TUBERCULOUS MENINGOENCEPHALITIS IN IMMUNOCOMPETENT CHILD

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Abstract. Tuberculous involvement of the central nervous system (CNS) is an important and serious type of extra-pulmonary involvement. It has been estimated that approximately 10% of all patients with TB have CNS involvement. The incidence of CNS tuberculosis is directly proportional to the prevalence of tuberculous infection in general. In developing countries CNS tuberculosis is a disease of younger age group, usually childhood. The high morbidity and mortality of tuberculous meningoencephalitis (TBM) warrants an early diagnosis and treatment.

In Constanța County in the first 3 months of the year 2007 we noticed the presence of 5 cases of TBM in children with ages ranging from 6 months to 6 years. In Romania BCG vaccine is mandatory and it has been proven to reduce the incidence of severe disseminated disease in children. In this context we report a case of TB meningoencephalitis (TBM), in a 2 years and 3 months old metiss child without BCG vaccine. We analyze the aspect of cerebrospinal fluids, electroencephalography (EEG), inflammatory blood tests and cerebral MRI examination.

Diagnosis of TBM was delayed in this case. In the first month of treatment the child presented a toxic hepatitis due to antituberculosis treatment. Hydrocephaly was present at the onset of the disease. In evolution, we noticed transient decrease of visual acuity, cranial nerve paralysis, and severe motor deficit.

Keywords: tuberculous meningoencephalitis (TBM), child, BCG vaccine

Introduction:

Most tuberculous infections of the CNS are caused by Mycobacterium tuberculosis. Mycobacterium tuberculosis is a non-motile, non-spore forming, and an obligate aerobic acid-fast bacillus (AFB), whose only natural reservoir is man. M. tuberculosis grows slowly both in vitro and in vivo, with a doubling time of about 15–22 h, and it requires an incubation of at least two weeks to grow on Lowenstein-Jensen (LJ) solid medium [1,2].

It is believed that the bacilli reach the CNS by haematogenous route secondary to disease elsewhere in the body. Rich and Mc Cordock [3] suggested that CNS tuberculosis develops in two stages, initially small tuberculous lesions (Rich's foci) develop in the CNS, either during the stage of bacteremia of the primary tuberculous infection or shortly afterwards. These initial tuberculous lesions may be in the meninges, the subpial or
subependymal surface of the brain or the spinal cord, and may remain dormant for years after initial infection. Later, rupture or growth of one or more of these small tuberculous lesions produces development of various types of CNS tuberculosis (see figure no. 1). [1, 4, 5]

The specific stimulus for rupture or growth of Rich's foci is not known, although immunological mechanisms are believed to play an important role. Rupture of the small tubercles into the subarachnoid space or into the ventricular system results in meningitis. The type and extent of lesions that result from the discharge of tuberculous bacilli into the cerebrospinal fluid (CSF) depend on the number and virulence of the bacilli, and the immune response of the host. [1]

The pathogenesis of localized brain lesions is also thought to involve haematogenous spread from a primary focus in the lung (which is visible on the chest X-ray in only 30% of cases). It has been suggested that with a sizeable inoculation or in the absence of an adequate cell-mediated immunity, the parenchymal cerebral tuberculous foci may develop into tuberculoma or tuberculous brain abscess (see figure no. 1). [1, 5]

**Tuberculous meningitis (TBM)**

TBM is characterized as a meningoencephalitis as it affects both the meninges and the brain's parenchyma together with its vasculature. In tuberculous meningitis there is a thick, gelatinous exudate around the sylvian fissures, basal cisterns, brainstem, and cerebellum. Microscopically diffuse exudates consist of polymorph nuclear leukocytes, macrophages, lymphocytes, and erythrocytes with a variable number of bacilli within a loose fibrin network, and as the disease progresses, lymphocytes and connective tissue elements predominate [1,5].

