

Central nervous system and spinal tuberculosis in children at a tertiary care center in Saudi Arabia

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BACKGROUND AND OBJECTIVES: Tuberculosis (TB) remains a global health problem. There is limited data on pediatric central nervous system tuberculosis (CNSTB) in Saudi Arabia on diagnosis and therapy.

DESIGN AND SETTING: Retrospective review of health record of pediatric patients <14 years old who were diagnosed as having CNSTB or spinal TB and admitted to a tertiary care center.

PATIENTS AND METHODS: Health records and microbiology data of pediatric patients diagnosed with CNSTB were over 20-year period were reviewed. Data on demographics, clinical presentation, surgical interventions, neuroimaging, mycobacterial cultures and susceptibility and treatment were collected.

RESULTS: Thirteen children were diagnosed with CNSTB or spinal TB. Tuberculoma was the most frequent in 8 cases (62%), followed by TB of the spine in 4 cases (31%), and one case of meningitis. Six patients had a history of TB contact (46%) and 8 (62%) patients had a positive tuberculin skin test (TST). Seizure and weakness was the most frequent symptoms (38% each), while fever was less frequently encountered (23%). Tissue cultures (brain tissues/spinal tissues) showed a high yield (92%) of *Mycobacterium tuberculosis* with positive cultures for 11 surgical specimens out of 12 for whom cultures were done. There were no surgical complications from biopsies. All of MTB isolates were sensitive to first-line agents.

CONCLUSIONS: Brain or spinal biopsy is safe and has a high culture yield for MTB so it is advisable to perform a biopsy for any child in whom CNSTB is suspected and when there is no other less risky involved site for biopsy. All MTB isolates in this series were sensitive to first-line anti-tubercular agents.

Tuberculosis (TB) is a major health problem worldwide. In 2011, WHO estimated 8.8 million new TB cases worldwide at an incidence rate of 128 per 100 000 with 1.1 million deaths (excluding HIV).¹ In Saudi Arabia, TB is still a major health problem with 4549 total reported cases in 2010, at an incidence of 18 per 100 000, with 30% extrapulmonary and 70% pulmonary tuberculosis. Children less than 15 years accounted for about 4% of the total.² The incidence of central nervous system tuberculosis (CNSTB) was not reported.

Other serious issue is the development of drug-resistant TB, either single agent resistance or multidrug resistance. In Saudi Arabia, there is no country-wide surveillance study; however, several hospital-based studies had addressed this issue with one study showing resistance

of 8.5% to any first-line agents and 2.5% multidrug resistance (resistance to both isoniazid and rifampicin).³ A meta-analysis of 12 published studies, primarily of adult patients showed that monoresistance to a single first-line agent was found in 10.9%, isoniazid resistance in 11% and multidrug resistance in 5.7%.⁴ TB meningitis and tuberculoma is a rare form of extrapulmonary TB, but most serious. Several reports addressed this illness among Saudi which seems to be rare among children.⁵⁻⁷ This report was a retrospective review of central nervous system TB (CNSTB) and spinal TB among children referred to King Faisal Specialist Hospital and Research Centre (KFSHRC), a major tertiary care referral center in Saudi Arabia. The main objectives were to assess clinical presentation, the diagnostic yield of tissue biopsy and treatment outcome.

PATIENTS AND METHODS

This was a retrospective case survey of patients admitted to KFSHRC over a 20-year period (1990-2010), who fulfilled criteria for the diagnosis of CNSTB. It was approved by the Research Advisory Council of KFSHRC. CNS tuberculoma was defined by suggestive neuroimaging finding (ring-enhancing lesion) supported by either growth of *Mycobacterium tuberculosis* from brain tissues, gastric aspirate or sterile body tissue or the finding of caseating granuloma in brain tissue with either a positive tuberculin skin test (TST) or positive microscopy for acid fast bacilli (AFB) from cerebrospinal fluid (CSF), gastric aspirate or sterile body site. Spinal TB was defined by a finding of destructive spinal lesion with growth of MTB from spinal/bone tissues or histopathological evidence of caseating granuloma on spinal/bone tissue with either positive TST and/or positive microscopy for AFB from sterile tissue or gastric aspirate. Criteria for diagnosis of tuberculous meningitis were the presence of increased lymphocyte in CSF ($>10 \times 10^6/L$) with high protein ($>400\text{mg/L}$) and low CSF/serum glucose (<0.6) with one of the following: 1) isolation of MTB from CSF 2) positive DNA amplification for MTB in CSF 3) positive AFB from CSF, gastric aspirate or sterile body sites. Cases were retrieved from medical records with a discharge diagnosis of CNSTB or spinal TB, and microbiology records were reviewed. Data were collected on the clinical, laboratory and demographic characteristics

