhans' giant cells with epithelioid cells and lymphocytes (high power X40).

tuberculous infection. Tuberculin test was advised for confirmation of underlying systemic disease. A positive skin reaction to purified protein derivative (PPD) test was found, suggesting tuberculous infection. While Mantoux test was found to be positive, the chest radiograph was normal and no foci of consolidation were found. Sputum examination for presence of acid fast bacilli was negative. However, Ziehl-Neelsen (ZN) staining of the serial sections was positive for acid fast bacilli (Fig. 4). Any other focus of tuberculosis could not be found. Routine blood counts were also within normal limits. ESR was 70mm in first hour. Patient was seronegative for HIV 1 and 2 antibodies.

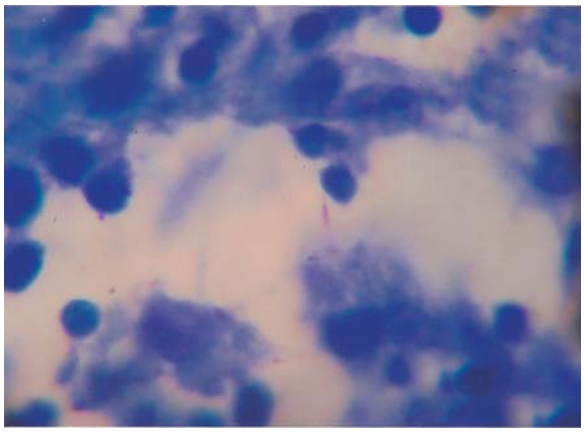

Figure 4: Acid-fast bacilli seen in histological section (ZN stain, Oil immersion X100).

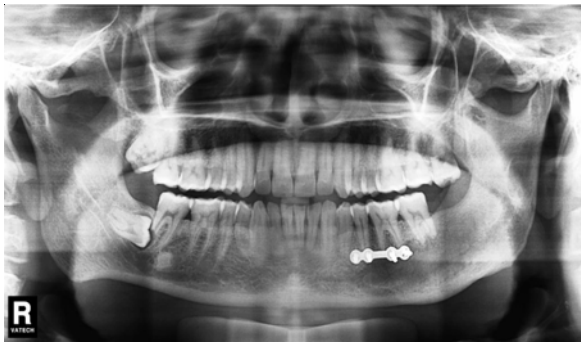

Figure 5: Postoperative radiograph showing healing of the lesion.

Based on the histopathological report, the patient was put on four drug anti-tubercular treatment (Rifampicin, Ethambutol, Pyrazinamide and Isoniazid). Follow-up at one month after treatment showed marked clinical improvement (Fig. 5). Primary tuberculosis of jaw was diagnosed. The patient was followed up till recently without evidence of recurrence.

DISCUSSION

We believe that it is important to add this new case for the following reasons; 1) despite three biopsies and specific bacterial stains, it was impossible to establish a definitive diagnosis; 2) the above case contrasts with previous reports in the literature in which every oral biopsy specimen securely pointed to underlying tuberculosis.

In the present case, it would appear that the original abscess from the cystic lesion could have been, in fact, underlying tuberculosis. This would seem a more probable explanation of the post-extraction recurrence of the pus discharge in the same site. Despite marsupialization followed by enucleation of the cyst, the bony defect failed to heal. Diagnosed first as a dentigerous cyst and then as an odontogenic keratocyst, underlying systemic diseases like tuberculosis was not suspected. The patient showed no history of cough, weight loss or fever. There was no past or family history of TB. In these circumstances, clinical suspicion of oral TB seldom arises, especially when a history of a systemic medical condition and therapy are denied. Interestingly, the prognosis was excellent as soon as antitubercular regimen was started based on the characteristic histopathology which suggested underlying tuberculous infection. The patient has been on a regular follow-up since last one and half a year and the lesional site wound has completely regressed.

In such cases, there are several important points to be remembered by the dental surgeon.

1) The necessity of taking a thorough medical history, especially so in, for example, tuberculosis which has a social stigma.

2) The advisability of surgical intervention in cases of long standing apparent residual sepsis.

3) The necessity of histopathological examination of all tissues removed in surgery.

4) The value of oral diagnosis to: a) the patient- leading to diagnosis and treatment of the pulmonary condition and b) the patient's contacts- for screening.[5]

The reported incidence of oral involvement in tuberculous patients ranges from 0.05% to 3.65%, when determined by clinical examination, and 20% when determined by postmortem examination. These findings suggest that a number of cases with oral manifestations are not diagnosed during routine clinical examination of the oral cavity.[1] The occurence of oral tuberculosis is extremely rare, despite the fact that sputum may be heavily contaminated with tubercle bacilli in pulmonary infection.[5]

Mycobacterium tuberculosis was demonstrated in periapical tissues while a case of dental cyst containing *M. tb* was also described.[5,6] Nagar *et al*[7] confirmed a case of primary tuberculosis of palate as any other foci of tuberculosis were not found.

