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Distinguished delegates, Ladies and Gentlemen

I am indeed happy to be amidst you this morning for the inauguration of the 68th National Conference on Tuberculosis and Chest Diseases organised under auspices of the Tuberculosis Association of India (TAI) in its Platinum Jubilee celebration year. At the very outset, I would like to extend my good wishes to the Tuberculosis Association of India and the National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi for organising this prestigious conference. The Tuberculosis Association of India, set up in 1939, is one of the oldest voluntary organisations having its affiliates all over the country.

As we are aware, India has the world’s highest burden of tuberculosis. TB kills one person every two minutes in India or almost 750 people daily. Global TB control is unattainable without controlling the incidence of TB in India. Nearly 20 years after WHO’s declaration of Tuberculosis as a global public health emergency, major progress has been made towards attainment of the global targets defined in the context of the Millennium Development Goals. India has been an able partner in this progress. The Revised National Tuberculosis Control Programme (RNTCP) has become one of India’s largest public health achievements. The overall vision of RNTCP is “A TB free India”. There is compelling evidence now that the tide has, indeed, turned in case of TB. The burden of TB has begun to fall, and there are now fewer TB-related deaths each year than previous years.
It is heartening to note that the Ministry of Health and Family welfare (MoHFW) have developed an ambitious National Strategic Plan 2012-17 for TB Control, with the goal of universal access to early diagnosis and effective treatment. These goals seem achievable primarily because the TB programme has established a robust programme management infrastructure, focused on effective implementation, decentralizing patient-friendly services to impoverished and vulnerable sections of the population, and improving quality of care for all.

The endeavor should now be to aim for universal access focussing on improved diagnosis of TB patients through improving outreach, vigorously expanding case-finding efforts among vulnerable sections of the society, deploying better diagnostics, and extending services to patients diagnosed and treated in both the public and private sectors. The emphasis also has to be on improving patient-friendly access to high-quality treatment for all diagnosed cases of TB, including scaling-up treatment for Multi-Drug Resistant-TB nationwide. In that context, I am glad to see that the ‘National Rural Health Mission’ (NRHM) has expanded its reach and public health management capacity. The NRHM has improved service delivery infrastructure from the hospital to the village level, and has developed an army of community health workers and volunteers that can be leveraged to promptly detect symptomatic persons who suffer from TB.

The Ministry of Health and Family Welfare’s programme-based research for development and incorporation of innovations into effective programme practice is similarly noteworthy. The prohibition on manufacture, sale, distribution and use of sero-diagnostic test kits for tuberculosis will have far reaching policy implications and would help streamline TB diagnostics in India. TB is now a notifiable disease. It mandates all healthcare providers to notify every TB case, diagnosed or treated, to local authorities on a regular basis. The Central TB Division in collaboration with National Informatics Centre has developed a case-based web platform - ‘Nikshay’, which is now being scaled up nationally. This will enable better surveillance and tracking of TB cases and shall prove to be an effective programme management tool.

I must also stress that no national level campaign is successful without the active participation of voluntary organisations. The role played by the Tuberculosis Association of India in supplementing the Government’s efforts in prevention and control of TB is indeed praiseworthy. It has been publishing a quarterly, the ‘Indian Journal of Tuberculosis’ exclusively devoted to the cause of TB. It also organizes a National level Conference on Tuberculosis every year and this year’s Conference commemorating the Platinum Jubilee is being organized at Delhi in association with the National Institute of Tuberculosis and Respiratory Diseases (NITRD). The annual TB Seal Campaign is a novel way of spreading awareness about tuberculosis.

While wishing both these organisations all success for the Conference, I would urge all stakeholders to contribute to this noble cause so that the scourge of Tuberculosis ceases to be a public health problem in India and every citizen of our country goes on to become a productive member of society, participating actively in nation building.

Non-tubercular respiratory diseases like asthma, COPD, lung cancer, silicosis, health hazards of smoking are emerging as an additional burden to public health services in India. Conferences like the NATCON could be the best fora to discuss these conditions and formulate recommendations to guide national policies for prevention and control of these diseases. Let us commit ourselves to continue to do our best for instituting health care systems in the country which are equitable, affordable and accessible by all sections of the society.
I am confident that when we put our hearts and minds together we shall be able to build an India free of Tuberculosis and other preventable diseases. With these few words, I wish the Conference and its deliberations all the very best.

Jai Hind

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**Abbreviations:**

COPD = Chronic Obstructive Pulmonary Disease
NATCON = National Tuberculosis Conference
FEMALE GENITAL TUBERCULOSIS-A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

Female Genital TB (FGTB) poses a great challenge for the treating clinicians in terms of diagnosis and treatment in a woman in her reproductive age, when she has the most important role in the family. In India, it causes significant morbidity, short and long term sequelae, especially infertility for the affected women in reproductive age in India. Genital TB is responsible for 1% of all gynaecological admissions in India and 17.4% in infertility clinics, seeking assisted reproduction. The age of presentation of FGTB is lower in developing countries than in developed countries possibly due to younger age at marriage and child-bearing. FGTB is caused by *Mycobacterium tuberculosis* in most cases and mostly occurs secondary to a focus elsewhere in the body which is usually healed or quiescent and becomes active after a long latent period. Chance of FGTB increases if the primary infection occurs near time of menarche. Primary focus is usually pulmonary (in 50% cases) or extra-pulmonary TB like lymph nodes (40%), bones and joints (5%), urinary or gastro-intestinal tract (5%). It is also estimated that 8-15% women with pulmonary TB may have co-existent genital TB which is usually silent. However, primary genital TB can rarely occur in women whose male partners have active genito-urinary TB (e.g. tuberculosis epididymitis) by transmission through infected semen. The spread of TB from lungs and other sites is usually by haematogenous or lymphatic route, less commonly by direct contiguous spread from nearby abdominal organs like intestines or abdominal lymph nodes can cause genital TB. The various genital organs affected by TB in order of frequency are fallopian tubes (90-100% cases), endometrium (50-80% cases), ovaries (20-30% cases), cervix (5-15%) and rarely vagina and vulva (1% cases).

Fallopian Tubes are involved in almost all (>90%) women with genital TB and the involvement is usually bilateral. In tuberculous endosalpingitis, the infection starts from endosalpinx and is usually through haematogenous route of spread. The fallopian tube is thickened, enlarged and tortuous. Sometimes, unilateral or bilateral pyosalpinx may be formed due to caseation in the tubal wall and the collection of the cheesy material in the lumen with blockade of both ends of fallopian tubes due to fibrosis. Dense pelvic adhesions are often formed around the tubes though some women may have tubo-ovarian mass without adhesions. Rarely, a persistent fistula may form spontaneously or iatrogenically due to surgical drainage and may fail to heal. Intestinal obstruction can occur due to adhesions. Endosalpinx may sometimes be hyperplastic or oedematous and may be totally destroyed or there may be fusion of papillae in the endosalpinx making women more prone to ectopic pregnancy and infertility. Sometimes, granulomatous lesion with chronic inflammatory infiltrate with or without caseation may be seen in the tube.

In tuberculous exosalpingitis, there is direct spread of the disease from intestines with disease starting in the muscularis mucosa of tube. Initially, there is congestion of fallopian tubes, ovaries and peritoneum of the pouch of Douglas with flimsy adhesions and miliary tubercles on their surface. In later stages, there are beaded tubes with calcification and tubal blockage, tubo-ovarian masses due to peri-oophoritis, hydrosalpinx, pyosalpinx or massive adhesion formation. Thickened vascular plastic adhesions are formed between tubes and adjacent pelvic organs, especially in adhesive or plastic type of peritonitis. In more severe cases, there may be multiple adhesions in peritoneal cavity with obliterated pouch of Douglas (Frozen pelvis). In interstitial tuberculous salpingitis, there is inflammation in the interstitial part of the tube with thickening of the tube while in
salpingitis isthmica nodosa, there is nodular thickening of the tube due to proliferation of tubal epithelium within the hypertrophied muscle layer as diagnosed on hysterosalpingography as small diverticulum.

Endometrium is involved in 50-80% (mean 70%) of cases. Initially, there is no macroscopic disease but caseation and ulceration occur later with progression of TB and in advanced stages, there may be distortion of cavity, varying from slight distortion to complete obliteration due to adhesions. Total destruction of endometrium may result in Asherman’s syndrome like picture resulting in amenorrhoea secondary to end organ failure. In fact, genital TB is an important cause of Asherman’s syndrome in India leading on to secondary amenorrhoea and infertility with poor prognosis for treatment. TB may involve pelvic or abdominal peritoneum with tubercles all over the peritoneum, intestines and omentum and may lead to ascites and abdominal mass. FGTB may masquerade as ovarian cancer and even CA 125 levels are raised in peritoneal TB, with CT scan and MRI also giving similar picture, the diagnosis may be made only on laparotomy done for suspected ovarian cancer. In such cases, ascitic fluid tapping for bio-chemical analysis and peritoneal biopsy may confirm the diagnosis of TB and thus avoiding a needless laparotomy. On laparotomy, there may be vague masses without a line of cleavage with adherent loops of bowel or omental masses mimicking secondaries from ovarian cancer. There may be perihepatic adhesions (Fitz Hugh Curtis syndrome) in female genital TB and peritoneal TB. Involvement of ovary cervix, vulva and vagina is rare.

The clinical presentation of genital TB depends upon the site of involvement of genital organs. There may be no symptoms or signs in early stages. Constitutional symptoms like fever, weight loss, loss of appetite, menstrual dysfunction (menorrhagia in early stages and oligomenorrhoea and amenorrhea later), abnormal vaginal discharge, abdominal and pelvic pain, lump abdomen and infertility can occur in FGTB. Infertility is the most common presentation of genital TB with reported incidence of infertility being between 40 to 80%. Both primary and secondary infertility may occur. The average incidence of genital TB in infertility clinics world over is 5-10 % and varies from 0.69 % in Australia, 1% in USA, and 17.4 % in India. The reason for infertility is involvement of fallopian tubes (blocked and damaged tubes), endometrium (non-reception and damaged endometrial with Asherman’s syndrome) and ovarian damage in TB with poor ovarian reserve and volume. Similarly, there may be no clinical signs in early stages. There may be fever, lymphadenopathy, chest crepitation, abdominal and pelvic masses, ascites, uterine and adnexal masses, vulvar or vaginal ulcers in some cases.

Since there may be no symptoms and signs in the early stages, diagnosis is generally delayed. A high index of suspicion is required during work up of infertility. The final diagnosis is made from good history taking, careful systemic and gynaecological examination and judicious use of diagnostic modalities like endometrial biopsy in conjunction with imaging methods and endoscopic visualization, especially with laparoscopy. Some authors have developed an algorithm for accurate diagnosis of FGTB by combining history taking, examination and investigations. The clinical picture can be confused in women coming with large pelvic abdominal masses and ascitis, or women with acute pain abdomen in the early postpartum period, getting admitted in the gynaecological wards as tuberculous or large tubo ovarian abscesses thus posing a great challenge in early management.

A high index of suspicion is required for early diagnosis and timely treatment of FGTB. The diagnostic approach used is history of TB or anti-tuberculous therapy (ATT) in the patient or family. History of HIV positivity is also important. Detailed general physical examination for any lymphadenopathy, any evidence of TB at any other site in body (bones, joints, skin, etc.), chest examination (PTB), abdominal examination (abdominal TB), examination of external genitalia (vulvar or vaginal TB), speculum examination (cervical TB), bimanual examination (endometrial or fallopian tube TB) help in the diagnosis of genital TB. 

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Complete hemogram may show anaemia, leucocytosis with lymphocytosis and raised ESR in TB, but is non-specific. Serological tests like monoclonal antibody based sandwiched enzyme linked immunosorbet assay (ELISA) are not sensitive and specific enough to be of great value in diagnosis of genital TB and are now banned. Levels of CA 125 are only moderately raised (<200 U/ml) in genital TB (normal levels <35 U/ml). Mantoux (Tuberculin) test has limited utility with sensitivity of 55% and specificity of 80%. Chest X-ray (posterior – anterior film) should be performed to exclude or confirm co-existing respiratory TB or old stigmata of previous pulmonary TB.

The diagnostic dilemma arises due to varied clinical presentations, diverse results on imaging and endoscopy. Available battery of bacteriological, serological, and histopathological tests are often required to get a collective evidence of diagnosis of genital tuberculosis. Imaging modalities have role in mainly tubo-ovarian masses. Ultrasonography (USG) has a very limited role in genital tuberculosis and may show bilateral solid adnexal masses with scattered small calcifications with free fluid in pouch of Douglas. Computerised axial tomography (CT scan) and Magnetic resonance imaging are useful modalities for tuberculous pelvic and abdominal masses with low density ascites, multiple pelvic, abdominal, hepatic or splenic lesions with or without lymphadenopathy. MRI has better resolution and shows the presence of hypodense masses with rim enhancement abutting the pelvic walls in FDG. Positron emission tomography (PET SCAN) demonstrates glucose uptake by tubercular lesions and is particularly useful to know whether the lesion is active TB or not especially in women with tubo-ovarian masses.

Endometrial biopsy, curettage or aspirate is done in the premenstrual phase for histo-pathological testing, acid fast bacilli (AFB) smear and culture and polymerase chain reaction (PCR). Demonstration of granuloma with or without Langerhans giant cells on histopathology is gold standard in diagnosis of genital TB. In the absence of typical epithelioid granuloma and caseation of TB, other features like dilatation of glands, destruction of epithelium and presence of inflammatory exudates in the lumen suggest tuberculous pathology. The sample is subjected to smear examination for AFB and culture on Lowenstein–Jensen (LJ) medium. Other rapid diagnostic methods are BACTEC 460 Mycobacteria growth inhibitor tube (MGIT) and specific gene probes contributing to more rapid identification and diagnosis. Polymerase chain reaction (PCR) is a rapid (1-2 days), sensitive and specific molecular biological method for detecting mycobacterial DNA (mpt 64 gene) on endometrial or peritoneal samples in FGTB patients and is positive in 56 % cases as compared to 1.6 % smear positive and 3.2 % culture positive cases in genital TB. It has been found to have high sensitivity and specificity and may be positive in presence of as low as 1-10 organisms per ml. However, due to high false positivity, ATT should not be started just on the basis of positive PCR unless there is some other evidence of FGTB on clinical examination or on investigations like presence of tubercles or other stigmata of TB on laparoscopy. In short, a good history taking, along with correct sampling using various imaging modalities and use of multiplex PCR does certainly contribute to allaying the difficulty of diagnosis.

Hysteroscopy is useful in FGTB. The endometrium is pale looking, the cavity is partially or completely obliterated by adhesions of varying grades (grade 1 to grade 4) often involving Ostia. There may be a small shrunken cavity. One has to be cautious while performing hysteroscopy in genital TB due to increased difficulty to distend the cavity and to do the procedure and increased chances of complications like excessive bleeding, perforation and flare up of genital TB. A laparoscopy is the most reliable tool to diagnose genital TB, especially for tubal, ovarian and peritoneal disease. The test can be combined with hysteroscopy for maximum information. In sub-acute stage, there may be adhesions in pelvic organs with multiple fluid filled pockets, congestion, oedema, miliary tubercles, white yellow and opaque plaques over the fallopian tubes and uterus. In chronic stage, there may be yellow small nodules on tubes (nodular salpingitis), short and swollen tubes with agglutinated fimbriae (patchy salpingitis), unilateral or bilateral hydrosalpinx with retort shaped tubes due to agglutination of fimbriae and pyosalpinx or caseosalpinx. Various types of adhesions covering genital
organs with or without omentum and intestines and perihepatic adhesions are seen on laparoscopy in FGTB cases. There are increased complications on laparoscopy for FGTB as compared to laparoscopy performed for non-tuberculous patients (31% vs 4%) like inability to see pelvis (10.3% vs 1.3%), excessive bleeding (2.3% vs 0%), peritonitis (8% vs 1.8%). The adhesions are typically vascular and adhesiolysis can increase the risk of bleeding and flare up of the disease.9

Multiple drug therapy in adequate doses and for sufficient duration is the mainstay in the treatment of TB including FGTB. In olden days, before rifampicin, the anti-tuberculous therapy (ATT) was given for 18-24 months with significant side-effects and poor compliance. Short course chemotherapy for 6-9 months has been found to be effective for medical treatment of FGTB. DOTS (Directly observed treatment short course strategy) treatment is favoured by WHO to prevent MDR and for better results and is available free in different DOT centres. WHO in its recent guidelines has removed category 3 and recommends daily therapy of rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) for two months followed by daily four-month therapy of rifampicin (R) and isoniazid (H).1 Thrice weekly dosing throughout therapy (2RHZE/4HR) can be given under DOTS where every dose is directly observed provided the patient is not HIV positive or living in an HIV prevalent setting.

The patient is first categorized to one of the treatment categories and is then given treatment as per guidelines for national programmes by WHO.11 Genital TB is classified under category 1 being seriously ill extra-pulmonary disease. To ensure quality-assured drugs in adequate doses, a full six-month course pack box is booked for an individual patient in the DOTS centre with fixed drug combipack (FDC) of isoniazid, rifampicin, pyrazinamide and ethambutol thrice a week for the first two months (intensive phase) under direct observation followed by combination blister pack of isoniazid and rifampicin thrice a week for the next four months (continuation phase). Rarely, FGTB, cases can have relapse or failure categorizing them into category II which includes two months intramuscular injections of streptomycin thrice weekly along with other four drugs (RHZE) of category I under direct supervision of DOTS centre health worker for the first two months followed by four drugs (RHZE) thrice a week for another month (Intensive phase), followed by continuation phase with three drugs isoniazid (H), rifampicin (R) and ethambutol (E) thrice a week for another five months.1,10,11 Patients not opting for DOTS treatment must take daily therapy of RHZE for two months (intensive phase) followed by RH for four months (continuation phase).1 Convenient and economic combo packs are available in market. Treatment of multi drug resistant (MDR) FGTB is the same as for pulmonary MDR-TB with second line drugs and is needed for long duration (18-24 months).1,11,12

The modern short course chemotherapy consisting of rifampicin and other drugs is highly effective for the treatment of FGTB with rare need of surgery. However, limited surgery like drainage from residual large pelvis or tubo ovarian abscesses, or pyosalpinx can be performed followed by ATT for better results. There are much higher chances of complications during surgery in women with genital TB like excessive haemorrhage and non-availability of surgical planes at the time of laparotomy with higher risks of injury to the bowel and other pelvic and abdominal organs. It is better to take biopsies from the representative areas and close the abdomen without pelvic clearance in cases of laparotomy done for suspected pelvic tumours but found to be tubercular at laparotomy followed by full medical treatment. Sometimes, even after a full six-month course of ATT, women with genital TB with infertility do not conceive when laparoscopy and hysteroscopy may be repeated to see any remaining disease. Outcome for fertility in FGTB is only good when ATT is started in early disease. However, cases of advanced TB with extensive adhesions in pelvis and uterus are usually untreatable with very poor prognosis for fertility. Tuboplasty performed after ATT does not help much with chances of flare up of the disease and risk of ectopic pregnancy, should a woman conceive. Surgical therapy usually consists of total abdominal hysterectomy and salpingoophorectomy in cases of persistence of pelvic masses after complete medical treatment.
Most women with genital TB present with infertility and have poor prognosis for fertility in spite of ATT. The conception rate is low (19.2%) with live birth rate being still low (7%). In vitro fertilization and embryo transfer (IVF-ET) appears to be the only hope for some of these women whose endometrium is not damaged with pregnancy rate of 16.6% per transfer. If after ATT, their tubes are still damaged but their endometrium is receptive (no adhesions or mild adhesions which can be hysteroscopically resected), IVF-ET is recommended. However, if they have endometrial TB causing damage to the endometrium with shrunken small uterine cavity with Asherman’s syndrome, adoption or gestational surrogacy is advised to them.

There has been a renewed interest in research in TB at global level. New and improved BCG vaccines are being developed. GeneXpert, line probe assay, and liquid culture can help in making early diagnosis. However, point of care best diagnostic test still is eluding the scientific world for making definitive diagnosis of FGTB. Research in FGTB is hampered due to lack of criteria for monitoring the therapeutic efficacy. New drugs, effective against strains that are resistant to conventional drugs and requiring a shorter treatment regimen, are being developed. By controlling TB, FGTB can also be kept at bay and treated early to prevent development of short term and long term sequelae of this menace.

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REFERENCES


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Adrenal deficiency, also described as Addison’s disease, is a relatively uncommon endocrine disorder with an estimated prevalence of 0.01 to 0.02% worldwide. It is gender non-specific with both males and females affected. It can present as an acute event (Addisonian crisis) or chronic with symptoms that have persisted for some time. The onset of this condition is commonly seen between 30 to 50 years. Secondary deficiency due to iatrogenic cause is frequently seen as a result of exogenous steroids, especially in patients managed in the Critical Care Unit. When Thomas Addison first described hypoadrenalism, tuberculosis (TB) accounted for 80% of the cases. This has changed with global incidence of TB dropping due to better surveillance and treatment modalities. Consequently, the incidence of TB related clinical hypoadrenalism has also dropped (20%).

Developing countries are still affected due to higher reported prevalence of TB. Latent and active TB infection in India is present in nearly 40% of the population; with 20% new cases diagnosed from this part of the world when compared worldwide. The burden that is faced in India, as in other developing countries, is exacerbated through inadequacy of primary health care, general lack of public awareness, co-existing HIV infection that complicates the rise in numbers from an epidemiological perspective. The view that only certain stratum of society is susceptible to contracting TB disease needs rethinking and public in India should be aware that it is very much a communicable disease.

The presence of multi drug resistant TB (MDR-TB) in India has added further challenges to management and escalated surveillance, timely treatment are mandatory for effective TB control. Arresting the spread of MDR-TB requires isolation and management with specific drugs which are obviously expensive. Specialized testing used for detection and interpretation of MDR-TB should be more widely available as currently this is only being offered by a limited number of laboratories nationally. The sequela of events due to delay in timely diagnosis, quality of care, intervention and follow up need not be overstated.

In active Tuberculosis, there is haematogenic spread of infection from the primary site that affects bilateral adrenal gland function. Manifestation of hypoadrenalism may be gradual with medullary loss seen more commonly than cortical function. Imaging studies usually reveal an enlarged adrenal gland due to the inflammatory process and fibrosis replacing normal gland tissue. The active gland tends to reduce in size with prolonged TB infection with attenuation of cortisol release and this in turn can indicate the severity of TB. The adrenal gland can regenerate and recover with consistent anti-fungal management but the prognosis and full recovery remains debatable.

Many reports in the Indian literature have documented the relationship of TB and sub-clinical adrenal deficiency and reversal with anti-TB treatment. A small study of five patients reported lack of reversal of adrenal deficiency while a second study on a larger group of patients has shown better prognosis after a three-year follow up. Using ACTH stimulation testing, data from a longitudinal follow up of HIV negative TB patients showed more than 70% improvement by six months with anti TB therapy; and dramatic normalization was seen after 24 months. The authors showed that reversal of adrenal function was seen in both pulmonary and extra-pulmonary TB. In another comprehensive study, prospective
analysis on 190 patients with HIV studied over six years showed frequent incidence of extra-pulmonary and disseminated TB which contributed to high mortality in these subjects. HIV has diverse implications on the adrenal gland and is a common secondary cause of Addison’s disease. Cytomegalovirus (CMV) along with cryptococcal infection that is present usually results in necrotising adrenalitis.

Autoimmune disease is now found to be increasingly associated with diagnosis of Addison’s with figures close to 70 to 90%. In autoimmune adrenalitis, the adrenal cortex function deteriorates due to humoral and cell-mediated antibodies. This immune process may extend to malfunction of one or more endocrine glands in approximately 50 - 60% of the cases. The term “polyglandular autoimmune syndrome” is used to describe this spectrum of presentation causing type 1 diabetes, thyroiditis including Hashimoto’s disease, Graves’ disease, hypopituitarism, hypogonadism, hypoparathyroidism and some gastrointestinal disorders.

Polyglandular autoimmune syndrome can also present as Type 1 or Type 2 (AIT-1 and AIT-2). Both are genetic disorders where AIT-1 is an autosomal recessive disorder seen rarely in some races of Jewish descent and sporadically in some European populations. Clinically, Type 2 is more common where antibodies to various steroidogenic enzymes are present. Other glands may be affected and it is important that if family members or first degree relatives of patients show clinical manifestations of this syndrome, appropriate management and follow up should be considered. The mode of inheritance of AIT-2 can be variable and is polygenic with gender preponderance of females over males has been noted.

Infectious adrenalitis of the adrenal gland(s) may occur through a primary or metastatic process and result in hypoadrenalism. This includes inflammatory disease in seriously ill patients with invasive cancer process, sepsis, adrenal haemorrhagic events caused by viral illnesses, anticoagulant or heparin therapy, thromboembolic disease, antiphospholipid syndrome resulting in infarction of the gland. Mycoses and use of anti-mycotic drugs like ketoconazole or fluconazole that inhibit cortisol biosynthesis, all tend to induce hypoadrenalism.

Presentation and investigations

The classical features of Addison’s are severe discomfort in the back and abdominal areas, diarrhoea, tachycardia, hypotension, fever and sometimes coma. Hyperpigmentation may be a clinical feature seen in severe deficiency.

Acute management begins with replacement of IV fluids along with glucose, IV steroid replacement and close monitoring to ensure that patient is stabilised. Baseline morning cortisol and ACTH levels should be tested where AM cortisol <100nmol/L is strongly suggestive of low adrenal reserve and >220 nmol/L would exclude diagnosis. Other abnormal laboratory results seen include low electrolytes, hypoglycaemia, abnormal LFT’s, in some cases increased calcium, increased lymphocytes and eosinophilia, normocytic anaemia.

Delineation of site of deficiency is required for long term management. Failure to produce adequate Cortisol could identify a primary cause – when the adrenal gland is affected, or a secondary cause where the pituitary gland is affected and fails to stimulate the adrenal gland. The ACTH stimulation test helps to interrogate the hypothalamic – pituitary - adrenal (HPA) axis function and predict the extent of adrenal function decline and onset of latent disease. This test provides 95% specificity and 97% sensitivity.

Post ACTH stimulation, cortisol level greater than 500 - 550 nmol/L; or a rise of more than 200 - 250 nmol/L from baseline level usually indicates adequate adrenal reserve. Exogenous steroid use can attenuate the cortisol response; so in this setting it is preferable to check HPA axis function post withdrawal of steroids.

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Conventional testing combined with more sensitive testing currently available can provide better outcomes for patients with adrenal insufficiency. Some laboratories offer inhibitory testing using metyrapone to establish normality of HPA axis dysfunction as this avoids unnecessary steroid replacement. The factors leading to adrenal insufficiency are variable and while prognosis is generally good, return to normal health is also dependent on the underlying aetiology leading to the clinical presentation.

**V. Parameswaran***

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**REFERENCES**


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INDbL RED CROSS INITIATIVE FOR TUBERCULOSIS CONTROL

S. P. Agarwal*

Tuberculosis is an ancient disease which has afflicted the mankind for the last many centuries. With the launch of Revised National Tuberculosis Control Programme (RNTCP) of the Ministry of Health and Family Welfare, Government of India, it is widely acknowledged that the prevalence of Drug Sensitive TB in India has been reduced from 465/ lakh population (1990) to 230/ lakh population in 2012 and TB mortality has been reduced from over 38/ lakh population in 1990 to 22/ lakh population in 2012. In spite of these gains, TB remains a major public health challenge in India, being responsible for the death of one person every two minutes i.e. about 750 deaths every day. It is also estimated to have caused a loss of 7.9 million DALYs (disability-adjusted life years) and a reduction of $ 23.7 billion in economic well-being. As per the World TB Report 2013 of the World Health Organization, 31% of the 2.9 Million TB cases missed globally are estimated to be in India. Further, India does account for the highest number of TB and MDR-TB cases in the world. With 17% of the global population, it contributes to 26% of the global TB burden. With 1.9 Million new cases every year in India, if left untreated, each case of lung TB can infect 10-15 persons every year. Drug Resistance Surveillance studies have revealed that in new TB cases and retreatment cases, the prevalence of MDR-TB (resistant to two powerful first line drugs INH and Rifampicin) is 3% and 15-17% respectively. Under nutrition, crowded habitations with poor ventilation and sunlight, smoking, alcohol or substance abuse, low immunity in addition to HIV, Diabetes are the causative factors promoting development of active Tuberculosis from amongst a large pool of nearly 40% of the population having latent Tuberculosis. Stigma and discrimination further afflict the TB patients.