of patients, as well as results of radiological investigations, type and duration of anti-tubercular therapy, and clinical outcome. Surgical samples were cultured for the presence of *Mycobacterium*. A BACTEC 460TB radiometric system (Becton Dickinson Diagnostic Systems, Spark, MD, USA) was used for *Mycobacterium* detection and drug susceptibility testing during the period 1981 to 2002. This system was subsequently replaced by BACTEC MGIT 960 (Becton Dickinson) in June 2002. Histopathological specimens were also stained and examined for the presence of AFB. DNA amplification using BD ProbeTec ET system (Becton Dickinson) was utilized to detect MTB in cerebrospinal fluid (CSF) for patients with meningitis in addition to culture. The information was entered into a data abstraction sheet and was subsequently entered into a computerized database using an Excel spreadsheet. Clinical information is presented by frequency tables and proportion. No comparative analysis was done.

RESULTS

Thirteen (13) children fulfilled the criteria of CNSTB or spinal TB, including 3 males and 10 females with a mean age of 9.2 years and an average duration of symptoms of 3 months. Eight children had tuberculoma (TB brain abscess), 4 had TB spine and only one had TB meningitis. All cases were diagnosed between years 1990 to 2005. In patients with spinal TB, two had thoracic involvement, one cervical and one thoracolumbar.

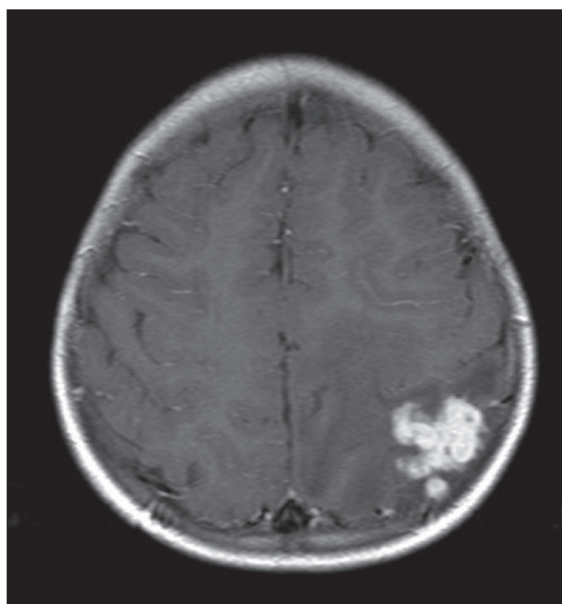


Figure 1. T1-weighted MRI image post contrast showing nodular enhancing brain lesion in left parietal area.

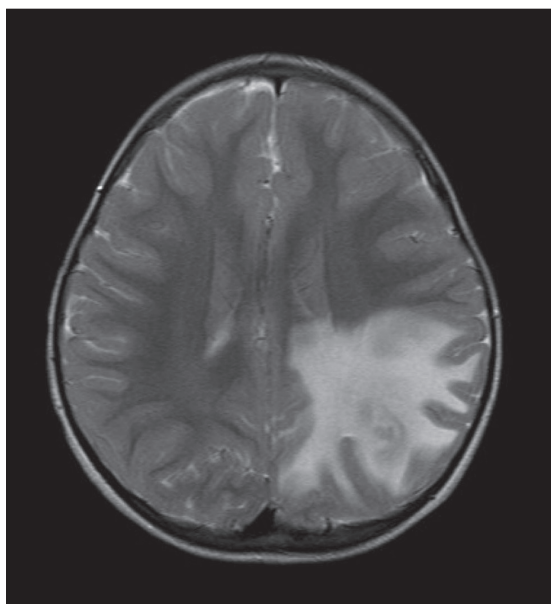


Figure 2. T2-weighted MRI image showing massive edema involving left parietal area surrounding the brain lesion.

The most common presenting symptoms were seizure in 5/13 (38%) and motor weakness in 5/13 (38%). Fever was present in only three patients (23%) while two patients (15%) had visual problem and two patients with aphasia. Six patients (46%) had contact with TB patients and eight patients (62%) had positive tuberculin skin testing (TST) with an induration more than 10 mm. Elevated ESR >20 mm/h was noted in ten patients (77%) while only two patients had abnormal chest x-ray (15%), one with hilar adenopathy and the other had chronic granulomatous disease (CGD) with disseminated MTB disease with lung, liver and brain involvement. In patients with tuberculoma, neuroimaging (CT/MRI) studies found a ring-enhancing mass lesion (Figures 1 and 2) with extensive edema located supratentorial in six and infratentorial in two. All of those patients except one were referred as having probable brain tumors. All patients but one underwent surgical biopsies without complications (craniotomy in seven patients, fine needle aspiration [FNA] from a vertebral abscess in one patient, cervical decompression in three patients, FNA of the liver in one immunodeficient patient [CGD] with CNS and liver involvement). One patient had TB meningitis, diagnosed as positive TB by the BD ProbeTec ET system in the CSF. No surgical complications encountered. Eleven patients out of 12 for whom cultures were done had MTB grown from brain (7), spinal (3) or liver (1) tissues (92%) while AFB smear was positive in only two (17%). The result of the BD ProbeTec ET system was positive in only one patient out of five for whom the test was performed (20%).

