

Case Report

A case of brucellosis displaying Parkinsonian-like tremor

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Abstract

We report a rare case of brucellosis with Parkinsonian-like tremor and simple partial motor seizure. This patient worked as a sheep butcher and the sheep were imported from brucellosis-endemic areas. He presented with classical manifestations of brucellosis; infection was confirmed using the Rose Bengal Plate and Standard Tube Agglutination tests. The patient also suffered from headache, partial seizures, changes of personality and static tremor of both upper limbs. After anti-infection therapy, but without the use of anti-Parkinson drugs, the patient fully recovered and remained free of Parkinsonian-like tremor. Brucellosis can present with atypical symptoms, clinicians should widen their diagnostic view of *brucella* infection.

Key words: brucellosis; Parkinsonian-like tremor

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Introduction

Brucellosis is a zoonotic infection caused by the Gram-negative coccobacillus *Brucella* and as many as 500 000 new cases are diagnosed globally each year [1]. Consistent with the global trend, the incidence of brucellosis in China is also increasing. Brucellosis is clinically characterized by fever, joint pain, night sweats, weight loss and hepatosplenomegaly. It is generally believed that only 4% of the patients have neurological manifestations accompanying these symptoms [2-5]; these conditions vary widely and include polyradiculitis, myelopathy, encephalitis, or meningitis [6], brain or epidural abscess [7,8], injury of cranial nerve [3,9-11], transient ischemic attack and other vascular diseases [12,13], altered mental status [14]. Parkinsonian-like tremor is rare. Here we report a case of brucellosis with this unusual manifestation.

Clinical Information

A 52-year-old man employed as a sheep butcher, was admitted to the Infectious Department, the First Affiliated Hospital with Nanjing Medical University, Jiangsu Province, China, with periodic episodes of fever, joint pain and night-sweat for more than eight months and persistent headache for two weeks. The patient also complained of weight loss during the long course of fever. Five months before hospitalization, he began to receive oxytetracycline; this treatment was based on the diagnosis of brucellosis which drawn

from positive serum Rose Bengal Plate and Standard Tube Agglutination tests performed by Yixing Center for Disease Control and Prevention (the latter is 1:400). Initial antibiotic treatment was ineffective. Two months prior to hospitalization, levofloxacin therapy was initiated; as a result, the patient experiences relief of the joint pain but fever continued. Two weeks before hospitalization the patient developed paroxysmal headache, partial seizures, increased irritability and bad temper.

Physical examination on admission was normal except for elevated temperature (38°C). Neurologic examination revealed static tremor of both upper limbs; this was aggravated when nervous, and relieved during exercise. Other nervous system-associated clinical manifestations such as bradykinesia, rigidity or gait disturbance were not detected.

Laboratory examinations revealed a mildly increased neutrophil population, mildly decreased lymphocyte number in blood and serum ferritin of 445.00ug/L. Cerebrospinal fluid (CSF) was colorless and clear appearance during examination, with a pressure of 90 drops per minute, positive Pandy's test and protein of 1.70g/L, glucose of 3.3mmol/L, chloride of 111.7mmol/L, and IgG of 0.194g/L. Furthermore, the WBC count of CSF was $95 \times 10^6/L$ with granulocytes accounting for 66%, lymphocytes 31%. Routine urine and stool, serum sodium, calcium, phosphorus, magnesium, glucose, liver enzymes,

creatinine, urea nitrogen, fibrinogen, antithrombin III, prothrombin time, activated partial thromboplastin time, C-reactive protein and erythrocyte sedimentation rate were within the normal ranges. Tests for *Mycobacterium tuberculosis* infection included the PPD test, γ -IFN and 38kD-IgG of in serum, and T-SPOT•TB which enumerated the number of effector T-cells responding to stimulation by peptides simulating ESAT-6 and CFP-10 antigens were all negative. Neither unenhanced nor enhanced 3T cranial magnetic resonance imaging showed any abnormal signals including the symmetrical abnormal signal. Unfortunately, the patient refused to allow EEG and cognitive tests to be performed.

Treatment with trimethoprim/sulfamethoxazole (TMP-SMZ) 160mg/800mg every twelve hours and daily levofloxacin (500mg/day) was initiated. Two weeks after initiation of therapy, CSF analysis was repeated and all of the abnormal indexes returned to the just outside the normal range. Antibiotic therapy was continued for three months. Patient follow-up after nine months indicated that the patient had fully recovered and remained free of fever, headache, seizure and tremor.

Discussion

Brucellosis is an endemic disease in many areas of the globe, including China. However, the disease is rare in Jiangsu Province, a non-brucellosis endemic area located in the east of China. But as the source of infection has not been effectively controlled and the business and exchange between different areas rapidly increases, imported cases and introduction of *brucella*-infected sheep from endemic to non-endemic areas are often reported [15,16]. Due to the lack of specificity of symptoms and signs, brucellosis with neurological manifestations is very easy to misdiagnose and is often followed by sequelae of nervous system and even death [17].

