

Diagnosis of Tuberculosis - Where We Stand?

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A mycobacterial disease important as a cause of disability and death in many parts of the world with resurgence in the developed world, has again renewed interest in it, although it has never been controlled in the so called underdeveloped world. The initial infection usually goes unnoticed, tuberculin sensitivity appears within a few weeks, lesions commonly heal, leaving no residual changes except pulmonary or tracheobronchial lymph nodes calcifications. It may progress directly to pulmonary tuberculosis or, by lymphadenomatogenous dissemination of bacilli, to produce pulmonary, miliary, meningeal or other extrapulmonary involvement. Serious outcome of the initial infection is more frequent in infants, adolescent and young adults. Extrapulmonary tuberculosis is less common than pulmonary.

A disease whose causative agent primarily resides in man or diseased cattle is not new to mankind. Tuberculosis has a very long history being described in the Chinese Huang Ti Nei-Ching written in the third millennium BC. Analyses of bones dating back to the Shang dynasty (c. 1650-1027 BC) have revealed traces of leprosy, typhoid fever and tuberculosis. According to estimates each year 10 million people develop tuberculosis worldwide and 30% die of it. The clinical features vary in children and adults.

The diagnosis of tuberculosis like any other infectious disease is based on the clinical presentation and must always be confirmed by laboratory findings. Clinical status is based mainly on the presence or absence of tubercle bacilli in the sputum and also on the nature of chest x-ray changes. Abnormal x-ray densities indicative of pulmonary infiltration, cavitation or fibrosis can occur before clinical manifestations. Fatigue, fever and weight loss may occur early, while localizing symptoms of cough, chest pain, hemoptysis and hoarseness become prominent in advanced stages. Tuberculosis in infants and children ranges from an asymptomatic primary complex which passes unnoticed through a locally progressive illness to miliary spread which may be fatal. Progression of the primary complex may be parenchymatous, leading to tuberculous bronchopneumonia, pleural effusion or bronchial obstruction. A child with tuberculous bronchopneumonia will be obviously ill, feverish and have a cough. If a pleural effusion develops, the onset is usually acute with breathlessness, fever and pleuritic pain. This complication is more likely in the older child. Enlarged lymph nodes compressing or eroding through bronchial wall sometimes present with wheezing, which may be mistaken for asthma or a foreign body or, alternatively, with paroxysms of coughing resembling pertussis. Miliary tuberculosis results from haematogenous dissemination of organisms throughout the body, usually from a caseating lymph node. This complication is more likely to affect infants and young children than older children and usually occurs within six months of the infection. Active primary complex in the lung is usually present. Symptoms are mostly non-specific and respiratory symptoms are uncommon. Physical signs which may be present include hepatosplenomegaly, choroidal tubercles and evidence of meningitis. Adult type tuberculosis is almost certainly due to reinfection by organisms which have lain dormant since the initial primary tuberculosis, the lesion is confined to the lung without lymph node involvement.

Tuberculosis in adults and the elderly may be asymptomatic, revealing itself on a chest radiograph taken for other purposes. More usually though, some or all of the classic symptoms i.e. fever, night sweats, lethargy, loss of weight, dry or productive cough, haemoptysis and chest pain may be present. A chronic cough in a smoker should never be attributed solely to chronic bronchitis unless a chest radiograph has excluded tuberculosis and, for that matter, lung carcinoma. The majority of patients with pulmonary tuberculosis have no physical signs.

When TB is suspected the first and foremost the clinician should ask for Mantoux (Tuberculin skin test) and must stress that the test be performed with Purified protein derivative (PPD) using 1, 10 or 100 units specially in areas where TB is endemic. The test is very valuable in persons at high risk.

Radiological studies are helpful in pulmonary TB although it is variable but usually radiographs show enlargement of hilar, mediastinal, or subcarinal lymph nodes and lung parenchymal changes. Newer modalities introduced such as CTscan may be helpful.

The specimen for haematological, microbiological or histopathological diagnosis of TB could be abscess contents, aspirated fluids, blood, body fluids, bone marrow, bronchoalveolar lavage, bronchial washings, bronchial brushing, CSF, gastric lavage, lymph nodes, skin lesion material, sputum, stool, urine, tissue biopsy sample, transtracheal aspirate and wound material.