All the *Mycobacterium* TB isolates were sensitive to first-line antituberculous agents. All patients received a minimum of one year of antitubercular therapy. Eight patients received isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) for 2 months followed by 10 months of H and R while 2 patients were treated with H,R,Z and streptomycin for 2 months then continued on H and R for 10 months more. One patient was treated with two months of H, R, Z, E followed by 10 months of Z and E while 2 patients started on three drugs (H, R, Z) for 4 months then continued on H, R for 12 months due to extensive disease. Steroids were used perioperatively only for a few days. All patients except two were started on four anti-TB drugs initially until sensitivity became available in 2 to 3 months. Nine patients were cured without sequelae, two patients had visual problems (one had homonymous hemianopsia and the other had poor visual acuity [central] on presentation) and two patients had residual motor weakness which persisted after a minimal 5 years of follow-up.

DISCUSSION

CNSTB is a rare and serious form of extrapulmonary TB. It is always difficult to diagnose and in many circumstances surgical specimens (which may not be available in many healthcare facilities) are required. Adding to the difficulty is a negative tuberculin skin test (TST) in 35% to 50% of patients and lack of evidence of pulmonary TB in a large proportion of patients.⁸

In Saudi Arabia, few studies have addressed CNSTB, which seems to be rare, in children.^{6,7} Only four cases of TB meningitis were encountered among 140 cases of children with meningitis⁶ and in another report, only two children were found among 39 cases of CNSTB.⁷ In this report, 13 cases of CNSTB confirmed by culture and/or histology. In this series, the majority of CNSTB were tuberculoma (60%) with only one case of meningitis. This contrasts with other reports where most cases of CNSTB were meningitis.^{9,10} This most likely reflects a referral pattern rather than a difference in epidemiology.

A history of contact with TB and positive TST are helpful in suspecting a diagnosis of CNSTB while fever was an infrequent symptom. Sixty-two percent had a positive TST, leaving 38% of confirmed CNSTB with negative TST. This is a little higher than reported previously,^{9,11} which probably is due to the high rate of TB infection in our country. Physicians should have high index of suspicion for TB in any child presenting with symptoms of a space-occupying lesion. They should consider TB exposure and perform a TST. However, for children with a space-occupying lesion for whom CNSTB is suspected, confirmation of the diagnosis is mandatory since other diseases, particularly tumors, may mimic CNSTB, as was evident from one published report from KFSHRC where only 10% to 15% of all cerebral mass lesions were tuberculoma,¹² which in support of an aggressive approach in obtaining a tissue diagnosis. In this series, this approach was associated with no complications and resulted in an excellent diagnostic yield with tissue culture being positive in 92% of cases. This is higher than what has been reported from a study in England with 39% positive CSF and 69% positive overall¹⁰ and a study from South Africa showing only 12% positive CSF and 30% overall from any site.¹³ This is probably due to the fact that only 13% of those reported patients in those two studies had tuberculoma alone while the rest had meningitis. In addition, it was not clear if any of these patients with tuberculoma underwent a brain biopsy.

This high culture yield was probably due to the aggressive approach in obtaining a surgical biopsy in

this series from any suspicious brain lesion since those lesions may be mistaken with tumors, and no lesions were treated empirically. It is also worth noting that all of the 12 MTB isolates were sensitive to first-line agents—isoniazid, rifampin, pyrazinamide, streptomycin and ethambutol. This may reflect rare resistance in CNSTB or that our sample was too small to detect rare resistance. The overall prognosis of CNSTB in this series was good with aggressive therapy, and all

survived.

In conclusion, issue biopsy has a very high culture yield for CNSTB and spinal TB and should be attempted for any child with a suspicious brain lesion if there is no extra-CNS involvement from which the biopsy can be easily obtained. Despite the fact that no drug-resistant TB was found in this cohort, it is hard to recommend initiation of three-drug regimens in the absence of a countrywide survey of TB sensitivity.

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