Indian Red Cross Society (IRCS) is the largest statutory humanitarian organization in the country with 700 State, District and Sub-district branches, having 12 million members/volunteers. Community health is one of its core functions. IRCS in collaboration with Tuberculosis Association of India, WHO, Central TB Division of the Ministry of Health and Family Welfare, Government of India, State and District TB officials and International Federation of Red Cross and Red Crescent (IFRC) has been working since 2009 through its volunteers for prevention and treatment of Tuberculosis including MDR-TB.

In collaboration with its partners, IRCS launched the TB Project (India) in 2009 in a few vulnerable communities in three states which has been extended to seven states in 2014, with the aim to increase community awareness on TB, MDR-TB, XDR-TB and TB/HIV through project advocacy, social mobilization, counselling, nutritional supplementation, ensuring treatment adherence and the involvement of cured TB patients as Red Cross volunteers to reduce stigma and discrimination associated with TB. The methodology of the Indian Red Cross TB project involves recruitment of volunteers, their training with the help of District TB Officers (DTOs), getting a list of registered TB patients from DTOs who have stopped treatment after one month for a variety of reasons including initial recovery, alcohol and substance abuse, intolerance to drugs, migration, failure to arrange transportation for getting medicines, etc. The volunteers visit these patients (defaulters/retreatment cases) and counsel the patients and their families that the TB is curable. In the acute phase, the concerned volunteer visits the patients three times a week, provides them nutritional supplementation, psychosocial support as well as the support for transportation to the DOTs centre. The volunteers also help the contact cases for TB screening. They also visit the work places of the TB patients and attempt stigma/discrimination reduction through
drama groups (nukkar nataks), testimonials, cured TB patients as well as community leaders. Community awareness activities are also undertaken regarding cough etiquette, necessity of completion of TB treatment and the message that the TB is fully curable through testing and drugs available at DOTs centres free of cost and also that it spreads by droplet infection in the air from the sputum positive cases. So far Indian Red Cross TB project through 170 trained volunteers at targeted state/district branches has been able to put back on treatment a total number of 2130 CAT II patients with 1670 (76.4%) being fully cured and thereby preventing 250 patients (15%) who otherwise would have developed MDR-TB. Considering the cost of treatment of one drug sensitive TB case being Rs. 600 in comparison to Rs.2 lacs for a MDR-TB case with much higher mortality, Indian Red Cross TB intervention is a cost-effective intervention in terms of lives saved, MDR-TB prevented, finding of missed cases, reduction of stigma/discrimination and the provision of psychosocial support.

With its unique network of thousands of volunteers throughout the country, the Indian Red Cross has the perfect platform to reach more vulnerable communities in India and help the TB programme provide universal access to TB care.

**Suggested Reading:**

- [http://who.int/mediacentre/factsheets/fs104/en/](http://who.int/mediacentre/factsheets/fs104/en/)
- WHO estimated; Source – TB India 2013, RNTCP Annual Status Report, MoHFW, Government of India
- [http://who.int/mediacentre/factsheets/fs104/en/](http://who.int/mediacentre/factsheets/fs104/en/)

Indian Journal of Tuberculosis
GLOBAL SCALE-UP OF THE PROGRAMMATIC MANAGEMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS

Charles L. Daley*

Summary: Worldwide, an estimated 8.6 million people develop tuberculosis (TB) each year resulting in 1.3 million deaths. Although rates of TB are declining in many areas of the world, the emergence of drug-resistant strains of M. tuberculosis threatens to undermine TB control programmes. Multidrug-resistant TB (MDR-TB), strains that are resistant to at least isoniazid and rifampicin, are more difficult to diagnose and treat than other forms of TB and are associated with a higher mortality rate. Unfortunately, most countries with a high burden of MDR-TB detect less than 25% of the estimated MDR-TB cases and among those detected only 82% are treated. Of the estimated 300,000 MDR-TB patients among notified TB cases, only 6% are eventually detected and treated successfully. There are many gaps in the programmatic management of drug-resistant TB (PMDT) that must be closed in order for us to successfully control TB and additional financing will be required. Through these new efforts, we hope to see more rapid scale up of PMDT activities and ultimately control and prevention of drug-resistant TB.

Key words: Tuberculosis, Multidrug-resistant, Control, World Health Organization, Xpert

INTRODUCTION

Tuberculosis (TB) continues to remain a major global health problem. Worldwide, there are an estimated two billion people infected with Mycobacterium tuberculosis from which 8.6 million people develop TB each year1. A staggering 1.3 million people die of TB annually including over 300,000 with HIV infection. Although rates of TB are declining in some areas of the world, the emergence of drug-resistant strains of M. tuberculosis threatens to undermine TB control programmes worldwide (Figure 1)1,2. Multidrug-resistant TB (MDR-TB), strains that are resistant to at least isoniazid and rifampicin, and extensively drug-resistant TB (XDR-TB), MDR-TB strains that are also resistant to a fluoroquinolone and second-line injectable drug, are more difficult to diagnose and treat than other forms of TB and are associated with a higher mortality rate. Unfortunately, most countries with a high burden of MDR-TB detect less than 25% of the estimated MDR-TB cases and among those detected only 82% are treated. New rapid molecular tests for the diagnosis of resistance are being implemented but enrollment into treatment programmes lags due to resource constraints. In order to achieve control of MDR-TB, high level political will and leadership will be needed to scale-up the programmatic management of drug-resistant TB (PMDT) on a global basis.

Figure 1: Drug-resistant tuberculosis. Most strains of Mycobacterium tuberculosis are drug susceptible but there are subsets of increasingly resistant strains. Source: Ref. 1

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CURRENT EPIDEMIOLOGIC SITUATION

By the end of 2012, data were available on drug resistance from 136 countries. Globally, an estimated 3.6% of new cases and 20.2% of previously treated cases have MDR-TB. The percentage of new cases with MDR-TB ranges from 2.2% in the Americas and South East Asian region to 16% in the European region. The highest levels of MDR-TB are in eastern Europe and central Asia where more than 20% of new cases and 50% of previously treated cases in some countries are estimated to have MDR-TB. In India, the WHO estimates that 2.2% (CI 1.4-2.5) of new cases and 15% (CI 11-19) of retreatment cases have MDR-TB.

Worldwide, there were an estimated 450,000 (300,000-600,000) new cases of MDR-TB in 2012 that resulted in 170,000 deaths. There were approximately 84,000 MDR-TB cases and 10,000 with rifampin resistance notified to WHO in 2012: more than half of these cases were in India, China and the Russian Federation. The notified cases represented only 28% of the 300,000 pulmonary TB cases estimated to have MDR-TB and 19% of the estimated 450,000 incident MDR-TB cases (Figure 2). The estimated number of MDR-TB cases in India in 2012 was 64,000 (49,000-79,000) but the notified cases were only 16,588 or 26% of the estimated cases. However, compared to 2009, the number of notified cases increased ten-fold.

Extensively drug resistant TB (XDR-TB) made headlines in 2006 when a cluster of HIV infected XDR-TB patients was reported from Kwa Zulu Natal in South Africa. Delays in diagnosis, inadequate treatment, and poor infection control policies led to rapid transmission of the drug resistant strains to others. By the end of 2012, XDR-TB was reported from 92 countries and accounted for an estimated 9.6% of MDR-TB cases. The number of XDR-TB cases reported worldwide increased from 1464 to 2230 between 2011 and 2012.

Figure 2: The many gaps in MDR-TB Control. Source Ref. 1
Within a year of the first reports of XDR-TB, there were isolated cases of patients from Italy that had resistance to all first-line and second-line drugs. This initial description was followed in 2009 by a report from Iran describing 15 such patients and more recently, a report from India describing four patients with “totally drug resistant tuberculosis” (TDR-TB). In order to address this emerging issue, the WHO convened an expert panel in March 2012 to review these reports and attempt to come up with a definition for TDR-TB. The expert panel felt that a new definition of resistance beyond XDR-TB was not recommended at this time given the technical difficulties with drug susceptibility testing of many anti-TB drugs and insufficient evidence to link such DST results to treatment outcomes.

### CASE DETECTION

Drug susceptibility testing (DST) on cultures (solid and liquid) of *M. tuberculosis* is used to detect resistance to first and second-line TB drugs. However, availability of laboratories capable of performing cultures and DST is greatly limited and methods lack standardization and reproducibility for many second-line drugs. Globally, only 5% of new cases and 9% of previously treated cases were tested for MDR-TB and only 23% of notified and confirmed MDR-TB cases had DST performed for both fluoroquinolones and second-line injectable drugs. The proportion of cases tested varies widely by region.

Clearly, availability of DST in high burden MDR-TB countries is grossly inadequate and improving coverage is urgently needed to improve detection of MDR and XDR-TB. The development of new rapid molecular tests offers the potential to identify genetic mutations that confer resistance in a fraction of the time that it takes phenotypic methods. Molecular methods have considerable advantages for scaling up PMDT and surveillance of drug-resistant TB because they offer speed of diagnosis, standardized testing, potential high through-put, and fewer requirements for laboratory biosafety. Two methods have been endorsed by the WHO: 1) line probe assays (LPA) including the Genotype MTBDR (Hain Lifescience, Nehren, Germany) and INNO-LiPA Rif.TB (Innogenetics, Zwijndrecht, Belgium) and 2) the Xpert MTB/RIF (Cepheid Inc, Sunnyvale, California). The Genotype MTBDR can detect mutations conferring resistance to isoniazid and rifampicin whereas the other tests can detect mutations associated with resistance to rifampicin only. In 2009, the Genotype MTBDRsl test was introduced for rapid determination of genetic mutations associated with resistance to fluoroquinolones, aminoglycosides (kanamycin, amikacin, streptomycin), cyclic peptides (capreomycin), and ethambutol. The WHO recommends that the Genotype MTBDRsl may be used as a rule-in test for XDR-TB but cannot be used as a replacement test for conventional phenotypic DST.

Xpert MTB/RIF is a fully automated diagnostic molecular test that can simultaneously detect *M. tuberculosis* and rifampicin resistance within two hours. The system has minimal biosafety requirements and training needs that allows the instrument to be used in non-conventional settings. The WHO recently published a policy update of their recommendations for the use of this technology after reviewing more than 85 peer-reviewed studies. The performance of Xpert MTB/RIF was excellent in many different testing situations as noted in the Table. Among extrapulmonary specimens, the pooled sensitivities were approximately 80% or above for lymph node tissue/aspirates, cerebrospinal fluid, and gastric lavage/aspirations but was only 43.7% for pleural fluid. Based on these results, the updated recommendations for use are as follows:

For the diagnosis of pulmonary TB and rifampicin resistance, WHO recommends that Xpert MTB/RIF should be used as the initial diagnostic test in adults and children presumed to have MDR-TB or HIV-associated TB. Xpert may also be used as the initial diagnostic tests in adults and children presumed to have TB if resources permit. Additionally, Xpert may be used as a follow-on test to microscopy in adults presumed to have TB but not at risk of MDR-TB or HIV associated TB, especially in further testing of smear-negative specimens.

For the diagnosis of extrapulmonary TB and rifampicin resistance, Xpert MTB/RIF should be used as the initial test in testing cerebrospinal fluid specimens from patients with presumed TB meningitis.
Additionally Xpert may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from patients presumed to have extrapulmonary TB\textsuperscript{10}.

This test is being rapidly adopted by countries and as of June 2013, 1402 machines and 3.2 million cartridges have been procured by 88 of 145 countries eligible for concessional pricing\textsuperscript{10}. South Africa has adopted Xpert MTB/RIF as the primary diagnostic test for TB to replace smear microscopy.

**LABORATORY SCALE-UP**

The Global Laboratory Initiative (GLI) was established in 2008 as a Working Group of the Stop TB Partnership\textsuperscript{11}. The GLI consists of over 100 international partners that serve as an independent, technical expert advisory group to WHO, the Stop TB Partnership, development and funding agencies, and countries. Some of the GLI priority activities for 2013-2014 are to strengthen laboratory capacity and infrastructure in resource-limited areas, support the global scale-up of rapid diagnostics, and improve quality of individual laboratories and laboratory networks\textsuperscript{11}.

Two highly successful GLI projects are EXPAND TB (Expanding Access to New Diagnostics for TB) and TBXpert. EXPAND TB was established in 2008 with the aim of accelerating the update of new TB diagnostic technologies such as liquid culture systems and rapid molecular tests in 27 high burden countries\textsuperscript{11}. Since 2011, 81 laboratories have been established and over 54,000 MDR-TB detected under this project. The TBXpert Project will provide approximately 1.4 million Xpert MTB/RIF test cartridges and over 220 GeneXpert instruments in 21 recipient countries in 2013-2015\textsuperscript{11}.

The WHO-GLI Supranational Reference Laboratory Network (SRLN) was established in 1994 to support a global project on anti-TB drug resistance surveillance\textsuperscript{12}. In the period 2013-14, 12 SRLs were funded and supported laboratory strengthening and DRS activities in 36 countries (18 high MDR-TB burden countries). To date, the GLI has been an outstanding example of how partners can work together to achieve remarkable success.

**MANAGEMENT OF MDR-TB**

The number of MDR-TB cases started on second-line treatment increased from 30,492 in 2009

### Table: Test characteristics of Xpert MTB/RIF under different testing situations*

<table>
<thead>
<tr>
<th>Test Situations</th>
<th>Studies/Participants</th>
<th>Pooled sensitivity</th>
<th>Pooled specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial diagnostic replacing smear microscopy</td>
<td>22/9008</td>
<td>88% (84-92)</td>
<td>99% (98-99)</td>
</tr>
<tr>
<td>Add-on test following a negative smear</td>
<td>23/7151</td>
<td>68% (61-74)</td>
<td>99% (98-99)</td>
</tr>
<tr>
<td>For smear positive, culture positive TB</td>
<td>23/7151</td>
<td>98% (97-99)</td>
<td>NA</td>
</tr>
<tr>
<td>For smear negative, culture positive TB</td>
<td>23/7151</td>
<td>68% (61-74)</td>
<td>NA</td>
</tr>
<tr>
<td>For people with HIV infection</td>
<td>7/1789</td>
<td>79% (70-86)</td>
<td>99% (98-100)</td>
</tr>
<tr>
<td>For people without HIV infection</td>
<td>7/1470</td>
<td>86% (76-92)</td>
<td>98% (96-99)</td>
</tr>
<tr>
<td>For detection of rifampicin resistance</td>
<td>24/2414</td>
<td>95% (90-97)</td>
<td>98% (97-99)</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expectorated or induced sputum – smear +</td>
<td>7/1083</td>
<td>96% (90-99)</td>
<td>NA</td>
</tr>
<tr>
<td>Expectorated or induced sputum – smear -</td>
<td>7/1083</td>
<td>55% (41-69)</td>
<td>55% (41-69)</td>
</tr>
<tr>
<td>Gastric lavage – smear +</td>
<td>6/1259</td>
<td>95% (83-99)</td>
<td>NA</td>
</tr>
<tr>
<td>Gastric lavage – smear -</td>
<td>6/1259</td>
<td>62% (44-80)</td>
<td>62% (44-80)</td>
</tr>
<tr>
<td>For detection of rifampicin resistance</td>
<td>3/176</td>
<td>86% (53-98)</td>
<td>98% (94-100)</td>
</tr>
</tbody>
</table>

* Source: Ref. 10

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to 77,321 in 2012 leaving at least 16,000 detected patients without treatment. In the 27 high burden MDR-TB countries, there was a 40% increase in enrollments during this time period. Much of these increases were accounted for by India where enrollments increased from 1136 in 2009 to 14,143 in 2012. PMDT services have been initiated in all 35 States/UTs of India. All the districts in the country had achieved complete geographical coverage by March 2013 and the country is now moving towards universal access to quality diagnosis and treatment of MDR TB patients. By June 2013, 31,350 MDR-TB patients and 284 XDR TB patients were reported to be initiated on treatment.

Unfortunately, the capacity to treat MDR-TB is lagging behind the capacity to diagnose MDR-TB. Diagnosis: treatment gaps of 5% or more are present in 14 of the high MDR-TB burden countries. The ratio of MDR-TB cases diagnosed to enrolled on treatment increased by >10% in China, Pakistan, and South Africa. There are many reasons for the gaps including a critical shortage of human resources, lack of availability to second and third line drugs, inadequate facilities for treatment and monitoring and ineffective TB control programs. Whatever the reasons, tight linkage between diagnosis and treatment of MDR-TB is critical for successful TB control.

Treatment of MDR-TB

The WHO published recommendations for the treatment of MDR-TB in 2007 and recently updated the recommendations. Most of the data supporting the updated recommendations derives from an individual patient meta-analysis that included over 9000 patients with MDR-TB. WHO recommends building a regimen that includes at least four second-line drugs likely to be effective (including a parenteral agent) (Figure 3) plus pyrazinamide in the intensive phase of the treatment regimen. Regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide) and either cycloserine or PAS if cycloserine cannot be used. A later generation fluoroquinolone such as moxifloxacin or high dose levofloxacin is recommended. An intensive phase of eight months is suggested with the total treatment duration of 20 months for most patients but the duration may be

![Figure 3: Building a treatment regimen for MDR-TB](image-url)
modified based on the patient’s response to treatment.

Treatment of MDR-TB is challenging for several reasons and the reader is referred to several excellent publications that address many of the practical issues that relate to treatment and managing adverse reactions, treatment in special situations and palliative care.

**Treatment Outcomes**

In 2012, a total of 107 countries reported outcomes for over 34,000 MDR-TB cases. The proportion of MDR-TB cases who were treated successfully was only 48%. Treatment success was the highest in the Eastern Mediterranean Region (56%) and Americas (54%) with success rates < 50% in the other regions. Deaths were the highest in the African Region (17%) and treatment failure the highest in the European Region (11%) with default a major contributor to poor treatment outcomes in all regions. The Global Plan’s target of achieving at least 75% treatment success for MDR-TB was achieved by only 37 of the 107 countries. Among 795 XDR-TB patients reported to WHO from 26 countries, treatment success was 20% overall with a mortality of 44%.

Recent systematic reviews and meta-analyses have reported treatment outcomes across a variety of settings. Orenstein and coworkers reported that the pooled treatment success rate from 34 studies was 62% (64% for individualized versus 54% for standardized treatment). Treatment outcomes were better when the duration of therapy was at least 18 months of duration and patients received DOT. Johnston and colleagues reported the same pooled success rate of 62% and noted better outcomes with surgical resection, no history of previous treatment and the use of fluoroquinolones. Among XDR-TB patients, Jacobson and colleagues reported a pooled success rate of 44% and importantly described better outcomes in those who took later generation fluoroquinolones.

**TREATMENT SCALE-UP**

The Green Light Committee Initiative (GLC) was established in 2000 with the aim of helping countries access quality-assured second-line anti-TB drug therapy for treatment of patients with MDR-TB. Between 2000 and 2010, the GLC approved the treatment of 105,140 patients from 133 projects in 83 countries and conducted over 300 technical assistance missions. However, only approximately 30,000 patients were actually enrolled over this time frame. Although enrollment into treatment was increasing, almost doubling between 2008 and 2009, the rate of enrollment was felt to be too slow. Therefore, a new framework was created that involved establishment of regional GLCs (rGLC) and a global GLC (gGLC) whose secretariat remained at WHO. Over two years, each of the rGLCs was established and all are now up and running. Recently, the MDR-TB Working Group and gGLC merged to become the Global Drug Resistance Initiative (GDI). This group will work closely with the Stop TB Partnership, WHO, and rGLCs to continue to scale up the programmatic management of MDR-TB worldwide, focusing on the high MDR-TB burden countries and working with the GLI to link diagnosis with appropriate and effective treatment.

The Global Drug Facility (GDF) is an initiative of the Stop TB Partnership that procures quality-assured TB drugs (and diagnostics). The second line drugs procured by the GDF are WHO pre-qualified and approved by stringent drug regulatory authorities. The GDF has increased the number of quality-assured drugs available, increased the number of suppliers of some drugs, implemented a strategic rotating stock pile to provide supplies rapidly in emergency situations, and improved forecasting tools. The GDF is an important component of both the GDI and GLI, providing quality-assured drugs and diagnostics at competitive prices.

**FINANCING OF TB CONTROL**

The WHO estimates that total funding for TB control activities in 2015 will require eight billion US dollars: about two thirds is needed for detection and treatment of drug susceptible cases, 20% for MDR-TB, 10% for rapid diagnostics and laboratory strengthening and 5% for collaborative HIV/TB activities. According to the WHO Global Report, the National TB Programme budget for India in 2013 was...
$182,000,000 (US), of which 37% was domestically funded and 57% internationally funded leaving a funding gap of about 6%. Of the total budget, $67,000,000 (US) were available for MDR-TB control. Unfortunately, large funding gaps exist globally. The funding gaps reported by NTPs add up to about one billion US dollars with approximately 13% of those gaps accounted for by gaps in the funding of MDR-TB control. In order to achieve global control of TB and MDR-TB, these gaps will need to be closed.

CONCLUSION

While nearly all countries have a national PMDT expansion plan, the actual number of MDR-TB patients diagnosed and treated is very low. Among the estimated 300,000 MDR-TB patients among notified TB cases, only 6% are eventually detected and treated successfully. There are many gaps in the global PMDT that must be closed in order for us to successfully control TB. Rapid implementation of new molecular diagnostics along with development of laboratory capacity is necessary to close the diagnosis gap (Figure 2). Ensuring access to quality-assured anti-TB drugs and developing infrastructure and human resources will be necessary for closing the treatment and success gaps. New initiatives such as the GLI and GDI will hopefully work in concert to link diagnosis and treatment and expand scale-up activities. Through these new efforts, we hope to see more rapid scale up of PMDT activities and ultimately control and prevention of drug-resistant TB.

REFERENCES


REACHING ALL TUBERCULOSIS PATIENTS IN INDIA WITH QUALITY CARE: CHALLENGES, OPPORTUNITIES AND THE WAY FORWARD TO ADDRESS THE MISSING MILLIONS

Suvanand Sahu*

TB is an ancient scourge that has caused untimely death of millions of people in the world, over several generations. The diagnosis of the disease using a microscope was demonstrated by Robert Koch over a century ago and medicines for cure have been available for over four decades. Yet, almost one million people die of TB globally each year, and an additional 0.3 million deaths occur due to tuberculosis in HIV positive people. In India alone nearly 0.3 million deaths occur annually due to TB. While efforts are ongoing for research and development of an effective vaccine, early detection and effective treatment remains the mainstay for preventing mortality, interrupting transmission and reducing the risk of further emergence of drug resistance.

India bears the highest burden of TB among all countries. Out of the estimated 8.6 million new cases of TB occurring annually, 2.2 million, i.e. more than one-fourth occurs in India alone. The decline in incidence of TB in India observed after 2005 is insufficient and it is unacceptable that a curable disease continues to kill hundreds of thousands of Indians during their economically productive years of life leading to considerable economic loss to the country.

The missing millions of TB patients

India’s Revised National Tuberculosis Control Programme started in 1997 and rolled out the internationally recommended DOTS strategy in a phased manner, reaching pan state and district coverage in 2006 (www.tbcindia.nic.in). Thereafter, efforts were made to improve access to TB care under the RNTCP while simultaneously launching and expanding services for drug resistant TB and HIV-associated TB. Private sector care delivery models were developed, awareness campaigns were launched and increased service delivery points were made available in areas with concentrated tribal population as well as urban poor population.

Results demonstrated increasing numbers of people tested for TB, increased number of patients diagnosed and registered for treatment and overall reasonably good treatment success rates. However, the increasing trend in case detection of incident TB cases (i.e. new and relapse cases) showed signs of stagnation in the late 2000s, remaining more or less flat, and even fell from 2011 to 2012. Meanwhile, the numbers of people with symptoms of TB that were tested with smear microscopy increased year-on-year, with a fall in smear positivity rate denoting greater effort being made to detect cases yet less cases actually detected. Under routine circumstances, this implies good progress in TB control, however there are three important factors that need to be kept in mind while interpreting these trends. First, this data and trend at the national level hides several different trends in data of states and districts and therefore cannot be interpreted with such simplicity. Second, and more importantly, the RNTCP has not been able to detect and treat a large number and proportion of the TB burden in the country. In the last few years, RNTCP has notified about 1.2 to 1.3 million incident TB cases annually leaving behind nearly one million incident TB cases from the estimated annual incidence of 2.2 million cases (Table). This nearly one million missing cases is an

Table: Incidence, notification and missing cases of TB

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated annual incidence</th>
<th>Notified incident cases (new &amp; relapse)</th>
<th>Missing cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>2,200,000</td>
<td>1,339,866</td>
<td>860,134</td>
</tr>
<tr>
<td>2011</td>
<td>2,200,000</td>
<td>1,323,949</td>
<td>876,051</td>
</tr>
<tr>
<td>2012</td>
<td>2,200,000</td>
<td>1,289,836</td>
<td>910,164</td>
</tr>
</tbody>
</table>

*Stop TB Partnership Secretariat, Geneva
Correspondence: Dr. Suvanand Sahu, Avenue Francois Besson 3, 1217 Meyrin, Geneva, Switzerland; Email: sahu.suvanand@gmail.com

Indian Journal of Tuberculosis
underestimate because this is only among incident TB cases and if prevalent TB cases are added this becomes even a higher number. These large numbers of TB patients are either managed by the non-RNTCP affiliated care providers, including a large and diverse private sector, or are not diagnosed and treated. In either case their diagnosis, treatment and outcomes remain undocumented and unknown.

Third, the notification data from India shows a large proportion and numbers of TB patients that are being treated again (re-treatment cases) which is unlike any other high TB burden country\(^1\). A number of studies have explored this issue but more information and understanding is required before we can concretely interpret the reasons for the increased numbers of retreatment cases.

While plans are being made in India to achieve universal access to quality services across all states and districts and services for drug resistant TB are being scaled up\(^5\), the issue of over a million TB patients missing from the notification and care services in India is a worry and presents a gigantic challenge, which if not addressed rapidly will be one of the major reasons for failing in the fight against TB.

This paper highlights the reasons and possible solutions for the missing millions of TB patients in India.

**Reasons for missing patients**

There are two broad reasons for missing TB cases from the notification system in India.

First and foremost is the fact that a substantial proportion of patients are managed by care providers that do not notify to RNTCP\(^6\). These care providers are mostly private sector care providers but could also be public sector care providers. The private sector care providers are diverse, ranging from individual clinicians to large hospitals, from unqualified practitioners to specialist doctors, and also include private laboratories and pharmacies. The public sector care providers who do not notify TB cases are more likely to be hospitals that are outside the primary health care system, especially in the urban areas, and health facilities that are under other government ministries or departments. Compounded to this problem is the reality of a large number of public sector doctors who also do private practice in their free time, and interestingly their prescription and notification practices in private practice are quite different.

Secondly, a number of TB patients fail to access appropriate care and in them TB is never diagnosed or treated. This could happen for people who are unable to access care because of barriers like distance to health facility, inability to pay for care or high opportunity cost for accessing free health care, elderly people who are immobile, people who do not for many reasons believe in modern medicine and populations with low awareness about TB. In addition, TB could be missed as a diagnosis in patients who seek care if the providers do not think about TB or do not rely on the correct diagnostics for TB. The widespread use of inaccurate and expensive serological tests for the diagnosis of TB is one such example which led to the Government of India ultimate banning them\(^4\). However, these tests are now quickly getting replaced by Interferon-Gamma Release Assays (IGRAs) which are again expensive and are not useful in the diagnosis of active TB disease. There are also patients who either drop out during the diagnostic process or after diagnosis of TB are not initiated on treatment\(^7\).