The haematological findings are generally low haemoglobin, normal or high white cell count and in majority of cases high ESR, which is also a good indicator or monitoring prognosis of the disease after therapy.

Microbiological diagnosis relies primarily on examination of acid fast stained or Z.N. stained smears from clinical specimens. It is still the easiest, least expensive and most rapid procedure for obtaining preliminary information. The limitation lies in the fact that there must be a minimum of 1000-10000 bacilli/ml and the sensitivity of Respiratory specimen is 30-70%, pleural fluid <20%, pericardial fluid <40% and CSF 10-40%. There are three methods of staining for TB bacilli. They are (1) Ziehl-Neelsen method which is the most widely used and most reliable (2) Kinyoun's method a slight modification of the classical method and is known as cold staining method the (3) is the Fluorochrome acid fast stain method in which Mycobacterium tuberculosis are seen as fluorescing but it must always be confirmed by the classical method.

Culture is still the gold standard for the diagnosis of TB. A number of methods are now in use for the cultivation of mycobacteria. Variations are in the media used for growth. There are two types of media (1) Solid media which are either Egg based or Agar based. The egg based media have a longer shelf life, and have the ability to neutralize the toxic material, but if contamination occurs they may get liquefied and sensitivity are difficult to perform. The agar based media promotes early growth as compared to the egg based one. Sensitivity are easy to perform, but are expensive and have a short shelf life. (2) Liquid media are media generally used in automated system which can detect growth of mycobacterium comparatively earlier. The systems are known as Continuous automated Mycobacterial liquid culture (CAMLiC) systems, so far three systems i.e. MB/Bact Bactec 9000 and MGIT 960 have been marketed. In performance all three systems are comparable, the difference being in sensing the growth cost, for each culture is very high in performance and rate of isolations manual as well as automated systems give similar results. The molecular methods are basically PCR based methods in which a target sequence is amplified usually the sequencing of 16S RNA or 65kDa heat shock protein. The identification methods uses, DNA-DNA hybridization, Sequencing, PCR-Restriction Fragment Length Polymorphisms (RFLP) and PCR Capture Probes while the Typing methods includes, Pulse-field gel Electrophoresis (PFGE), Random amplification of polymorphic DNA (RAPD), Repetitive Element Southern Blotting and Repetitive Element PCR.

Polymerase chain reaction (PCR) is a new diagnostic technique which works on the principle of DNA amplification that uses specific DNA sequences as markers for microorganisms. In theory this technique can detect a single microorganism in a specimen such as sputum, gastric aspirate, pleural fluid, cerebrospinal fluid or blood. Recent publications show that various PCR techniques, most using the mycobacterial insertion element IS6110 as the DNA marker for M. tuberculosis complex organisms, have a sensitivity and specificity greater than 90%. It appears that PCR may have a useful but limited place in the diagnosis of TB. A negative PCR never eliminates TB as a diagnostic possibility, and a positive result does not confirm it. A number of patients with inactive tuberculosis and contacts had specimen that were PCR positive, presumably because of the presence of very small numbers of live or dead bacteria that may be present in Macrophages. Despite a number of studies

published over the past decades, serology has found little place in the routine diagnosis of TB. The IMMUNOLOGICAL Tests available for the diagnosis of TB includes The Tuberculin Test which is probably the most useful immunological method provided it is carried out by using Purified derivative and not general screening method which is in common use now. The other method in use is ANDA test and Andaelisa both of which have either very limited value or no value and should not be asked for. Tuberculin test has a limited significance while other serological tests have not proved to be of value.

Finally, we can say that in routine use Acid Fast staining and Culture are the best method if performed by experienced microbiologist, they are economical and reliable. PCR based methods are only of epidemiological importance while Haematological methods can be use for monitoring the prognosis of TB. In the years to come some rapid diagnostic methods will also be introduced but in the developing world because of the cost framework these methods may not be that easily available, hence AFB smears and Cultures would still remain a gold standard for some times to come.