Rapidly Progressing Fatal Neurobrucellosis in a Healthy Child in an Endemic Area in Southern Israel

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KEY WORDS: brucellosis, meningitis, encephalopathy, Bedouin, imaging, seizures, thrombosis

Meningitis and encephalitis are among the most severe life-threatening conditions the pediatric emergency physician may face. Prompt recognition and early treatment may be lifesaving. We would like to raise awareness to a relatively rare pathogen whose high prevalence in our geographic area should be taken into consideration in cases of severe meningitis.

We present a case of rapidly progressing fatal neurobrucellosis in an otherwise healthy child in southern Israel and the associated challenges in early diagnosis and treatment.

PATIENT DESCRIPTION

An 8 year old previously healthy and fully immunized Bedouin Muslim boy was admitted to the emergency room with a 2 day history of fever > 39°C and weakness that worsened during 24 hours prior to admission, accompanied by shaking chills and occasional vomiting. The family denied diarrhea, presence of animals in the household, or consumption of unpasteurized milk products. There was no family or personal history of hypercoagulability states, immune deficiency, diabetes or other metabolic disorders.

On admission the child was confused, unable to talk fluently and responded only partially to vocal commands. No rash was noticed. Vital signs were fever 38.0°C, heart rate 139 beats per minute, blood pressure 118/68 mmHg and oxygen saturation 100% in room air. Physical examination revealed a well-developed child who opened his eyes only to pain, was non-verbal and unable to localize pain. The Glasgow Coma Scale score was 8/15. Nuchal rigidity was not present. Neurological examination demonstrated that he was encephalopathic with dilated pupils reactive to light, and the presence of corneal and gag reflexes, trismus, hyperactive tendon reflexes without clonus and bilateral positive Babinsky reflexes. No focal neurological deficits were detected. Laboratory investigation showed hemoglobin 11.8 g/dl, white blood cell count 10000/mm³ with 58.3% neutrophils and 27.0% lymphocytes, and a platelet count of 261,000/mm³. Serum glucose was 195 mg/dl, and electrolytes and liver function tests were within normal limits. The patient deteriorated rapidly to stupor with choreoathetotic limb movements. A lumbar puncture was not performed due to his impaired consciousness, and intravenous ceftriaxone (100 mg/kg) was administered empirically. During transfer to brain computed tomography (CT), he had three short focal seizures which stopped spontaneously. Brain CT + angiography was normal without signs of increased intracranial pressure, meningitis, stroke or sinus thrombosis. He was admitted to the Pediatric Intensive Care Unit and treated with benzodiazepines and acyclovir. The electroencephalogram showed diffuse slowing of background activity, without epileptiform activity, compatible with encephalopathy.

Five hours after admission the patient developed tonic posturing of the arms and legs accompanied by opisthotonus, which did not respond to intravenous midazolam or phenytoin. He was unconscious, with sunset eyes, absent corneal reflexes, pupils not reactive to light and absent gag reflex. The tendon reflexes were hyperactive in the upper limbs and absent in the lower limbs, without clonus; no focal neurological deficits were present. The patient was intubated and ventilated. Seven hours post-admission brain magnetic resonance imaging (MRI) including MRA + MRV showed normal ventricular size, normal intra- and extra-cortical blood flow without sinus thrombosis and evidence of leptomeningeal enhancement compatible with meningitis [Figure 1]. Shortly after the MRI, his pupils were dilated, equal and fixed and no longer responding to painful stimuli. An ophthalmologic examination revealed normal disks. A bedside intracranial pressure monitor device measured a pressure of 50 mmHg which soon rose to 100 mmHg. Aggressive neuroprotective management aiming to reduce intracranial pressure (30 degree elevation and midline position of the head, deep sedation and analgesia, mild hyperventilation, hyper-osmolar therapy with intravenous 3% hypertonic saline and mannitol 20% boluses) was initiated with no clinical improvement. The patient’s condition worsened and 24 hours after admission he was considered brain dead. CT angiography showed severe brain edema with no blood supply to the brain and massive thrombosis of sagittal, horizontal and sigmoid brain sinuses as well as bilateral jugular veins. A lumbar puncture performed 24 hours post-admission revealed a white
blood cell count of 45 cells/mm³ with 55% lymphocytes, 35% mononuclears and 10% polymorphonuclears, a glucose level of 104.7 mg/dl and a protein concentration of 1140 mg/dl. No organisms were recovered in the cerebrospinal fluid.

A blood culture drawn on admission grew pleomorphic Gram-negative bacilli which 24 hours later were identified as *Brucella* spp. Serology to *Mycoplasma* and *Rickettsia* and serum polymerase chain reaction for West Nile fever, herpes simplex and cytomegalovirus were negative. The Rose-Bengal test was positive; *Brucella* serology (standard tube agglutination test) was initially 1/320 and rose to 1/4800 24 hours later.

**COMMENT**

Our patient suffered from neurobrucellosis. This was evidenced by the clinical manifestations of meningo-encephalitis accompanied by the positive blood culture and extremely elevated serum IgM titer for *Brucella*. Neurobrucellosis can present in many ways. Our patient presented with fever, confusion, vomiting and seizures, as described in 57%, 18%, 17% and 8% of the cases of neurobrucellosis, respectively [1]. None of the anamnestic, physical, imaging or early laboratory results were suspicious or diagnostic for brucellosis or neurobrucellosis, except for the patient’s ethnicity.