Detecting all cases alone is not enough, detecting them early and initiating them on effective treatment is what is needed to make an impact on transmission. A number of studies have pointed out the late diagnosis and treatment of TB in India and the related shopping for care which results in excessive out-of-pocket expenses for patients\(^8\).

To increase case detection and notifications, RNTCP has implemented several initiatives and some of them have been reasonably successful, but not enough to address the enormous challenge of the missing cases.

One such example is the involvement of all care providers through different models of
public-private collaborations. This initiative, started in early 2000s, did increase case detection and notifications in targeted population and some of the projects are still ongoing. But progress was limited because the models could not be scaled up and compliance of all providers of care could not be ensured due to a variety of reasons linked to the characteristics and drivers of the private sector health care market in India. Even a large number of government doctors during their private practice often resorted to treating TB without notification. It is a well-established fact that most patients, including the poor, in India first seek care in the private sector with willingness to pay out of pocket. From the patient’s perspective, care provided free of cost by the government is often not perceived as good quality, is sometimes difficult to access and comes with an opportunity cost of lost wages. In contrast, care provided by the private sector is readily available and easy to access in terms of time, place and choice of care providers. The quality of TB care provided by the private sector care providers varies considerably. Diagnosis is often delayed, missed or comes at a high cost due to unnecessary and inappropriate tests. Treatment is complicated due to prescription practices, drug quality issues and lack of a system for treatment adherence. RNTCP collaborated with the Indian Medical Association to train practitioners and more recently made TB a disease that is mandatorily notifiable. It is interesting to note that a year after the policy of mandatory notification case detection did not increase but actually fell marginally. This points to the fact that in a country like India regulatory mechanisms alone are not sufficient because policies and regulations are difficult to implement and enforce. More recently the National Strategic Plan of RNTCP has proposed a new approach of working with the private sector care providers with minimal disruption to the private sector market principles and allowing an interface agency to bridge the gap between RNTCP and the private sector care providers.

Other initiatives of RNTCP included additional service delivery points and provision of additional human resources in urban areas and tribal areas. This has helped in providing greater access to the urban poor and indigenous populations. However, there are many more vulnerable and underserved groups that are yet to be systematically identified and reached.

Actions needed to detect and notify all TB cases in India

The actions that are needed to detect and notify all TB patients in India are numerous. However, the top three action points are notification, private sector business models and active case finding.

1. Notification: The mandatory TB notification policy needs to be implemented. This will require education of care providers, incentives for notifications and user-friendly electronic and mobile phone based tools for notifications. The government has started an excellent web-based notification system called “NIKSHAY” (http://nikshay.gov.in/User/Login.aspx). Considering the widespread use of mobile phones in India and relative difficult access to computers the next step is to develop a mobile phone based data entry and retrieving system which should be simple and friendly. Such a notification system should include doctors, laboratories and pharmacies. Positive results in diagnostic laboratory tests such as the Xpert MTB/RIF tests should trigger automated notifications and such systems are today available (http://www.stoptb.org/global/awards/tbreach/xpertsms.asp). In clinics, doctors making a diagnosis of TB should be able to notify using mobile phone based applications or messaging systems. Further work is needed to trigger notifications from pharmacies on sale of anti-TB medicines, again using mobile phone based applications.

2. Private sector business models: Innovative, sustainable and scalable business models for TB care in the private sector are urgently needed. The traditional RNTCP models of public-private collaborations have relied heavily on referral of patients to the public sector, use of only RNTCP drug regimen and provision of free services in
the private health care sector. New models are required where the private sector manages the TB cases themselves, using the best available diagnostics and standard internationally recommended drug regimen, and notifies the patients to the government through the NIKSHAY system. To be sustainable and effective such models should work with, and not against, the principles and forces of the private sector market. Separate business models may be required for laboratories, pharmacies and clinics. There are examples of such models taking shape in India on laboratories and elsewhere on clinics and this is an opportunity to think out-of-the-box. The anti-TB medicine market in the private sector in India far exceeds that of the public sector. This is an opportunity for intervening in the private sector market by introduction of quality assured patient-wise TB drug box to ensure correct dosage and complete treatment. This could not only improve quality and affordability of TB drugs in the private market but also has the potential of triggering notification as a drug box moves from the shelf of the private pharmacy to the patient. To implement any of these models a private sector interface agency will be required and it is encouraging to note that the RNTCP national strategic plan recognized this. One such model with an interface agency has just started to function in Mumbai and there is much to be learnt from this project.

3. **Active TB case finding.** Active screening and case finding needs to be considered as a strategy to increase case detection and more importantly to diagnose TB patients early in their course of illness. This should be prioritized for high risk, vulnerable and underserved population groups. New approaches in care delivery needs to be planned and implemented for key affected population groups such as migrants, urban slum dwellers, indigenous population groups, mining affected population, etc. These approaches include systematic screening, mobile outreach and effective use of community volunteers in care delivery.

In addition to the above three important action points, diagnosis and treatment of all forms of TB need to be included in the package of services under the Universal Health Coverage agenda of India, and the government budgetary allocation for TB prevention and care should be increased.

In May 2014, the World Health Assembly will consider a new post-2015 strategy with bold targets.

**By bold innovations in care delivery, India can make rapid progress towards early and enhanced TB case detection and has an opportunity to lead the fight against TB globally, along with other BRICS countries which account for more than half of the TB burden globally.**  

**REFERENCES**


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**THE TUBERCULOSIS ASSOCIATION OF INDIA**

**NATCON 2014**

The 69th National Conference on Tuberculosis and Chest Diseases (NATCON 2014) will be held in association with the Maharashtra State Anti-TB Association at Mumbai.

The timings and other details will be announced in due course.
Original Article

REASONS FOR INTERRUPTION OF ANTI-TUBERCULAR TREATMENT AMONG THE RETREATMENT PATIENTS IN CATEGORY II OF RNTCP IN CHANDIGARH, NORTH INDIA

Sandeep Singh Sarpal1*, Naveen Krishan Goel2*, Dinesh Kumar3* and Ashok Kumar Janmeja4**

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Summary

Introduction: More re-treatment TB patients are notified in India than any other country in the world, and default among this group is a serious public health problem. Adherence to the long course of TB treatment is a complex, dynamic phenomenon with a wide range of factors impacting on treatment taking behaviour. The main aim of the study was to study the basic clinical and demographic profile of the defaulters and the reasons for discontinuation of treatment among these retreatment patients in category II of RNTCP.

Methods: A longitudinal study was designed and the patients registered under RNTCP category II from June 2010 to December 2011 at various centres in Chandigarh formed the study cohort. Out of total 607 patients registered during this period under category II of RNTCP in Chandigarh, 545 consented to participate in the study. These were followed up to September 2012 till the completion of treatment. 32 patients among the registered 545 defaulted from the treatment during the period. These patients were traced in the community and information regarding reasons for interruption and barriers to treatment was obtained from them using a pre-structured pre-tested questionnaire. Data were analysed using SPSS 18 statistical software package.

Results: 32(5.9%) patients defaulted from the treatment under RNTCP category II. 29(90.6%) were pulmonary patients while 3(9.4%) were extra-pulmonary patients. 46.9% of the defaulters were in the age group of 20-35 years, followed by 31.3% in the age group of 36-50 years. 21.9% went to traditional healers for cure while 12.5% tried herbal medicine during the treatment. 25% (eight) patients did not have faith on the DOTS treatment. Most common side effects of treatment complained by the patients were GI upset (62.5%), fatigue (59.4%), drowsiness (34.4%) and itching (31.3%). 46.8% believed that ATT induced side-effects were the main reason for treatment interruption. Maximum treatment interruption was seen at the end of the third month (31.3%).

Conclusions: Maximum interruptions were found to occur by end of third month of ATT. ATT induced side-effects were the main reason for treatment interruption. Efforts need to be made to improve the pre-treatment counselling, increase proportion of patients treated by community-based DOTS providers, repeated health education to the patients emphasizing the need to continue treatment.

[Indian J Tuberc 2014; 61: 121-128]

Key words: Tuberculosis, Treatment interruption, Anti-tubercular Treatment, RNTCP

INTRODUCTION

There were an estimated 8.8 million incident cases of TB (range, 8.5 million—9.2 million) globally in 2010 equivalent to 128 cases per 1,00,000 population. Most of the estimated number of cases in 2010 occurred in Asia (59%) and Africa (26%). There were an estimated 12.0 million prevalent cases (range, 11.0 million—14.0 million) of TB in 2010. This is equivalent to 178 cases per 1,00,000 population. India, however, disproportionately accounts for nearly half of the retreatment TB cases notified globally. Default among re-treatment group is a serious public health problem. The notification rate of re-treatment TB in India has slowly but steadily increased over the past decade, from 14 cases per 100,000 population in 2001 to 25 cases per 100,000 population in 2009. At present by achieving the 70% case detection and 85% cure rate, only 59% of the patients are being cured and 41% of the cases remain undetected in the community. Thus the long term goals of RNTCP

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cannot be met by curing only 59% patients. Therefore, the focus must remain on dealing with the important reasons of default and timely retrieval of the patients who interrupt treatment.4

Adherence to the treatment in patients of TB is a complex process and many factors are implicated on having an impact on the treatment taking behaviour. Many studies have been conducted across the world to study the reasons for default from ATT 5, 6, and some are also reported from India (mostly done under RNTCP setting). 3-10

The main aim of study was to study the basic clinical and demographic profile of the defaulters and the reasons for discontinuation of treatment among these retreatment patients in the category II of RNTCP.

MATERIAL AND METHODS

Chandigarh, a Union Territory (UT) is also the capital of Punjab and Haryana situated in the northern part of the country. RNTCP was launched in Chandigarh on 25th January 2002. RNTCP is implemented in the UT through District Tuberculosis Centre (DTC) located in Sector 34. There are three Tuberculosis units (TU). A longitudinal study was designed and the patients registered under RNTCP category II from June 2010 to December 2011 at the various centres in Chandigarh formed the study cohort. Out of total 607 patients registered during this period under category II of RNTCP in Chandigarh, 545 consented to participate in the study. These were followed up to September 2012 till their completion of treatment. Both pulmonary and extra-pulmonary patients were enrolled, irrespective of their sputum status. From the cohort of 545 patients enrolled in the study, information regarding their socio-demographic profile, educational and occupation status was obtained.

RNTCP defines default as a patient who has not taken anti-TB drugs for more than two months consecutively any time after starting treatment.4 32 patients among the registered 545 defaulted from the treatment during the period. These patients were traced in the community and information regarding the reasons for interruption and barriers to treatment was obtained from them using a pre-structured pre-tested questionnaire. The study instrument was specifically designed/developed with slight modifications in regional context, by reviewing the relevant literature and previously used standardized instruments and protocols.

In addition to the personal and socio-demographic data, treatment history was recorded in detail. In case of the patients having changed address/migrated, phone numbers of the patients recorded in RNTCP registers were utilised or contacts were obtained from the patients neighbours/guardians and telephonic interview was carried out for that patient.

Patients of category I, transferred out, transferred in during the period were excluded from the study. Informed consent was taken from the respondents (or guardians in case of minors) and ethical guidelines under Declaration of Helsinki were followed. The institutional Ethical Committee also approved the study.

Characteristics of the defaulters and non-defaulters were compared by using statistical tests of significance. A simple descriptive analysis was done for the variables which were of interest. Odds ratios, along with 95% confidence intervals, were calculated. Differences in proportions were assessed by using the Chi-square test of significance. p values of <0.05 were considered as statistically significant, all the p values being two-sided. Analysis of variance (ANOVA) technique was used for testing variability between several groups. Relative risk estimate along with their 95% confidence interval were used for investigating risk factors of treatment default/interruption. Logistic regression model was also used for estimating the probability of default. Data was analysed using SPSS 18 statistical software package.

RESULTS

Characteristics of defaulters

Thirty two (5.9%) patients defaulted from the treatment under category II of RNTCP. A majority (29) were the pulmonary patients while the rest (3) were extra-pulmonary patients. Sixteen (50%) were relapse patients, five (15.6%) were failures, nine (28.1%)
were treatment after default (TAD) while 2(6.3%) belonged to the Others category. A majority of the defaulters were males (31). The mean age of defaulters was 38.47±14.06 years. A large number of the defaulters were residing in the slum areas (19) while eight were residing in the urban areas.

Most of the defaulters were Hindus (29). 24 of the defaulters were married. Among the defaulters, 34.3% were in service, 31.3% were labourers, 12.5% were in business, and 3.1% were housewives in the present study (Table 1). Seven (21.9%) patients went to the traditional healers for cure while four (12.5%) tried herbal medicine during the treatment.

Eight (25%) patients did not have faith on the DOTS treatment. Eleven (34.4%) patients were currently using tobacco. The mean duration of smoking was 20.48±12.22 years. Ten (31.3%) were currently consuming alcohol. The mean duration of alcohol consumption was 20.5±12.3 years. Analysis of the socio-demographic profile of retreatment patients revealed that among the male patients, 16 (8.9%) were treatment interrupters and 26 (6.6%) of the total patients were treatment interrupters and married. 24 (6%) of the patients residing in the rural and slum areas were treatment interrupters (Table 2).

### Table 1: Socio demographic profile of the defaulters

<table>
<thead>
<tr>
<th>Age of the patient</th>
<th>No (%)</th>
<th>Yes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-19</td>
<td>1(3.1)</td>
<td></td>
</tr>
<tr>
<td>20-35</td>
<td>15(46.9)</td>
<td></td>
</tr>
<tr>
<td>36-50</td>
<td>10(31.3)</td>
<td></td>
</tr>
<tr>
<td>51-65</td>
<td>5(15.6)</td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>1(3.1)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31(96.9)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1(3.1)</td>
<td></td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hindu</td>
<td>29(90.6)</td>
<td></td>
</tr>
<tr>
<td>Sikh</td>
<td>2(6.3)</td>
<td></td>
</tr>
<tr>
<td>Muslim</td>
<td>1(3.1)</td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>6(18.8)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>24(75)</td>
<td></td>
</tr>
<tr>
<td>Widow/Widower</td>
<td>2(6.3)</td>
<td></td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slum</td>
<td>19(59.4)</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>8(25)</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>5(15.6)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>5(15.6)</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>12(37.5)</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>4(12.5)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>7(21.9)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>3(9.4)</td>
<td></td>
</tr>
<tr>
<td>Graduate</td>
<td>1(3.1)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Socio-demographic characteristics of the retreatment patients

<table>
<thead>
<tr>
<th>Socio Demographic characteristic</th>
<th>Treatment Interrupters</th>
<th>Chi Square value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>No (%)</td>
<td>Yes (%)</td>
</tr>
<tr>
<td>Below 35</td>
<td>300(94.9%)</td>
<td>16(5.1%)</td>
<td></td>
</tr>
<tr>
<td>Above 35</td>
<td>213(93.0%)</td>
<td>16(7.0%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>196(99.5%)</td>
<td>1(0.5%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>317(91.1)</td>
<td>31(8.9%)</td>
<td></td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hindu</td>
<td>435(93.8%)</td>
<td>29(6.3%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>78(96.3%)</td>
<td>3(3.7%)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>147(96.1%)</td>
<td>6(3.9%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>366(93.4%)</td>
<td>26(6.6%)</td>
<td></td>
</tr>
<tr>
<td>Type of family</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear</td>
<td>409(94.2%)</td>
<td>25(5.8%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>104(93.7%)</td>
<td>7(6.3%)</td>
<td></td>
</tr>
<tr>
<td>Socio Economic Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>333(95.1%)</td>
<td>17(4.9%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>180(92.3%)</td>
<td>15(7.7%)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>445(94.3%)</td>
<td>27(5.7%)</td>
<td></td>
</tr>
<tr>
<td>Literate</td>
<td>68(93.2%)</td>
<td>5(6.8%)</td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>140(94.6%)</td>
<td>8(5.4%)</td>
<td></td>
</tr>
<tr>
<td>Rural and Slum</td>
<td>373(94.0%)</td>
<td>24(6%)</td>
<td></td>
</tr>
</tbody>
</table>

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Table 3: Side effects of drugs as perceived by the defaulters

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI upset</td>
<td>20 (62.5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (59.4%)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>11 (34.4%)</td>
</tr>
<tr>
<td>Itching</td>
<td>10 (31.3%)</td>
</tr>
<tr>
<td>Joint Pains</td>
<td>6 (18.8%)</td>
</tr>
<tr>
<td>Burning in Hands and Feet</td>
<td>4 (12.5%)</td>
</tr>
<tr>
<td>Dizziness and Loss of Balance</td>
<td>4 (12.5%)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (3.1%)</td>
</tr>
</tbody>
</table>

Table 4: Mode of the spread of tuberculosis according to defaulters

<table>
<thead>
<tr>
<th>Mode of spread of Tuberculosis</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coughing</td>
<td>15 (46.9)</td>
</tr>
<tr>
<td>Contact</td>
<td>13 (40.6)</td>
</tr>
<tr>
<td>Sneezing</td>
<td>11 (34.4)</td>
</tr>
<tr>
<td>Don’t Know</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Curse</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Heredity</td>
<td>1 (3.1)</td>
</tr>
</tbody>
</table>

Table 5: Bivariate analysis of risk factors for treatment interruption

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Interrupters</th>
<th>Non Interrupters</th>
<th>OR</th>
<th>Chi Square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;35</td>
<td>16</td>
<td>213</td>
<td>1.41</td>
<td>0.57</td>
<td>0.44</td>
</tr>
<tr>
<td>&lt;35</td>
<td>16</td>
<td>300</td>
<td>(0.65-3.04)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31</td>
<td>317</td>
<td>19.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>196</td>
<td>(2.71-380.6)</td>
<td></td>
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</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hindu</td>
<td>29</td>
<td>435</td>
<td>1.73</td>
<td>0.41</td>
<td>0.52</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>78</td>
<td>(0.49-7.32)</td>
<td></td>
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<tr>
<td>Marital Status</td>
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<td></td>
<td></td>
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<tr>
<td>Single</td>
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<td>147</td>
<td>0.57</td>
<td>1.01</td>
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<tr>
<td>Others</td>
<td>26</td>
<td>366</td>
<td>(0.21-1.51)</td>
<td></td>
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<tr>
<td>Type of Family</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nuclear</td>
<td>25</td>
<td>409</td>
<td>0.91</td>
<td>0.05</td>
<td>0.99</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>104</td>
<td>(0.36-0.38)</td>
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<tr>
<td>SES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>17</td>
<td>333</td>
<td>1.63</td>
<td>1.34</td>
<td>0.24</td>
</tr>
<tr>
<td>Others</td>
<td>15</td>
<td>180</td>
<td>(0.75-3.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slum</td>
<td>24</td>
<td>373</td>
<td>1.13</td>
<td>0.01</td>
<td>0.93</td>
</tr>
<tr>
<td>Urban</td>
<td></td>
<td></td>
<td>(0.47-2.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>8</td>
<td>140</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>5</td>
<td>68</td>
<td>1.21</td>
<td>0.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Literate</td>
<td>27</td>
<td>445</td>
<td>(0.39-3.46)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Logistic regression

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Odds Ratio</th>
<th>95% C.I. for EXP(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&gt;35 yrs</td>
<td>-.296</td>
<td>.432</td>
<td>.469</td>
<td>1</td>
<td>.493</td>
<td>.744</td>
<td>.319 - 1.734</td>
</tr>
<tr>
<td>Male</td>
<td>1.922</td>
<td>1.144</td>
<td>2.821</td>
<td>1</td>
<td>.093</td>
<td>6.836</td>
<td>.726 - 64.409</td>
</tr>
<tr>
<td>Hindu</td>
<td>.487</td>
<td>.642</td>
<td>.575</td>
<td>1</td>
<td>.448</td>
<td>1.627</td>
<td>.462 - 5.723</td>
</tr>
<tr>
<td>Unmarried</td>
<td>.005</td>
<td>.555</td>
<td>.000</td>
<td>1</td>
<td>.993</td>
<td>1.005</td>
<td>.339 - 2.981</td>
</tr>
<tr>
<td>Nuclear Family</td>
<td>-.158</td>
<td>.478</td>
<td>.110</td>
<td>1</td>
<td>.740</td>
<td>.853</td>
<td>.334 - 2.178</td>
</tr>
<tr>
<td>Residence</td>
<td>-.143</td>
<td>.471</td>
<td>.092</td>
<td>1</td>
<td>.761</td>
<td>.867</td>
<td>.345 - 2.180</td>
</tr>
<tr>
<td>Illiterate</td>
<td>-.061</td>
<td>.550</td>
<td>.012</td>
<td>1</td>
<td>.911</td>
<td>.941</td>
<td>.320 - 2.763</td>
</tr>
<tr>
<td>Addiction</td>
<td>1.493</td>
<td>.636</td>
<td>5.504</td>
<td>1</td>
<td>.019</td>
<td>4.449</td>
<td>1.278 - 15.481</td>
</tr>
<tr>
<td>Constant</td>
<td>-5.675</td>
<td>1.289</td>
<td>19.374</td>
<td>1</td>
<td>.000</td>
<td>.003</td>
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</tr>
</tbody>
</table>
Table 7: Reasons for treatment interruption

<table>
<thead>
<tr>
<th>S.No</th>
<th>Reasons for Treatment Interruption*</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>ATT induced side effects</td>
<td>15(46.8)</td>
</tr>
<tr>
<td>2.</td>
<td>Loss of wages/work</td>
<td>12(37.5)</td>
</tr>
<tr>
<td>3.</td>
<td>No improvement</td>
<td>11(34.3)</td>
</tr>
<tr>
<td>4.</td>
<td>Lack of faith on DOTS</td>
<td>8(25.0)</td>
</tr>
<tr>
<td>5.</td>
<td>Early Improvement</td>
<td>7(21.8)</td>
</tr>
<tr>
<td>6.</td>
<td>Long duration of treatment</td>
<td>5(15.6)</td>
</tr>
<tr>
<td>7.</td>
<td>Others</td>
<td>4(12.5)</td>
</tr>
<tr>
<td>8.</td>
<td>Alcohol</td>
<td>2(6.3)</td>
</tr>
</tbody>
</table>

*Multiple responses

Most common side-effects of the treatment complained by the patients were GI upset (62.5%), fatigue (59.4%), drowsiness (34.4%) and itching (31.3%) (Table 3). 47% of the defaulters believed that coughing was the main mode of spread of tuberculosis, 40.6% believed contact while 25% didn’t know the mode of spread of tuberculosis (Table 4).

Barriers in treatment

Only 14(43.8%) of the patients were eating with their family. A majority of the patients (24) said that they had to stop going to work at some point during the course of the treatment due to poor health. 11(34.4%) said that they had to stop going to work for three-six months during the course of treatment while 6(18.8%) had to stop work for a period of more than six months. Most patients (26) said that they experienced social stigma during the course of the treatment. Only 3(9.4%) of the patients agreed that attitude of others during the course of therapy was helpful.

Reasons for treatment interruption

Odds ratio showed that male sex was a significant risk factor for treatment interruption/default. However, the type of family, residence, and education level were not found to be significant correlate with treatment interruption (Table 5). Risk factors obtained on the basis of bi-variate analysis may be interrelated and hence logistic regression was also done to confirm the risk factors (Table 6).

Table 8: Relationship of treatment interruption with duration of treatment

<table>
<thead>
<tr>
<th>Treatment Interruption</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Month</td>
<td>5(15.6)</td>
</tr>
<tr>
<td>2nd Month</td>
<td>7(21.8)</td>
</tr>
<tr>
<td>3rd Month</td>
<td>10(31.3)</td>
</tr>
<tr>
<td>4th Month</td>
<td>6(18.7)</td>
</tr>
<tr>
<td>&gt;4th month</td>
<td>4(12.5)</td>
</tr>
</tbody>
</table>

Fifteen (46.8%) believed that ATT induced side-effects were the main reason for treatment interruption. 11(34.3%) said no improvement after therapy as a reason for treatment interruption. 8(25%) patients did not have faith on DOTS (Table 7). Maximum treatment interruption was seen at the end of the third month (31.3%) (Table 8).

DISCUSSION

This study describes the characteristics and risk factors for default among the re-treatment TB patients in Chandigarh. Among the defaulters, 96.9% were males in the present study. Earlier researchers have also shown male sex as a risk factor for default. The main reason for default among the males could be due to financial /occupational constraints due to which they cannot spare time to visit the DOTS centres.

A majority (90.6%) of the defaulters in the present study were pulmonary patients while the rest (9.4%) were extra-pulmonary patients. Jha et al had reported 97.7% pulmonary cases and 2.2% extra pulmonary cases among the defaulters in their study. Their findings collaborate with the present study. Lower default rates among the extra-pulmonary patients could be due to more concern of the patients towards the symptoms leading to a better compliance pattern.

28.1% of the defaulters in the present study belonged to treatment after default category. Similar findings have been shown by Sachdeva KS et al where 25.5% were treatment after default and Jha et al had reported that 37.6% were treatment after default in their study. Thus TAD constitutes an important group.
among the defaulters in retreatment patients and it is imperative to provide repeated health education to these patients emphasizing the need to continue treatment. Special counselling and motivational sessions for this group of patients should be planned and one-to-one counselling sessions may be provided to the individual patients in the TAD group.

Twenty five per cent of the defaulters in the present study did not know the mode of spread of tuberculosis. This calls for strengthening the efforts for implementation of International Standards of TB Care (ISTC) at peripheral level. ISTC expects good inter-personal communication to educate the patients about the disease and its treatment including the duration and importance of completion of treatment.15

Only 14.3% patients were eating with their family. 81.2% believed that they had experienced social stigma due to the disease. Family members can potentially provide the general care and psychological support for TB patients; hence involvement of family members in the treatment can be an effective strategy to increase treatment success among tuberculosis patients.

In the present study, maximum treatment interruption was seen at the end of the third month (31.3%). Sixty nine per cent treatment interruption had occurred by the end of the third month. Many other studies have also reported that maximum number of patients interrupted their treatment by the end of second or third month. Gupta S et al reported (72.17%) treatment interruptions occurred by the third month of ATT.16 Chan-Yeung et al found that 45% of those who defaulted did so in the first two months of treatment.17 Kaona et al reported that up to 39% patients had stopped taking their medication within the first two months of commencing treatment.18 On the contrary, some other investigators have reported higher default rate after third month of ATT.19,20 Logically, the cumulative risk of default depends on the duration for which patients suffering from any medical condition are required to take medication. This effect would be exacerbated in the case of retreatment TB because the patients are required to take medication long after they feel well. DOT therapy assumes that patients who proved themselves adherent during the initial phase may be trusted to go on partly self-administered therapy subsequently in continuation phase. However, based on findings in our study, we would suggest retreatment patients, particularly in the TAD group, being maintained on DOT (thrice or twice weekly intermittent therapy) during the continuation phase until treatment completion for better compliance pattern and decreasing the default rate.

Among the various reasons cited by the defaulters for the treatment interruption, 46.8% said that ATT induced side-effects were the main reason for treatment interruption. Similar findings were reported by Jaggarajamma et al in their study where 42% of the patients defaulted due to drug-related problems.11 Mittal C found that 43.2% patients were non-compliant in their study due to side-effects of the drugs.3 Wares et al found the most common reason for stopping treatment being the adverse effects of ATT.21

Among the ATT induced side-effects, GI upset (62.5%) was the most common side-effect reported in the present study followed by fatigue (59%) and drowsiness (34%). Similar findings have been reported in earlier studies.22,23 Efforts should be made for the availability of medicines to the patients for promptly treating the commonly observed side-effects during the anti-TB therapy.

