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Tuberculous Meningitis in the Differential Diagnosis of Cns Infection and the Urgency of Antituberculosis Treatment

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Abstract

Tuberculosis is a chronic necrotizing granulomatous disease caused by *Mycobacterium tuberculosis*, causes morbidity and mortality worldwide, and affects children as in all age groups. Tuberculous meningitis (TM) is the most severe form of the disease. The pathogenesis of TM is poorly understood and the best management has not been established. We report 17-years old female patient, who was referred from Somalia with a suspected intracranial mass lesion accompanied by poor general condition, reduced consciousness, hypertension and bradycardia, diagnosed as TM after brain biopsy with result of positive PCR and culture for *M. tuberculosis*. But the patient died after diagnosis of tuberculous meningitis in the last phase. The aim of this case report is to remind that TM must be considered in the differential diagnosis of intracranial infection in patients from endemic areas and the treatment should be initiated rapidly to prevent delayed diagnosis and lethal complications.

Keywords: Children; Meningitis; Mycobacterial infection; Tuberculosis

Introduction

Tuberculous meningitis is a common disease in young children killing or disabling almost half of patients affected [1]. Diagnosis is challenging because clinical features are non-specific, laboratory tests are not sensitive and hence treatment delay is the greatest risk factor for death. The best approaches to prevent, diagnose and treat tuberculous meningitis are still inadequate [1,2]. Tuberculous meningitis is one of the most serious infections of central nervous system especially in developing countries with high morbidity and mortality rates [3,4]. In a study Ruslami et al. determined that 50% of the patients with tuberculous meningitis were mortal [5]. The incidence of pulmonary tuberculosis is directly related to frequency of tuberculous meningitis, for that reason the best way of prevention is optimisation of global tuberculosis control [6]. Bacillus Calmette Guerin (BCG) vaccination protects children against disseminated forms of childhood tuberculosis like meningitis [7]. Although early diagnosis and treatment of tuberculous meningitis has been known as the most important factor determining the outcome for a long time, early clinical diagnosis is hard and often delayed with serious complications. The diagnosis is difficult because of the non-specific symptoms are present rather than classic signs of meningitis; i.e. neck stiffness is usually absent during early disease in patients of all ages. In young children these symptoms also include headache, fever, developmental delay, vomiting, malaise and confusion [1,8]. Therefore early, curable disease may progress to coma, opisthotonus and finally death because once the signs of complex disease such as meningeal irritation, coma, seizures, raised intracranial pressure, cranial nerve palsies, hemiparesis, and movement disorders are observed, the diagnosis is evident but unfortunately the patient has more sequelae [1,9]. Therefore our purpose of presenting this case report is to remind that tuberculous meningitis must be considered in the differential diagnosis of intracranial infection in patients from endemic areas of tuberculosis and the treatment should be initiated rapidly in order to prevent delayed diagnosis and lethal complications.

Case Report

Seventeen years old female patient was admitted to our hospital with fever, reduced consciousness and vomiting on December 2013. It was learned from her history that; she was coming from Somalia where she was hospitalized with symptoms of headache, fever, confusion and drowsiness previously. Her father was receiving malaria treatment because it was an endemic infection in the region and therefore she was initiated treatment for malaria on admission. During the follow up her confusion has increased and cranial MRI was performed and there she was found to have three lesions 15 x 10mm in size, located in parietooccipital region, suggesting intracranial mass or abscess requiring further examination resulting with referral to our hospital.

