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Prognostic Indicators in Patients with Intracranial Tuberculoma: a review of 102 Cases

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Abstract

Objective: To see the characteristics, course and outcome of patients suffering from intracranial tuberculoma.

Methods: Retrospective review of 102 patients diagnosed as intracranial tuberculoma at a tertiary care center over 10 years.

Results: A total of 102 cases were seen with an age range of 1 to 75 years (mean, 30 years). Predisposing factors included Diabetes mellitus (8 patients) and pregnancy or puerperium (7 patients). Five pediatric patients had tuberculoma despite documented BCG vaccination. Fever (59%), headache (57%), meningeal irritation (36%) were the commonest presenting features; one-third of patients were drowsy or comatose at presentation. Cerebrospinal fluid analysis was performed in 63 patients, of whom 88% had elevated protein, 83% had low glucose, and 84% had pleocytosis (one-third with neutrophilia). Forty-nine (50%) patients had clinical or laboratory evidence of concomitant tuberculous meningitis, Chest radiographs showed active or old tuberculous infection (25%), with a miliary pattern in 20%. Two-thirds of subjects had multiple tuberculomas (mean, 4.5 lesions per patient) on contrast CT or MRI scan. Hydrocephalus was present in 37 (37%) patients of which 21 required shunt surgery. Thirty-nine patients had > 9 months of follow up; 17 patients showed complete recovery, 20 patients had partial recovery, and 2 patients had no response. Coma at presentation and miliary pattern on chest X-ray were predictors of poor prognosis.

Conclusion: The study demonstrates that fever, headache, signs of meningeal irritation and cranial nerve palsies are common presenting features. Complete recovery was seen in 40% patients. Coma and military TB are predictors of poor prognosis (JPMA 54:83;2004).

Introduction

Although the lungs remain the major primary sites of *Mycobacterium tuberculosis* infection, many organs are potentially affected. Approximately 5-10% of cases of tuberculosis have central nervous system (CNS) involvement. Intracranial tuberculosis has two related pathologic processes: tuberculous meningitis and intracranial tuberculoma. The two conditions are separate clinical entities, with only 10% of patients with tuberculoma having detectable meningeal involvement.¹ Although tuberculomas are amongst the rarest intracranial space-occupying lesions in developed countries, they account for a significant proportion of intracranial mass lesions both in HIV -infected and uninfected individuals in tuberculosis endemic areas.²⁻⁴ Intracranial tuberculomas are histologically composed of granulomatous tissue and result from hematogenous spread from a distant focus of tuberculous infection. Unlike malignant tumors of the central

nervous system, tuberculomas often grow without permanently destroying the surrounding neural tissue, thus potentially enabling a good clinical recovery. However, tuberculomas may rupture into the subarachnoid space causing meningitis and affecting the brain parenchyma and cerebral blood vessels. 1 The purpose of this study was to determine the clinical, laboratory, radiographic, and treatment features and outcome in HIV -uninfected Pakistani patients with intracranial tuberculoma.

Patients and Methods

The medical records of 242 patients with a diagnosis of central nervous system tuberculosis seen at the Aga Khan University Hospital, between 1988-1999 were retrospectively reviewed. Patients were included in the study if one or more contrast-enhancing lesions were identified on computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain (102 patients), and these space-occupying lesions were diagnosed as intracranial tuberculoma based on one or more of the following criteria: 1) clinical and/or radiographic response to antituberculous chemotherapy (n = 59); 2) microbiologic or histopathologic or radiographic evidence of active pulmonary or systemic tuberculosis (n = 24); 3) histopathologic features of granulomatous formation (n = 19) of the biopsied/excised CNS lesion. Variables studied included patient demographics, clinical features, laboratory investigations, radiologic findings, and outcome. Multiple logistic regression model was used to identify predictors of poor prognosis. The odds ratio and confidence interval were also calculated for each factor in relation to mortality. Data was statistically analyzed using an SPSS software program (version 8.0, copyright @ SPSS Inc; 1989-97).