Hydrocephaly may occur as a consequence of the obstruction of the basal cisterns, outflow of the fourth ventricle, or occlusion of the cerebral aqueduct. Hydrocephaly frequently develops in children and is associated with a poor prognosis. The basal exudates of TB are usually more severe in the vicinity of the circle of Willis, and produce a vasculitis-like syndrome. Cerebral infarctions are most common around the sylvian fissure and in the basal ganglion. Haemorrhagic transformation of infarcted tissue is not unusual [1, 5, 7, 8, 9]

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**Figure 1.** Pathogenesis of CNS lesions in TB meningoencephalitis—adapted by Rich and Mc Cordock
In most patients with tuberculous meningitis there is a history of vague ill health lasting 2–8 weeks prior to the development of meningeal irritation. These nonspecific symptoms include malaise, anorexia, fatigue, fever, myalgias and headache. The prodromal symptoms in infants include irritability, drowsiness, poor feeding, and abdominal pain. Eventually, the headache worsens and becomes continuous. Neck stiffness is reported by about 25% of patients, but meningismus is detected in a higher number of patients at the time of examination. Bulging fontanelles develop in infants, who become increasingly irritable. Nausea, vomiting and altered sensorium may develop. [1]

Continuous low-grade pyrexia is typically present in about 80% of patients. A prior history of TB is present in approximately 50% of children with tuberculous meningitis and 10% of adult patients [7, 9, 10].

Cranial nerve palsies occur in 20–30% of patients and may be the presenting manifestation of tuberculous meningitis. The sixth cranial nerve is most commonly affected, and less frequently the third, fourth, seventh and eighth cranial nerves [11]. Vision loss due to optic nerve involvement may occasionally be a dominant and presenting illness. [1]

Ophthalmoscopic examination may reveal papilledema. Fundoscopy may reveal choroid tubercles, yellow lesions with indistinct borders present either singly or in clusters [8, 12].

Hemiplegia may occur at the onset of the disease or at a later stage. Quadriplegia secondary to bilateral infarction or severe cerebral edema is less common and occurs only at an advanced stage in a few patients. At times, abnormal movements may dominate the clinical picture, more commonly in children than in adults. Seizures, either focal or generalized, may occur during acute illness or months after treatment [12]. Behavioral changes consisting of apathy, confusion, or bizarre behavior, tend to progress to increasing lethargy, stupor, and coma.

In TB meningitis CT or MRI of the brain may reveal thickening and intense enhancement of meninges, especially in the basal regions. Ventricular enlargement is present in the majority of patients. The degree of hydrocephaly correlates with the duration of the disease [13]. Infarctions are another characteristic imaging feature of tuberculous meningitis [10].

Thick basilar exudates appear on CT as intensely enhanced areas in the basal cisterns (spider-leg appearance) and in the sylvian fissures [10]. The thickening of the meninges is better visualized by MRI after enhancing the contrast with gadolinium. MRI shows marked linear enhancement of the ependymal surface of the ventricle following gadolinium injection [14].

Case presentation

AM, female, 2 years 3 months old, was hospitalized in our clinic on January 19, 2007 for high fever (39–40°C), headache, disphagia, vomiting, somnolence, symptoms that were present for 3 weeks. In ambulatory, the patient received antibiotic treatment po with Amoxicillin/Clavulanic acid and then Clarithromycine.

The personal physiological history emphasized that the child was born in Spain and was adopted in Romania by a Romanian family (the child lived in Romania since one year). The immunization schedule was Spanish (similar with the Romanian one, but with absence of BCG vaccine).

General examination revealed profoundly altered clinical status, metiss child with fever, somnolence, incoherent, disorientated, neck stiffness and Kernig II signs present, tachycardia, crackles on both pulmonary areas.

We performed lumbar puncture (LP): CSF hypertensive, 1000 elements/mmc (60% polymorphonuclear cells, 40% mononuclear cells), Pandy reaction +++, albumin level = 2.64 g‰, chlorites level = 6.42 g‰, glucose level = 0.23 g‰. Blood analysis revealed Leukocytes = 32 300/mmc (PMN=91.8%). (see table no. 1) In the beginning, we evaluated the bacterial meningitis already treated with antibiotics and we initiated treatment with Meropenem 500 mg every 8h for 14 days associated with antiedematous treatment and steroids.

After a period of 4 days of amelioration (consciousness preserved, cooperate, but with fever and intense neck stiffness) the child presented generalized seizures 2-5 min x2/day – 2 days, followed by paralysis of cranial nerves.

LP performed on the fourth day revealed: 400cells/mmc (Ly =95 %), Pandy reaction +++, albumin level =0.99 g‰, chlorites level =6.54 g‰, glucose level =0.53 g‰. (see table I)

Contact tracing revealed a contact with adopted maternal uncle diagnosed with pulmonary TB and absence of BCG vaccination (the child was born in Spain); IDR at 2 U PPD – positive at 72h (presence a nodules of 11-12 mm). In order to sustain
the TB etiology of the meningitis we performed Quantiferon TBgold which was positive on the 10th day of hospitalization.