Though, there is a debate regarding the portal of entry of infecting organisms, hematogenous and lymphogenous mechanisms are the most probable routes of infection. The bacilli are possibly transferred from a primary focus in another part of the body and localized in, for example, jaw, after trauma.[5] The systemic factors that favour the chances of oral infection in tuberculosis include lowered host resistance and increased virulence of the organisms. The local predisposing factors may be poor oral hygiene, local trauma, dental abscess and jaw fractures.[8]

In the present case of intraosseous mandibular lesion like odontogenic keratocyst, the mode of inoculation of the tubercle bacilli can be the hematogenous route. Also, inoculation can be sometimes by direct extension or even after tooth extraction. In our case, the spread of infection might have been through an extraction socket of 38, which could have made an occult tubercular focus in the mandible. Moreover, the patient was of lower socio-economic conditions with poor oral hygiene which might have been a predisposing factor. If a primary focus has not been discovered, it is described as clinically primary. Since no other primary focus was found in the present case, the case was diagnosed as primary manifestation of tuberculosis presenting as non- healing bony defect.

Persistent pus discharge may usually be associated with soft tissue actinomycotic, fungal, bacterial or tubercular osteomyelitis. Tubercular osteomyelitis of the mandible is extremely rare and is generally the result of the hematogenous spread of pulmonary tuberculosis. Tuberculous osteomyelitis frequently occurs in the later stages of the disease and has an unfavourable prognosis. [9] Our patient had no history of pulmonary or osseous tuberculous lesions. The underlying mandibular bone was not involved as the radiographs showed a well-defined radiolucency. There was neither appearance of blurring of trabecular details nor any irregular areas of radiolucency. Whenever a discharging pus is observed, which does not respond to removal of aetiological factors and antibiotic treatment, TB can be suspected.

In our case, histopathological examination of the biopsy specimens was an important aid in the diagnosis of the disease, because both cultures and smears from the lesional site for acid-fast bacilli were negative. According to different authors, difficulty in microbiologic detection of the tubercle bacilli may be due to the high immunity of the patients resulting in the destruction of the bacilli, their enclosure by local tissue reaction, the very small numbers of tubercle bacilli in oral lesions, hence direct examination of scrapings stained with Ziehl- Neelsen stain usually negative, and previous long time treatment with antibiotics.[9-11] In such cases, it is essential to attempt to locate a primary site of the disease elsewhere in the body before oral tuberculosis can be considered primary. The source of infection was not obvious in the present case. A possibility of occult primary site is not ruled out.

Because of the absence of other symptoms in primary TB, a problem of great significance is the risk of dissemination during dental procedures and the possibility that the dental staff may contract an infection while treating such patients. The prognosis of primary oral tuberculous infection is excellent, and therapy is shorter in relation to secondary disease.[12]

The case reported here shows the importance of a dentist in detecting a systemic disease manifested first in the mouth as non-healing wound. The case presented thus shows the importance of a biopsy in any suspected or even unsuspected oral lesions. Oral cavity tuberculosis is often a consequence of active pulmonary tuberculosis and is relatively rare. However, tuberculosis must be included in the differential diagnosis of both oral mucosal and bony lesions to avoid any serious complications.

CONCLUSION

Attention is drawn to the clinicians as to how oral tuberculous lesions could be missed in a busy practice, especially in the absence of any history or clinical signs and symptoms of tuberculosis.

Because of the absence of other symptoms in primary tuberculosis, a problem of great significance is the risk of dissemination during dental procedures and the possibility that the dental staff may contract an infection while treating such patients. It would not be wrong to say that the infected host is a walking "time bomb", in whom at any moment progressive disease may develop and, in many cases, serve as a nidus for the spread of the infection to other members of the community.

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Case Report

CO-EXISTENCE OF HIV, ACTIVE TUBERCULOSIS AND ASPERGILLOMA IN A SINGLE INDIVIDUAL - A CASE REPORT

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***Summary*:** Tuberculosis (TB) is a disease as old as mankind, whereas in India the first case of Human Immunodeficiency Virus (HIV) was reported in 1986. HIV and TB are so closely connected that their relationship is often described as a co-epidemic. Aspergilloma (Fungal Ball, Mycetoma) represents a saprophytic growth of aspergillus that colonizes in the preformed cavities commonly due to pulmonary tuberculosis (PTB). We report a case of HIV, active pulmonary tuberculosis and aspergilloma occurring in the same patient. Despite our best efforts, we could not lay our hands on any similar case in the medical literature. **[*Indian J Tuberc 2013; 60:* 55 - 58]**

Key words : Aspergilloma, HIV, Active tuberculosis

INTRODUCTION

Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) have been closely linked since the emergence of Acquired Immunodeficiency Syndrome (AIDS). HIV infection has contributed to a significant increase in the worldwide incidence of TB[1]. TB is the most common opportunistic infection affecting HIV-seropositive individuals and is the most common cause of death in patients with AIDS[2].

The term 'aspergilloma' was first used by Dave to describe a discrete lesion that classically colonizes the cavities of healed pulmonary tuberculosis and other fibrotic lung diseases[3]. Aspergilloma consists of masses of fungal mycelia, inflammatory cells, fibrin, mucus and tissue debris. Although other fungi may cause the formation of fungus ball (e. g. zyomycetes and fusarium), aspergillus spp (esp. A. fumigatus) are by far the most common etiologic agents[4]. Aspergillomas with active pulmonary tuberculosis (PTB) have rarely been reported [5]. Although there have been several case reports of mycetomas in HIV-infected individuals [6-8], till now there is no report of all the three entities (HIV, Active PTB and Aspergilloma) occurring together in one patient. Hence this case report.