Brucellosis is endemic in Mediterranean and Middle East regions. In Israel, the disease caused by *B. melitensis* is endemic in the Negev area, being almost exclusively diagnosed in the Bedouin Muslim population living in close proximity to unvaccinated sheep and goats and consuming unpasteurized dairy products from these animals [2,3]. An overall incidence of 7 cases per 100,000 was reported in Israel in 2008 among Bedouins compared with 0.2/100,000 in the Jewish population [2]. Recently, an 83% increase in the overall number of brucellosis cases was reported by the Israel Ministry of Health (595 cases, 7.3 cases/100,000 in 2014 compared with 325 cases, 4.0 cases/100,000 in 2013) [unpublished data, Israel Ministry of Health, Department of Epidemiology]. In children, an unproportionally high incidence of 16 cases/100,000 was reported during 2005–2010 among Bedouin children < age 18 years living in southern Israel [3]. Death from *Brucella* infection occurs in < 1% of cases.

Neurobrucellosis is a less common manifestation of *Brucella* infection and is found in only a minority of cases [4]. Physical findings commonly seen in systemic brucellosis, such as hepatomegaly and splenomegaly, are rare in cases with *Brucella* central nervous system involvement. In an overview of 187 patients aged 10–77 years diagnosed with neurobrucellosis reported in the Turkish literature during 1998–2007, headache, fever, sweating, weight loss and back pain (57%, 57%, 30%, 28% and 23% of all cases, respectively) were the predominant symptoms, while meningeal irritation, confusion, hepatomegaly, hyposthesia, splenomegaly and convulsions (37%, 18%, 15%, 12%, 11% and 8%, respectively) were the most common clinical findings [1]. The major complications of neurobrucellosis in these patients were cranial nerve involvement, polyneuropathy/radiculopathy, depression, paraplegia, stroke and abscess formation (19%, 7%, 5%, 4%, 3.2% and 3%, respectively) [1]. Death as a result of neurobrucellosis occurs in only about 0.5% of cases [4].

Should empiric antibiotic treatment for *Brucella* be administered in high risk patients? Could it have changed the fatal outcome? Recently, two cases of neurobrucellosis (one presenting with positive meningal signs, papilledema and hydrocephalus and the second with a cerebral mass) were described in two Bedouin patients aged 6 and 13 years [5]. In both cases, prompt (before microbiological confirmation) initiation of anti-*Brucella* antibiotic treatment (gentamicin, cotrimoxazole, rifampin and doxycycline, and gentamicin, rifampin and doxycycline, respectively) was associated with a favorable outcome. Our patient developed intracranial hypertension which progressed to brain death within 10 hours from hospital admission and approximately 48 hours since onset of symptoms. Such rapid death due to neurobrucellosis is highly unusual (0.5%). As far as we know, this is the fastest neurobrucellosis disease progression described in the literature. It is unclear whether empiric antibiotic treatment could have slowed or stopped the process.

While an early CT angiographam was unsuccessful in detecting meningitis, the MRI and the second CT performed later supported the diagnosis, emphasizing the need for repeated imaging as good medical practice in such cases. Brain imaging findings...
in neurobrucellosis may be normal or may reveal inflammation as well as white matter changes or vascular changes. The second CT angiography showed severe brain edema with no blood supply to the brain and massive thrombosis of sagittal, horizontal and sigmoid brain sinuses as well as bilateral jugular veins. The cerebrovascular involvement in neurobrucellosis may be due to a possible rupture of a mycotic aneurysm or to the inflammatory process occurring in the vessels (particularly arteritis, with resultant infarcts, hemorrhages or venous thromboses) [1]. Cerebral venous thrombosis is extremely rare in brucellosis [1,4,5].

In conclusion, a high index of suspicion of neurobrucellosis is advised when encountering patients living in endemic areas and presenting with obscure, confusing and mixed constitutional, neurologic or psychiatric symptoms without any other obvious explanation. Anti-Brucella empiric treatment should be considered in these cases.

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References

“If God exists, I hope he has a good excuse”

Woody Allen (born 1935), American actor, author, filmmaker, comedian, playwright and musician, whose career spans more than six decades. As a comedian, he developed the persona of an insecure, intellectual, fretful nebbish, which he maintains is quite different from his real-life personality. In 2004, Comedy Central ranked Allen in fourth place on a list of the 100 greatest stand-up comedians, while a UK survey ranked Allen as the third greatest comedian. By the mid-1960s Allen was writing and directing films, first specializing in slapstick comedies before moving into dramatic material influenced by European art cinema during the 1970s, and alternating between comedies and dramas to the present. He often stars in his films, typically in the persona he developed as a standup. Some best-known of his over 40 films are Annie Hall, Manhattan, and Hannah and Her Sisters. In 2007 he said Stardust Memories, The Purple Rose of Cairo, and Match Point were his best films. Critic Roger Ebert described Allen as “a treasure of the cinema”