TUBERCULOUS MENINGITIS MIMICKING ACUTE POLYRADICULONEVRITIS

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ABSTRACT

Romania has the highest prevalence of tuberculosis (TB) among all the Central European countries. Involvement of the central nervous system (CNS) by the TB accounts for approximately 1% of all cases of tuberculosis. CNS TB includes two clinical categories: intracranial and spinal. We report two cases of tuberculosis meningitis with hemorrhagic CSF. Diagnosis was based on clinical signs, complementary investigations and response to early treatment with antituberculosis medication with adjunct of steroid therapy. Some mild neurological sequels persisted.

Key words: tetraparesis; multiple cranial nerves palsy; bilateral abducens nerve palsy; bilateral peripheral facial palsy; horizontal diplopia; dysfagia; dysphonia; confusion; tuberculous meningitis; radiculomyelitis; immunocompetent

INTRODUCTION

Involvement of the central nervous system (CNS) by the TB accounts for approximately 1% of all cases of tuberculosis (1). Romania has the highest prevalence of tuberculosis (TB) among all the Central European countries with an incidence of 99.9/ 100.000 population in 2009. CNS TB includes two clinical categories: intracranial and spinal (table 1).

Table 1. *Classification of CNS tuberculosis (2)*

Classification of CNS tuberculosis
Intracranial
Tuberculous meningitis (TBM)
Tuberculous encephalopathy
Tuberculous vasculopathy
CNS tuberculoma (single or multiple)
Tuberculous Brain Abcess
Spinal
Pott's spine and Pott's paraplegia
Non-osseous spinal tuberculoma
Spinal meningitis

CASE REPORT

Case 1

A 63 years old woman, Caucasian, presented to the emergency department after one week of progressive onset of distal parestesia ("pins and needles"), motor deficit, multiple cranial nerves palsy with bilateral peripheral facial palsy (left side> right side), dysarthria, dysphonia, dysphagia. She also had sphincters incontinence.

Her past medical history includes bilateral hip congenital luxation and arterial hypertension. The patient was non-smoker and did not consume alcohol. She denied any history of trauma, rashes, travel abroad or exposure to tick bites.

Clinical examination revealed no nuchal rigidity, bilateral complete lower motor neuron type of facial palsy, dysarthria, dysphonia, dysphagia, tetraparesis, complete loss of thermal and pain sensibility, complete loss of osteotendinous reflexes, cutaneous plantar reflexes were absent. The patient was apyretic during the hospitalisation.

Full blood count was normal. ESR was 52 mm/h. Blood cultures were negative. LDH level was 195U/L. All others laboratory data were in normal limits excepting a mild hyponatremia (132 mEq/L).

Cerebrospinal fluid (CSF) studies showed albumin-cytological dissociation, a protein level of 300 mg/L (normal 15-45) with white blood cell count of 1096/μL. Glucose level of 43 mg/dl(normal 40-70) (plasma glucose 152 mg/dl). There CSF had a

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hemorrhagic aspect, which initially was interpreted as a puncture incident; red blood count in CSF was 122000/ μL. CSF and sputum specimen was negative for acid-fast bacilli. Chest X-radiography was clear.

EEG was normal. Nerve conduction studies showed prolonged F wave and prolonged distal motor latency with decreased velocity from the bilateral peroneal nerve and right tibial nerve, suggestive for an Acute Inflammatory Demyelinating Polyneuropathy (AIDP).

With the characteristic albumin-cytological dissociation, a diagnosis of the Guillain-Barre syndrome (AIDP) was made. We started to treat her with immunoglobulin infusion (0,4 mg/kg body weight) from day 1 and intravenous corticotherapy (Dexamethasone 8 mg twice a day, daily).

On the 3rd day of treatment she started to be confused, with hallucinations and no clinical amelioration of the motor deficit.

Contrast enhanced brain MRI showed some diffuse white matter abnormalities hyperintense FLAIR frontal bilateral, suggestive for chronic vascular lesions, irrelevant in the present context. The spinal MRI showed a subacute hematoma T8-L3 (possible post lumbar punction). (Fig.1)