CASE REPORT

A 45-year-old man, a known case of HIV and a treated case of PTB, was admitted with complaints of cough, haemoptysis and fever for the past 15 days. The cough was minimal, accompanied with purulent expectoration. The haemoptysis was off and on, moderate in quantity. The fever was low grade and not accompanied by rigors or chills. There was history of loss of appetite and generalised weakness. General physical examination revealed pallor, clubbing and posterior cervical lymphadenopathy. In chest, there were increased resonance and bronchial breath sounds with a few coarse crepitations in the left infraclavicular area. Routine investigations revealed haemoglobin 7.5g/dl and white cell count of 10800 cells/mm^3 with 60% neutrophils, 38% lymphocytes and 2% eosinophils. His CD4+ count was 350/mm^3. A cavitary lesion in the left upper lobe was found on chest radiograph (Fig.1). The lesion showed the "air crescent sign" suggestive of aspergilloma (Fig 2). A CT scan of the chest revealed a cavity with an intracavitary mass in the left upper lobe (Fig 3). His two sputum samples were positive for acid fast bacilli (AFB). His bronchoscopy was done and bronchoalveolar lavage (BAL) fluid showed fungal hyphae of Aspergillus spp. and was also positive for AFB.

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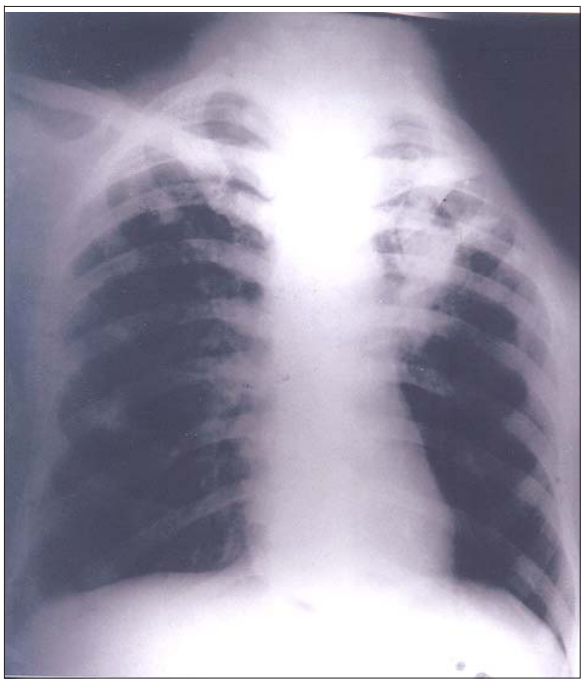

Figure 1: X-ray chest showing a cavitary lesion with a intracavitary mass in left upper-zone.

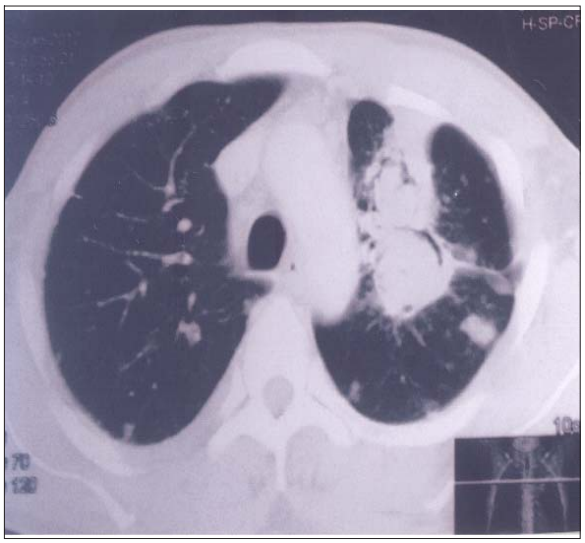

Figure 3: CT chest showing cavity with aspergilloma and parenchymal lesion in left upper lobe.

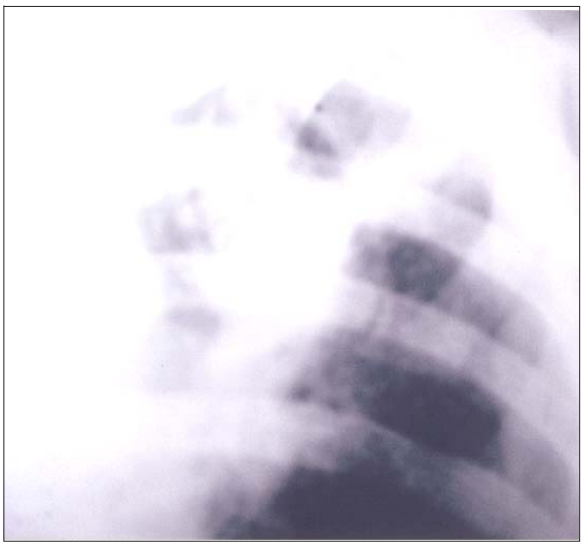

Figure 2: X-ray chest showing a aspergilloma in the cavity on the left upper zone with "Air Crescent Sign".