Thirty seven per cent patients cited loss of wages/work as second most common reason for default. Financial instability is a hindering factor among the retreatment patients as due to long duration of treatment, social stigma attached with the disease and poor health they tend to lose job/wages. This affects treatment compliance among the defaulters as they tend to change address, migrate to other areas and follow up of such patients becomes difficult which was observed during the present study. In addition to the DOTS therapy, food and housing subsidies, and keeping the job position during their treatment course may be needed by the patients to improve treatment outcomes.24, 25

Thirty four per cent patients said no improvement as a reason for default from ATT in the present study. In a study by Mittal C, et al, 10.8% patients were non-compliant due to no improvement
in symptoms. This can be attributed to the long duration of treatment, emergence of drug resistant bacteria and development of psychiatric co-morbidities such as depression in the retreatment group. Future researchers should focus on the quality of life of the retreatment patients in Indian scenario.

Twenty five per cent patients in the present study defaulted due to lack of faith on the DOTS. Long duration of treatment and associated side-effects of therapy, ill health, social stigma and financial losses can lead to a situation where patients lose faith on the therapy even though the treatment is provided free of cost by the government. Health personnel should be sensitive to this issue and evolve suitable motivation strategies. Possibilities of mobilizing Non-Governmental Organizations’ (NGO) support in the community should be explored.

Twenty two per cent said early improvement as a reason to treatment interruption in the present study. However, on the contrary, many authors have reported early improvement as the main reason for treatment interruption. Gupta S et al reported that the most common reason for treatment interruption was a feeling of early improvement reported by the patients (30.05%). Social problems and feeling of improvement were the top two reasons for patients to default in study by Demissie et al. 15.6% patients defaulted due to long duration of treatment. The long duration of treatment can lead to patients seeking health options from different health care providers. India has a huge and poorly regulated private medical sector and it has been reported that, nearly 50-70% of TB patients continue to prefer private healthcare. Therefore, further strengthening of the Public Private Mix (PPM) activities of RNTCP is needed. The responsibility of the community DOTS providers, the government health agencies and the NGOs in educating, counselling and motivating the retreatment patients and their family members to continue the treatment is crucial for the success of RNTCP.

CONCLUSIONS

Defaulting from the treatment is common among the large number of re-treatment patients in India. Maximum interruptions were found to occur by the end of third month of ATT. More than one reason was often reported for discontinuation of treatment. ATT induced side-effects were the main reason for treatment interruption. Early management of side-effects due to ATT may also be taken care of to further improve the compliance. Efforts need to be made to improve the pre-treatment counselling, increase the proportion of patients treated by community based DOTS providers, repeated health education to the patients emphasizing the need to continue treatment. Default occurring due to long duration of treatment calls for the introduction of drugs that may further shorten the duration of chemotherapy.

ACKNOWLEDGEMENTS

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REFERENCES

7. Vijay S, Balasangameshwar VV, Srikantharamu N. Treatment Dynamics and Profile of Tuberculosis Patients under the District Tuberculosis Programme (DTP) – A Prospective Cohort Study. Indian J Tuberc 1999; 46: 239-49.
from the Urban setting of Delhi, India. *Tropical Medicine and International Health* 2003; 8: 625-33.


Original Article

RNTCP IN GUJARAT: A COMPARATIVE STUDY BETWEEN TRIBAL AND NON-TRIBAL AREAS

Shridhar V. Rawal*

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INTRODUCTION

The state of Gujarat has a considerable 14.8% of tribal population.1 As we know, tribal people live in geographical isolation mostly in remote, difficult to reach areas. They are referred as backward and are forming poorest of the poor of India. 2 The accessibility and utilization of RNTCP services in different areas are found to be different in several studies.3 It would be useful to identify the areas, which really need to be paid more attention to in Gujarat as now WHO is aiming for “Universal access to TB care”.4

Gujarat is one of the pioneer states in implementation of RNTCP in India. The pilot project was implemented in rural area of Chansma of Mehsana district in 1993. The pre-dominantly tribal areas like Narmada, Dang, Chhota udepur and vyara were lately covered and whole state was covered by the end of March 2004.

To improve the accessibility and utilization of RNTCP services, several measures are taken in different areas. These include incentives to basic health workers as well as patients in the tribal areas. Tribal action plan of RNTCP-II had already proposed to pay additional salary of Rs. 1,000/- over and above the regular salary to contractual STS and STLS posted at TUs with tribal area DMC as a tribal area allowance. Other incentives like travel cost, etc., were also suggested. The patients completing treatment are also rewarded with an incentive of Rs.250/- in tribal area.2

Thus, tribal population has its own problems and the programme has tried to reach them with feasible solutions. Now, it should be assessed whether these measures taken by the programme has really made a dent in tribal area or the universal access to TB care will require further initiatives. In this context, a comparative study was carried out in tribal and non-tribal areas to assess the impact of RNTCP in these areas.

Summary

Background: Tribal population resides in difficult to reach terrain. It is vital to know, in context of “Universal care approach”, whether they are equitably benefited by RNTCP.

Objective: To compare RNTCP performance in tribal areas with non-tribal areas and to detect whether the difference in performance indicators is statistically significant.

Methods: A comparative analysis of RNTCP performance indicators like total case detection rate, new smear positive case detection rate, etc., was carried out using annual data of last three years in tribal and non-tribal areas. T-test was applied to confirm statistically significant difference.

Results: The performance of tribal area is better in terms of suspects examined per lakh population per year, total case detection rate, NSP case detection rate and success rate. The difference was close to statistically significant difference at 95% confidence limit and the difference was significant at 90% confidence limit. The extra-pulmonary case notification rate was significantly higher in non-tribal areas with understandable reasons.

Conclusion: Significantly high previously treated smear positive case notification rate in tribal area is a matter of concern. The incentives to tribal areas appear to reap better results and these need to be supported and sustained. [Indian J Tuberc 2014; 61: 129-133]

Key words: Annual total case detection rate, Annual new smear positive case detection rate, Success rate, Operational capacity, Tribal area, Non-tribal area, T-test.

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MATERIAL AND METHODS

The annual reports of the last three years i.e. 2009 to 2011 were analysed. The state is divided into 30 districts for RNTCP programme. Based on population presentation, out of 237 talukas, 47 are labelled as tribal talukas. As per RNTCP organizational structure, TU is the basic unit. For the purpose of this study, TU was used to define tribal and non-tribal areas. Out of total 138 TUs, 38 TUs were tribal TUs and remaining were non-tribal TUs. The performance indicators for TU level were compiled from quarterly performance reports published by State TB Cell. The study has focused on infectivity and operational capacity aspects. The primary statistics used includes percentages, mean & standard deviation (SD). As MS excel was used to detect statistically significant difference, t-test based on F-test values was calculated to detect whether difference is significant or not. With the help of F-test, homogeneity of the data was decided first and then t-test was applied. Though the data was derived from a large number of TUs in tribal and non-tribal areas, for different years, for comparison, their summary statistics is used and so these tests are applied. Considering the small sample size, confidence limit of 90% is accepted for certain parameters.

RESULTS

As a first step, RNTCP tries to find the TB patients by detecting TB suspects from OPDs in different health facilities. The indicator used for this is: suspects examined /lakhs population per quarter (Table 1).

The expected rate is 150 suspects examined/lakh population per quarter. In tribal regions, this indicator suggests that the suspect examination rate is far higher. For tribal areas, the mean and SD values were 202 SEPL and 19.67. For non-tribal areas, the respective values were, 182.33 and 2.51. The difference of variance was found to be statistically significant among two areas, while t-test was non-significant.

The other parameter used to measure operational performance in RNTCP now is total case detection rate (Table 2). This includes both pulmonary and extra-pulmonary TB case detection. The mean and SD values for tribal areas were found to be 148.33 and 10.50 respectively. For non-tribal areas, the summary statistics values were 130 and 4.58. The difference was very close to statistically significant (p=0.07). In other words, at 90% confidence limit, the tribal areas have significantly higher total case detection rate than non-tribal areas.

The rate of transmission of tuberculosis is reflected by new smear positive cases. The new smear positive case detection rate in tribal and non tribal areas was not found to be statistically different. Though again, at 90% confidence limit, the NSP case detection rate was significantly higher in tribal areas than non-tribal areas (p=0.09).

The patient registered for RNTCP is followed up at two and three months, based upon category and smear positivity, for sputum examination. The 3-month conversion rate is thus an indicator of effectiveness and efficiency of treatment. This was found to be more than 90% in both tribal and non-tribal areas (Table 3).

RNTCP measures its completeness in terms of drug effectiveness and patient compliance by
This combined rate is called success rate (Table 4). The mean success rate in tribal and non-tribal areas was found to be 89% and 87% respectively. Considering 90% confidence limit, the difference was statistically significant (p=0.06).

Sputum smear negative cases are those who are having two initial negative sputum results, whose symptoms persist after two weeks of broad spectrum antibiotics and whose repeat sputum examination results are also negative along with radiological abnormalities suggestive of active TB. The mean NSN case notification rate observed in tribal and non-tribal areas are 21.82 and 15.62 per lakh population respectively. The difference is found to be statistically non-significant at 95% confidence limit.

Other operational parameters (Table 6) studied were percentages of all smear positive patients who started RNTCP DOTS within seven days of diagnosis and percentages of all types of TB patients registered, receiving DOTS through community.

The parameter of increasing importance in context of MDR-TB is previously treated smear positive case notification rate. The mean notification rates were found to be 33.63 and 26.68 per lakh population in tribal and non-tribal areas respectively. The difference is significantly higher (p<.05) in tribal area, which is a matter to be worried about.

Table 3: Smear conversion rate at 3-months in NSP in tribal and non-tribal areas

<table>
<thead>
<tr>
<th>Year</th>
<th>Tribal(%)</th>
<th>Non-Tribal(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>93.00</td>
<td>91.00</td>
</tr>
<tr>
<td>2010</td>
<td>93.00</td>
<td>91.00</td>
</tr>
<tr>
<td>2011</td>
<td>92.00</td>
<td>91.00</td>
</tr>
<tr>
<td>mean</td>
<td>92.67</td>
<td>91.00</td>
</tr>
</tbody>
</table>

Table 4: Treatment success rates in tribal and non-tribal areas

<table>
<thead>
<tr>
<th>Year</th>
<th>Tribal</th>
<th>Non-Tribal</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>89%</td>
<td>87%</td>
</tr>
<tr>
<td>2010</td>
<td>90%</td>
<td>88%</td>
</tr>
<tr>
<td>2011</td>
<td>88%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Table 5: NSN, Extra-pulmonary and previously treated Sm +ve case notification rates

<table>
<thead>
<tr>
<th>Year</th>
<th>Tribal</th>
<th>Non-Tribal</th>
<th>Tribal</th>
<th>Non-Tribal</th>
<th>Tribal</th>
<th>Non-Tribal</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>27.03</td>
<td>16.83</td>
<td>11.7</td>
<td>20.32</td>
<td>36.91</td>
<td>28.06</td>
</tr>
<tr>
<td>2010</td>
<td>20.45</td>
<td>14.01</td>
<td>11.35</td>
<td>19.00</td>
<td>33.98</td>
<td>27.00</td>
</tr>
<tr>
<td>2011</td>
<td>18.00</td>
<td>16.00</td>
<td>10.00</td>
<td>20.00</td>
<td>30.00</td>
<td>25.00</td>
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</table>

Table 6: Operational parameters of RNTCP

<table>
<thead>
<tr>
<th>Year</th>
<th>Tribal</th>
<th>Non-Tribal</th>
<th>Tribal</th>
<th>Non-Tribal</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>86%</td>
<td>90%</td>
<td>63%</td>
<td>40%</td>
</tr>
<tr>
<td>2010</td>
<td>89%</td>
<td>91%</td>
<td>70%</td>
<td>50%</td>
</tr>
<tr>
<td>2011</td>
<td>90%</td>
<td>92%</td>
<td>56%</td>
<td>54%</td>
</tr>
</tbody>
</table>

P=0.11 P=0.06
volunteers. The mean value for the earlier parameter was higher in non-tribal area, while the mean value for the later parameter was found to be more in tribal area.

**DISCUSSION**

The analysis of the last three years reveals an important finding in terms of case finding. The suspect examination rate is higher in tribal area as compared to non-tribal area. This finding provides support to a similar observation made by Jyoti Patnaik et al in their study in Orissa.

The total case detection rate is also high in tribal areas as compared to non-tribal areas. The availability of services helpful to detect extra-pulmonary cases, the awareness about the need for treatment of these conditions, the acceptability can be some of the factors requiring attention in wide non-tribal area.

This is followed by the very important observation about new sputum smear positive cases detected in both areas. This rate is substantially high in tribal areas. It clearly suggests that the laboratory services are functioning optimally in these difficult terrains. Though, a one-year-data review mentions that the case detection activity was similar in both areas. The lesser availability of private practitioners in these areas might also be claimed for these high rates. Additionally, increased infection transmission and high burden of TB can also be a reason.

The new smear negative case detection rate findings are in favour of tribal area. As per definition, their detection depends upon radiological investigation. It requires further study of availability of functional x-ray facility in both areas. Though it is believed that non-tribal area will have more x-ray facilities available compared to tribal area, the functional status in terms of both machine and manpower needs to be explored. As these cases are believed to get converted to smear positive cases later on, their detection and treatment are equally important.

Though till now, more attention is paid on pulmonary tuberculosis, recently, the focus is changing towards detection of all types of TB cases. So, detection and treatment of extra-pulmonary TB cases are also important. As the findings suggest, the rate of detection of EP cases is significantly higher in non-tribal area. The reason can be lack of awareness about the form of TB in tribal area. Also, less availability of facilities required for diagnosis of this type of condition can lead to lesser detection rate. The finding suggests that for universal access to TB care, in terms of availability of diagnosis of extra-pulmonary tuberculosis, tribal area needs to be paid attention.

As per guidelines on programmatic management of drug resistant TB in India, all smear positive previously treated pulmonary TB cases are to be included as MDR-suspects. This increases the importance of reviewing this indicator. The study finding of higher rates of 34 per lakh in tribal area needs to be attended to. As, now, these patients will be subject to tests for MDR detection i.e LPA test. The programme expects that if an area has good quality DOTS implemented, this rate should decline gradually. The data of tribal area is in the same line, which is indicative of good quality DOTS there, and raises hope that the rates will continue to fall in coming years.

The 3-month smear conversion rate is good in both areas. This finding is important from programmatic point of view as it suggests that the sustained efforts are required for the follow-up of patients, particularly in non-tribal areas.

Success rate in both areas is suggestive of successful acceptance, availability and sustained efforts of government facilities through programme. It can be attributed to the high percentage of patients receiving DOT though community volunteers in tribal areas, who are from the local areas and provided additional incentives. Similarly, success rate of 86% was reported in Madhya Pradesh, with predominantly tribal area. Though probably due to difficulties of the topography, the rate of patients put on DOTS within seven days of diagnosis is little lesser in tribal areas as compared to non-tribal areas. In addition to remoteness from health facility, in-availability or partial availability of manpower can also be the reason.
While considering above results, attention should also be paid to the fact that Government of India has made special provisions in tribal sub-plan to have one PHC per 20,000 population instead of 30,000 population, one sub-centre for 3000 instead of 5000 people, provision of more mobile clinics, allopathic, ayurvedic and homeopathic dispensaries.10

CONCLUSION

Among performance indicators, suspect examination rate, case detection rate, success rate and NSN case notification rate and previously treated smear positive case notification rate were significantly high in tribal areas. Extra pulmonary case detection rate was found to be high in non-tribal areas.

SUGGESTIONS

The study is based on data of three years’ annual reports. A study using data of more years may provide better idea. It would be more useful to carry out an analysis to detect factors that lead to better or poor results of parameters e.g. role of community volunteers in success rate. Availability of patient-wise data may help to do it.

ACKNOWLEDGEMENTS

We are deeply grateful to Dr. Paresh Dave, Additional Director (Health), for providing guidance and support to carry out the study.

REFERENCES

5. Central TB Division. Director General of Health services. MOHFW. New Delhi Revised National Tuberculosis control program. 2012; Module 2. page 19.
USE OF COMPLEMENTARY AND ALTERNATIVE THERAPIES AMONG RURAL TB PATIENTS IN NALGONDA, ANDHRA PRADESH: A QUALITATIVE STUDY

B Venkatraju¹ and Sheela Prasad²

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Summary

Background: A considerable number of studies have been conducted on health seeking behaviour of TB patients in different parts of the world. However, these studies largely ignored the prevalence and use of complementary and alternative medical practices (CAM) among TB patients. This present study was prompted by the recognition that, an understanding of different factors influencing CAM use in a medically pluralistic setting has important implications for providing patient-centred comprehensive care, and improving the quality of life for TB patients.

Aim: The objective of the study was to explore the reasons and motivations for the use of Complementary and Alternative Medicine (CAM) therapies among rural TB patients.

Methods: A sample of 110 respondents were recruited purposively from two selected rural TB units at Yadagirigutta and Chintapally in Nalgonda district in Andhra Pradesh (A.P.). Semi-structured interview schedule and case study methods were used for the collection of primary data. A qualitative content analysis method was employed to analyse and interpret the data.

Results: TB patients employed a variety of alternative therapies such as massage, prayer, amulets, diet, faith or spiritual healing, restriction in alcohol consumption and smoking, abstinence from sex, and herbal teas as an adjunct to biomedical TB treatment. Engaging in alternative medical practices resulted in a sense control and relief from physical and psychological suffering and trauma associated TB illness.

Conclusion: There is a need on the part of the health care professionals and health policy managers to gain insight into the motivations and reasons for CAM use among the TB patients. Such a shift in thinking will impact on reducing non-compliance, and identifying and dealing with unmet needs of patients which are seen as major deterrents to successful TB control programmes. [Indian J Tuberc 2014; 61: 134-141]

Key words: Tuberculosis, Complementary and alternative medicine, Prayer, Witchcraft, Evil eye, Faith healing.

INTRODUCTION

In recent years, the popularity of Complementary and Alternative Medicine (CAM) therapies increased, particularly among patients suffering from serious and chronic diseases such as cancer¹, arthritis², psychiatry³, and HIV⁴. These studies clearly suggest that sick individuals diagnosed with chronic and life threatening diseases actively try alternative therapies exclusively, simultaneously or alternatively in their quest for better cure. CAM refers to healing practices that do not fall within the framework of modern biomedicine. CAM recognizes that there are many approaches to health care including conventional western medicine. Today in many parts of the West, there is an acceptance of the relevance of CAM by the medical/scientific community. In the USA, the National Centre for Complementary and Alternative Medicine (NCCAM) is a part of the National Institutes of Health. The NCCAM promotes integrative medicine which combines mainstream modern medicine and CAM. In India, there is a long history of using CAM along with modern medicine for treatment of various health problems. One of the most attractive features of CAM therapies is the holistic nature of treatment, in the sense that healing involves the whole person, not simply the diseased organ of the human body which is the main focus of biomedicine.

The paper would like to argue for a strong rationale for use of CAM therapies in the treatment of some diseases, specifically TB in the context of India. The high levels of economic disparity and socio-cultural diversity along with an unevenly distributed modern healthcare system create a climate where modern medicine is not always able to deliver. In the

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Indian Journal of Tuberculosis
case of TB, the long drawn nature of treatment, the stigma attached and the higher prevalence among the poor, all challenge modern medicine. The limited success of the National TB control programme has to be understood against this background. In such a situation, with the number of TB cases on the rise, there is an urgent need to encourage and view CAM therapies favourably in the treatment of the disease.

Research studies conducted on the use of CAM therapies indicate that patients and their family members are often reluctant to disclose use of CAM therapies to their clinicians for fear of ridicule or rejection, and this may negatively affect the doctor-patient communication and compliance with treatment regimen. Review of literature related to health seeking behaviour of TB patients reveals that very little is known about the use and prevalence of CAM medical practices among TB patients, the factors influencing its use, and the perceptions and beliefs of TB patients towards CAM therapies. This area largely remains unexplored in Indian context in particular. Health policy makers and medical practitioners need to be aware of motivations for use of CAM therapies by TB patients for various reasons. For instance, a better awareness of the factors influencing use of CAM therapies among TB patients can play an indispensable role in improving the treatment programmes that focus on adherence to standard TB treatment, and health education in communities. Furthermore, an understanding of cultural beliefs and perceptions that influence CAM use in a medically pluralistic setting has important implications for providing patient-centred holistic care and improving patient-physician communication.

This paper makes a strong case for justifying the use of CAM in the treatment of TB in India. The objective of the study was to explore the reasons and motivations for the use of CAM therapies among rural TB patients. An important outcome of this research is to sensitise the medical community to the various dimensions of CAM therapy in treatment of TB, in an effort to gain more acceptance for it among doctors.

MATERIAL AND METHODS

The field-work for this study was conducted during the year 2008 - 2009 in rural Nalgonda district as part of a larger study on the ‘Perceptions and Experiences of Rural Patients with Tuberculosis’. A sample of 110 newly registered TB patients were selected using purposive sampling method from a list of patients registered for treatment in two selected rural TB Units (Chintapally and Yadagirigutta) of Nalgonda district, Andhra Pradesh, South India. As the aim of the study was to explore subjective personal meanings, emotional subtleties, and experiences associated with the use of CAM therapies, a qualitative method was chosen for this study. Selection of participants was based on those who were above 18 years and who were residents of the study area. Oral informed consent was obtained from all the respondents before administering the research tools. Semi-structured interview schedule and case study methods were used for the collection of data, and in-depth interviews were conducted face-to-face with the patients. The main interview question was ‘what types of alternative treatments are used in the management of your TB illness?’ Interview questions were designed based on the tripartite model of local health care system framework (i.e., popular, folk and professional health care sectors) suggested by Arthur Kleinman. Interviews with the patients were conducted in native language (Telugu), and interviews were transcribed into English. Data was analyzed based on the principles of grounded theory proposed by Strauss and Glasser. Content analysis method was employed to analyse and interpret the data. Field notes were analyzed inductively, and data analysis was carried out following multi-step procedure that consisted of data reduction, coding, and identification of themes.

RESULTS

Sample characteristics

Of the total 110 respondents, 73.6% and 26.3% were males and females respectively. The mean age of the patients was 39 years. Of the total respondents, 72 (65.45%), were smear positive, 27 (24.5%) were smear negative and 11 (10%) were
extra-pulmonary cases. Of the total cases, 5.45% were found to be co-infected with HIV and TB. The socio-demographic characteristics of the sample are summarized in Table 1.

**Table 1: Socio-demographic characteristics of the patients (n=110)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in Groups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-25</td>
<td>14</td>
<td>12.7</td>
</tr>
<tr>
<td>26-35</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>36-45</td>
<td>26</td>
<td>23.6</td>
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<td>46-55</td>
<td>28</td>
<td>25.4</td>
</tr>
<tr>
<td>56-65</td>
<td>16</td>
<td>14.5</td>
</tr>
<tr>
<td>66-72</td>
<td>4</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>SEX</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>81</td>
<td>73.6</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>26.3</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>92</td>
<td>83.6</td>
</tr>
<tr>
<td>Widow/Widower</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Single</td>
<td>8</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-literate</td>
<td>67</td>
<td>61</td>
</tr>
<tr>
<td>Primary</td>
<td>26</td>
<td>23.6</td>
</tr>
<tr>
<td>Secondary</td>
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<td>12.7</td>
</tr>
<tr>
<td>College</td>
<td>3</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agriculture</td>
<td>38</td>
<td>34.5</td>
</tr>
<tr>
<td>Labor</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>Self-employed</td>
<td>24</td>
<td>21.8</td>
</tr>
<tr>
<td>Private employee</td>
<td>6</td>
<td>5.4</td>
</tr>
<tr>
<td>Student</td>
<td>2</td>
<td>1.8</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>6.4</td>
</tr>
</tbody>
</table>

**Table 2: Alternative treatment practices among rural TB patients in Nalgonda**

<table>
<thead>
<tr>
<th>Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Religious rituals (e.g., prayer)</td>
</tr>
<tr>
<td>Restriction in use of alcohol and smoking</td>
</tr>
<tr>
<td>Herbal remedies (e.g., ginger and pepper tea, hot baths)</td>
</tr>
<tr>
<td>Faith or spiritual healing (e.g., witches, diviners, priests)</td>
</tr>
<tr>
<td>Abstinence from sex</td>
</tr>
<tr>
<td>Over-the-counter medicines (e.g. pain relievers: cough syrup)</td>
</tr>
<tr>
<td>Diet (e.g. meat, eggs, milk)</td>
</tr>
<tr>
<td>Restriction of certain foods (e.g., potato, sweet diet, brinjal, dry fish)</td>
</tr>
</tbody>
</table>

**Alternative medical practices among TB patients:**

In response to the question, “what types of alternative treatments are used in the management of your TB illness?”, the respondents reported using a variety of CAM treatment strategies such as massage, prayer, protein rich diet, faith healing, abstinence from sex, restriction in smoking and alcohol consumption and herbal teas to cope with their illness (Table 2).

In this study, the most commonly employed CAM therapies by patients were prayer, massage, diet, and abstinence from sex. Of the total 110 patients, 17% of patients resorted to faith healing practices after embarking upon TB treatment. Faith-based healing was generally sought by patients who attributed their illness to supernatural agents such as divine retribution, witchcraft or evil eye.

Alternative medical practices used by the TB patients are discussed in more detail in the following sections:

**i) Faith Healing**

The patients who attributed causation of their TB illness to supernatural forces made use of both allopathic treatment and faith healing services simultaneously. In this study, it was found that patients usually consulted faith healers when a variety of other resources, particularly, anti-TB medicines had failed to provide expected relief. Although patients reported faith in modern TB medicine, as they did not get expected respite from their symptoms, they looked to faith healing as a complementary source of help with biomedicine. A few case studies are presented below in order to demonstrate how patients understand use of faith healing services, the meanings they attached to these faith healing therapies, why they found them appropriate, and what results they expected to get from using these therapies.
Case Study 1 – Witchcraft

In the following case study, a 45-year-old patient gave reasons for attributing his TB to witchcraft, and turning to a witch for help. He said:

I have taken TB medicines for more than two months. But, these medicines did not provide much relief to me. Instead, they caused severe vomiting and drowsiness. I found side-effects of TB medicines intolerable, and I dropped out of TB treatment for more than 20 days. My physical condition deteriorated over a period of time. At this stage, I really got very much frustrated. I felt something was really wrong with me. My family members suspected the role of evil forces in the causation of my illness. You know, if it is a natural illness, I could have got cured with injections and tablets. But this did not happen at all. Two years back, I had quarreled with my brother over sharing the agricultural land. Fierce arguments have been taking place between my and my brother’s family since last two years. Last year my healthy child died in mysterious circumstances. Soon after, I was diagnosed with TB and HIV. I strongly suspected that my brother might have bewitched me and my child. I went to a witch to find out the underlying cause of my illness. He went into trance and told me that a close blood relative of mine bewitched me out of hatred and jealousy. The explanation given by the healer confirmed my suspicion. He performed rituals and told us that he expelled evil spirits which interfered with my health. On the advice of witch, a goat was sacrificed to appease the evil spirits. Since then, there has been a considerable improvement in my health condition. You see, modern medicine is useful for treating symptoms but not the underlying cause of illness.