When admitted to our pediatric intensive care unit, on physical examination, she had fever of 37.8°C, moderate-to-poor general condition, she was unconscious only localizing painful stimuli and direct light reflex was present on both eyes. At the same time she had hypertension and bradycardia suggesting increased intracranial pressure. The patient didn't have a household member previously treated for pulmonary tuberculosis and the indicative scar for BCG vaccination was not present. Lumbar puncture could not be performed for differential diagnosis such as meningitis and encephalitis because of suspected intracranial mass lesion. Ampiric antibiotics were initiated. In laboratory tests, hemoglobin was 12.5 g / dL, white blood cell count: 10,100/mm^3, platelet count: 401,000/mm^3, C reactive protein (CRP): 12:31 mg/lt, aspartate aminotransferase (AST)/ alanin aminotransferase (ALT) levels: 43/202 U/L and levels of other biochemical markers were within normal limits. Blood gases, coagulation parameters, and immunoglobulin levels were normal. Viewed as a diagnostic for malaria Giemsa-stained thick or thin blood films was not compatible. Plasmodium dipstic and hydatid cyst (echinococcus) serology was negative and she was considered to be tuberculosis. Tuberculosis polimerase chain reaction (PCR) assay in blood and sputum and acid-fast bacilli (AFB) determination in gastric lavages were negative whereas tuberculin skin test was positive (≥ 10 mm) because the induration of our patient was measured 28 x 13 mm. Blood culture and deep tracheal aspirate cultures were negative. Patient was intubated upon the start of generalized tonic-clonic seizures and cranial MRI imaging was repeated. MRI images showed common parenchymal intracranial calcification, hydrocephalus, increase in brain edema and especially revealed a hyperdense

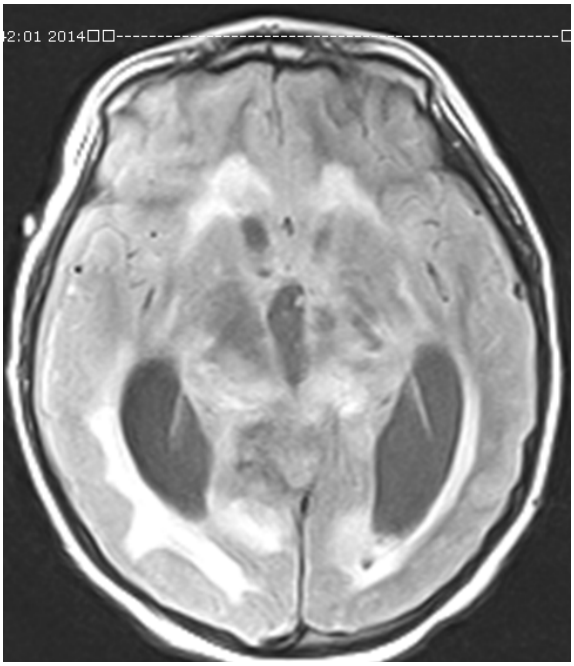

Figure 1: MRI image showing common parenchymal intracranial calcification, hydrocephalus, increase in brain edema and a hyperdense appearance in favor of temporal region involvement.

appearance thought to be in favor of temporal region involvement (Figure 1). By consulting with neurosurgery department, patient was inserted shunt for hydrocephalus and brain biopsy was performed. After shunt operation, cerebrospinal fluid (CSF) protein level was 223 mg/dl, CSF glucose: 27 mg/dl, concurrent blood sugar level:139 mg/dl and 10 lymphocytes was observed in CSF cell count. Tbc CSF PCR was negative and brain biopsy pathologic specimens were observed to have granuloma regions characterized by CD 68 positive epithelioid histiocytes. Granuloma structure of the lesion and subsequent necrosis was thought to be granulomatous disease; primarily tuberculosis. . Besides the treatment of antibiotics quadruple antituberculosis treatment was initiated after the diagnose was considered including INH, rifampin, pyrazinamide and ethambutol with optimal doses according to recommended guidelines (10). Brain biopsy PCR and cultures were positive for mycobacterium tuberculosis and antibiogram was found to be sensitive to isoniaside (INH), rifampicin, ethambutol, pyrazinamide and streptomycin. Steroid treatment previously initiated due to brain edema was continued with appropriate dosage (10). During follow up diabetes incipitus was developed, her general condition deteriorated and she became unconscious completely. Despite of all curative and supportive treatments patient could not be recovered and died.