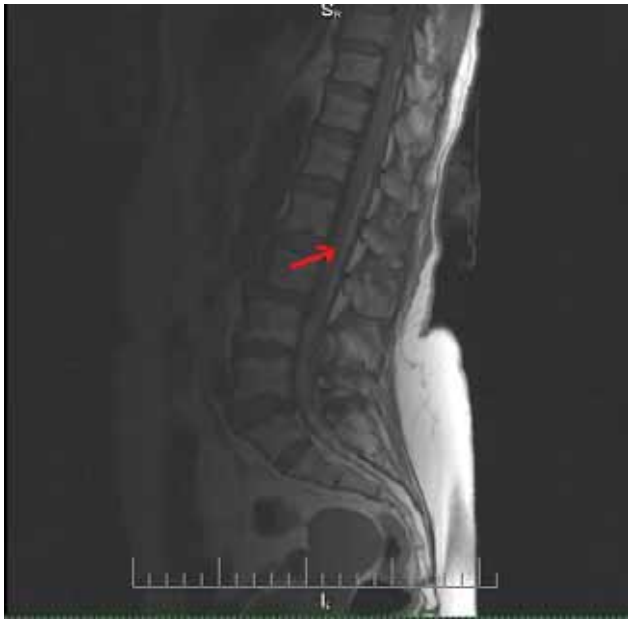

Figure 1. *Sagital T1 lumbar spine MRI; hyperintense signal corresponding to subdural hematoma*

Repeated CSF study showed albumin-cytological dissociation, a protein level of 70 mg/L (normal 15-45) with white blood cell count of 22/μL (76% lymphocytes). Low glucose level of 17 mg/dl (normal 40-70), concomitant plasma glucose 146 mg/dl). The aspect of CSF persisted to be hemorrhagic with red blood count of 25.000. There were no malignant cells at the CSF studies.

Based on low level of glucose in the CSF, a diagnosis of tuberculosis meningitis was suspected. We interrupted the administration of immunoglobulin, and we started the treatment with Hidrazide, Rimfapicin, Pyrazinamide and Ethambutol (treatment according to the standard doses, see table 2). The symptoms spectacularly improved, after the first 24 hours. She was discharged on day 10 to the regional neurology department, with remission of the superior limb paresis and of the right peripheral facial palsy, significant improvement of the inferior limb paresis and quasi complete remission of the sensitive signs. She continued her treatment with antituberculosis drugs.

At two month, she progressively improved, with complete recover of her motor deficit with muscle strength grade 5/5(Medical Research Council MRC grade), her ankle reflexes returned bilaterally. She has a residual facial palsy on her left side.

Case 2

A 31 year old Caucasian female, immunocompetent, was referred to our department with subacute onset (3 days ago) of headache, low-grade fever (37,3°C-37,7°C) diarrhea, vomiting, dizziness, blurred vision with horizontal diplopia.

Her past medical history includes Helicobacter Pylori gastritis.

On examination she was conscious, had horizontal left diplopia, dysphagia for solids, normal osteotendinous reflexes.

Laboratory data showed a syndrome of inappropriate antidiuretic hormone secretion (serum sodium 121 mEq/L). The leukocyte count was normal, while ESR was 40 mm/h. Blood culture was negative. All other laboratory data were in normal limits.

CSF studies showed albumin-cytological dissociation, a protein level of 1017 mg/L (normal 15-45) with white blood cell count of 18/μL. Glucose level of 67 mg/dl (normal 40-70) (plasma glucose 103 mg/dl). The aspect of CSF was slightly hemorrhagic. No contrast enhanced brain MRI was normal. Chest X-radiography was clear.

As the presentation was highly suggestive for Guillain-Barre syndrome we started the intravenous immunoglobulin infusion and corticotherapy. Her clinical state did not improve in the following days, on contrary; she became confused, complaining of headache, horizontal diplopia with bilateral abducens palsy, bilateral ptosis, dysphagia, dysphonia.

Nerve conduction studies were in normal range (no argument for AIDP). We attempted a second lumbar puncture which revealed a decreased CSF pressure, suggesting a complete blockage of CSF around the spinal cord. The aspect was of xanthochrom CSF, a protein level of 41 mg/L (normal 15-45) with no white blood cell count of. Glucose level of 50 mg/dl (normal 40-70) (plasma glucose 147 mg/dl). Repeated nerve conduction studies was in normal range.

The contrast enhanced spinal MRI showed pachymeningitis with decliv CSF and contrast enhanced of cauda equina. (Fig. 2 & 3).

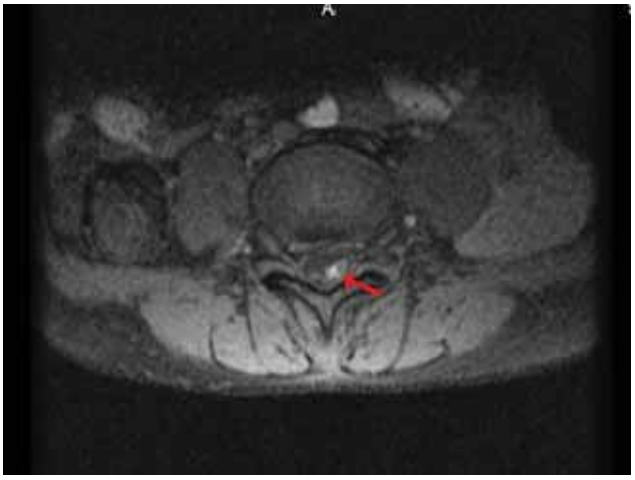

Figure 2. *Axial T1 lumbar spine MRI; hyperintense signal corresponding to contrast enhancement of cauda equina*