Case Study 2 – Evil Eye

In the following case study, a 52-year-old woman described evil eye as a possible cause of her illness, and shared the following reasons for consulting a faith healer:

I have been suffering from TB illness for the last one year. Initially, TB medicines caused more harm than good. Medicines made my symptoms worse, and caused severe side-effects (dizziness and acidity). You know, sometimes, I felt that I may die of this horrible problem at any moment. In fact, TB illness crippled me physically and mentally. A series of misfortunes also occurred in my family - my husband had a heart stroke suddenly and mysteriously. My adult son became very rebellious. I became restless and nervous. I was worried, could not sleep, and had lost lot of weight. I consulted different practitioners including herbalists and medical physicians, but none of them were able to cure my illness completely. This indicated to me that there was some underlying cause behind my illness. On the advice of my close relatives, my husband took me to a Muslim priest. Sayab (Muslim priest) at dargah explained to me that evil eye was the cause of my illness. My family members totally agreed with his diagnosis for different reasons. You see, many people in my village are jealous of my family. You see, my husband is a central government employee. He had constructed one of the best houses in my village. He also purchased three acres of fertile agricultural land which is very close to my house and village. Because of these reasons, many people are very jealous of my family’s economic growth. They want to harm us so that we no longer remain financially stable. I strongly feel that my relatives or neighbours caused harm to my family by casting an evil eye. Muslim priest gave amulets to all my family members. He sprinkled holy water and ash on me, my husband and son. And he chanted prayers and told me that he expelled the evil spirits from my body. After this ritual, I am feeling better. TB medicines were working better. I strongly felt that expulsion of evil spirits strengthened the efficacy of TB medicines. Since then, I had gained considerable weight, and the problem of breathlessness and cough lessened to a considerable extent now. My son got married, and he is leading a responsible life. My husband also recovered from heart stroke. I believe that Sayab performed a miracle in my life.

Case Study 3 - Divine Retribution

A TB patient in his late forties, explained reasons for consulting a priest to appease angry goddess Uppalamma. He said:

For the last one and half year, I had been suffering from intermittent fever. You know, I had tried...
TB medicines, self-care remedies and a variety of herbal medicines, but all these remedies provided very little relief. My symptoms remained, and my health condition worsened day by day. I vomited a lot. I became very much restless. I dropped out of treatment for some time. My wife and I began to think why this illness has not been responding to different types of treatments. We thought over this issue for some time seriously. Several questions came to my mind: Is there a person who dislikes us? Have I had arguments with my neighbours? I can’t think of any person who may have reasons to harm me. You see, we are poor people and we don’t have any valuable assets. So I never suspected the role of witches in the causation of my illness. However, I suspected that some mystical force was behind my illness. If it was a natural illness, my illness could have responded to TB medicines for sure. I had consulted a local priest to find out the underlying cause of my illness. He told me that mother goddess Uppalamma was angry with me because I had offended her in some way. You know, the explanation given by the healer made a perfect sense to all my family members. I remembered that my illness began soon after the relocation of the shrine of Uppalamma from inside of my house to the backyard. Now it became very clear to me that Uppalamma was not happy with me at all. She certainly cursed me for offending her. The priest performed prayers, and rubbed enchanted lemons all over my body. I felt relived from mental agony soon after the rubbing of lemons all over my body. He performed rituals at my house to appease goddess Uppalamma, and gave amulets to all my family members. Priest asked me to sacrifice a goat to appease angry goddess Uppalamma. I had offered a goat to Uppalamma. I had also spent one week in a healing temple of lord Venkateswara. I took part in the daily prayers in the temple. I am feeling much better now because of the fact that I propitiated Uppalamma. This is because, the priest removed causal agent responsible for my misery. This is the first time in my life that I had turned to God for help. I understood the supreme powers of Almighty. I have been performing special prayers in the name of Uppalamma every Saturday of the week. You know, if I had not appeased Uppalamma, I would have died of this deadly disease. I returned to TB treatment after close to two months of lapse in treatment. My illness is responding to TB medicines well now.

The above case studies illustrate the belief that supernatural causes were responsible for causing a person to become seriously sick, is almost invariably the reason why an ailing individuals go to visit a priest or witch. It was found that patients who sought faith healing services initially attributed the aetiology of their TB illness to natural and individual factors such as exposure to cold weather, alcohol consumption, smoking, hereditary, infection, diet or mental stress, but later gave different interpretations when there was little improvement in their health condition despite being on TB medication for a considerable period of time. Such changes in initial tentative categorization of illness causation from natural and individual factors to supernatural factors is not unique to the people of Nalgonda district, but are reported in a number of studies in different countries. Patients who sought treatment from faith healers stated that they felt better after seeking treatment from traditional healers.

ii) Prayer

Prayer was one of the most common complementary therapies employed by the study patients with almost all patients (>85%) seeking some kind of psychological benefits from this therapy, most commonly having a sense of control over their illness. Patients described that they offered prayers at homes or in religious centres such as temples, churches and muslim darghas in the hope that gods/goddesses would listen to their appeal for help in overcoming illness and adversity. Many patients, in particular, reported that they coped with their predicament by praying and putting their fate in God’s hands. Patients’ narrative accounts suggested that prayers played a central role in enhancing hope and coping abilities.

Case study 4 – Prayer

A 45-year-old, widow, HIV positive TB patient, attributed her recovery from illness to prayer. She described it this way:

I became very confident and hopeful after attending the prayers at a faith healing church in Karnapuram village. Prayers brought me inner peace, enhanced my self-confidence. I remained confident that Jesus would listen to my prayers. You know, if I hadn’t
prayed, I would not have survived. Then, my children would have become orphans by now. I am grateful to Jesus for his miraculous healing powers. I am no longer a depressed person. I have been seeking more comfort through prayer, and asking God to give me strength and energy to overcome this illness. I feel that Jesus had performed a miracle in my life. I am indebted to Christ for his help in saving me and my children.

iii) Dietary Therapies

All the patients mentioned that dietary observations play an indispensable role in the treatment of TB illness. It appears that the rationale for food recommendations and restrictions for treatment of TB illness is more culturally-oriented. There is a strong and universal belief among the rural people that a healthy body is seen as state of proper balance, and ill health as state of imbalance. In rural Nalgonda, like in many parts of the world, foods and illnesses are classified metaphorically as hot or cold according to their affects on the body, and are used therapeutically to restore humoral equilibrium or balance in the body. It is believed that a person with hot disease should avoid hot foods and should take only cold foods, on the other hand, a person suffering from cold disease should take only hot foods, and must avoid cold foods in order to restore body balance.

Meat, eggs and milk came up as the most recommended food items that a person suffering from TB should take. TB is basically viewed as a disease involving excessive coldness in the body, and the hot foods' (such as meat, eggs, ginger tea) intake is mainly aimed to counteract this coldness effect. All the patients and their family members considered that protein rich diet is important for building up physical strength and thereby improving their health. On the other hand, foods such as brinjal, potato, sugar, dry fish, banana, custard apple, guava, sugar, and tamarind is avoided. Because foods such as sugar, jaggery, banana, guava, orange, cucumber, and custard apple are categorized as cold foods, and hence avoided. All the patients reported that foods such as potato, brinjal, gongura (Hibiscus sudariffa), and dry fish, would aggravate cough, fatigue, and muscle aches, and hence are restricted.

iv) Massage Therapy

Self massage therapy is one of the most popular CAM therapies noticed among majority of the TB patients. Patients complained that muscle aches and cramps, fatigue, and weakness were the most distressing symptoms of their illness, and these symptoms had a considerable impact on their everyday lives. Massage is believed to have significant therapeutic effects. It is believed that massaging the body for example, with oil help in removing stiffness and soreness in the joints and muscles. It is understood that massage loosens the blood vessels and muscles thereby allowing free flow of blood to the body which results in relaxation of body muscles.

v) Restriction in use of alcohol and smoking; Abstinence from sex

For many respondents, having TB illness meant modifications in their life styles. During the course of treatment, almost all the married patients said that they avoided sexual intercourse with their respective partners as it is believed to be detrimental to the health of both partners. Most patients with the history of alcohol consumption and smoking expressed that they quit or restricted smoking and alcohol after being put on TB treatment. There is a universal belief among the people that mixing alcohol and TB drugs can be injurious to the health, and could result in death.

DISCUSSION

The study results indicate that the use of alternative medical practices is common among the TB patients. Engaging in alternative medical practices such as prayer, massage, faith healing, etc., resulted in a sense control and relief from physical and psychological suffering and trauma associated TB illness. The study findings suggest that for almost all patients TB illness represented a situation of anxiety and profound psychological depression. In other words, TB illness disrupted an individual’s taken-for-granted world of everyday ongoing life. In this study, patients in desperate situation turned to different healers in the hope of getting respite from the illness. Results suggest clearly that patients are interested in the management of their illness and will explore all avenues
to try and overcome the illness. This study clearly
demonstrates and endorses the view suggested by
medical anthropologist Kleinman\(^8\) that patients
actively shop for a variety of treatment options in their
search for cure. Over the course of TB treatment,
patients utilized different healing therapies moving
freely from one sector of health care to another
depending upon their accumulated knowledge and
suggestions gathered from family members, relatives,
and neighbours.

In rural Nalgonda like in many other parts of
the world, it is believed that biomedical treatment is
ineffective when dealing with illnesses perceived to
be caused by witchcraft, evil eye or other supernatural
forces. It is understood that such an illness will not be
cured permanently and effectively as long as the
witches, evil spirits, or deities are not appeased and
propitiated appropriately. Patients who adhered to this
type of belief system did not reject modern medical
treatment. Instead, they explained that lasting cure is
possible only when the patient undergoes faith healing.
Patients’ narrative accounts revealed that resort to faith
healers was not the first resort, but rather a ‘desperation
measure’, after various treatments had brought very
little relief.

The study findings clearly suggest that for
the rural patients, alternative health care systems
are not mutually exclusive, rather they seem to
serve complementary functions. For them, the
practice of medical pluralism is complementary and
not competitive, and patients see no conflict or
dichotomy between these plural systems. None of
the CAM therapies posed any major threat to the
health of TB patients. However, patients who
attributed their TB illness to supernatural factors
discontinued the mainstream treatment for more
than two weeks, which is a major cause of concern
as far as adherence to TB medication is concerned.
The likelihood of developing drug-resistant TB
increases among such patients.

Despite the tremendous progress made in TB
care and awareness programmes over the years
under the biomedical framework, the study results
demonstrate the continued existence of folk theories
(e.g., witchcraft, evil eye, divine retribution,
consumption of cold foods) of disease causation.
Patients perceived diet as major factor in the treatment
of TB illness. While the lay beliefs recommended meat,
eggs, and milk, this diet is endorsed by modern
medicine too. A diet rich in proteins was seen as one
of the ways to counter TB during the sanatorium era\(^{12}\).
It is only after the emergence of antibiotics that modern
TB treatment ignored nutrition as a major factor in
facilitating the recovery from TB illness. Most of the
patients said that although they prefer to eat meat, eggs,
milk, etc, but they can’t afford these foods because of
their poor economic position.

During the course of this research, none of
the patients refused mainstream TB treatment,
rather, alternative treatments were used as an adjunct
to conventional TB treatment. Findings of this study
suggest that in a way TB patients do sense the
limitations of Western medicine while recognizing
its efficacy. While the TB drugs treat the disease,
alternative therapies to heal the self are seen as
equally important in the treatment of TB. The study
findings clearly support earlier observations made
by various scholars in the field of medical
sociology and anthropology that the major emphasis
on TB diagnosis and treatment rather than
communication with the patients and community
members appears to one of the major shortcomings
of TB control programmes in several non-western
countries. For instance, health care workers
consider TB basically a biological problem with
major impact on the patient’s physical body. In this
study, patients, on the other hand, emphasized the
problems in the psychosocial domain like fears
about disease relapse, anxiety, social
discrimination, depression, loss of self esteem,
harmful side-effects, little relief from the
symptoms, persistence of symptoms, fear of
spreading disease to family members, future of
children, loss of family support, God’s punishment,
breach of religious taboos, jealousy, hatred,
disruption in interpersonal relationships, witchcraft
or fears about death. These differing perceptions
between the physicians and patients clearly imply
that practitioners must make an effort to understand
their patients’ psychosocial world, and reasons or
motivations for use of CAM therapies in order to
identify and deal with the felt needs of the patients.
CONCLUSION

The study results indicate that concurrent anti-TB treatment does not seem to be a deterrent to the use of different CAM therapies. It can be argued that CAM are attractive because they are seen as more compatible with patients’ cultural values, worldview, and spiritual/religious beliefs. Practitioners need to make an endeavour to elicit and acknowledge alternative medical practices, and should avoid cultural stereotypes and victim blaming. A major question that needs to be posed is, ‘What is appropriate care”? In the biomedical model, only allopathy is seen as good care and not be questioned. In other words, allopathy is the only system seen as appropriate, while all other systems of health care are unscientific, inadequate, not recognized, and to be discouraged. While resorting to different faith healers may be seen as irrational and superstitious from health care practitioners’ point of view, however, when one considers the alternative treatments in desperate conditions, the rationality of patient’s health seeking behaviour becomes clear.

To provide culturally sensitive care, the practitioners must be prepared to address pathophysiological and psychosocial problems as experienced by the patient and his/her family members. Health care workers need to be aware of traditional health beliefs and treatment practices, and employ comprehensive and holistic models of treatment that incorporates not just pathophysiological, but psychological, social and cultural factors. The results of this study also provide information on the culturally based misconceptions about causes of TB. Health care professionals need to be sensitized to the different socio-cultural contexts and belief systems that their patients come from which determine variations in health seeking behaviour. This qualitative study has certain limitations. The samples were not selected randomly, and hence, they are not statistically representative of populations beyond them. A bias towards under-reporting of utilization of faith healers cannot be ruled out. However, the findings of this study provide valuable information for planning client-centered integrative care and for rural TB patients.

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We wish to sincerely thank TB patients, who participated in this study. We would like to express our sincere thanks to Joint Director (TB), District TB Officer, Nalgonda, and TB staff who lent us support and co-operation.

REFERENCES

INTERLEUKIN-3 AND INTERLEUKIN-17 DO NOT PLAY A DYNAMIC ROLE IN THE IMMUNOPATHOGENESIS OF OSTEOARTICULAR TUBERCULOSIS

Urvashi Tiwari1*, V.G.Ramachandran2*, Shukla Das2* and Sudhir Kumar3**

(Received on 18.6.2013; Accepted after revision on 21.1.2014)

Summary

Background: Osteoarticular tuberculosis accounts for one to three per cent of all cases of active TB. IL-3 stimulates the proliferation, differentiation and survival of pluripotent stem cells. IL-17 has shown to promote inflammatory cell recruitment and granuloma organization throughout infection with Mycobacterium tuberculosis. During the chronic phase of the infection, a balance between Th1 and Th17 responses needs to be achieved to limit immunopathology.

Aim: To correlate the serum levels of IL-3 and IL-17 at presentation and after completion of treatment in clinicoradiologically proven cases of osteoarticular tuberculosis.

Methods: 32 clinicoradiologically confirmed cases of osteoarticular tuberculosis were included. Archived serum samples of eight patients of osteoarticular tuberculosis of an earlier study, confirmed by PCR, AFB smear or by histopathology with previously determined IL-12 and TGF-β levels were available. A detailed history was noted and their general physical, local and relevant systemic examination was performed. Various laboratory parameters including IL-3 and IL-17 levels in serum were estimated at presentation and at six months of DOTS CAT-1 treatment.

Results: There was a significant improvement in the clinical and radiological parameters after treatment. No correlation was found between IL-3 and IL-17 levels before and after treatment. A significant correlation (p value= 0.022) was shown between levels of IL-3 and IL-12 after six months of treatment.

Conclusions: Qualitative and quantitative fluctuations in IL-3 and IL-17 levels were not able to serve as useful indices of disease activity.

Key words: Cytokines, Osteoarticular TB, Interleukin-3, Interleukin-17, DOTS

INTRODUCTION

Tuberculosis (TB), one of the oldest known diseases in history, continues to be a major health problem in developing countries like India. Tuberculosis can affect all tissues of the body and therefore can present in various forms. Osteoarticular TB accounts for one to three percent of all cases of TB with active clinical disease, indicating the burden of disease in the community3.

Mycobacterium tuberculosis is a facultative intracellular bacterium which characteristically resists intracellular killing and has the ability to lie dormant inside the host cell. Mycobacterial epitopes are presented on the surface of antigen presenting cells in conjunction with MHC-II causing the CD4+ T cells to undergo activation and clonal proliferation. CD4+ T cells produce a variety of cytokines that activate the immune cells and express cytolytic properties.

Cytokines are involved in the effector phase of all inflammatory diseases. The effect of a particular cytokine on a given cell depends on the nature of cytokine, its extracellular abundance, the presence of the complementary receptor on the cell surface, and downstream signals activated by receptor binding. A number of parameters can affect adequate and reliable measurements of cytokine levels in biological specimens including the timing of sampling, sample handling and storage, and the choice of plasma or serum. As cytokines reflect the local or systemic milieu, they could serve as biomarkers for disease severity and as targets for therapy.

Th1 cells mainly produce interferon-gamma (IFN-γ) which is a regulator of cellular immunity and provides protection against intracellular microorganism. Th1 cytokines, IFN-γ, IL-12 and TNF-α, are critical for controlling infection with Mycobacterium tuberculosis. Th2 cells produce IL-
IL-5 and IL-13 which is a regulator of humoral immunity. Th2 cytokines, IL-4 has anti-inflammatory effect, and IL-10 and TGF-β suppresses T cell responses. Th17 cells produce IL-17 which has been found to be secreted early in tuberculosis. Internal microenvironmental stimuli include a combination of TGF-β, IL-6 and IL-21 which induce the differentiation of naïve T cells into Th17 cells. The development of latter is inhibited in the presence of Th1 or Th2 cytokines. Regulatory T cells (Tregs) play a crucial role in dampening immune responses against pathogens and in maintaining self-tolerance and immune surveillance. Tregs are found to be increased during active TB. B lymphocytes function as APCs and may have immunoregulatory roles in TB. Multifunctional T cells secreting IFN-γ, TNF-α and IL-2 are more frequent in TB patients than in latent TB infection. Patients with active TB frequently have decreased levels of IFN-γ and IL-2, and high levels of immunomodulatory cytokines IL-10 and TGF-β in response to mycobacterial antigens. IL-3, a cytokine secreted by activated T lymphocytes, stimulates the proliferation, differentiation and survival of pluripotent hematopoietic stem cells. Th17 cells also participate in early inflammatory response to mycobacterial infection and has been shown to be associated with reactivation of latent TB infection. Following Mycobacterial tuberculosis infection, the early recruitment of neutrophils to lungs is associated with early granuloma formation. IL-17 may play a role in granuloma formation and inflammation. During primary tuberculosis, both IFN-γ and IL-17 producing cells are induced, both are potent inflammatory cytokines capable of inducing expression of chemokines that promote cell recruitment and granuloma organisation throughout infection. During the chronic phase, a balance between Th1 and Th17 responses needs to be achieved to control bacterial growth and limit immunopathology.

Moreover, IL-3 inhibits RANKL induced osteoclast differentiation by direct action on osteoclast precursors. IL-3 inhibits RANKL induced osteoclast differentiation and diverts the cells to macrophage lineage. IL-17 induces the synthesis of osteoclast differentiation factor (ODF) via a COX-2 mediated PGE₂ synthesis by osteoblasts which in turn stimulate osteoclast like multinucleated cell (OCL) formation. IL-17 synergizes potently with other inflammatory cytokines. It also promotes osteoclastogenesis via induction RANKL.

The aim of this study was to correlate the serum levels of Interleukin-3 and Interleukin-17 at presentation and after completion of treatment i.e. after six months of DOTS (Directly observed treatment shortcourse), in clinicoradiologically proven cases of osteoarticular tuberculosis.

MATERIAL AND METHODS

The study was conducted at the University College of Medical Sciences & GTB Hospital, Delhi from November 2011 to December 2012. 32 clinicoradiologically confirmed cases of osteoarticular tuberculosis were included. Archived serum samples of 35 patients of osteoarticular tuberculosis included in an earlier study, confirmed by molecular method (PCR), smear for acid fast bacilli (AFB smear) or by histopathology with previously determined IL-12 and TGF-β levels were also available. Out of these 35 cases, eight cases with positive CRP were included for comparison. Patients suffering from spinal tuberculosis or any co-existing systemic illness were excluded from the study. A detailed history was noted and their general physical, local and relevant systemic examination was performed and the following parameters were analyzed. The parameters included haemoglobin estimation, total leucocyte count, differential leucocyte count, erythrocyte sedimentation rate, C-reactive protein, Chest X-ray, X-ray of the affected part and estimation of Interleukin-3 and Interleukin-17 levels in serum.

The patients were given DOTS CAT-1 regimen and the indicated orthopaedic management was carried out. The patients were reviewed at the end of two months to assess any untoward reaction of the antitubercular chemotherapy. Again at the end of six months, patients were re-reviewed and same investigations were repeated. IL-3 (Raybiotech, USA) and IL-17A (GEN-PROBE Diaclone, France) were assayed using specific ELISA kits. Values less than the sensitivity of the kit were taken as zero for statistical analysis. All the samples were held under same storage conditions, assayed with kits.
of the same batch number and under same testing conditions.

**Statistical analysis**

Paired t-test was used to compare IL-3 and IL-17 levels before initiating and after completion of ATT in patients of osteoarticular tuberculosis. Paired t-test was used to compare quantitative variables before and after treatment. McNemar test was used to compare qualitative variables before and after treatment. Pearson correlation was used to correlate the levels of various interleukins in the study.

**RESULTS**

The study population comprised 40 patients of osteoarticular tuberculosis. All patients completed the full course of CAT-1 DOTS regimen. In our study population, 62.5 per cent of patients were between 10-29 years of age. The extremes of age i.e less than nine years and more than 50 years of age, constituted 20 per cent of the enrolled patients. Male-Female ratio in our study was 3:2. Out of 40 patients, nine had affliction of the elbow and that of knee joint each. Five patients had foot involvement, four had wrist and that of hip involvement each. Three patients had sacroiliac joint involvement and same number had affliction of ankle. Two patients had hand involvement while one patient had rib involvement. The clinical and radiological data of the patients in the study population are summarized in Table 1.

The quantitative data of the patients in the study population is given in Table 2.

Fourteen out of 40 patients had positive C-reactive protein (CRP) values before the start of

**Table 1: Clinical and Radiological data in the study population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 Month (n=40)</th>
<th>2 Month (n=40)</th>
<th>6 Month (n=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain</td>
<td>40</td>
<td>26</td>
<td>3</td>
<td>0.000</td>
</tr>
<tr>
<td>Cold abscess</td>
<td>14</td>
<td>8</td>
<td>1</td>
<td>0.000</td>
</tr>
<tr>
<td>Joint effusion</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0.063 (NS)</td>
</tr>
<tr>
<td>Restriction of motion</td>
<td>21</td>
<td>15</td>
<td>4</td>
<td>0.000</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>27</td>
<td>23</td>
<td>8</td>
<td>0.000</td>
</tr>
<tr>
<td>Decreased joint space</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0.125 (NS)</td>
</tr>
<tr>
<td>Lytic lesion</td>
<td>13</td>
<td>7</td>
<td>0</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>NS- nonsignificant values</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Quantitative Laboratory Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At start of therapy</th>
<th>At 2 months follow up</th>
<th>At 6 months follow up</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
<td>Mean</td>
<td>S.D.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.763</td>
<td>1.718</td>
<td>12.265</td>
<td>1.128</td>
</tr>
<tr>
<td>Total leucocyte count (/cum)</td>
<td>8457.5</td>
<td>2352.7</td>
<td>7818.5</td>
<td>1684.9</td>
</tr>
<tr>
<td>Differential neutrophil count (%)</td>
<td>66.58</td>
<td>5.931</td>
<td>67.35</td>
<td>4.6107</td>
</tr>
<tr>
<td>Differential lymphocyte count (%)</td>
<td>28.78</td>
<td>5.873</td>
<td>29.2</td>
<td>4.6641</td>
</tr>
<tr>
<td>Differential monocyte count (%)</td>
<td>2.38</td>
<td>1.821</td>
<td>2.425</td>
<td>2.2633</td>
</tr>
<tr>
<td>Differential eosinophil count (%)</td>
<td>2.23</td>
<td>1.747</td>
<td>1.225</td>
<td>1.2707</td>
</tr>
<tr>
<td>ESR (mm/1st hour)</td>
<td>38</td>
<td>22.439</td>
<td>23.8</td>
<td>14.207</td>
</tr>
</tbody>
</table>

NS - Non-significant values  SD – Standard Deviation  ESR – Erythrocyte sedimentation rate
treatment. At the end of two months of treatment, positivity persisted in only one patient. CRP became negative after six months of treatment in all patients in whom it was positive before the initiation of treatment.

The levels of IL-3 registered a decrease at six months follow-up in six patients. In two patients, however, there was a rise in the levels of IL-3. IL-17 levels in serum were detectable in only one patient, which became undetectable post-treatment. There was no significant change in the levels of Interleukin-3 and Interleukin-17 before and after treatment (Table 3).

In the eight retrospective samples in which levels of IL-12 and TGF-β were available, a significant correlation was shown between IL-3 and IL-12 levels at six months (p value=0.022). Correlation between rest of the cytokines was not significant (Table 4).

Six out of 40 patients had partial recovery i.e. the treatment was extended in these patients beyond six months. Rest were cured i.e. there was an improvement in the above-mentioned clinical and radiological parameters, after six months of ATT.

**DISCUSSION**

Tuberculosis is a chronic disease. Latent infection and dormancy of tubercle bacilli adds to the complexity of the disease. The gene expression and the antigens expressed by the bacilli are different in case of active or latent infection. Therefore, the immune response varies during the course of the disease at different intervals of time and it is very difficult to predict the immunoregulatory response in this disease. In the present study, there was a significant improvement in the clinical and radiological parameters after completion of six months of antitubercular therapy, which is consistent with the previous studies. Acute phase reactants such as CRP and ESR showed a decrease with treatment providing a valuable index of activity of the disease.

In our study, IL-3 levels in six patients were found to decrease post treatment i.e. after six months
of antitubercular therapy. The initial (before treatment) values of IL-3 were very high, probably due to high Th1 response. These values decreased to very low levels which were not detectable by the commercially available ELISA kit used, thereby suggesting their probable role in the pathogenesis of the disease. But to elucidate their exact role, further studies with a higher sample size should be considered. In two patients, the IL-3 levels showed a rise after treatment. This could be due to some secondary infection which was not yet diagnosed. However in a majority of patients, IL-3 levels in serum samples were found to be below 20pg/ml. In the eight retrospective samples in which serum levels of IL-12 and TGF-β were available, a significant correlation is seen between IL-3 and IL-12 levels at six months. Previous studies have shown that IL-3 induces the formation of multinucleated giant cells in TB and results in a decrease in bacterial numbers28. IL-12, also a Th1 cytokine enhances phagocytosis and cytotoxic activity of neutrophils in TB29. Hence, both of these cytokines appear to be protective. Therefore, a positive correlation suggests a synergistic effect of these two in initiating inflammation, although qualitative differences may exist between the two which needs to be studied further. IL-17 is a Th17 cytokine, the exact role of which in TB still remains unknown. IL-17 associated immune responses can be protective in containing the infection or could have a deleterious effect in TB and may lead to tissue damage along with massive inflammation and influx of neutrophils37. Th17 cells have been shown to contribute to adaptive immune response in exposed persons and in patients with active disease30. In our study, IL-17 was detectable in only one patient, before starting treatment. After treatment, however, the value came down to undetectable levels i.e. less than 3.3pg/ml. In our study, we had quantified only IL-17A as the studies done previously had shown its role in TB31. But IL-17 family consists of six cytokines, namely IL-17 A-F32. Since the quantification has not been done for other five cytokines, it is difficult to comment on the exact nature of Th17 response in osteoarticular TB. In our study, no correlation was found in the serum levels of IL-3 and IL-17, before and after treatment.

In TB, regulation of Th1 and Th17 responses is essential to promote antimycobacterial immunity and prevent extensive immunopathological consequences31. In our study, the patients having high IL-3 had undetectable levels of IL-17 in their serum samples, suggesting a Th1/Th17 balance. In this study we have studied only two cytokines, namely IL-3 and IL-17. These cytokines are regulated by a variety of other cytokines and internal microenvironment. Previous studies have shown that IL-3 and IL-17 genes are highly unregulated in tuberculosis along with genes such as IL-22, IL-6 and Th17 responses in various infections33.