The past history revealed that he was a known case of HIV and had been treated for PTB two years back. The HIV infection had been diagnosed during this period and his CD4+ count was 467/mm^3 .The patient had been advised to complete ATT before initiating Anti Retroviral Therapy (ART). Routine chest radiographs taken during that time showed heterogenous opacity in the left upper zone. Patient had been given ATT Category 1 as per RNTCP guidelines. The treatment was uneventful and the patient was declared cured at the end of treatment. The patient was not given ART at that time as per the WHO 2006 guidelines[9] regarding treatment of HIV as his CD4+ count was > 250/ mm^3.

Treatment with anti-tubercular drugs (Cat II as per RNTCP guidelines) was started and opinion of a surgeon was sought regarding Aspergilloma who advised surgery on completion of the intensive phase of ATT or when the sputum for AFB turned negative, but the patient refused surgery and was given oral itraconazole (400mg/day) along with ATT. Patient's haemoptysis subsided and his general condition improved with treatment. At the end of

extended intensive phase, his sputum was negative for AFB. Currently, patient is on continuation phase of ATT and has been advised to take ART as per the WHO 2010 guidelines[10] regarding treatment of HIV patients.

DISCUSSION

Our case is exceptional in the aspect that the patient was harbouring HIV, active pulmonary tuberculosis and concomitant aspergilloma, an association of the three pathologies in the same patient. To the best of our knowledge, such an association has not been reported till date.

TB is the most common opportunistic infection in HIV patients and is the manifestation of AIDS in more than 50% of cases in developing countries[11]. TB can occur at any time during the course of HIV infection. Unlike other opportunistic infections which occur at CD4+ counts below 200/mm^3, active TB can occur throughout the course of HIV disease[12]. Clinical presentations of TB in HIV-infected individuals depend on the level of immune-suppression resulting from HIV infection. In patients with relatively intact immune function (CD4+count > 200/mm^3), PTB is more frequently seen than extra-pulmonary tuberculosis[13]. In these patients, chest radiographic findings include upper lobe infiltrates and cavitation, similar to those in HIV negative individuals with PTB[14]. Sputum smears are often positive for acid-fast bacilli in these patients.

Despite effective treatment for tuberculosis being available, the recurrence of TB is more common than would be expected among HIV-infected patients[15]. Various studies have shown that patients with extensive disease (measured by initial bacterial count, smear positivity, time to sputum conversion, radiological severity of disease and cavitation), are more likely to have recurrence than those without extensive disease[16].

Though allergic bronchopulmonary aspergillosis is rarely known to mimic a number of pulmonary conditions like PTB[17], aspergillomas occur most commonly in pre-existing healed tuberculous cavities and usually affect the upper lobe. There are only a few case reports of an association of aspergillomas with active PTB[5]. It has been suggested that Aspergillus and Mycobacteria are unable to grow simultaneously in a cavity in the lung[18], explaining the uncommon occurrence of aspergilloma with active tuberculosis. There have been several case reports of mycetomas in HIV-infected individuals[6-8]. The presentation and clinical course of pulmonary mycetoma in the HIV-infected patients differ in several ways from those in the immunocompetent patients. These patients have a high risk of disease progression, including the development of possible semi-invasive disease [19]. Despite there being various case reports of two-by-two associations of "TB with Aspergilloma" and "HIV with Aspergilloma" there is no case report describing the association of the three pathologies (HIV, active PTB and Aspergilloma) concurrently in one patient.

Our patient was a known case of HIV, having recurrence of sputum positive pulmonary tuberculosis along with an Aspergilloma which was residing in a cavity in the left upper lobe. The CD4 + count which was always above 200/mm^3, may be the reason of his having typical symptoms, involvement of upper lobe with cavitation on X-ray and sputum being positive for AFB. The presence of fungal hyphae of aspergillus spp. in bronchoalveolar lavage fluid pointed towards the colonization of the cavity by an aspergilloma.

The co-existence of an aspergilloma along with active pulmonary tuberculosis in a HIV patient, is an occurrence which has not been reported earlier. Thus, this case is reported to create an awareness amongst clinicians, that if they come across such a combination in their practice, treatment of all the three co-morbidities concurrently is essential to minimize complications and reduce mortality.

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Short Communication

HIV POSITIVITY IN TB SUSPECTS - AN OBSERVATIONAL, NON-RANDOMIZED STUDY

Parminder Kaur[1], Poonam Sharma[2] and Aruna Aggarwal[3]

(Received on 5.10.2011; Accepted after revision on 28.9.2012)

Summary

Aims: The present study was carried out to determine the prevalence of TB, HIV, and TB- HIV co-infection in 618 patients who attended the health institute for TB diagnosis and treatment at a rural tertiary care hospital in Punjab.

Methods: Pulmonary T.B was diagnosed by sputum smear microscopy, culture and extra-pulmonary TB was diagnosed by X-ray, CT and other methods.HIV diagnosis was made by testing the sera by 3E/R/S (ELISA/RAPID/SIMPLE) tests as per NACO guidelines.

Results: Of the total 618 patients, 74(12%) were patients of pulmonary TB, out of whom 72 were diagnosed by Ziehl Neelsen (ZN) staining and two were diagnosed by culture as the ZN stained smear was negative, 169(27.3%) were cases of extra-pulmonary TB. Three out of 618 were HIV positive. 1.23% were TB- HIV co-infected.