In first week of hospitalization we performed a cerebral MRI which showed: contrast substance in cisternal and pericerebral liquidian space suggestive for meningitis; pontin ischemic lesions (acute stage); internal hydrocephaly with minimum edema of transependimar resorption.

All clinical and biological data and cerebral MRI (see fig. no. 2, 3) suggested diagnosis of TB meningoencephalitis. In the 5th day of hospitalization we started treatment with tuberculostatic drugs (association of 5 antituberculous drugs in a daily regimen for 2 months).

In accordance with the initial aspect of the CSF (1000 cells/mmc with predominance of polymorphonuclears-60%), high level of leukocytosis, other bacterial etiology couldn't be excluded. (see table II) Since the child had received antibiotics prior to hospitalization we couldn't identify the second bacteria that were involved in meningitis in this case.

The evolution of the CSF was slowly favorable (see table no. 1).

Pulmonary X-ray revealed changes suggestive for interstitial pneumonia and absence of lesions specific for TB.

Ophthalmoscopical examination performed on the 4th day of hospitalization revealed papilledema. Fundoscopy didn’t show the presence of choroid tubercles.

**Evolution over period of hospitalization**

The neurological evolution worsened, with new paralysis of cranial nerves and right hemiparesis, coma for the next 14 days. When she recovered from the coma, she was blinded. After 1 month of tuberculostatic treatment we noticed the presence of automatic movements and myoclonia with short periods of exacerbation. We intensified the antiepileptic treatment with Convulex and Lamictal.

The performed electroencephalogram evidenced: presence of theta –delta rhythm (more frequent delta) combined with alpha rhythm posterior (according with age), but with presence of length wave (cca 4-5 episodes) in the cortical temporo-parieto-occipital right aria. (see figure no. 4)

The febrile syndrome disappeared after 5 days of tuberculostatic treatment but the leukocytes remained increased over the whole period of hospitalization.

In addition to tuberculostatic drugs and antibiotics she received antiedematous treatment, antithermic drugs, antalgics and antiepileptic drugs, vitamins from group B, neurotrophic drugs (Encephabol, Cerebrolysine), and steroids (Dexamethasone for the first 17 days).

During hospitalization the child presented an...
episode of toxic hepatitis related with Rifampicin and Isoniaside which was resolved with hepatotrophic drugs (Essentiale and Silimarim). (see table III and table no. IV)

The pediatric neurologist consult after 1 month of hospitalization evidenced: Right hemiparesis, paresis of VI right cranial nerve, right peripheral facial paresis and paroxysm with partial seizures on the right hemimorphy facial and crural, clonus, extrapyramidal syndrome, myoclonic seizures, and symptomatic epilepsy. The pediatric neurologist recommended treatment with Synacten 1 vial every 2 days, Convulex (3.5 ml twice per day) and Lamictal (2 mg twice per day).

One week before hospital discharge we performed an MRI which showed sequelae of the initial pontin lesions, and communicant ventriculomegaly.

Two days before hospital discharge we performed a neurosurgical examination which established that as long as the patient presented cytolological and biochemical changes in the CSF, the opportunity of CSF drainage was compromised.

**Right VI\(^{th}\) cranial nerve paresis**

**Evolution after hospital discharge:**

The opportunity of CSF drainage was not accepted by the neurosurgeon.

She completed antituberculous treatment for one year and she recovered from a neurological point of view: after one year and 3 months she could walk with little difficulties; facial paralysis still evident when she smiled and talked (fig. 5); still presenting difficulties in visual acuity.

![Facial paralysis (photo taken with the mother's permission)](image)

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**Table III.** Evolution of biochemical constants in blood

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**Table IV.** Cultures and serologic tests during hospitalization

**Particularities of the case**

The child was born in Spain without BCG vaccine but was living in Romania (adopted by a Romanian family), country with high TB endemicity. The child presented a sporadic contact with maternal grandfather who was diagnosed with pulmonary TB.

Evolution of TB meningitis in this case was precipitated by another bacterial disease that couldn't be identified because the child had received antibiotics prior to hospitalization.

**Conclusions**

Bacterial meningitis with double etiology is very rare in clinic but when present can worsen disease evolution.

TBM still represents a threatening disease in infants.

Severe forms of TBM were present in children less than 3 years old and without BCG vaccine.

It draws attention to the importance of TBM as differential diagnosis in children with suspected viral meningoencephalitis or partially treated bacterial meningoencephalitis.
Any delay in the specific treatment of TBM can associate severe neurologic sequelae or death.

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