Discussion

Tuberculous meningitis is a serious and challenging problem worldwide [4,9]. Our patient was coming from Somalia where tuberculosis is endemic. Diagnosis is challenging due to its non-specific clinical presentation [4]. Children with headache, fever, vomiting and altered sensorium should be evaluated quickly for tubercular meningitis [11]. Consistent with the literature, our patient had only symptoms of fever, reduced consciousness and vomiting. The existing laboratory techniques has restricted sensitivity and smear microscopy and culture are unfortunately negative in an important proportion of cases [4]. On CSF, moderate pleocytosis with lymphocyte predominance, increased protein content and low glucose concentration might suggest tuberculosis just like our patient, but clinical and radiological findings are still necessary for the diagnosis [4,9]. Although tuberculin skin test was positive, blood and deep tracheal aspirate cultures were negative in our patient. Tuberculosis PCR assay in blood and sputum were also negative. The diagnostic function of CSF Ziehl-Neelsen staining and microscopy for acid-fast bacilli is variable and often very weak [1], because CSF contains low organism numbers limiting diagnosis [4]. In our patient acid-fast bacilli (AFB) determination in gastric lavages were negative as in the literature. Tbc CSF PCR was also negative. Eventually, brain biopsy PCR and cultures positive for mycobacterium tuberculosis confirmed the diagnosis.

Tuberculomas are frequently unsuspected lesions so that, a focal seizure might be the most common symptom of tuberculosis in endemic populations. They can also manifest with focal neurological signs or raised intracranial pressure due to obstruction of CSF pathways [9,12]. Our patient had a suspected intracranial mass lesion suggesting tuberculoma and reduced consciousness was the first symptom at admittance. Also she had hypertension and bradycardia showing increased intracranial pressure. Our patient was intubated upon the start of generalized tonic-clonic seizures and cranial magnetic resonance imaging (MRI) was repeated. MRI images of our patient showed suggestive features for tuberculous meningitis. At defining the neuroradiological features of tuberculous meningitis MRI was found to be superior to computed tomography (CT), particularly when they involve the brainstem [13]. At the same time, MRI is important for the identification and monitoring of tuberculous meningitis related cranial neuropathies [14]. Hydrocephalus is the most common complication of tuberculous meningitis occurring in 50-80% of pediatric patients at admission [15] as a result of a basal adhesive meningeal reaction and the obliteration of arachnoid villi [11]. Hydrocephalus, stroke, and tuberculoma formation are the major complications of tuberculous meningitis which develop within the first 3 months of treatment and can be mortal if not detected and treated rapidly [9]. Neurosurgery is a significant addition to the approach of central nervous system (CNS) tuberculosis especially with complications such as moderate/severe hydrocephalus requiring ventriculo-peritoneal shunting. Besides this, resection of tuberculomas and drainage of tuberculous abscesses ends with better results [16]. Our patient also required shunt operation for hydrocephalus as expected.

The principles of tuberculous meningitis treatment include starting antituberculosis therapy as early as possible with isoniazid and rifampicin as the key parts. Drug resistant disease must be detected quickly to initiate alternative drugs and hence to prevent death [9,17]. Improved clinical outcomes depends on timely diagnosis and proper medication with optimal doses reducing the morbidity and mortality [5,11]. We were lucky that antituberculosis therapy was initiated immediately after the diagnosis was suspected and antibiogram revealed sensitive to our drugs; because it is stated that patients with drug resistant disease have usually died before the results were obtained. Nowadays the rapid way to diagnose drug-resistant tuberculous meningitis is recommended by CSF nucleic acid amplification tecniques (NAATs) and the discovery of genetic mutations that can give drug resistance. On the other hand, this method is limited by the low sensitivity of CSF NAATs and there are doubts about which mutations would best predict resistance for some drugs [9,18]. Addition of corticosteroids to antituberculous therapy are known to decrease death and disability by about 30% [19]. Actually national guidelines recommend adjunctive corticosteroids for all patients with the disease [10]. They are believed to decrease brain edema and cytokine production reducing long term neurologic sequelae [20]. Based on the literature steroid

was administered to our patient. Nevertheless the outcomes include death in 50% of cases of tuberculous meningitis [5] and survivors might have considerable neurological sequelae including failure to thrive, seizures, hydrocephalus, and cranial nerve palsies [15].

On conclusion; despite of all curative and supportive treatments our patient could not be recovered. Tuberculous meningitis is still known as the most mortal form of tuberculosis. Early diagnosis and treatment improves survival rate but currently available diagnostic tests are still inadequate. Tuberculous meningitis must be considered in the differential diagnosis of intracranial infection in patients from endemic areas of tuberculosis and the treatment should be initiated at once to prevent delayed diagnosis and lethal complications.

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