Conclusion: The risk of developing TB increases in patients with HIV. So, HIV and TB programmes should be collaborated together and should be closely integrated with medical care to curb the spread of these deadly diseases. **[*Indian J Tuberc 2013; 60:* 59 - 60]**

Key words : Prevalence, HIV, Tuberculosis, TB–HIV co-infecton

INTRODUCTION

HIV is the strongest risk factor for developing tuberculosis (TB) disease in those with latent or new *Mycobacterium tuberculosis* infection[1]. The risk of developing TB is between 20 and 37 times greater in people living with HIV than among those who do not have HIV infection.[1] Since 1980, much of the increase in the incidence of TB has been attributable to the impact of HIV/AIDS.[2]

The adverse interaction between human immunodeficiency virus (HIV) infection and tuberculosis (TB) poses difficult challenges to public health programmes.[3]

India is the highest T.B burden country accounting for 1/5th (20%) of global incidence. About 40% of Indian population is infected with T.B. It has been estimated that in 2007, about 4.85% of the incident TB cases in India were HIV positive.[4]

MATERIAL AND METHODS

We estimated the prevalence of TB, HIV, and TB and HIV co-infection in patients who came to the Microbiology Department (for TB diagnosis) of a rural tertiary care medical institute. The study was carried over a period of one year i.e. from April 2010 to March 2011 in the Department of Microbiology at SGRDIMSAR. Two sputum (First spot-early morning) samples were collected from 618 TB suspects in standardised sputum containers, and were processed on the same day. Smears were prepared from mucopurulent/thick portions of specimens, stained with ZN stain and then, for culture, the samples were inoculated on Lowenstein Jensen (LJ) medium. Extra-pulmonary TB was diagnosed by X-ray, CT and other methods. Sera from all 618 patients were screened for HIV sero-positivity. Pre-test counselling and HIV test were performed after informed consent. The sera were tested by 3E/R/S (ELISA/RAPID/SIMPLE) tests as per NACO guidelines.

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Table: Distribution of patients according to diagnosis

Patients enrolled	Pulmonary TB (sputum smear positive+sputum smear negative but culture positive)	Extra pulmonary TB	HIV positive	TB-HIV Co-infection
618	72+2=74	169	3	3

RESULTS

Total 618 patients were enrolled as TB suspects, of whom 74(12%) were patients of pulmonary TB. Sputum smear microscopy was positive in 72 patients and in two patients, sputum smear was negative but the LJ culture report after eight weeks was positive. One hundred sixty nine (27.3%) were cases of extra-pulmonary TB, diagnosed by X-ray, CT and other methods. Three out of 618 were HIV positive. 1.23% were TB-HIV co-infected (Table).

DISCUSSION

On the basis of the present study, the HIV-TB co-infection came out to be 1.23% which is in accordance with the 2007 survey conducted by NACO in which the prevalence of HIV among TB patients varied between 1% and 13.8%.[5] A study from western India showed 57/64 HIV seropositive cases having tuberculosis (TB)[6], while a study from South India has found ELISA HIV seropositivity in cases of tuberculosis to the tune of 1.3% only.[7] The risk of developing TB increases in patients with HIV. The TB-HIV co-epidemic is a major public health problem and is increasing cause of morbidity worldwide.

The control of both TB and HIV will be most successful if the RNTCP (for TB) and the NACP (for HIV) collaborate together and these are closely integrated with medical care.

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ABSTRACTS

Evaluation of nutrient agar for the culture of *Mycobacterium tuberculosis* using the microcolony detection method

L. Satti, S. Abbasi and U. Faiz. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(7)**: 908-10.

We evaluated nutrient agar using the microcolony detection method for the recovery of *Mycobacterium tuberculosis* on 37 acid-fast bacilli (AFB) positive sputum specimens, and compared it with conventional Löwenstein-Jensen (LJ) medium. Nutrient agar detected 35 isolates compared to 34 on LJ medium. The mean time to detection of mycobacteria on nutrient agar and LJ medium was respectively 9.6 and 21.4 days. The contamination rate on nutrient agar and LJ medium was respectively 5.4% and 2.7%. Nutrient agar detects *M. tuberculosis* more rapidly than LJ medium, and could be an economical, rapid culture method in resource-poor settings, provided our findings are confirmed by further studies.

Asthmatic Granulomatosis: A Novel Disease with Asthmatic and Granulomatous Features

Sally E. Wenzel, Catherine A. Vitari, Manisha Shende, Diane C. Strollo, Allyson Larkin and Samuel A. Yousem. *Am J Respir Crit Care Med* 2012; **186**: 501-07.