Therefore, determination of Th2 response needs to be done, to comprehend their interplay. Also the interleukin levels were undetectable after treatment, in cases of partial or incomplete cure i.e. where the treatment was extended beyond six months. Further studies with a higher sample size spanning over a longer duration is required to draw inferences. Secondary education of post-thymic T cells permits means for matching immune response to signals from innate immune system. IL-17 family of cytokines is believed to coordinate innate and adaptive immunity to certain pathogens.

The basic premise of the present investigation that non-specific signals stemming from cells of innate immune system are to be perceived, and provides a directional maturation while simultaneously coordinating with the evolving adaptive response requires a precise role of IL-17. But our data do not support this notion. However other factors may be at play; for example ROR-γt deficiency results in decreased Th17 activity and decreased expression of IL-1734. However on the basis of data presented here, IL-3 and IL-17 per se do not seem to play a decisive role in osteoarticular tuberculosis contrasting with other studies33. The limitation imposed by restricting the analysis of immune response as influenced by two chosen cytokines may perhaps be overcome by studying a larger repertoire of the cytokines.

ACKNOWLEDGEMENTS

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REFERENCES

and


MULTI-DRUG RESISTANT TUBERCULOSIS AMONG CATEGORY I TREATMENT FAILURES - A RETROSPECTIVE STUDY

Niti Singh¹, Zeeshan Sidiq², Manpreet Bhalla³, V.P. Myneedu⁴ and Rohit Sarin⁵

(Received on 18.7.2013; Accepted after revision on 13.2.2014)

Summary

Background: Tuberculosis (TB) remains a major global health problem and ranks as the second leading cause of death worldwide. An important cause of TB epidemic is the emergence of multi drug resistant (MDR) strains of Mycobacterium tuberculosis. Despite the availability of treatment that is expected to cure most cases of TB, levels of MDR-TB remain worryingly high in India.

Objective: This study was carried out to ascertain the prevalence of MDR-TB among category I pulmonary TB treatment failure patients.

Methods: This was a retrospective study involving 750 pulmonary tuberculosis patients enrolled at six district centres of Delhi State under RNTCP who failed to respond to CAT I treatment and whose sputum samples were submitted for culture and drug sensitivity testing (DST) over a period of three years (2009-2012). MDR-TB was defined as TB caused by bacilli showing resistance to at least isoniazid and rifampicin.

Results: Out of the total 750 patients included in the study, 470 (62.6 %) were culture positive. Of these, 377 (80.2%) were subjected to DST and rest 93 (19.7%) were excluded. Ultimately, DST result was available for 353 (93.6 %) cases. 239 (68%) cases were detected as multi drug resistant TB.

Conclusion: High proportion of MDR-TB (68%) among culture positive CAT I treatment failure cases highlights the need for rapid diagnostic tests which will enable the detection of MDR-TB at an early stage and will thus minimize the risk of transmission as well as the possible errors associated with the treatment.

Key words: Tuberculosis, CAT-I, Multi-drug resistance, DST.

INTRODUCTION

Tuberculosis (TB) remains a major global health problem and ranks as the second leading cause of death worldwide, after the human immunodeficiency virus (HIV). In 2011, there were almost nine million new cases and 1.4 million TB deaths worldwide¹. India is the second-most populous country in the world and is ranked first among the 22 high burden countries which accounts for 80% of all estimated incident cases of TB worldwide. In 2009 alone, two million TB cases were estimated to have occurred in India, accounting for one fifth of the global burden of TB². An important cause of TB epidemic is the emergence of multi drug resistant (MDR) strains of Mycobacterium tuberculosis. In 2011, almost 60,000 cases of multi drug resistant tuberculosis (MDR-TB) were reported worldwide. According to WHO, the incidence of MDR-TB in India is less than one in ten but is expected to scale up within the next three years. The Revised National TB Control Programme (RNTCP), based on the internationally recommended Directly Observed Treatment Short-course (DOTS) strategy, was launched in India in 1997. Despite the availability of treatment that is expected to cure most cases of TB, levels of MDR-TB remain worryingly high in India.

Since prevalence of MDR-TB mirrors the functional state and efficacy of tuberculosis control programme in the country also, the present study was aimed at determining effectiveness of DOTS by accessing the prevalence of MDR-TB among patients who had completed Category-I (CAT-I) treatment and were regarded as failures (CAT-I failures) and thus were put on CAT II and the samples were submitted for culture and DST to look for MDR.

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MATERIAL AND METHODS

This retrospective study was conducted at the Department of Microbiology, National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi. Apart from being a 550-bedded tertiary care hospital dedicated for the treatment of tuberculosis and other respiratory diseases, NITRD is also a National Reference Laboratory (NRL) for Revised National Tuberculosis Control Programme (RNTCP) and provides referral support to six districts of Delhi state and has a DOTS-Plus site for the treatment of MDR patients. The laboratory is efficiently going through the regular rounds of proficiency testing, for both first and second line drug sensitivity by the Supra National Reference Laboratory, Institute of Tropical Medicine; Antwerp, Belgium for solid as well as for liquid cultures.

A total of 750 pulmonary tuberculosis patients enrolled at six district centers of Delhi State under RNTCP who failed to respond to CAT I treatment and whose sputum samples (two consecutive sputum samples) were submitted for culture and drug sensitivity testing (DST) over a period of three years (2009-2012) were recruited in this study. Standard definitions for treatment failure were used3.

All the sputum samples were screened for the presence of acid fast bacilli (AFB) by Ziehl-Neelsen’s method and processed for culture by digestion, decontamination and concentration following modified Petroff’s method and were inoculated onto two slopes of Lowenstein-Jensen (L-J) medium and were incubated for eight weeks at 37°C. The isolates were identified by growth rate, colony morphology and P-nitrobenzoic acid (PNB) susceptibility testing.

Drug susceptibility testing for Isoniazid (INH), Rifampicin (RIF), Ethambutol (EMB) and Streptomycin (SM) was done for the culture positive samples by 1% Proportion Method as per RNTCP guidelines and H37Rv was used as the standard reference strain.

RESULTS

Out of the total 750 patients screened, culture results revealed that 470 (62.6%) were culture positive and 258 (34.4%) were culture negative. 22 (2.9%) got contaminated during the incubation period.

Of the total culture positive patients (n=470), 377 (80.2%) were subjected to first line DST and rest 93 (19.7%) were excluded due to the presence of less number of colonies than those required for DST (as per RNTCP guidelines, the number of colonies should be 20 or more). Ultimately, DST result was available for 353 (93.6 %) cases. Remaining 24 (6.36%) DSTs were rejected due to contamination.

Of the 353 cases subjected to DST, 239 (68%) were detected as multi drug resistant TB (MDR-TB i.e. resistant to both INH and Rif). Amongst the MDR patients (67.7 %), the proportion of resistance to three or more drugs including HR (86.1%) was greater than that of resistance to HR only (13.8%) (Table 1). Monoresistance was highest to H at 6.6% (22/353) and lowest to R at 1% (6/353) with 0.5% resistant to E (2/353). If resistance to rifampicin is taken as a surrogate for MDR-TB, then an additional 1.6% (6/353) cases of MDR-TB can be reported. Majority of the MDR patients were males (64.4%) as compared to females (35.6%).

The pattern of anti-tuberculosis drug resistance among category II (entry level) pulmonary TB patients is shown in Table 1.

A marked difference of 37.3% (750 vs 470) was observed between the cases declared as treatment failures according to the programme and the true failures (as identified by the culture results).

Table: Pattern of drug resistance among CAT I failure patients prior to putting on CAT II

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>Number of Patients (%age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHRE</td>
<td>151 (42.7)</td>
</tr>
<tr>
<td>SHR</td>
<td>43 (12.1)</td>
</tr>
<tr>
<td>HRE</td>
<td>12 (3.4)</td>
</tr>
<tr>
<td>HR</td>
<td>33 (9.3)</td>
</tr>
<tr>
<td>R</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>H</td>
<td>22 (6.6)</td>
</tr>
<tr>
<td>S</td>
<td>20 (5.6)</td>
</tr>
<tr>
<td>E</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

Indian Journal of Tuberculosis
DISCUSSION

In our study, the prevalence of MDR-TB among culture positive CAT I failures was found to be (68%) which is significantly higher than the earlier reports from Delhi \(^8,9\). The problem of MDR-TB among treatment failure patients in India has previously been highlighted in numerous studies \(^4-8\). Unfortunately, such data continues to be overlooked. This study with its emphasis on screening of CAT I treatment failures under RNTCP was analyzed to find out the prevalence of drug resistance among these patients.

Very less data is available regarding the prevalence of MDR-TB among CAT I failures hence, this study carries significant importance. High levels of MDR-TB amongst CAT I failures as shown in this study suggest that a high degree of resistant strains are already circulating in the community and it is possible that a proportion of CAT I treatment-failures may have had initial drug resistance, which was undetected.

In this study, the difference observed between the programme failures and the true failures was high (37.3%). This could be explained on the basis of standards used at various district centres for defining treatment outcome. Most of these centres lack the facility for culture and DST and hence smear conversion at the end of intensive phase of treatment is the only deciding factor available for judging the treatment outcome. This finding is in consistent with several previous studies which reported the percentage of smear positive but culture negative cases in the range of 20-35% \(^10,11\). This study therefore highlights the need for more improved diagnostic methods at district centers for the screening of treatment failure cases.

This study was associated with certain limitations. Firstly, culture was used as a reference in defining the failures which is associated with certain drawbacks like harsh decontamination, sensitivity less than 100%, and the need for good laboratory practices. Secondly, since our institute is a referral centre, sampling bias could have been there, thus leading to potential under- or over-estimate of the prevalence of MDR-TB among CAT I failures. These results therefore cannot be extrapolated to Category I patients in other parts of the country.

CONCLUSION

Although our study is not the representative of whole country but a significantly high proportion of MDR-TB (68%) among CAT I failures tested for susceptibility against the anti-tuberculosis drugs is a matter of concern. Drug resistant TB surveillance should be incrementally achieved, through regular systematic studies that randomly sample TB patients and supplement sputum microscopy with ranked risk evaluations and/or DST \(^12\).

It is a well-established fact that resistance is due to naturally occurring genetic mutations, but treatment errors such as adding a single drug to a failing regimen e.g. prescribing CAT II for failures of CAT I, failure to recognize the signs of treatment failure in time, treatment with an inadequate regimen and standardized first line regimens for patients with undiagnosed MDR-TB select mutants which grow into resistant strains.

Finally, the findings of this report highlight the strong need for better and rapid diagnostic methods with good quality control which will enable the detection of MDR-TB at an early stage and will thus minimize the risk of transmission as well as the possible errors associated with the treatment even at the periphery.

REFERENCES


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I, Shri Tejinder Ahluwalia, Secretary-General of the Tuberculosis Association of India, 3, Red Cross Road, New Delhi - 110 001, hereby declare that the particulars given above are true to the best of my knowledge and belief.

Tejinder Ahluwalia, Secretary-General On behalf of the Tuberculosis Association of India
Original Article

EVALUATION OF HORMONAL CHANGES IN MENSTRUAL CYCLE OF WOMEN INFECTED WITH PULMONARY TUBERCULOSIS IN NNEWI, SOUTH EASTERN NIGERIA

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Summary

Background & objective: The present study was designed to evaluate the hormonal changes in menstrual cycle of premenopausal women infected with pulmonary tuberculosis in Nnamdi Azikiwe University Teaching Hospital Nnewi.

Material and Methods: A prospective study involving sixty-seven (67) female participants within the child-bearing age were randomly recruited and grouped based on their tuberculosis status as: Symptomatic TB infected females (n=20), Symptomatic TB infected females on ATT (n=20) and Control females (n=27). After due consent, a detailed medical history was obtained and routine investigations of pulmonary tuberculosis and confirmation using Ziehl Neelsen and sputum culture techniques for AFB and chest x-ray were done. Blood samples collected from the participants were used for hormonal assay using immunoenzymometric method.

Results: The results showed that the serum levels of FSH and LH (µIU/ml) were significantly higher while progesterone and estradiol were significantly lower in Symptomatic TB females compared to Symptomatic TB females on ATT at follicular and luteal phases of menstrual cycle (P<0.05). The serum levels of FSH and LH were significantly reduced in Symptomatic TB females on ATT while progesterone and estradiol were significantly increased at follicular and luteal phases of menstrual cycle (P<0.05). FSH was significantly higher at follicular phase while estradiol was significantly higher at luteal phase of menstrual cycle in Symptomatic TB females on ATT.

Conclusion: Tuberculosis induced hypergonadism in affected women which seemed to be reversed on treatment. Routine investigation for Tuberculosis should be done for women presenting with infertility, since early treatment can reverse the abnormality.

Key words: Pulmonary tuberculosis, Hormonal abnormality, Menstrual cycle, Anti-tuberculosis Therapy.

INTRODUCTION

Mycobacterium tuberculosis is one of the most important opportunistic infections affecting subjects with HIV infection. In most cases, the infection manifests as pulmonary tuberculosis but in some occasions, extrapulmonary tuberculosis has been demonstrated in other organs including the female reproductive system. Endocrine involvement by tuberculosis has been blamed for the high incidence of menstrual disorders1. Hassan and Darwish4 reported a high prevalence rate of 66% menstrual abnormalities in TB subjects with secondary amenorrhea, ranking high among the irregularities observed.

Tuberculosis is believed to produce menstrual irregularities by causing hormonal imbalance on one hand, and by direct effect on the female reproductive tract thereby causing amenorrhea and infertility in affected women5. It has been shown that most of the irregularities are reversible once the subjects have been treated with anti-tuberculosis drugs6. Failure to reverse suggests genital tuberculosis6,7.

The present study therefore seeks to evaluate the hormonal changes occurring in women of child-bearing age who have pulmonary tuberculosis.
MATERIAL AND METHODS

SUBJECTS

A total of sixty-seven (n=67) female participants within the child-bearing age (15-45 years) with parity levels 0-6 were randomly recruited for the study. Forty (n=40) female participants with confirmed pulmonary tuberculosis were recruited at the Tuberculosis/Chest (DOTs) clinic of Nnamdi Azikiwe University Teaching Hospital Nnewi and grouped into: (i) Symptomatic TB infected (n=20) (ii) Symptomatic TB infected on anti-tuberculosis therapy (ATT) (n=20). The remaining twenty-seven (n=27) participants who were apparently healthy women were recruited among the hospital staff and served as controls. A detailed medical history was obtained from each of the participants using a structured questionnaire. Routine investigations for TB were done using concentrated sputum for microscopy and Ziehl Neelsen staining techniques for AFB. Chest x-ray examination results of participants who have been placed on ATT before the commencement of the study were obtained from their respective EPI data files for confirmation of pulmonary tuberculosis and results of Laparoscopic and Mycobacterium tuberculosis Polymerase Chain Reaction studies. Blood sample collected from all the participants were double-screened for malaria parasite infection using the rapid P. falciparum antigen detection method and Giemsa stained thick and thin blood smears for microscopic detection of malaria parasite and HIV infection using the rapid immunoaassay and immunochromatographic techniques respectively to exclude those with malaria parasite and HIV infection. Assessment of hormonal profile based on the phases of their menstrual cycle (follicular 7th to 13th day and luteal 21st to 23rd) phases was done using immunoenzymometric method. Classifications into different groups were based on the results of Tuberculosis screening and CDC criteria for staging TB infection as: (i) Symptomatic Tuberculosis-infected group not on Anti-TB drugs (n=20). These participants were Tuberculosis positive with signs and symptoms of tuberculosis infection but have not been placed on Anti-TB drugs. (ii) Symptomatic Tuberculosis infected group on Anti-TB drugs (n=20). These participants were TB positive and have been placed on Anti-TB drugs for not less than eight months. (iii) Control group (n=27). These participants were apparently healthy women and had neither HIV nor TB infections.

A structured questionnaire was also designed and self administered to the participants to obtain their menstrual cycle pattern, fertility and obstetrics history. Their individual folders were also retrieved for results of medical and laboratory investigations and treatments.

The ethics committee of NAUTH Nnewi approved the study design and the participants gave informed consent.

Exclusion criteria: Only the participants adjudged as pulmonary TB subjects participated in the present study. Patients with extra-pulmonary tuberculosis were excluded. Malaria and HIV infected participants were excluded. Also excluded were women on contraceptives and women who were having previous history of infertility before the commencement of the study.

METHODS

Determination of (FSH, LH, Prolactin, Progesterone and Estradiol) by Microplate Immunoenzymometric assay method

Principle: The hormone test is based on a sandwiched enzyme-linked immunosorbent assay (ELISA). The FSH, LH, Testosterone, Progesterone, Prolactin, Estradiol or Cortisol antigens and biotinylated monoclonal antibody specific for the FSH, LH, Testosterone, Prolactin, Progesterone, Estradiol and Cortisol were simultaneously incubated, after washing; the enzyme (streptavidin-peroxidase) was added, which reacts with antigen bound monoclonal antibody, the substrate solution acts on the bound enzyme to induce colour reaction product. The colour product is directly proportional to the concentrations of FSH, LH, Progesterone, Prolactin and Estradiol present in the sample.
Procedure: The procedure used was as described by the manufacturer of the kits (Monobind Inc USA). After formatting the microplate wells for each serum reference, control and patient specimen to be assayed in duplicate, 0.050 ml (50 µl) of the appropriate serum reference, control or specimen was pipetted into the assigned wells. 0.100ml (100 µl) of enzyme reagent solution was added to all the wells and were swirled gently for 20-30 seconds to mix and then covered and incubated for 60 minutes at room temperature. The content of the microplate was discarded by decantation and the plates blotted dry with absorbent paper. 300 µl of wash buffer was added and decanted, tapped and blotted for three washes. 0.100 ml (100 µl) of working substrate solution was added to all wells in the same order without shaking the plate and incubated at room temperature for 15 minutes. 0.050 ml (50 µl) of stop solution was added to each well and gently mixed for 15-20 seconds and the absorbance in each well was read at 450nm (using a reference wavelength of 620-630nm to minimize well imperfection) in a microplate reader and the results read within 30 minutes of adding stop solution.

Statistical Analysis

The version 16 of SPSS package was used in statistical analysis. The variables were expressed as mean (±SD). The student t-test and analysis of variance (ANOVA) and post-hoc (LSD) were used to assess significant mean differences. Graph Pad Prism version 5.03 was used for graph presentation. The level of significance was considered at P<0.05.

RESULTS

Levels of anterior pituitary hormone levels in test groups and control group at follicular and luteal phases of menstrual cycle

The mean serum FSH value (mIU/ml) in symptomatic TB female subjects was not significantly different between follicular (29.9±11.5) and luteal (23.5±14.2) phases of menstrual cycle (P>0.05). On the other hand, the mean serum FSH value (mIU/ml) in symptomatic TB females on ATT was significantly higher at follicular phase (21.8±10.3) compared to luteal phase (17.8±6.1) of menstrual cycle (P<0.05).

The mean (±SD) serum LH level (mIU/ml) in symptomatic TB females was not significantly different between follicular (13.1±4.8) and luteal (14.5±10.8) phases of menstrual cycle (P>0.05). There was no significant mean difference in mean (±SD) serum LH level (mIU/ml) between follicular (10.7±4.7) and luteal (11.9±6.2) phases of menstrual cycle in symptomatic TB females on ATT (P>0.05). However, the mean LH level (mIU/ml) in control females was significantly higher at follicular phase (7.9±6.3) compared to luteal phase (4.4±1.9) of menstrual cycle (P<0.05).

The mean (±SD) serum LH level (mIU/ml) in symptomatic TB females (13.1±4.8, 14.5±10.8) was significantly higher compared to Control females (7.9±6.3, 4.4±1.9) at both follicular and luteal phases of menstrual cycle (P<0.05). The mean (±SD) serum LH level (mIU/ml) in Symptomatic TB on ATT (11.9±6.2) was significantly higher compared to Control females (4.4±1.9) at luteal phase of menstrual cycle (P<0.05).

The mean (±SD) serum Prolactin concentration (ng/ml) in Symptomatic TB females was not significantly different between follicular (28.6±3.1) and luteal phases (29.5±4.7) of menstrual cycle (P>0.05). No significant difference was observed when the mean serum prolactin level (ng/ml) in Symptomatic TB females on ATT was compared between the follicular (19.5±3.9) and luteal (19.4±3.9) phases of
menstrual cycle (P>0.05). Similarly, no significant difference was also observed in the mean serum prolactin level (ng/ml) in Control females between follicular (18.3±4.4) and luteal (18.1±3.4) phases of menstrual cycle (P>0.05).

The mean (±SD) serum Prolactin concentration (ng/ml) in Symptomatic TB females was significantly higher compared to Control females at follicular and luteal phases of menstrual cycle (P<0.05). Similarly, the mean (±SD) serum Prolactin concentration (ng/ml) in Symptomatic TB females (28.6±3.1, 29.5±4.7) was significantly higher compared to Symptomatic TB females on ATT (19.5±3.9, 19.4±3.9) at follicular and luteal phases of menstrual cycle (P<0.05) (Fig. 1).

Levels of Steroid Hormones (Progesterone and Estradiol) in Tests groups and Control group at follicular and luteal phases of menstrual cycle

The mean (±SD) serum Progesterone concentration (ng/ml) in Symptomatic TB females was not significantly different between follicular (2.0±1.2) and luteal (2.3±0.3) phases of menstrual cycle (P>0.05). Similarly, the mean (±SD) serum Progesterone concentrations (ng/ml) in Symptomatic TB females on ATT was not significantly different between follicular (3.7±3.4) and luteal (2.2±0.4) phases of menstrual cycle (P>0.05). The mean serum progesterone level (ng/ml) in Control females was significantly lower at follicular (4.4±2.5) than luteal (8.7±4.9) phase of menstrual cycle (P<0.05).

The mean (±SD) serum progesterone level (ng/ml) in symptomatic TB females (2.0±1.2, 2.3±0.3) and symptomatic TB females on ATT (3.7±3.4, 2.2±0.4) were significantly lower compared to the values observed in control females (4.4±2.5, 8.7±4.9) at both follicular and luteal phases of menstrual cycle (P<0.05 respectively). However, the mean (±SD) serum progesterone level (ng/ml) in symptomatic TB females was significantly lower compared to the values observed in control females (4.4±2.5, 8.7±4.9) at both follicular and luteal phases of menstrual cycle (P<0.05 respectively). However, the mean (±SD) serum progesterone level (ng/ml) in symptomatic TB females was significantly lower compared to the values observed in control females (4.4±2.5, 8.7±4.9) at both follicular and luteal phases of menstrual cycle (P<0.05 respectively).

![Figure 1](image_url)

**Figure 1:** Comparison of mean (±SD) serum levels of FSH, LH and prolactin in test groups and control group at follicular and luteal phases of menstrual cycle.
ml) in symptomatic TB females on ATT (3.7±3.3) was significantly higher compared to symptomatic TB females (2.0±1.2) at follicular phase of menstrual cycle (P<0.05).

The mean (±SD) serum estradiol level (pg/ml) in symptomatic TB females was not significantly different between follicular (24.9±13.0) and luteal (25.1±8.0) phases of menstrual cycle (P>0.05). However, the mean (±SD) serum estradiol level (pg/ml) in symptomatic TB females on ATT was significantly lower at follicular phase (45.0±29.0) compared to luteal phase (63.0±39.0) of menstrual cycle (P<0.05). Similarly, the mean serum estradiol value (pg/ml) in Control females was significantly lower at follicular (80.9±50.1) compared to luteal phase (94.1±36.6) of menstrual cycle (P<0.05).

The Mean (±SD) serum estradiol level (ng/ml) was significantly lower in symptomatic TB females (24.9±13.0, 25.1±8.0) and symptomatic TB females on ATT (45.0±29.0, 63.0±39.0) compared to their corresponding control females (80.9±50.1, 94.1±36.6) at both phases of menstrual cycle (P<0.05 respectively). The mean (±SD) serum estradiol level (pg/ml) in symptomatic TB females on ATT (45.0±29.0, 63.0±39.0) was significantly higher compared to symptomatic TB females (24.9±13.0, 25.1±8.0) at both phases of menstrual cycle (P<0.05) (Fig. 2).

Figure 2: Comparison of mean (±SD) serum levels of progesterone and estradiol in test groups and control group at follicular and luteal phases of menstrual cycle

HORMONAL CHANGES IN MENSTRUAL CYCLE OF WOMEN INFECTED WITH PULMONARY TUBERCULOSIS

Indian Journal of Tuberculosis
DISCUSSION

The present study showed that the mean serum levels of FSH, LH, progesterone and estradiol in Symptomatic TB female participants were not significantly different between follicular and luteal phases of menstrual cycle. This contrasts the observation in apparently healthy subjects where differences in hormonal levels exist between the two phases of the menstrual cycle. However, the significantly higher estradiol at luteal phase compared to follicular phase of menstrual cycle in Symptomatic TB females on ATT is consistent with the finding in Control females. FSH and LH are usually higher at the follicular phase and peak at the mid cycle to enable ovulation to take place while Progesterone and estradiol levels are usually higher at the luteal phase than the follicular phase with the former being referred to as the ‘hormone of pregnancy’. The absence of this normal physiological balance in some Symptomatic TB female subjects may bring about menstrual and reproductive irregularities such as reduced flow (Oligomenorrhea), increased flow (Polymenorrhea), excessive flow (menorrhagia) and delayed ovulation. These menstrual irregularities have been found to be prevalent in TB subjects.

The research also showed that the serum levels of FSH and LH were significantly higher while progesterone and estradiol levels were significantly lower in Symptomatic TB and Symptomatic TB on ATT compared to Control female subjects at both follicular and luteal phases of menstrual cycle. This strongly indicates a state of primary hypogonadism. The reduced ovarian function may lead to increased incidence of menstrual disorders as mentioned previously. Among the TB subjects studied, the level of FSH at follicular phase was significantly higher in symptomatic TB group who were not on drugs when compared to their counterparts on anti-TB drugs. The LH level at follicular phase did not vary significantly among the TB groups considered. These observations clearly suggest a degree of hormonal imbalance existing among TB infected women at the different stages of the disease. The significantly higher FSH and LH at follicular phase of TB subjects suggest that ovulation may occur earlier in these women compared to the control. This may shorten the length of the menstrual cycle in such women or increase the frequency of menstruation.

The significantly reduced levels of progesterone and estradiol (the two major female sex hormones) probably as a result of TB infection sent a positive feedback to the anterior pituitary glands causing them to over secrete FSH and LH. Since progesterone is the main hormone of the luteal phase of the menstrual cycle, any deficiency in its secretion will affect the cycle and cause menstrual abnormalities which have been reported by previous studies. Progesterone and estradiol levels normally fall at the follicular phase of the cycle to enable the rise in FSH which initiates the next cycle. In this study, however, the levels of these two hormones were low at the luteal phase resulting to alteration of menstrual cycle since these hormones are normally elaborated during the luteal phase. This signifies a form of ovarian hypo function which may be a problem in TB infected individuals.

The significant improvement in levels of the parameters observed in Symptomatic TB females on ATT compared to their counterparts who were not on treatment implies that there would be significantly reduced incidence of hypogonadism with its associated menstrual and reproductive disorders. This implies that the treatment had some beneficial effects on the pituitary gland and gonads causing increased levels of progesterone and estradiol with consequent reduction in the levels of FSH and LH. The higher prolactin level at the follicular and luteal phases of menstrual cycle in symptomatic TB females signifies hyperprolactinaemia which has been associated with menstrual irregularity. Previous studies have also associated ATT with menstrual irregularities. Thus, the menstrual abnormalities which have been reported in TB infected women, may have their origin in hormonal imbalance at both phases of the menstrual cycle. It has been reported that TB induced menstrual irregularities become abated once such patients have been treated for tuberculosis. This is consistent with the finding in symptomatic TB females on ATT in the present study. However, if the menstrual abnormality continues after anti-TB treatment, this raises the suspicion of genital tuberculosis, which is often
latent and difficult to diagnose. This highlights the importance of early diagnosis and prompt treatment of affected subjects so as to improve their menstrual and reproductive function.