The patient in this study worked as a sheep butcher handling sheep that were imported from brucellosis-endemic areas, such as Inner Mongolia, Shanxi and Heilongjiang. Based on the clinical features and laboratory results, definite diagnosis of brucellosis was made in this case. Taking the long duration of symptoms into account, we believed that the patient was in the sub-acute phase of brucellosis. And neurological disorders together with high protein level and increased cell number in CSF indicated that there was something wrong with the central nervous system. However, diagnosis of neurobrucellosis was improbable because we didn't carry out the CSF

agglutination test for brucellosis and the CSF brucella culture was negative.

Although there are reports about involuntary muscular movement during brucellosis [18-20], Parkinsonian-like tremor is rare. In this case, the tremor associated with the upper limbs manifested as static tremor which became aggravated when nervous but relieved during exercise; the symptoms disappeared after antibiotic treatment for brucellosis, in the absence of treatment with any anticholinergic drugs or levodopa. MRI examination of this patient excluded intracranial tumors, cerebral hemorrhage, Fahr syndrome and other neurological syndromes. As to the CSF examination, clear and colorless appearance, high protein content, increased IgG values and decreased chloride were consistent with many chronic central nervous system infections including neurobrucellosis [5,13,21]. But contrary to previous studies, the increase of CSF cell in this patient was mainly attributed to neutrophils and this may be relevant to the long duration of symptoms and the long-term use of antibiotics. Not surprisingly, CSF cultures were negative for *Brucella*; this has been documented previously [5,21]. CSF changes associated with *Brucella*-infected patients are similar to those observed for tuberculous-associated meningitis, therefore we conducted several tests to rule out *M. tuberculosis* infection, all of which were negative. Collectively, these results suggest that the Parkinsonian-like tremor associated with this patient was likely to be caused by the brucellosis infection. Our interpretation is consistent with limited reports available in the literature. Mousa *et al.* found one patient had temporary Parkinsonian-like tremor in ten patients with *Brucella*-associated meningitis [5]. Molins *et al.* revealed that an increasing slow and unsteady gait with tremor in both hands appeared in one patient two months after complete recovery who was suspected to suffer with brucellosis [22]. Levodopa and bromocriptine treatment based on the diagnosis of Parkinson's disease did not help but anti-infection therapy with doxycycline, rifampin and streptomycin resulted in resolution of the hand tremor [22]. Doctors must widen their diagnostic perspective when faced with atypical cases like this one, including a diagnosis of brucellosis to explain all of the observed clinical manifestations.

Our observation suggests that the pathogenesis of temporary static tremor in brucellosis is different from that associated with Parkinson's disease. It may be a focal encephalitis with circumscribed symptoms, related to concurrent treatment, owing to an

idiosyncratic immunological reaction [22,23]. Molins *et al.* argues a post-synaptic dopamine receptor lesion might be involved, such as corpus striatum vascular inflammation similar to that observed in syphilitic Parkinsonism, since the tremor was unresponsive to levodopa and bromocriptine [22]. Together these results suggest that the key to the treatment of brucellosis with Parkinsonian-like tremor is anti-infection therapy; anti-Parkinson drugs are unlikely to be effective.

Like tubercle bacillus, *Brucella* species are facultative intracellular bacteria. Elimination of the bacteria is essential to block direct damage mediated by the organism itself or indirect damage mediated by possible delayed hypersensitivity or demyelination originating from the repeated stimulation of the immune system caused by bacterial components such as toxins or metabolites [24]. Previous studies indicated that, for early treatment of neurobrucellosis has a greater impact on positive patient outcome, patients suffering from a long infection of brucellosis more often respond to treatment slowly and with accompanied sequelae [25]. This patient didn't receive any antibiotic until he was diagnosed with brucellosis two months after the onset of fever. Another problem in the treatment at local hospitals was that the doctors made up a prescription of monotherapy with Oxytetracycline or Levofloxacin, this treatment strategy had been proven to be ineffective [5,26-28] and would promote the generation of drug-resistance easily. Therefore, in our opinion, doctors should follow the principles of chemotherapy of tuberculosis "early, regular, entire journey, sufficient quantum and combination", in other words, early treatment to rapidly kill the bacteria, regular medication to avoid drug resistance, entire journey of treatment to reduce recurrence, sufficient quantum to prevent resistance and reduce the drug toxicity, and combination therapy to enhance efficacy. Given the resistance associated with use of oxytetracycline and the side effects after long-term use of streptomycin and rifampin, we recommend the combination therapy of levofloxacin and TMP-SMZ; this is also in agreement with the guideline issued by the Public Health Directorate, European Commission, Luxembourg [29] The above two kinds of drugs could penetrate effectively into cells, maintain an effective therapeutic plasma drug concentration for a long time, but with a low relapse rate [12, 16, 25, 29-32].

In summary, clinical manifestations of brucellosis are complex and easily misdiagnosed. Neurological disorders manifesting as Parkinsonian-like tremor in

patients with brucellosis are rare but clinicians should fully understand the patient's medical history, especially the epidemiological information, and should consider brucellosis in the differential diagnosis in high-risk populations.

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