Severe asthma represents 5–10% of all asthma, yet remains problematic and poorly understood. Although it is increasingly recognized as consisting of numerous heterogenous phenotypes, their immunopathology, particularly in the distal airways and interstitium, remains poorly described. The objective was to identify the pathobiology of atypical difficult asthma. We report 10 from a total of 19 patients (17 women and two men) meeting asthma and severe asthma definitions, requiring daily systemic corticosteroid (CS) use, with inconsistent abnormalities on chest computed tomography scans, who underwent video-assisted thoracoscopic biopsies for further diagnosis and management. The pathology of 10 of the 19 cases revealed small airway changes consistent with asthma (eosinophilia, goblet cell hyperplasia), but with the unexpected finding of interstitial non-necrotizing granulomas. These patients had no evidence for hypersensitivity pneumonitis, but 70% of cases had a personal or family history of autoimmune-like disease. The 10 cases were treated with azathioprine, mycophenolic acid, methotrexate, or infliximab. Nine of 10 showed decreased CS requirements and improved or maintained FEV1 despite lower CS doses. Of the remaining nine patients, six manifested asthmatic small airway disease, alone or in combination with alveolar septal mononuclear cells, but no granulomas, whereas three manifested other pathologic findings (aspiration, pneumonia, or thromboemboli). These data suggest that a subset of severe "asthma" manifests a granulomatous pathology, which we term "asthmatic granulomatosis." Although identification of this disease currently requires a thorascopic biopsy, alternative approaches to therapy lead to improvement in outcomes.

Effect of Vitamin D and Inhaled Corticosteroid Treatment on Lung Function in Children

Ann Chen Wu, Kelan Tantisira, Lingling Li, Anne L. Fuhlbrigge, Scott T. Weiss and Augusto Litonjua. *Am J Respir Crit Care Med* 2012; **186**: 508-13.

Low vitamin D levels are associated with asthma and decreased airway responsiveness. Treatment with inhaled corticosteroids improves airway responsiveness and asthma control. The objective was to assess the effect of vitamin D levels on prebronchodilator FEV1, bronchodilator response, and responsiveness to methacholine (PC20, provocative concentration of methacholine producing a 20% decline in FEV1) in patients with asthma treated with inhaled corticosteroids. We measured

25-hydroxyvitamin D levels in the serum of children with persistent asthma at the time of enrolment in the Childhood Asthma Management Programme. We divided subjects into the vitamin D sufficiency (>30 ng/ml), insufficiency (20–30 ng/ml), and deficiency (<20 ng/ml) groups. Covariates included age, treatment, sex, body mass index, race, history of emergency department visits, hospitalizations, and season that vitamin D specimen was drawn. Our main outcome measures were change in prebronchodilator FEV1, bronchodilator response, and PC20 from enrolment to 8–12 months. Of the 1,024 subjects, 663 (65%) were vitamin D sufficient, 260 (25%) were insufficient, and 101 (10%) were deficient. Vitamin D-deficient subjects were more likely to be older, African American, and have a higher body mass index compared with the vitamin D-sufficient and insufficient subjects. In the inhaled corticosteroid treatment group, prebronchodilator FEV1 increased from randomization to 12 months by 140 ml in the vitamin D–deficient group and prebronchodilator FEV1 increased by 330 ml in the vitamin D insufficiency group and by 290 ml in the vitamin D sufficiency group (P = 0.0072), in adjusted models. In children with asthma treated with inhaled corticosteroids, vitamin D deficiency is associated with poorer lung function than in children with vitamin D insufficiency or sufficiency.

Obesity and Asthma: An Inflammatory Disease of Adipose Tissue Not the Airway

Olga Sideleva, Benjamin T. Suratt, Kendall E. Black, William G. Tharp, Richard E. Pratley, Patrick Forgione, Oliver Dienz, Charles G. Irvin1 and Anne E. Dixon. *Am J Respir Crit Care Med* 2012; **186**: 598-605.

Obesity is a major risk factor for asthma; the reasons for this are poorly understood, although it is thought that inflammatory changes in adipose tissue in obesity could contribute to airway inflammation and airway reactivity in individuals who are obese. The objective was to determine if inflammation in adipose tissue in obesity is related to late-onset asthma, and associated with increased markers of airway inflammation and reactivity. We recruited a cohort of obese women with asthma and obese control women. We followed subjects with asthma for 12 months after bariatric surgery. We compared markers in adipose tissue and the airway from subjects with asthma and control subjects, and changes in subjects with asthma over time. Subjects with asthma had increased macrophage infiltration of visceral adipose tissue (P < 0.01), with increased expression of leptin (P < 0.01) and decreased adiponectin (p < 0.001) when controlled for body mass index. Similar trends were observed in subcutaneous adipose tissue. Airway epithelial cells expressed receptors for leptin and adiponectin, and airway reactivity was significantly related to visceral fat leptin expression (rho = -0.8; P < 0.01). Bronchoalveolar lavage cytokines and cytokine production from alveolar macrophages were similar in subjects with asthma and control subjects at baseline, and tended to increase 12 months after surgery. Obesity is associated with increased markers of inflammation in serum and adipose tissue, and yet decreased airway inflammation in obese people with asthma; these patterns reverse with bariatric surgery. Leptin and other adipokines may be important mediators of airway disease in obesity through direct effects on the airway rather than by enhancing airway inflammation.

Vitamin D Deficiency, Smoking, and Lung Function in the Normative Aging Study

Nancy E. Lange, David Sparrow, Pantel Vokonas and Augusto A. Litonjua. *Am J Respir Crit Care Med* 2012; **186**: 616-21.