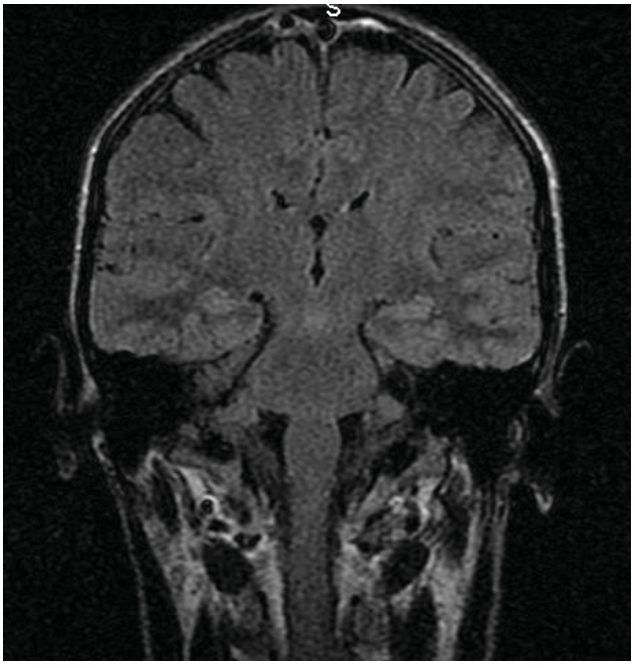

Figure 3. *Coronal FLAIR MRI section; normal brain aspect*

We raised the suspicion of TBM (based on clinical aspect, low-grade fever, MRI and CSF aspects) and started the four antituberculostatic drugs (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, treatment according to the standard-doses, see table 2), even without a firm microbiological diagnosis. The patient improved clinically, with no dysphagia, no dysphonia, but, mild bilateral ptosis, horizontal diplopia (right > left).

DISCUSSION

The two cases raised a few differential diagnosis problems.

First, the clinical presentation was highly suggestive for Guillain-Barre Syndrome (CSF studies showed albumin-cytological dissociation, and in one case also the nerve conduction studies were concordant with the diagnosis of acute polyradiculonevritis). They hadn't responded to treatment with Immunoglobulin infusions. Bilateral facial nerve palsy has an incidence of only 1 per 5 million population/year (3), and usually it draws attention to infectious diseases (borreliosis, tuberculosis) or to sarcoidosis or acute polyradiculonevritis. We had to exclude potential vasculitis (Behcet, Wegener, Sjogren, and lupus erithematosus), sarcoidosis, infections, metabolic disorders; traumatic, neoplastic, drug-induced acute polyneuropathies. The auto-antibody screen was negative for the inflammatory autoimmune disorders. Hashimoto thyroiditis was excluded by normal thyroid function. The patient's presentations and the brain and spinal MRI imaging made CNS carcinoma and lymphoma unlikely. The screening for HIV and syphilis was negative. Lyme's disease is a common cause of facial palsy, but our patients had no history of exposure to tick bites or recent travel abroad. Screening for Herpes viruses and infectious CMV was negative.

The two cases had atypical features of CNS TBM that may have confounded early diagnosis. Typically, CNS TBM is described as chronic meningitis with insidious onset. In contrast our patients had a subacute onset.

The CSF study found an atypical aspect. Typical CSF in TBM should be as clear as a similar test tube filled with water. The patients' CSF was hemorrhagic. This could be explained by the vascular lesions in acute TBM.

Early diagnosis and treatment correlates with better outcomes. Given the difficulties in obtaining a rapid diagnosis, therapy must often be initiated empirically (13).

Tuberculous meningitis is still one of the common infections of central nervous system and poses significant diagnostic and management challenges (4). Tuberculous radiculomyelitis (TBRM) is a complication of neurological tuberculosis that is rarely reported (5). We searched the PUBMED database for all articles published from 1966 throught 2011 that dealt specifically with TBRM and TBM. We found 92 cases.

PATHOGENESIS

TBM has two stages in the pathogenesis: first a bacterial seeding of the meninges and subpial regions of the brain with the formation of tubercles, followed by the rupture of one or more of the tubercles and the discharge of bacteria into the subarachnoid space (6).