Results

The study included 102 patients (male; 45, females; 57). The mean patient age was 30 years, with a majority of patients between 15 and 45 years (range, 1 to 75 years). Only 6% patients were more than 60 years old, while 5% were below 5 years of age. Almost 70% patients had no prior history of tuberculosis or contact with a patient with tuberculosis. Predisposing factors for tuberculosis included diabetes mellitus (8 patients), pregnancy or a puerperal state (7 patients), and the use of systemic corticosteroids or cytotoxic therapy (3 patients). Five pediatric patients had intracranial tuberculoma despite documented Bacillus- Calmette-Guerin (BCG) vaccination as per World Health Organization guidelines. The median duration of symptomatology before diagnosis was 20 days in children and 45 days in adults. Eight patients were comatose, and 27 were drowsy at the time of presentation. Fever (59%) and headache (57%) were the most common presenting symptoms, while meningeal irritation (36%), cranial nerve palsies (33%; most commonly involving the facial or abducent nerves), and papilledema (19%) were the most common clinical signs. Peripheral leukocytosis was seen in one-half of the study cohort, while laboratory-documented anemia occurred in 30 (30%) patients. The erythrocyte sedimentation rate was recorded in only 60 patients and was found to be elevated in 41 (61%) subjects. Cerebrospinal fluid (CSF) analysis was performed in 63 patients, and 49 (84%) had CSF pleocytosis (65% with mononuclear predominance and 35% with neutrophilic predominance). Cerebrospinal fluid protein was elevated in 53

(88%) and glucose was low in 48 (83%) patients. Cultures of CSF were positive for *Mycobacterium tuberculosis* in only 3 out of 63 patients. Clinical features and CSF parameters were suggestive of meningeal involvement (concomitant tuberculous meningitis) in 49 (49%) patients. Histopathologic evaluation was performed in 19 patients. Specimens were obtained by either biopsy or surgical resection of intracranial tuberculoma, and the final diagnosis was based upon the presence of caseation necrosis with granulomata formation. Chest x-rays were performed in all subjects; active or healed tuberculosis was identified in 25 (25%) patients out of which, 20 (20%) patients had a miliary pattern. Computed tomography of the head was performed in 62 patients while 40 patients underwent MRI scanning. More than two-thirds (69%) of patients had multiple tuberculomas, and the locations of lesions were supratentorial (56%), infratentorial (12%), or both (32%). The number of tuberculous lesions ranged from 1 to more than 100 (mean, 4.5 per patient), and occurred as follows: solitary lesion, 31 patients; 2-5 lesions, 46 patients; > 6 lesions, 25 patients. The diameter of the largest [(0)] tuberculoma was 5 centimeters. Hydrocephalus was present in 37 (37%) patients and 21 required decompressive shunt surgery (Figures 1-5). [(1)] Eleven (11%) patients died. Fifty-one patients were lost to follow up after a variable period (2 weeks to 7 months). Long-term follow up of nine months or more was available for only 39 patients. All of these patients received isoniazid, rifampicin, and pyrazinamide. Patients also received ethambutol and/or streptomycin in all but two instances. Duration of treatment was 9-12 months in these 39 patients. Thirty one patients concomitantly received systemic corticosteroids. Twelve patients developed adverse drug effects, and antituberculous therapy was temporarily interrupted or discontinued in six patients, Seventeen patients had complete clinical and radiographic recovery, 20 patients had partial recovery (clinical and/or radiographic), and two patients had no clinical improvement. Most common neurologic sequelae were seizures (6 patients) and hemiplegia/monoplegia (5 patients). Follow up CT scans were available in seven patients. Follow up period ranged from one month to seven months. Three patients had complete resolution of tuberculoma while three patients showed a decrease in number and/or size of tuberculoma. One patient had no change in size of lesion. This lesion was subsequently excised and histopathology was consistent with tuberculoma. Follow-up MRI scans were available for only 13 patients; four of these had complete resolution of lesions after 6-12 months of therapy, while four patients had a decrease in the number and/or size of their tuberculoma(s) on repeat scan. Four patients had no change in the number and/or size of their space-occupying lesion 18 months after initiation of treatment. Two subjects had complete clinical recovery, one had partial recovery, and one had no clinical improvement. In one additional patient, the size of the tuberculoma increased after one year of treatment despite partial clinical recovery. Five of these 12 patients had no radiological improvement despite complete treatment. The diagnosis of tuberculoma in these patients was established on the basis of coexisting evidence of pulmonary tuberculosis. None of these patients underwent biopsy. A multiple regression analysis identified that coma at presentation (Odds ratio, 2.7, 95% confidence interval, 1.8 to 5.6) and military pattern on chest -x ray (Odds ratio, 3.0, 95% confidence interval, 1.6 to 6.6) were independent predictors of mortality (P= 0.01). The size, location and number of tuberculoma (Odds ratio 1.2, Confidence interval 95%, 0.6-2.2, P=0.2), hydrocephalus (Odds ratio 1.3, 95 % confidence interval, 0.8-2.2, P=0.12) and

concomitant tuberculous meningitis (Odds ratio 1.8, 95 % confidence interval, 0.8-2.6, P=0.08) were not found to be independent predictors.