Vitamin D has immunomodulatory and antiinflammatory effects that may be modified by cigarette smoke and may affect lung function. The objective was to examine the effect of vitamin D deficiency and smoking on lung function and lung function decline. A total of 626 men from the Normative Aging Study had 25-hydroxyvitamin D levels measured at three different times between 1984 and 2003 with concurrent spirometry. Vitamin D deficiency was defined as serum level ≤ 20 ng/ml. Statistical analysis was performed using multivariable linear regression and mixed effects models. In the overall cohort, there was no significant effect of vitamin D deficiency on lung function or on lung

function decline. In both cross-sectional and longitudinal multivariable models, there was effect modification by vitamin D status on the association between smoking and lung function. Cross-sectional analysis revealed lower lung function in current smokers with vitamin D deficiency (FEV1, FVC, and FEV1/FVC; $P \leq 0.0002$), and longitudinal analysis showed more rapid rates of decline in FEV1 ($P = 0.023$) per pack-year of smoking in subjects with vitamin D deficiency as compared with subjects who were vitamin D sufficient. Vitamin D deficiency was associated with lower lung function and more rapid lung function decline in smokers over 20 years in this longitudinal cohort of elderly men. This suggests that vitamin D sufficiency may have a protective effect against the damaging effects of smoking on lung function. Future studies should seek to confirm this finding in the context of smoking and other exposures that affect lung function.

Relevance of Latent TB Infection in Areas of High TB Prevalence

Surendra K. Sharma, Sandeep Mohan and Abhishek Sharma. *Chest* 2012; **142(3)**: 761-73.

About one-third of the world population has latent TB infection (LTBI), the majority of which is distributed in 22 high-burden countries. Early diagnosis and treatment of active TB remains the top priority in resource-poor countries with high TB prevalence. Notwithstanding, because LTBI contributes significantly to the pool of active TB cases later on, its diagnosis and treatment is essential, especially in high-risk groups. The lack of a gold standard and several limitations of currently available tools, namely the tuberculin skin test and interferon-ã release assays, are major constraints for LTBI diagnosis. In areas with high TB prevalence, interferon-ã release assays have not shown superiority over the conventional tuberculin skin test and are yet to be systematically studied. Decisions regarding LTBI treatment with isoniazid preventive therapy should be made, keeping in mind the high prevalence of isoniazid resistance in these settings. Although efforts to shorten the LTBI treatment duration are encouraging, most trials have focused on adherence and toxicity. Future trials on short-duration regimens in high-burden settings should address drug efficacy issues as well. LTBI management, therefore, should comprise a targeted screening approach and individualization of LTBI treatment protocols. In addition, efforts should focus on airborne infection control measures in high-burden countries. A high prevalence of drug-resistant TB, the HIV epidemic, and delays in the diagnosis of active TB cases are other major concerns in areas of high TB prevalence. There is ample space for further research in these countries, whose outcomes may strengthen future national guidelines.

Fluoroquinolone exposure prior to tuberculosis diagnosis is associated with an increased risk of death

Y. F. van der Heijden, F. Maruri, A. Blackman, E. Holt, J.V. Warkentin, B.E. Shepherd and T.R. Sterling. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(9)**: 1162-67.

Fluoroquinolone (FQ) exposure before tuberculosis (TB) diagnosis is common, but its effect on outcomes, including mortality, is unclear. Among TB patients reported to the Tennessee Department of Health from 2007 to 2009, we assessed FQ exposure within six months before TB diagnosis. The primary outcome was the combined endpoint of death at the time of TB diagnosis and during anti-tuberculosis treatment. Among 609 TB cases, 214 (35%) received FQs within six months before TB diagnosis. A total of 71 (12%) persons died; 10 (2%) were dead at TB diagnosis and 61 (10%) died during anti-tuberculosis treatment. In multivariable logistic regression analysis, factors independently associated with death were older age (OR 1.05 per year, 95%CI 1.04-1.07), human immunodeficiency virus infection (OR 8.08, 95%CI 3.83-17.06), US birth (OR 3.03, 95%CI 1.03-9.09), and any FQ exposure before TB diagnosis (OR 1.82, 95%CI 1.05-3.15). Persons with FQ exposure before TB diagnosis were more likely to have culture- and smear-positive disease than unexposed persons. Among this patient population, FQ exposure before TB diagnosis was associated with an increased risk of death. These findings underscore the need for cautious use of FQs in persons with possible TB.

Predictors of recurrence of multidrug-resistant and extensively drug-resistant tuberculosis

K. Blondal, P. Viiklepp, L.J. Guðmundsson and A. Altraja. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(9)**: 1228-33.

The objective was to assess the treatment outcome of the first Green Light Committee (GLC) approved countrywide management of multidrug-resistant (MDR-) and extensively drug-resistant tuberculosis (XDR-TB) in Estonia and to evaluate risk factors contributing to TB recurrence over eight years of follow-up. The design was prospective assessment of MDR- and XDR-TB patients starting second-line anti-tuberculosis drug treatment between 1 August 2001 and 31 July 2003, with follow-up until 31 December 2010. In 211 MDR- and XDR-TB patients, treatment success was 61.1%; 22.3% defaulted, 8.5% failed and 8.1% died. TB recurrence among successfully treated patients was 8.5%, with no significant difference between XDR-TB and MDR-TB. TB recurrence was associated with resistance to all injectables (HR 2.27, 95%CI 1.16-5.06, P = 0.046), resistance to a greater number of drugs (HR 1.35, 95%CI 1.11-1.64, P = 0.003), and sputum smear positivity (HR 2.16, 95%CI 1.16-4.00, P = 0.016). A history of previous TB treatment was associated with TB recurrence among successfully treated patients (HR 4.28, 95%CI 1.13-16.15, P = 0.032). The internationally recommended Category IV treatment regimens are sufficiently effective to cure 75% of adherent MDR- and XDR-TB patients. A history of previous treatment, resistance to all injectable agents and resistance to a greater number of drugs increase the recurrence of MDR- and XDR-TB.