The mechanism of action of tuberculosis in producing menstrual abnormalities is not clear but the female genital tract has often been involved in active tuberculosis which has been associated with amenorrhea and infertility in affected women. Advanced HIV disease has been linked to extra-pulmonary TB involving the genital tract and is believed to be responsible for some of the menstrual disorders reported in TB patients. Genital tuberculosis has been associated with high incidence of infertility in Nigeria. This study concludes that tuberculosis has adverse effects on the ovarian function which manifest with menstrual and reproductive irregularities. Early diagnosis and treatment of affected individuals is necessary to reduce the incidence of these abnormalities.

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REFERENCES

PRIMARY CUTANEOUS TUBERCULOSIS OF THE PINNA: AN UNUSUAL PRESENTATION

Kumar V1*, Mehra B1** and Meher R2*

(Received on 15.7.2013; Accepted on 11.1.2014)

Summary: Cutaneous tuberculosis is an uncommon form of extra-pulmonary tuberculosis. A young female presented with chronic, non-healing ulceration involving the left pinna. Serology and skin biopsy suggested tuberculosis. Anti-tubercular therapy resulted in complete resolution of lesions. The recent increase in tuberculosis has led to myriad forms of the disease which often mimic non-specific dermatitis in morphology. The diagnostic dilemma encountered in such clinical settings has prompted us to present this unusual case. On review of literature, we could find only three case reports of ulcerative form of primary tuberculosis of pinna. [Indian J Tuberc 2014; 61: 159-161]

Key words: Tuberculosis, Cutaneous, Pinna

INTRODUCTION

Cutaneous tuberculosis (CTB) forms only a small proportion of extrapulmonary tuberculosis1. Indian studies report a prevalence of CTB as 0.26%-0.59%2. Still rare is the primary form of CTB with very few cases reported in literature. In tropical countries including India, the usual sites of affection are the buttocks and trunk3 and as a result, tuberculosis is not usually considered in the differential diagnosis of cutaneous lesions involving the face. We report here a case of primary CTB with an unusual site of affection involving the pinna. This report seeks to highlight the need for increased awareness of atypical presentations of CTB, which would allow for the correct diagnosis and timely management of this unusual skin disorder.

CLINICAL RECORD

A sixteen-year old female presented to the Otorhinolaryngology Department with complaints of non-healing, painless ulcers involving the left pinna, for the past three years. The lesions were associated with serous discharge and itching. There were no systemic complaints. Local examination revealed areas of skin ulceration with discharge and crusting involving the entire lobule and lower pole of helix and anti-helix of the pinna. The surrounding skin was red and indurated but non-tender (Figure 1).

Figure 1: Clinical photograph of the patient showing tubercular ulcers involving the lower pole of the left pinna. Thick crusts can be seen on and around the areas of ulceration. Note the well demarcated zone of involvement separated from the rest of the normal pinna.

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There was no cervical lymphadenopathy. The patient was earlier diagnosed variably by private clinicians as having contact allergic dermatitis and later as chronic atopic dermatitis, and had received different therapies such as corticosteroids and anti-fungal drugs.

Routine haematological investigations were normal, except the E.S.R which was 42 mm (1st hour). The mantoux test after 72 hours was 10 mm x 12 mm. The chest X-ray was normal. KOH mount from the scrapings was negative for fungus. Subsequently, an incisional skin biopsy was taken which revealed epithelioid granulomas along with areas of caseation necrosis (Figure 2). Ziehl Neelsen (ZN) staining and culture of the discharge fluid from the ulcers were negative for acid fast bacilli (AFB). Further, an IgM enzyme linked immunosorbent assay (ELISA) for mycobacteria was performed which was found to be reactive at 1:200 dilutions. Thus, a diagnosis of Lupus vulgaris (LV) was made.

The patient was administered a four-drug regimen of isoniazid, rifampicin, ethambutol and pyrazinamide for the first two months, followed by isoniazid and rifampicin maintenance therapy for another five months. The cutaneous lesions healed completely with no residual deformity.

DISCUSSION

Lupus vulgaris (LV) is widely described as the most common form of CTB with a multitude of presentations. In some instances, lupus appears over a primary inoculation site, but more than half of the cases follow other tuberculous disease foci. The face is the most commonly affected site in Western countries with a frequent affliction of the nose and cheeks. In India, however lower extremities especially buttocks are most frequently affected. Involvement of pinna in our case did not follow either form of known presentations.

Though LV can be either primary or re-infectious types, in India it is generally re-infectious type only. Our case appears to be a primary infection of pinna, with no evidence of tuberculosis found at any other site during evaluation.

A typical feature of LV is its extremely chronic course. Although plaque type is the common form, many other variants such as vegetative, ulcerative, hypertrophic papular and nodular forms are also described. Our case presented with the ulcerative form of primary LV, only three cases of which involving the pinna have been reported so far. Atrophic scarring is a prominent feature of LV. In view of absence of atrophic scarring, LV seemed an unlikely diagnosis in our case.

As LV is a paucibacillary form of CTB, acid fast staining of smears or culture on Lowenstein–Jensen (LJ) medium seldom yields positive results. Thus, variations in the clinical presentation and the low rate of positive bacterial isolation lead to misdiagnosis and delayed treatment.

Many similar skin disorders like discoid lupus, lupoid leishmaniasis, pyoderma gangrenosum, sarcoidosis also show granulomas on biopsy and thus definitive
diagnosis does not rely on histopathology alone. While earlier case reports have emphasized the role of ELISA as a confirmatory test in such cases, we would like to highlight the fact that serological tests have variable sensitivity and specificity and are thus imprecise and inconclusive for diagnosis. Keeping this in view, the WHO has recently issued an advisory banning these serological tests. The diagnosis thus depends on a positive culture, and molecular techniques like polymerase chain reaction (PCR). In developing countries, PCR is not always readily available and therefore physicians must rely on a positive response to anti-TB drugs to diagnose difficult cases.

CONCLUSION

The adverse socio-economic conditions, high rates of migration of infected people, co-existent HIV epidemic and the emergence of multi-resistant Mycobacterium tuberculosis have added to the burden of TB in developing countries. Thus, even rare forms of TB like CTB should be considered in patients presenting with atypical skin lesions. The diagnosis in a country like India still relies on tests like mantoux, chest x-ray, sputum examination and serology, none of which is absolute in terms of diagnosis. Molecular tests should be supplemented where feasible, to increase the sensitivity as well as specificity of detection of atypical cases of primary CTB.

We suggest that the ubiquitous presence of mycobacteria and the distinct Indian culture of repeated unhygienic ear-piercing of girls in childhood, exposing the traumatized skin to the environment in rural settings predisposes to mycobacterial seedling and development of tubercular lesions in an otherwise immunocompetent host.

REFERENCES

TOTAL REPLACEMENT OF A LUNG BY TUBERCULOSIS PNEUMATOCELE - AN UNUSUAL POST-TUBERCULOSIS SEQUEL

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(Received on 30.7.2013; Accepted on 9.12.2013)

Summary: Total replacement of a lung by pneumatocele in pulmonary tuberculosis is rare. The formation of pneumatoceles in adult pulmonary tuberculosis can occur before, during or after anti-tuberculosis treatment. A case of pneumatocele formation in a 19-year young female following pulmonary tuberculosis is reported. The left lung was completely replaced by pneumatocele. Total replacement of a lung by pneumatocele inspite of successful chemotherapy of tuberculosis is rare and should be considered as one of the differential diagnosis for acquired cysts of the lung. [Indian J Tuberc 2014; 61: 162-165]

Key words: Pneumatocele, Tuberculosis, Post-tuberculosis sequel, Pneumothorax

INTRODUCTION

Pulmonary pneumatoceles are thin-walled, air-filled cysts that develop within the lung. Most often, they occur as a sequel to acute pneumonia, commonly caused by Staphylococcus aureus and are found more frequently in infants and young children. In adults, pneumatoceles are seldom reported. A case of complete replacement of left lung with the formation of pneumatocele is described in a 19-year young female following treatment of pulmonary tuberculosis. Isoniazid has been implicated as a cause for lung cysts in isolated cases. The rarity of bullous lesions prior to the use of INH is attributed to the spontaneous closure of the broncho-cavitary junction during the process of healing. Tuberculosis pneumatoceles often have unpredictable outcome. In some cases, the cysts are reversible or may persist even after successful completion of chemotherapy for tuberculosis. These lesions should not be evacuated with needle aspiration since this could lead to tension pneumothorax. Complications such as rupture, suppuration, and hemorrhage require surgical intervention.

CASE REPORT

A nineteen-year young female presented with complaints of cough and breathlessness on exertion since two years. She was treated for pulmonary tuberculosis (sputum smear positive for acid fast bacilli) four years ago. Two years later, she developed cough with minimal mucoid expectoration and breathlessness on moderate to severe exertion. There was no history of fever or any history of thoracic trauma or sudden chest pain suggestive of a pneumothorax. Her blood pressure was 122/74 mmHg and pulse rate was 92 beats/min. Her respiratory rate was 20 breaths/min with pulse oxygen saturation of 98% at room air. There was no pallor, cyanosis, clubbing peripheral edema or raised JVP. On examination, breath sounds were diminished over the left hemi thorax which was hyper-resonant. Vocal and tactile fremitus were noticeably decreased over the left hemi thorax. Heart sounds were maximally audible over the right hemi thorax. Routine laboratory investigations revealed normal baseline blood tests. Two sputum samples for acid-fast bacilli by Ziehl Neelsen staining were negative. Chest radiography revealed hyperlucency of the left hemithorax, radiologic pattern seen with pneumothorax; without any signs of mediastinal shift (Figure 1 A). Review of patient’s old radiographs taken four years back, when she was treated as smear positive pulmonary tuberculosis, revealed multiple non-homogenous opacities with areas of cavitations on the left side and multiple 2-3 mm nodular infiltration of right upper, mid and lower zone (Figure 2 A).
Radiographs after one year of anti-tuberculosis treatment revealed that left-sided opacities had been replaced by giant thin-walled lesions with a few thin-walled cystic lesions in left zone; fibrotic and small cystic shadows were also noted on right side (Figure 2 B). CT chest demonstrated the presence of large radiolucent lesion suggestive of large bullus replacing the left lung parenchyma along with a few scattered tractional bronchiectatic, bullus and linear parenchymal fibrotic lesions on right side (Figure 1 B). There was

**Figure 1 A**: Chest radiograph showing hyperlucency of the left hemithorax, radiologic pattern seen with pneumothorax; without any signs of mediastinal shift

**Figure 1 B**: Chest computed tomograph of showing the presence of large radiolucent lesion suggestive of large bullus lesion replacing the left lung parenchyma along with few scattered tractional bronchiectatic, bullus and linear parenchymal fibrotic lesions on right side

**Figure 2 A**: Chest X-ray PA view showing multiple non homogenous opacities with areas of cavitations on the left side and multiple 2-3 mm nodular infiltration of right upper, mid and lower zone and shift of mediastinum to the left.

**Figure 2 B**: Chest X-ray PA view showing radiographs after anti-tuberculosis treatment revealed that left sided opacities had been replaced by giant thin-walled lesions with multiple thin-walled cystic lesions in left lower lobe; fibrotic and small cystic shadows were also noted on right side.

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164  PNEUMATOCELE AS A POST-TUBERCULOSIS SEQUEL

Figure 3: Two years' follow up chest radiograph showing spontaneous regression of pneumatocele

no evidence of any mediastinal lymphadenopathy. She was managed conservatively and her two years' follow-up chest radiographs showed spontaneous regression of pneumatoceles (Figure 3).

DISCUSSION

Cysts in the lung are air spaces lined by epithelia, which usually have the characteristics of bronchial epithelia. A variety of lung diseases can cause or mimic thin-walled air-containing cysts in the lung. Cysts may be classified as congenital and acquired. The commoner congenital causes for cysts in lung diseases include central and peripheral bronchogenic cysts, intralobar pulmonary sequestrations, congenital cystic bronchiectasis, cystic adenomatoid malformation of lung, and tracheobronchial papillomatosis. Cystic lung disease may be acquired in conditions like histiocytosis-X, bullous emphysema, pneumatoceles, and post-infectious states. Tuberculosis may present with atypical radiological manifestations in one-third of the cases, and multiple thin-walled cysts are one such rare manifestations of tuberculosis. Lung cysts in tuberculosis may occur as a result of tuberculosis infection, and may persist after sputum conversion, or conversely, tuberculosis may be a secondary invader of a pre-existing lung cyst. If tuberculosis secondarily infects the cysts, it may either lead to a progressive disease or may be a coloniser in the cysts. Pneumatoceles are thin-walled (<1mm), gas-filled space in the lung developing in association with acute pneumonia, such as staphylococcal, and frequently transient. Tuberculous pneumatoceles may represent either the cavity devoid of its caseous material, or cavity formation not necessarily in areas of tuberculous parenchymal involvement.

The pathogenesis involves formation of a ball valve mechanism at the site of the bronchocavitary junction due to edema, partial occlusion of the lumen by the inflammatory exudate, stenosis and distortion of the draining bronchus, or extra luminal pressure from enlarged lymph nodes. Granulomatous involvement of the bronchioles may lead to a check-valve mechanism leading to cyst formation. Other factors contributing are: destruction and/or dilatation of alveolar structures due to primary disease and constant pull due to mechanical changes such as pleural adhesions.

In isolated cases, isoniazid has been implicated as a cause for lung cysts. The advent of chemotherapy resulted in the development of "open cavity" healing with epithelialization of the bronchocavitary junction. This permitted the bronchial lumen to remain patent, thereby enhancing the extrusion of caseous material. The phenomenon is especially seen with INH therapy, which has been shown to have a lytic effect on the caseous material. Partially liquefied caseous material, due to the effect of INH, can plug the lumen at the broncho-cavitary junction to produce a ball valve during the process of extrusion. The rarity of bullous lesions prior to the use of INH is attributed to the spontaneous closure of the bronchocavitary junction during the process of healing. Most of the patients developing lung cysts with tuberculosis have an extensive bilateral infiltrative and an exudative kind of disease and in some cases the cyst may persist following an episode of active tuberculosis. Total replacement of one lung by a pneumatocele inspite of successful chemotherapy, like in our case, is rare but previously reported.
The management of these pneumatocele lesions remains controversial. Most of these regress during medical treatment. In our case, complete resolution of pneumatocele on chest X-ray was seen after two years (Figure 3). However, in a previously reported case of total replacement of one lung by large bullae, no change in chest radiograph was noticed for two years’ follow up. Complications such as rupture, suppuration, and hemorrhage are reasons for resection. Some authors are of the view that blebs or bullae occupying one-third or more of the hemithorax should be resected whether or not productive of symptoms. These lesions should not be evacuated with needle aspiration since this could lead to tension pneumothorax and rapid death. Therefore, the roentgen differentiation between pneumatocele and pneumothorax is most important. Our patient was referred for management of pneumothorax but review of her previous chest radiographs and stable general condition without any cardiac and respiratory distress prompted us to consider the possibility of pneumatocele and manage the patient conservatively. In exceedingly rare cases, tuberculous pneumatoceles have extrathoracic involvement due to transpleural fistulous communication. Sealed visceral and parietal pleura due to inflammation allow escape of air at a pre-existing weak point into subcutaneous tissue without involving the pleural cavity. The subcutaneous air pocket may gradually decrease in size or may persist. Tuberculosis pneumatoceles often have unpredictable outcome, in some cases the cysts are reversible and in others the cysts remain static without progression and may persist even after successful completion of chemotherapy for tuberculosis. It is likely that in our case the cyst in the lung developed probably due to ball valve mechanism produced at the broncho-cavitary junction by the partially liquefied caseous material. Later on, the cyst regressed either due to extrusion of caseous material or closure of broncho-cavitary junction due to healing or fibrosis. In conclusion, though rare, tuberculosis should be considered in the differential diagnosis of cystic lung lesions.

REFERENCES

A RARE CASE OF AN ISOLATED INTRAVENTRICULAR TUBERCULOMA WITH A DISMAL OUTCOME: AN UNUSUAL LOCATION OF A COMMON PATHOLOGY AND LESSONS LEARNT

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Summary: Isolated involvement of the ventricle by tuberculosis is extremely rare and only nine cases have been reported till now. We report a 13-year-old immuno-competent boy who presented with features of raised intracranial pressure with altered sensorium. Computed Tomography showed a ring enhancing intraventricular lesion with obstructive hydrocephalus. Gross total resection of the lesion was achieved and diagnosis was confirmed histologically. The patient had medical complications in the postoperative period and succumbs five days after the surgery. This report presents the unusual location of a common disease with a review of its clinical, radiological and histopathological features as well as the treatment modalities available.

Key words: Isolated, Ventricular, Tuberculoma.

INTRODUCTION

Central nervous system (CNS) involvement by Mycobacterium tuberculosis ranges from 0.5%-5% in the literature.¹⁻³ In the developing countries intracranial tuberculomas account for 4% of all intracranial space occupying lesions, whereas in the developed countries the incidence of intracranial tuberculoma is only 0.15%-0.18%.²⁻⁵ CNS tuberculosis can present as either diffuse basal leptomeningitis variety or localized variety in the form of tuberculoma, abscess or cerebritis. The common sites of tuberculomas are cerebellum, basal ganglia and cerebral hemispheres especially in the frontoparietal region. Other rare sites are quadrigeminal cistern, corpus callosum, suprasellar region. Isolated involvement of the ventricle by tuberculosis is extremely rare and only nine cases have been reported till now.²⁻⁷

We present another such case of an isolated ventricular tuberculoma in a 13-year-old immuno-competent boy with review of the current literature.

CASE REPORT

A 13-year-old male was admitted to the emergency department with complaints of headache and vomiting of one week duration. The headache was gradual in onset and was progressively worsening. The patient also had an episode of sudden loss of consciousness one day back and was in altered sensorium since then. There was no history of fever, seizures, head trauma or any other associated symptoms. However, patient had decreased appetite with weight loss since last one month.

On general examination, the patient was dehydrated, underweight for his age and features suggestive of malnutrition were present. Neurological examination revealed the patient with altered sensorium. Both the pupils were reacting equally to light. Fundus examination did not reveal any abnormality and there was no neck rigidity.

On hematological examination, hemoglobin was 9 gm/dl and total leucocyte count was normal. The Erythrocyte sedimentation rate was 60mm at one hour and Mantoux test was negative. There was severe hyponatremia of 110 meq/l on serum biochemical analysis. The boy was immuno-competent with the negative HIV result.

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CT (computed tomography) scan of the brain with and without contrast revealed a mass attached to the septum pellucidum in the midline and projecting into the left lateral ventricle at the level of foramen of Monro. The lesion was isodense to the brain parenchyma on plain CT scan and was showing a ring enhancement at the periphery on contrast medium administration. Secondary obstructive hydrocephalus was present due to the obstruction of foramen of Monro. Multiple adhesions were present between the lesion and the wall of the lateral ventricles (Fig. 1 & 2).

Fig.1: CT scan of the brain without contrast a & b) axial view showing a lesion attached to the septum pellucidum in the midline and projecting into the left lateral ventricle at the level of the foramen of Monro with obstructive hydrocephalus. Multiple adhesions can also be seen within the lateral ventricles.

Fig. 2: CT scan of the brain with contrast a & b) axial view showing a ring enhancing lesion attached to the septum pellucidum in the midline and projecting into the left lateral ventricle at the level of the foramen of Monro.
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X-ray of the chest revealed a loculated hydro-pneumothorax at the right costophrenic angle.

On lumbar puncture, the opening pressure was 180 cm of water and cerebrospinal fluid (CSF) was turbid in appearance. The total cell count was 230 cells/mm³ and 95% of the cells were lymphocytes. The sugar level was 54 mg/dl and protein level was 36 mg/dl. Both the Acid Fast stain and fungal stain did not reveal any abnormality. CSF culture also did not grow any acid fast bacilli. CSF adenosine deaminase (ADA) levels were within normal limits.

After correcting the electrolyte abnormalities and optimizing physiological and clinical condition, the patient was operated upon using the interhemispheric, anterior transcallosal approach with the aim of achieving a tissue diagnosis. The lesion was pearly white in appearance and densely adherent to the septum pellucidum, foramen of Monro and the choroid plexus. The lesion was avascular and firm in consistency. In view of the dense adhesions to the surrounding critical structures, near total excision of the tumor was achieved and the capsule was left behind. The septum pellucidotomy was performed at the end of the procedure. The external ventricular drain was inserted to monitor the intracranial pressure and drain the CSF if required.

Histopathological examination (Fig. 3) revealed an extensive areas of necrosis interspersed with epithelioid cells, lymphocytes and multinucleated giant cells. Atypical cells or features suggestive of malignancy were absent. These features were suggestive of chronic granulomatous inflammation such as tuberculoma.

In the immediate postoperative period, the patient was electively ventilated and gradually weaned off the ventilator on the first postoperative day. However, the patient developed diabetes insipidus at the time of weaning which was medically managed with fluids and vasopressors. Postoperative CT scan (Fig. 4) showed near complete excision of the lesion with a hypodensity...
in the right hypothalamus region suggestive of an infarct. The patient again deteriorated after two days and succumb to the complications five days after the surgery.

**DISCUSSION**

CNS tuberculomas account for 4% of all intracranial space occupying lesions in the endemic regions, whereas in the developed countries the incidence of intracranial tuberculoma is only 0.15%-0.18%. However, with the emergence of HIV infection, its incidence is increasing in the developed countries too. Isolated involvement of the ventricles by the mycobacterium bacilli is rare which may be related to the greater immunity to the infection. Despite this immunity, the bacilli can gain access into the ventricles through the choroid plexus, which is the most accepted pathway. The inflammation of choroid plexus (characterized by gelatinous exudates), ependymitis and asymmetric hydrocephalus (due to the formation of dense adhesions and septae) are the various manifestations of the ventricular involvement by bacilli. Tubercle foci (Rich Focus) can cause inflammation of the ventricular ependymal lining and the choroid plexus, as well as leptomeningitis by rupturing into the subarachnoid space. However, well-formed tuberculoma within the ventricle is extremely rare.

Most of the patients with CNS tuberculomas present before their third decade of life. Berthier et al had described four cases of intraventricular tuberculoma in patients less than ten years of age. The differential diagnosis of such isolated intraventricular lesion is difficult. The history of systemic tuberculosis is present in only 50% of the patients with such lesion at the time of presentation. Moreover, the tuberculous bacilli cannot be isolated from all the CSF samples or even the resected lesions. Factors such as presence of constitutional symptoms, low grade fever, weight loss, presence of systemic infection, in an endemic region are all indicators of intraventricular tuberculoma. Other modalities such as chest x-rays, tuberculin test, erythrocyte sedimentation rate, CSF smear, culture and polymerase chain reaction for TB also help in establishing the diagnosis.

The characteristic CT scan finding of tuberculoma is a “target sign” which consists of isodense to hypodense region of central necrosis with peripheral enhancement and moderate to severe perilesional edema. Assymetrical ventricular dilatation (secondary to the scarring and traction on the septum pellucidum), basal enhancing exudates and other tuberculomas within the brain parenchyma are other CT scan findings suggestive of Tuberculoma. On MRI scan, the peripheral rim appears isointense on T-1 weighted images, hypointense on T-2 weighted images and shows enhancement with contrast medium. Whereas the central necrotic portion appears hypointense on T-1 weighted images with no enhancement on contrast.

The management options for CNS tuberculosis are medical and surgical. However, in cases with a strong suspicion and features suggestive of the systemic tubercular disease, multidrug chemotherapy regimen is very effective with high cure rates. There may be transient increase in the intracranial pressure on starting the chemotherapy, secondary to the paradoxical increase in the size of the lesion. Surgical management has a definitive role in the management of intracranial tuberculomas. First is to establish the histological diagnosis, especially in unusual locations, as in our case. Second, to relieve the hydrocephalus by CSF diversion procedures. Minimally invasive techniques (endoscopic or stereotactic) to biopsy, the lesion may help to establish the diagnosis and start chemotherapy. However, surgical excision of the lesion is recommended in cases with failed medical treatment after six weeks and increasing intracranial pressure either due to the mass effect of the lesion or obstructive hydrocephalus.

**CONCLUSION**

Isolated intraventricular tuberculoma is a rare entity and should be considered in the differential diagnosis of intraventricular lesions, especially in endemic regions and with features suggestive of systemic tuberculosis. Multidrug therapy is the preferred management for intracranial tuberculomas, however surgical intervention is indicated in establishing the
diagnosis, to relieve mass effect or hydrocephalus and after failed medical treatment. In addition, major surgical intervention should be avoided and kept as minimally invasive as possible after optimizing the patient’s physiological and clinical conditions.

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REFERENCES


GENEXPERT BRINGS NEW HOPE FOR CHALLENGES TO TUBERCULOSIS 2050

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INTRODUCTION

Tuberculosis (TB) has been daunting the human race since centuries. To combat the epidemic of tuberculosis, plenty of research has taken place. In attempts to reverse this epidemic, the disease has evolved with complications such as Multi-Drug Resistant Tuberculosis (MDR-TB) and co-infection with Human Immunodeficiency Virus (HIV) infection.

It has been almost more than 125 years since microscopy has remained the primary diagnostic test for detecting Mycobacterium Tuberculosis (MTB), and culture remaining the gold standard. There has been a lot of advancement in technology and molecular methods have gained popularity in the diagnosis of tuberculosis. The advent of Nucleic Acid Amplification Technology (NAAT) has brought a revolution in the arena of medical diagnostics with Polymerase chain reaction (PCR) being very common in use.

The GeneXpert system, launched in 2004, simplified molecular testing by fully integrating and automating the three processes (sample preparation, amplification and detection) required for real-time PCR-based molecular testing. The GeneXpert platform is currently the only one of its kind which uses a cartridge-based system. The Xpert MTB/RIF is an automated diagnostic test that can detect MTB and resistance to rifampicin (RIF) conferring mutations directly from sputum, within two hours’ time frame.1

As per the WHO Global TB Report 2013, in 2012, globally there were an estimated 8.6 million incident cases of TB, equivalent to 122 cases per 100,000 population. Asia and Africa contribute 58% and 27% to the total burden of disease respectively. India accounts for 26% of the global cases. South Africa, Indonesia and Pakistan are major contributors as well.2 To eliminate tuberculosis as a public health problem by 2050, is a challenge to humanity, incidence will have to fall by an average of 16% per year for the next 40 years.3 New cases of TB have been falling since 2006 and fell at rate of 2% in 2012.2

HIV co-infection has put another hurdle in the path of combatting this menace. In 2012, TB among people living with HIV was estimated to be 13% of the total estimated burden. The proportion of TB cases co-infected with HIV was the highest in countries in the African Region. Mortality among TB patients was approximately 1.3 million people out of which nearly 28% being HIV deaths. It was estimated that there were 450,000 new cases of MDR-TB worldwide in 2012.2

In comparison to the conventional methods, Xpert MTB/RIF has proven its efficacy as a result WHO has strongly recommended it as the initial test for diagnosing and also may be used as a follow-up test to microscopy in settings where MDR and/or HIV is of lesser concern, especially in smear-negative specimens. These recommendations support the use of one sputum specimen for diagnostic testing, acknowledging that multiple specimens increase the sensitivity of Xpert MTB/RIF but have major resource implications. These recommendations also apply to children, based on the generalization of data from adults and acknowledging the limitations of microbiological diagnosis of TB (including MDR-TB) in children.1,4
In the coming six years, Xpert MTB/RIF will increase the number of TB cases diagnosed per year by 30%-37% and the number of MDRTB cases diagnosed by 69%–71%. In PLHIV, Xpert has been proven to increase detection rate, improve quality of rapid TB diagnosis and facilitate earlier and reduced time to initiate TB treatment. A UNITAID funded TB Xpert Project is proposed for year 2013-2015 enabling to provide approximately 1.4 million Xpert MTB/RIF test cartridges and over 220 GeneXpert instruments in 21 recipient countries for the rapid detection of TB and rifampicin resistance in mainly high burden countries. Till December 2013, 98 out of 145 countries have received the XpertMTB/RIF instruments and cartridges for concessional rates in this project.