Discussion

Intracranial tuberculosis is an important CNS infection in developing countries where tuberculosis is endemic. 1,5 In these regions, tuberculosis is the most common infectious cause of CNS space-occupying lesions in persons with and without HIV infection. 3 In Pakistan, HIV infection is rare and patients in our study cohort lacked historical and physical features suggestive of associated HIV / AIDS. As reported in the literature, most of our patients were late adolescents and young adults. 4 In view of its suppressive effects on cellular immunity, pregnancy is suggested to be a precipitating factor in at least 1% patients with CNS tuberculosis. 4 In our study, seven patients (8%) were either pregnant or in the puerperium, thus identifying these individuals as seriously at-risk for CNS tuberculoma. Fever was present more frequently (59%) in our patients than in previous series (10-25%). 4 This finding could reflect the higher incidence of concomitant tuberculous meningitis in our patients (50%) than in previous reports. 1 As observed by others, papilledema and focal neurologic signs were more common in children, and signs of meningeal irritation were more common among adults. 4 Cranial nerve involvement was also seen more frequently in our study cohort than in other literature series, and is likely due to the increased incidence of meningeal involvement. 6 Cerebrospinal fluid evaluation is not always possible in patients with CNS tuberculoma because of the frequent increased intracranial pressure present which is a contraindication for lumbar puncture. Where spinal taps were performed, our patients exhibited typical CSF findings of mononuclear pleocytosis, elevated protein, and hypoglycorrachia, although 35%> of subjects had neutrophilic CSF pleocytosis. 7-9 As noted in other studies, 25% of our patients had evidence of pulmonary tuberculosis, either active or inactive, on chest x-ray. 6 Magnetic resonance imaging is increasingly recognized as a better diagnostic modality for the diagnosis of tuberculoma, especially for brainstem tuberculoma. 10 In literature, 15% to 40% patients are reported to have multiple tuberculomas 4,11 ; in our study, 69% cases had multiple CNS lesions. The mean number of lesions (4.5 per patient) in our study appears to differ notably from the number of lesions (2.1) seen in patients with concomitant HIV infection. 3 Locations of lesions were supratentorial (56%), infratentorial (12%), or both (32%); supratentorial lesions and brainstem tuberculoma (198/0) were more common in our series than in previous reports. 4,12 In India and Africa, the incidence of brainstem tuberculoma varies from 2-8%. 4,5 These differences could be explained by the increased utility of MRI in the diagnosis of intracranial mass lesions in our study cohort (more than one-third of our patients underwent MRI) compared to studies in the pre- or early-MRI era. 4,5 Previous studies have suggested that most patients with intracranial tuberculoma can be treated successfully with antituberculous therapy without surgical intervention.11,13,14 Isoniazid and pyrazinamide have better CSF penetration compared to rifampicin, streptomycin, and ethambutol. 15,16 Empiric antituberculous therapy, pending drug susceptibility results, should take into account local resistance patterns and typically includes four-drugs, isoniazid, pyrazinamide and rifampicin plus streptomycin or ethambutol. Such regimens are also effective for patients with concomitant tuberculous meningitis.6 The

recommended duration of antituberculous therapy for intracranial tuberculoma is 9 to 18 months. 17,18 As for patients with meningeal involvement, the judicious use of corticosteroids is indicated for selected patients with CNS tuberculoma including those with clinical signs or symptoms of mass effect and increased intracranial pressure, and patients with large lesions. 19,20 More than one-quarter of our patients received adjunctive corticosteroids. The prognosis of intracranial tuberculoma cannot be reliably predicted from our study due to the unavailability of long-term follow up in a majority of subjects. Mortality was at least 11% and may have been higher because long-term outcomes were available in only 39 patients. Of these, 17 (41 %) patients had complete recovery. The radiographic outcome of patients with intracranial tuberculomas is variable and does not always appear to correlate with length of treatment or clinical recovery. Tuberculomas may resolve, decrease or increase in number and size, or remain unchanged after completion of therapy. 21 Complete clinical recovery was seen in some patients despite persistence of lesions, while some patients had no recovery despite complete resolution of tuberculomas.

Aknowledgement

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