Trend in tuberculosis infection prevalence in a rural area in South India after implementation of the DOTS strategy

C. Kolappan, R. Subramani, V. Chandrasekaran and A. Thomas. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(10)**: 1315-9.

Three tuberculin surveys were conducted at intervals of five years following the implementation of a DOTS-based programme in 1999 in Tiruvallur District, South India. The objective was to estimate the trend in the prevalence of tuberculosis (TB) infection among children and to evaluate the impact of the DOTS strategy. Children aged 1-9 years in the sample for each survey were registered and administered one tuberculin unit of purified protein derivative RT 23 with Tween 80 by intradermal injection on the volar aspect of the left forearm. The induration diameter of the reaction was measured in mm after 72 h (three days) and the prevalence of TB infection estimated. The induration data of Bacillus Calmette-Guerin (BCG) vaccinated and non-vaccinated children were analysed using the mixture model. The estimated prevalence of TB infection among non-BCG-vaccinated children in the three tuberculin surveys were respectively 19.4%, 13.8% and 11.4%, with an average annual decline of 5.2% (95%CI 3.6-6.8). The prevalence of TB infection among BCG-vaccinated children decreased, with an average annual decline of 5.4% (95%CI 10.0-18.6). A significant declining trend in the prevalence of TB infection among children was observed following the implementation of the DOTS strategy in the area.

Rapid molecular detection of pulmonary tuberculosis in HIV-infected patients in Santiago, Chile

M.E. Balcells, P. García, L. Chanqueo, L. Bahamondes, M. Lasso, A.M. Gallardo and L. Cifuentes. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(10)**: 1349-53.

Santiago, Chile, has a mean annual tuberculosis (TB) rate of 13 per 1,00,000 population; however, TB incidence in human immunodeficiency virus (HIV) infected individuals is at least 20 times higher. The objective was to assess the accuracy of rapid molecular testing for pulmonary TB (PTB) detection in routine care in HIV-infected patients. It was a cross-sectional study, conducted prospectively in five hospitals

between March 2010 and June 2011. HIV-positive subjects with suspected PTB provided sputum or mouth wash samples that were directly processed for acid-fast smear, mycobacterial cultures and Xpert® MTB/RIF. Positive test results were reported on the same day. We enrolled 166 subjects into the study; 50.6% provided two sputum samples, 33.1% only one sputum sample and 16.3% a mouth wash sample. The prevalence of TB was 8.1% (13/160). Diagnostic sensitivity increased from 66.7% (95%CI 39.1-86.2) for acid-fast smear to 91.7% (95%CI 64.6-98.5) for Xpert MTB/RIF, with comparable specificity at 98.6% (146/148, 95%CI 95.2-99.6) and 99.3% (147/148, 95%CI 96.3-99.9). Xpert MTB/RIF allowed early detection of rifampicin resistance in 16.6% of cases, with rapid adjustment to multidrug-resistant treatment. Xpert MTB/RIF provided earlier TB diagnosis in 25% more cases than acid-fast smear alone. Its implementation should be considered for TB diagnosis in HIV-positive patients even outside TB-endemic areas.

Diagnostic yield of tuberculosis using sputum induction in HIV-positive patients before antiretroviral therapy

S. D. Lawn, A.D. Kerkhoff, Pahlana, M. Vogt and R. Wood. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(10)**: 1354-7.

Adults (n = 602) enrolling in a South African antiretroviral treatment clinic underwent culture-based screening for tuberculosis (TB), regardless of symptoms. For those unable to spontaneously expectorate a 'spot' sample (n = 124), sputum induction with nebulised hypertonic saline was used to obtain a first sample and also to rapidly obtain a second sample from all patients. Collection of both samples typically took 10-15 minutes. The prevalence of culture-positive TB was 15.6% (95%CI 12.8-18.8). Spontaneously expectorated spot samples yielded 79.8% of all culture-positive TB diagnosis. The incremental yield from those needing an induced first sample was 5.3% and the yield from induced second samples was 14.9%.

What To Do For Quitting Smoking ?

After making a firm resolve to quit smoking, you may take the following steps:

1. **Consult your doctor. He/She is best placed to show you the way and help you medically at crucial junctures.**

2. **Join or form a group/an association of smokers who have successfully quit, like the *Alcoholics Anonymous* for drinkers.**

3. **Read guide book about quitting smoking.**

4. **Keep trying instead of thinking how difficult it is to quit or the pleasure you might get from just a single cigarette.**

5. **Talk freely to other smokers about how you are already succeeding. And advise the vulnerable non-smokers why they should never start the habit. This activity will help boost your own morale.**

6. **Finally, have full faith in your own self. You are the one who is going to succeed. Do not deprive yourself of some therapies that are available for 'nicotine replacement', if your doctor so advises.**

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