TBRM may develop in one of three ways: as a primary tuberculous lesion; as a downward extension of TBM; and as a secondary extension from vertebral tuberculosis (7). Primary tuberculous radiculomyelitis starts as a hematogenous focus or foci, either in the meninges or in the spinal cord, and subsequently spreads to the subarachnoid space secondary to rupture of the lesion. In contrast, in tuberculous radiculomyelitis secondary to intracranial tuberculous meningitis, the spread of infection is apparently via the CSF pathway (8).

PATHOLOGY

Macroscopically, one of the most remarkable features of the CNS TB is the presence of exudates that is usually described as extensive, copious and tenacious. It involves the bases of the cerebral hemispheres, the cranial nerves and the entire space between the spinal dura mater and the leptomeninges. Microscopically, the main pathological feature is the inflammatory process and the immune reaction.

Fibrinoid degeneration was observed in areas where the inflammatory exudates exist. The vascular fibrinoid is present in the subintimal zone and media of the involved vessels. The invasion of the blood vessels begins in the periadventitial region. The media is the most resistant portion of the vessel wall. The internal elastic lamina may become fibrillar and frayed. Occasionally there is a complete rupture (14).

CLINICAL FINDINGS

TBRM is characterized by the subacute onset of paraparesis. Symptoms include root pain, paraesthesias, bladder disturbance and muscle wasting; subsequent paralysis develops, usually after a few days. It is not uncommon to find absent deep tendon reflexes with flaccidity in the lower limbs and the presence of Babinski sign (9). TBM is characterized by low-grade fever, malaise, headache, lethargy, confusion and stiff neck, with Kernig and Brudzinski signs. Signs of cranial nerves involvement may be present at the time of admission to the hospital (6).

Diagnosis of CNS TB is usually suspected on the basis of clinical, CSF studies and CT/MRI findings.

CSF examination revel increased opening pressure, contains between 50-500 white cells/μL with lymphocytes predominance, protein 100-200 mg/dL, or higher, glucose < 40 mg/dL. The serum sodium and chloride and CSF chloride are often reduced, because of inappropriate ADH secretion or an addisonian state due to tuberculosis of the adrenals. CSF can also demonstrate the presence of acid-fast bacilli by Ziehl-Neelsen method. Mycobacterium tuberculosis can be identified specifically by PCR, DNA amplification (6).

Most common MRI findings are basilar meningitis, parenchymal lesions, tuberculomas (usually T2 hypointense, enhances strongly), ventriculitis, spinal involvement (10). All patients should have a chest X-ray.

The **treatment** for CNS tuberculosis is a medical emergency. It consists of four drugs: Isoniazid, Rifampicin, Pyrazinamide and Ethambutol, taken daily either individually or in combination.

Table 2. *Recommended treatment regimen for CNS tuberculosis caused by fully susceptible M. tuberculosis (11)*

Drug	Daily Dose Children	Daily Dose Adults	Duration
Isoniazid	10-20 mg/kg	300 mg	10 to12 months
Rifampicin	10-20 mg/kg	450 mg (< 50 kg) 600 mg (> 50 kg)	10 to12 months
Pyrazinamide	15-30 mg/kg	1.5 g (< 50 kg) 2 g (> 50 kg)	2 months
Ethambutol	15-20 mg/kg	15 mg/kg	2 months

Therapy is generally divided in to an intensive for 2 month and continuation phase, until 10-12 month. Studies showed that corticosteroids may be used, only in conjunction with antituberculostatic drugs (6).

Some patients, who present hydrocephalus or intracranial tuberculoma may require surgical intervention.

During the last years there was identified a phenomen known as the "paradoxical reaction". This phenomen refers to observation of clinical or radiological worsening of previous TB lesions or development of new lesions after at least one month of TB treatment in patients who initially responded to anti TB therapy (12).

CONCLUSION

TBRM is a rare complication of TBM. Tuberculosis can cause diffuse CNS infection in immunocompetent individuals. Early recognition and timely treatment are very important. The treatment should be started as soon as possible, for minimum 10 month. We consider that the steroids treatment is probably indicated, given the inflammatory process.

The particularities of the two cases consist of the clinical aspect of tuberculous meningitis mimicking strongly a Guillain-Barre Syndrome and the hemorrhagic aspect of the CSF in both cases, which did not respect the classical appearance of cerebrospinal fluid in tuberculous meningitis, but is explained by the vascular involvement of the vessels during tuberculous infection. Together with previous reports, our report indicates a good response to therapy, if started earlier. The overall prognosis of TBM remains poor – 10-20 % case fatality (worse if treatment is delayed and the patient is comatose) and 20-30% long term morbidity (cognitive and behavioural impairment, epilepsy, cranial nerve palsies and paresis) (15).

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