But for successful implementation, especially in high TB burden countries, proper management techniques and strong political commitment and prioritizing nation’s health as one of the major pillars in the progress of a nation needs to be emphasized upon.

The diagnostics can only work if it is supported by timely treatment, hence there will be a need for translating this early diagnosis to early treatment with uninterrupted supply of drugs. Xpert MTB/RIF with proven results for pulmonary TB, MDR TB and co-infection with HIV, may also fetch good results in cases of extra-pulmonary as well as pediatric TB and may give bright light to these dark corners of TB.

CONCLUSION

This assay has marked a new era in the diagnostics world of TB. With Xpert MTB/RIF, there will be a major reduction in the transmission and is a miracle for “Early diagnosis and treatment” (Secondary Prevention) against TB. This assay further boosts research and gives us hope that time may not be far when we will have a perfect win over tuberculosis.

REFERENCES

Role of the QuantiFERON®-TB Gold In-Tube test in the diagnosis of intrathoracic childhood tuberculosis


The objective of the study was to compare the performance of the QuantiFERON®-TB Gold In-Tube test (QFT-GIT) with that of the tuberculin skin test (TST) in the diagnosis of intrathoracic childhood tuberculosis (TB). Children with intrathoracic TB were enrolled in a randomised controlled trial studying micronutrient supplementation in intrathoracic TB. They underwent TST and QFT-GIT before starting daily anti-tuberculosis treatment. Of 362 children (median age 115.5 months, IQR 73–144, 55% girls) enrolled in the study, microbiological confirmation of TB was obtained in 128 (35%). The TST was positive in 337 (93%, 95%CI 90–95.5) and QFT-GIT in 297 (82%, 95%CI 77.8–85.6). Sensitivity of TST and QFT-GIT in culture-confirmed TB cases was respectively 90.5% (95%CI 84.1–94.5) and 82.6% (95%CI 74.9–88.4). QFT-GIT positivity rate correlated with TST induration (P < 0.001). TST was influenced by the disease spectrum (P = 0.004) and the age of the children (P = 0.002); QFT-GIT remained unaffected by these factors. Bacillus Calmette-Guérin immunisation status, weight-for-age Z-scores and microbiological confirmation of Mycobacterium tuberculosis did not influence the performance of either test. In high-burden countries, QFT-GIT is comparable to TST and offers no added advantage in the diagnosis of childhood intrathoracic TB.

Comparison of molecular and immunological methods for the rapid diagnosis of smear-negative tuberculosis


The rapid diagnosis of pulmonary tuberculosis (TB) can be challenging if acid-fast bacilli are not detected by sputum smear microscopy. The objective was to compare the results of the GeneXpert® MTB/RIF assay on a single sputum or bronchoalveolar lavage (BAL) specimen test with local immunodiagnosis from the site of disease using the T-SPOT®.TB assay on BAL (BAL T-SPOT). The Xpert and BAL T-SPOT tests were compared in 96 patients suspected of having sputum smear-negative pulmonary TB admitted to a referral centre in Germany. BAL T-SPOT identified 10 of 11 patients with pulmonary TB (including 3/4 patients with culture-confirmed TB) with a negative Xpert test. Using Xpert, the sensitivity, specificity and positive and negative likelihood ratios (LRs) were respectively 60.0%, 97.4%, 30.0% and 0.4% in culture-confirmed cases and 42.1%, 97.4%, 21.1% and 0.6% in all TB patients. In contrast, using BAL T-SPOT, the sensitivity, specificity and positive and negative LRs were respectively 80.0%, 62.6%, 2.1% and 0.3% in culture-confirmed cases and 89.4%, 62.6%, 2.4% and 0.2% in all TB patients. In sputum smear-negative TB suspects, a positive Xpert result is strongly indicative of culture confirmation; however, a negative result is insufficient to rule out active TB. Where clinical suspicion of pulmonary TB persists despite a negative Xpert result, local immunodiagnosis using T-SPOT on BAL may increase diagnostic accuracy.

Cost-effectiveness of a 12-dose regimen for treating latent tuberculous infection in the United States


A large randomized controlled trial recently showed that for treating latent tuberculous infection (LTBI) in persons at high risk of progression to
tuberculosis (TB) disease, a 12-dose regimen of weekly rifapentine plus isoniazid (3HP) administered as directly observed treatment (DOT) can be as effective as nine months of daily self-administered isoniazid (9H). The objective was to assess the cost-effectiveness of 3HP compared to 9H. A computational model was designed to simulate individuals with LTBI treated with 9H or 3HP. Costs and health outcomes were estimated to determine the incremental costs per active TB case prevented and per quality-adjusted life year (QALY) gained by 3HP compared to 9H. Over a 20-year period, treatment of LTBI with 3HP rather than 9H resulted in 5.2 fewer cases of TB and 25 fewer lost QALYs per 1000 individuals treated. From the health system and societal perspectives, 3HP would cost respectively US21525 and 4294 more per TB case prevented, and respectively 4565 and 911 more per QALY gained. 3HP may be a cost-effective alternative to 9H, particularly if the cost of rifapentine decreases, the effectiveness of 3HP can be maintained without DOT, and 3HP treatment is limited to those with a high risk of progression to TB disease.

Clinical and pathological features of adult pulmonary tuberculosis with reversed halo sign


The objective was to understand the pathological correlation of the reversed halo sign (RHS) in adult pulmonary tuberculosis (PTB) patients, and to compare the clinical characteristics of PTB patients with RHS with those without RHS. The study included 80 patients consecutively diagnosed with PTB by pathology or smear-positive sputum or bronchoalveolar lavage fluid from 1 January to 31 August 2012. All patients underwent high-resolution computed tomography (HRCT) scan, and were divided into two groups based on HRCT findings: RHS and non-RHS. All patients in the RHS group underwent CT-guided transthoracic lung biopsy to evaluate histopathological abnormalities. Clinical features such as smoking history, TB-related symptoms and comorbidities were compared. The ‘ring’ in the RHS corresponded to granulomata, with or without acid-fast stain positivity, and with or without caseating necrosis. Compared with the non-RHS group, patients in the RHS group were significantly younger, were less likely to have a smoking history and had fewer TB-related symptoms and comorbidities. Our study shows that younger PTB patients with relatively better baseline status tended to present with RHS on HRCT, have fewer TB-related symptoms and present atypically.

Antiretroviral therapy uptake among adult tuberculosis patients newly diagnosed with HIV in Nyanza Province, Kenya


In 2008, the Kenya tuberculosis (TB) programme reported low (31%) antiretroviral therapy (ART) uptake among human immunodeficiency virus (HIV) infected TB patients. The objective was to confirm ART coverage and identify factors associated with HIV clinic enrollment and ART initiation among TB patients. The design was a retrospective chart abstraction of adult TB patients newly diagnosed with HIV and eligible for ART at 58 Nyanza Province TB clinics between October 2006 and April 2008. TB data were linked to HIV clinic data at 50 facilities that provided ART. Associations with HIV clinic enrollment and ART were evaluated. Among 1137 ART-eligible TB patient records sampled, 32% documented HIV clinic enrollment and 29% ART. Date fields were largely incomplete; 11% of the patient records included HIV testing dates and <1% had dates for cotrimoxazole prophylaxis, HIV clinic enrollment and ART initiation. Adding HIV clinic data increased HIV clinic enrollment and ART documentation to respectively 62% and 44%. Among TB patients in HIV care, female sex, older age group and baseline CD4 documentation were associated with ART initiation. Linking data increased documentation of HIV clinic enrollment and ART documentation to respectively 62% and 44%. Among TB patients in HIV care, female sex, older age group and baseline CD4 documentation were associated with ART initiation. Linking data increased documentation of HIV clinic enrollment and ART uptake. Continued efforts are required to improve the documentation of HIV service delivery, especially in TB clinics. Interventions to increase ART uptake are needed for younger patients and men.
Screening for tuberculosis in pregnancy: do we need more than a symptom screen? Experience from western Kenya


The objectives were to explore the utility of tuberculosis (TB) symptom screening for symptoms of ≥2 weeks’ duration in a routine setting, and 2) to compare differences in TB diagnosis between human immunodeficiency virus (HIV) infected and non-HIV-infected pregnant women in western Kenya. It was a comparative cross-sectional study among pregnant women with known HIV status screened for TB from 2010 to 2012, in Eldoret, western Kenya. Of 2983 participants, respectively 34 (1%), 1488 (50.5%) and 1461 (49.5%) had unknown, positive and negative HIV status. The median age was respectively 30 years (interquartile range [IQR] 26–35) and 26 years (IQR 24–31) in HIV-infected and non-infected participants. A positive symptom screen was found in respectively 8% (119/1488) and 5% (67/1461) of the HIV-infected and non-infected women. The median CD4 count at enrolment was 377 cells/l (IQR 244–530) for HIV-infected women. One non-HIV-infected patient was sputum-positive. For HIV-infected women, TB was presumptively treated in 1% (16/1488) based on clinical symptoms and chest X-ray. Cumulatively, anti-tuberculosis treatment was offered to 0.6% (17/2949) of the participants. This study does not seem to demonstrate the utility of TB symptom screening questionnaires in a routine setting among pregnant women, either HIV-infected or non-infected, in western Kenya.

Pretreatment sputum smear grade and positivity during follow-up of TB patients in Ahmedabad, India


In Ahmedabad, India, a retrospective record review was undertaken among 2842 sputum smear-positive tuberculosis patients registered for treatment from April to September 2011 to assess the association of pretreatment sputum smear grade with sputum positivity and the additional yield of a second sputum sample during each follow-up examination. Respectively 39%, 26%, 28% and 7% of patients had pretreatment sputum grade 3+, 2+, 1+ and scanty. The higher the pretreatment sputum grade, the higher the proportion found positive during various follow-up periods. Overall, the additional yield of the second sputum sample was <2%; it did not vary with pretreatment smear grading.

Factors associated with treatment delay among tuberculosis patients referred from a tertiary hospital in Dhaka City: a cross-sectional study


The study was conducted at the tertiary medical college hospital in Dhaka City Corporation area, Dhaka, Bangladesh. The objective was to identify factors associated with treatment delay among tuberculosis (TB) patients referred from a public diagnostic centre to various DOTS treatment centres in Dhaka City Corporation area, Bangladesh. It was a cross-sectional study conducted among 123 patients referred from the Dhaka Medical College Hospital to different DOTS treatment centres during July–October 2012. Factors associated with treatment delay (>1 day between referral and initiation of DOTS treatment) were identified. Among the 123 patients referred from the hospital, treatment delay was found to range between 2 and 17 days (median 2). In bivariate analysis, treatment delay was found to be significantly associated with the patient’s diagnostic category. In multivariate analysis, World Health Organization (WHO) Category II patients were found to be four times more likely to have treatment delay than WHO Category I patients, and married patients were much more likely to have treatment delays than unmarried patients. The study findings suggest that the main factors contributing to treatment delay among TB patients were history of previous anti-tuberculosis treatment, marital status and age. Patients should be given extensive information about the dangers of treatment delay before referring them to DOTS treatment centres.
Association of socio-economic status with family history in adult patients with asthma


Socio-economic status is associated with increased morbidity in patients with asthma. The aim of the present study was to assess the association between socio-economic status and family history of asthma in adult asthma patients. The study included 200 adults with asthma and 400 non-asthmatic controls. Socio-economic status was determined based on income. Regression analysis was used to estimate odd ratios in relation to socio-economic class, using age, gender, family history of asthma and smoking habits. The highest occurrence of having any family history of asthma was observed in the high class group (88.2%), followed by upper middle class (79.5%), lower middle class (60%) and the lowest in the low class group (34%). Having any family history of asthma was an important risk factor in both univariate and multivariate analyses in lower middle class, upper middle class and high class, but not in the low class group. The results indicated a positive association between having a family history of asthma and higher socio-economic status. Further studies on a large representative sample need to be conducted to confirm these findings.

Effects of different methods of decontamination for successful cultivation of *Mycobacterium tuberculosis*


There has been an extensive invasion of tuberculosis at the global level by multidrug resistant as well as extensively drug resistant organisms. Attempts to recover the pathogen in pure culture have frequently failed since the specimens are often highly contaminated and also due to use of insufficient or over-active decontamination procedures. Hence in the present study, different methods of decontamination were tested to evaluate their independent efficacies for culture of *Mycobacterium tuberculosis*. A total of 359 samples (241 sputum, 59 urine, 50 endometrium biopsy, nine pus samples) from clinically suspected cases of tuberculosis were subjected to four different methods of decontamination followed by inoculation in Lowenstein-Jensen medium (LJM), and bilayered medium (BLM) and Kirchner’s liquid medium (KLM) to determine the influence of differential decontamination processes. Sputum scanty and positive specimens were graded and each sample was subjected to decontamination by four different techniques. Treatment of specimens with 4 per cent NaOH yielded minimum recovery of pure cultures, while use of 2 per cent NaOH produced higher number of contaminants compared to other methods of decontamination. Addition of N-acetyl L-cystein (NALC) coupled with 2 per cent NaOH to the samples for decontamination provided fairly reasonable recovery, but the highest number of *M. tuberculosis* cultures could be obtained when the specimens were treated with tri-sodium phosphate and benzalkonium (TSPB). Among the sputum positive cases, recovery of growth of *M. tuberculosis* was higher with greater number of bacilli present in the specimens. Regarding the influence of culture media, BLM produced not only rapid growth, but reasonably higher rate of isolation of *M. tuberculosis*. Although use of TSPB was found to be an efficient method of decontamination for successful isolation of *M. tuberculosis* from contaminated samples, both NALC+ 2 per cent NaOH and TSPB also showed significant recovery of *M. tuberculosis* cultures in BLM that can facilitate early diagnosis and initiation of treatment.

Treatment outcomes and moxifloxacin susceptibility in ofloxacin-resistant multidrug-resistant tuberculosis


The setting was a tertiary referral centre in Seoul, South Korea. The objective was to investigate the effect of moxifloxacin (MFX) susceptibility and later-generation fluoroquinolone (FQ) use on the treatment outcomes of ofloxacin (OFX) resistant multidrug-resistant tuberculosis (MDR-TB). Of 223
patients diagnosed with MDR-TB between January 2006 and December 2012, 70 (31.4%) patients with OFX-resistant MDR-TB were enrolled in this retrospective cohort study. Their treatment outcomes were analysed. The mean age (standard deviation) of the 70 patients was 40.6 (12.9) years; 43 (61.4%) were males and 26 (37.1%) had extensively drug-resistant TB. Of the 70 patients, 22 (31.4%) had MFX-susceptible TB, while the remaining 48 (68.6%) were MFX-resistant. The MFX-susceptible and -resistant groups were comparable in terms of baseline characteristics (including age, sex and radiological severity), and respectively 90.9% (20/22) and 70.8% (34/48) were treated with later-generation FQ-containing regimens (P = 0.074; mainly MFX [40/54, 74.1%]). Treatment success was achieved in 72.7% (16/22) of the MFX-susceptible patients and in 41.7% (20/48) of the MFX-resistant patients (P = 0.021). Treatment failure was significantly higher in the MFX-resistant group (41.7% [20/48] vs 9.1% [2/22]; P = 0.006). Patients with OFX-resistant MDR-TB had significantly better treatment outcomes when susceptible to MFX. This probably reflects the effect of later-generation FQ treatment.

Use of biomass fuel in households is not a risk factor for pulmonary tuberculosis in South Ethiopia


The study was conducted in rural settings of Sidama Zone in southern Ethiopia. The objective was to investigate the association between exposure to biomass fuel smoke and tuberculosis (TB). It was a matched case control study in which cases were adult smear-positive pulmonary tuberculosis (PTB) patients on DOTS-based treatment at rural health institutions. Age-matched controls were recruited from the community. Of 355 cases, 350 (98.6%) use biomass fuel for cooking, compared to 801/804 (99.6%) controls. PTB was not associated with exposure to the biomass fuel smoke. None of the factors such as heating the house, type of stove, presence of kitchen, presence of adequate cooking room ventilation, light source and number of rooms in the house was associated with the presence of TB. However, TB determinants such as sex, household contact with TB, history of TB treatment, smoking and presence of a smoker in the household have previously shown an association with TB. We found no evidence of an association between the use of biomass fuel and TB. Low statistical power due to the selection of neighbourhood controls might have contributed to this negative finding. We would advise that future protocols should not use neighbourhood controls and that they should include measurements of indoor air pollution and of exposure duration.

Association between vitamin D deficiency and tuberculosis in a Korean population


Several in vitro studies have been conducted regarding the immunomodulatory and mycobactericidal roles of vitamin D in tuberculous infection. However, discrepancies exist among epidemiological studies. We compared vitamin D deficiency between patients with tuberculosis (TB) and healthy control subjects and identified risk factors for vitamin D deficiency. This was an age- and sex-matched case-control analysis of 94 TB cohort and 282 Korean national survey participants. The median baseline 25-hydroxyvitamin D (25[OH]D) level in the TB group (9.86 ng/ml, IQR 7.19–14.15) was lower than in controls (16.03 ng/ml, IQR 12.38–20.30, P < 0.001). The prevalence of severe vitamin D deficiency was higher in patients with TB (51.1%) than in controls (8.2%, P = 0.001). The median 25(OH)D level increased from 11.40 ng/ml (IQR 7.85–15.73) to 13.18 ng/ml (IQR 10.60–19.71) after treatment completion (P = 0.037). On multivariate analysis, presence of TB and history of TB were independently associated with severe vitamin D deficiency. Patients with TB had a higher prevalence of vitamin D deficiency than control subjects in a Korean population. The median 25(OH)D level increased after TB treatment. Further studies are needed to establish a causal relationship.
Improved survival in multidrug-resistant tuberculosis patients receiving integrated tuberculosis and antiretroviral treatment in the SAPiT Trial


The therapeutic effects of antiretroviral treatment (ART) in patients with multidrug-resistant tuberculosis (MDR-TB) and human immunodeficiency virus (HIV) infection have not been established. The objective was to assess therapeutic outcomes of integrating ART with treatment for MDR-TB. It was a subgroup of MDR-TB patients from a randomised controlled trial, the SAPiT (Starting Antiretroviral Therapy at Three Points in Tuberculosis) study, conducted in an out-patient clinic in Durban, South Africa, from 2008 to 2012. Clinical outcomes at 18 months were compared in patients randomised to receive ART within 12 weeks of initiating standard first-line antituberculosis treatment with those who commenced ART after completing anti-tuberculosis treatment. Mycobacterium tuberculosis drug susceptibility results were available in 489 (76%) of 642 SAPiT patients: 23 had MDR-TB, 14 in the integrated treatment arm and nine in the sequential treatment arm. At 18 months, the mortality rate was 11.9/100 person-years (py; 95%CI 1.4–42.8) in the combined integrated treatment arm and 56.0/100 py (95%CI 18.2–130.8) in the sequential treatment arm (hazard ratio adjusted for baseline CD4 count and whether MDR-TB treatment was initiated: 0.14; 95%CI 0.02–0.94, P = 0.04). Despite the small sample size, the 86% reduction in mortality due to early initiation of ART in MDR-TB patients was statistically significant.

Attitudes towards involuntary incarceration for tuberculosis: a survey of Union members


Policies involving the use of involuntary incarceration for tuberculosis (TB) are highly ethically controversial. To encourage ethical reflection within the International Union Against Tuberculosis and Lung Disease (The Union), the Ethics Advisory Group (EAG) surveyed members regarding their attitudes and values relating to involuntary incarceration for TB. Members of the Union TB section were invited to respond to an anonymous web-based survey. The survey included both multiple choice questions describing a range of scenarios regarding involuntary incarceration, and free-text fields inviting respondents to provide general comments on ethical issues. The survey was completed by 194 participants, 33 (17%) of whom were opposed to involuntary incarceration on principle. The age and sex of the respondents was not associated with likelihood of principled opposition; respondents from North America were least likely to be opposed to involuntary incarceration (P = 0.02). Respondents were most likely to consider involuntary incarceration for persons with known multidrug-resistant TB or a history of previous treatment default, and least likely where people lived alone, were university-educated or the main income provider for their families. This survey found a wide range of viewpoints regarding involuntary incarceration, and highlights a number of key elements in ethical engagement with the tensions surrounding involuntary incarceration. We provide commentary on approaches to ethical policy making in the light of these findings.

Reasons for defaulting from drug-resistant tuberculosis treatment in Armenia: a quantitative and qualitative study


The study was conducted in Armenia, a country with a high prevalence of drug-resistant tuberculosis (DR-TB). The objective was to identify factors related to default from DR-TB treatment in Yerevan. Using a retrospective cohort design, we compared defaulters with patients who were cured, completed or failed treatment. Patients who initiated DR-TB treatment from 2005 to 2011 were included in the study. A qualitative survey was conducted including semi-structured interviews with defaulters and focus group discussions with care providers. Of
381 patients, 193 had achieved treatment success, 24 had died, 51 had failed treatment and 97 had defaulted. The number of drugs to which the patient was resistant at admission (aRR 1.16, 95%CI 1.05–1.27), the rate of treatment interruption based on patient’s decision (aRR 1.03, 95%CI 1.02–1.05), the rate of side effects (aRR 1.18, 95%CI 1.09–1.27), and absence of culture conversion during the intensive phase (aRR 0.47, 95%CI 0.31–0.71) were independently associated with default from treatment. In the qualitative study, poor treatment tolerance, a perception that treatment was inefficient, lack of information, incorrect perception of being cured, working factors and behavioural problems were factors related to treatment default. In addition to economic reasons, poor tolerance of and poor response to treatment were the main factors associated with treatment default.

**Low prevalence of positive interferon-gamma tests in HIV-positive long-term immigrants in Norway**


The objective was to determine the prevalence and predictors of positive interferon-gamma release assays (IGRAs) and tuberculin skin tests (TSTs) in human immunodeficiency virus (HIV) infected patients in Norway, a low tuberculosis (TB) endemic country. It was a multicentre cross-sectional study of 298 HIV patients tested with QuantiFERON®-TB Gold In-Tube (QFT-GIT), T-SPOT®.TB (T-SPOT) and TST. A total of 77/298 (26%) QFT-GIT, 29/117 (25%) T-SPOT and 52/217 (24%) TSTs (>5 mm) were positive. The median CD4 count was 427 cells/l. Three QFT-GIT results but no T-SPOT results were indeterminate. Of 52 TST-positive patients, 34 (65%) were QFT-GIT-positive (median interferon-gamma [IFN-] 4.38 international units [IU]/ml), compared to 16% of the TST-negative patients (median INF- 0.81 IU/ml, P < 0.001). Origin from a TB-endemic country, previous active TB and TB exposure were associated with a positive QFT-GIT (P 0.01). Patients from TB-endemic countries living in Norway for ≥10 years had lower odds of a positive QFT-GIT (12%; OR 0.17, 95%CI 0.060.53, P 0.002) than patients with 03 years’ residence (49%). The prevalence of positive IGRAs in HIV-infected patients was high in this low TB endemic setting. Lower QFT-GIT positivity in long-term residents from TB-endemic countries may reflect a waning of TB-specific immune responses.

**Correlation of plasma anti-tuberculosis drug levels with subsequent development of hepatotoxicity**


The objective was to compare the free and total plasma drug concentrations of rifampicin (RMP), isoniazid and pyrazinamide in subjects with or without anti-tuberculosis drug-induced hepatotoxicity (DIH). A total of 110 tuberculosis (TB) patients were administered daily anti-tuberculosis treatment and were prospectively followed for the development of DIH. Plasma drug levels were measured at 0, 1, 2 and 4 h on days 1, 7 and 14 of treatment. Plasma drug levels in 15 patients who developed DIH (cases) were compared with 95 patients who did not (controls). Female sex, body mass index < 17 kg/m² and baseline serum albumin < 4 g/dl predicted risk of DIH on univariate analyses. Free and total plasma RMP levels (Cmax and AUC0–4) on days 1, 7 and 14 were significantly higher in cases compared to controls and predicted development of DIH. Day 7 total RMP Cmax and AUC04 were higher in cases (mean 26.73, standard deviation [SD] 5.72 and 47.58, SD 33.10) than in controls (7.87, SD 10.95 and 14.01, SD 10.69, respectively). Plasma RMP levels were higher in cases than in controls and independently predicted subsequent development of DIH. The Cmax of Day 7 total RMP level (cut-off 12.50 mg/l) predicted subsequent development of DIH in 93.3% of the patients.

**Predominance of modern Mycobacterium tuberculosis isolates in North India**

Although India accounts for the highest tuberculosis (TB) burden in the world, the diversity in prevalent *Mycobacterium tuberculosis* strains is very poorly documented. Tuberculosis specific deletion 1 (TbD1) is a marker that has been used to differentiate ancient from modern strains. We report for the first time TbD1-based diversity in clinical *M. tuberculosis* isolates circulating in the North Indian states of Himachal Pradesh and Punjab. The present study documents a very high prevalence of modern strains in North India, which is in contrast to earlier studies that emphasised the predominance of ancestral strains for the majority of TB cases in India.

**Second-line drug susceptibility breakpoints for *Mycobacterium tuberculosis* using the MODS assay**


The objective was to establish breakpoint concentrations for the fluoroquinolones (moxifloxacin [MFX] and ofloxacin [OFX]) and injectable second-line drugs (amikacin [AMK], kanamycin [KM] and capreomycin [CPM]) using the microscopic observation drug susceptibility (MODS) assay. It was a multinational study conducted between February 2011 and August 2012 in Peru, India, Moldova and South Africa. In the first phase, breakpoints for the fluoroquinolones and injectable second-line drugs (n = 58) were determined. In the second phase, MODS second-line drug susceptibility testing (DST) as an indirect test was compared to MGIT™ DST (n = 89). In the third (n = 30) and fourth (n = 156) phases, we determined the reproducibility and concordance of MODS second-line DST directly from sputum. Breakpoints for MFX (0.5 µg/ml), OFX (1 µg/ml), AMK (2 µg/ml), KM (5 µg/ml) and CPM (2.5 µg/ml) were determined. In all phases, MODS results were highly concordant with MGIT DST. The few discrepancies suggest that the MODS breakpoint concentrations for some drugs may be too low. MODS second-line DST yielded comparable results to MGIT second-line DST, and is thus a promising alternative. Further studies are needed to confirm the accuracy of the drug breakpoints and the reliability of MODS second-line DST as a direct test.
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अपने विभिन्न कार्यों से कोल इण्डिया प्रज्वलित कर रहा है
भारत के आर्थिक विकास के सफर को

हम लोगों के जीवन, उनके स्तर को निरंतर बेहतर बनाने में सक्षम हुए हैं। ज्ञान, अन्न, स्वास्थ्य और अन्य बुध्धियाँएवं शुभोऽक्षणीय प्रदान करते हुए, हम लोगों के जीवन को बेहतर बनाने में सक्षम प्रयास करते हैं। हम अपने सबके एवं निविष्टचर्य प्रभावों से देश के कई शहरों और गांवों के लोगों के जीवन में सुधार लाते हैं। जहाँ तक एक सामाजिक आशीर्वाद निर्माता के रूप में हमारी भूमिका की बात है, तो विज्ञान के सबसे बड़े कौशल उत्पादक के रूप में हमने सम्पूर्ण प्रतिबद्धता के साथ अपने काम को उन्मूलन से बिगड़कर निपटाया है।

हमारा विश्वास है कि, राहें लम्बी एवं कुर्सी हो सकती है, पर अंत में उम्मीदें रोजन होंगी
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