

Case Report

***Mycobacterium tuberculosis* infection with clinically mild encephalitis/encephalopathy accompanied by reversible splenium lesion of the corpus callosum: a case report and analysis**

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Received November 6, 2016; Accepted December 8, 2016; Epub April 15, 2017; Published April 30, 2017

Abstract: Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) of the corpus callosum is caused by many factors, and the main pathogenesis is due to virus infection. However, *Mycobacterium tuberculosis* has not been regarded as a pathogenesis. To explore the association between *M. tuberculosis* and MERS, a patient with MERS in our hospital was analyzed to investigate the association. The pathogenic microorganism in the patient was diagnosed as *M. tuberculosis*, and its clinical symptoms were similar to the viral infection. Magnetic resonance imaging of the brain showed that the disease was characterized by reversible and isolated lesions of the splenium of the corpus callosum and disappeared in a short duration with good prognosis. MERS is also caused by *M. tuberculosis*.

Keywords: *Mycobacterium tuberculosis*, encephalitis, encephalopathy, corpus callosum

Introduction

The clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) of the corpus callosum, a syndrome, is common in febrile illness of Japanese children. This disease is characterized by reversible lesions of the splenium of the corpus callosum from the magnetic resonance imaging (MRI) of the brain, and sometimes white matter lesions of bilateral symmetry are involved. The clinical symptoms are mild and can be fully resolved within a month [1], without sequelae. This disease was at first reported by Tada, Japanese, and since 2008 relevant studies were also reported from China [2]. The lesions of the corpus callosum occur due to many causes such as inflammation, infarction, tumor, demyelination, status epilepticus, reduction in the excessive long-term use of antiepileptic drugs, etc.

The major cause for MERS is virus infection and the pathogen could not be identified in 40% of patients. In the patients where pathogens are found, the two most common pathogens are the influenza viruses A and B, followed by

mumps virus, adenovirus, and rotavirus, *Streptococcus*, and *Escherichia coli*. Moreover, other researchers have documented that the disease is also associated with varicellazoster virus, Epstein-Barrvirus, *Legionella pneumophila*, and *Staphylococcus aureus*. The reasons for infection include *Mycoplasma pneumoniae* accompanied with rotavirus infection, adenovirus infection, *Cryptococcus neoformans*, swine influenza virus infection, mumps vaccine, and pneumococcal infection. However, at present, no clinical study related to MERS caused by *Mycobacterium tuberculosis* infection is available. In the present study, a retrospective analysis of a patient who was diagnosed with MERS in our department was performed to explore the pathogenesis and imaging features, improving clinical diagnosis of the disease.

Case report

Case

A 39-year-old male patient had major complaints of acute mouth askew and slurred speech for 2 days before hospitalization, and

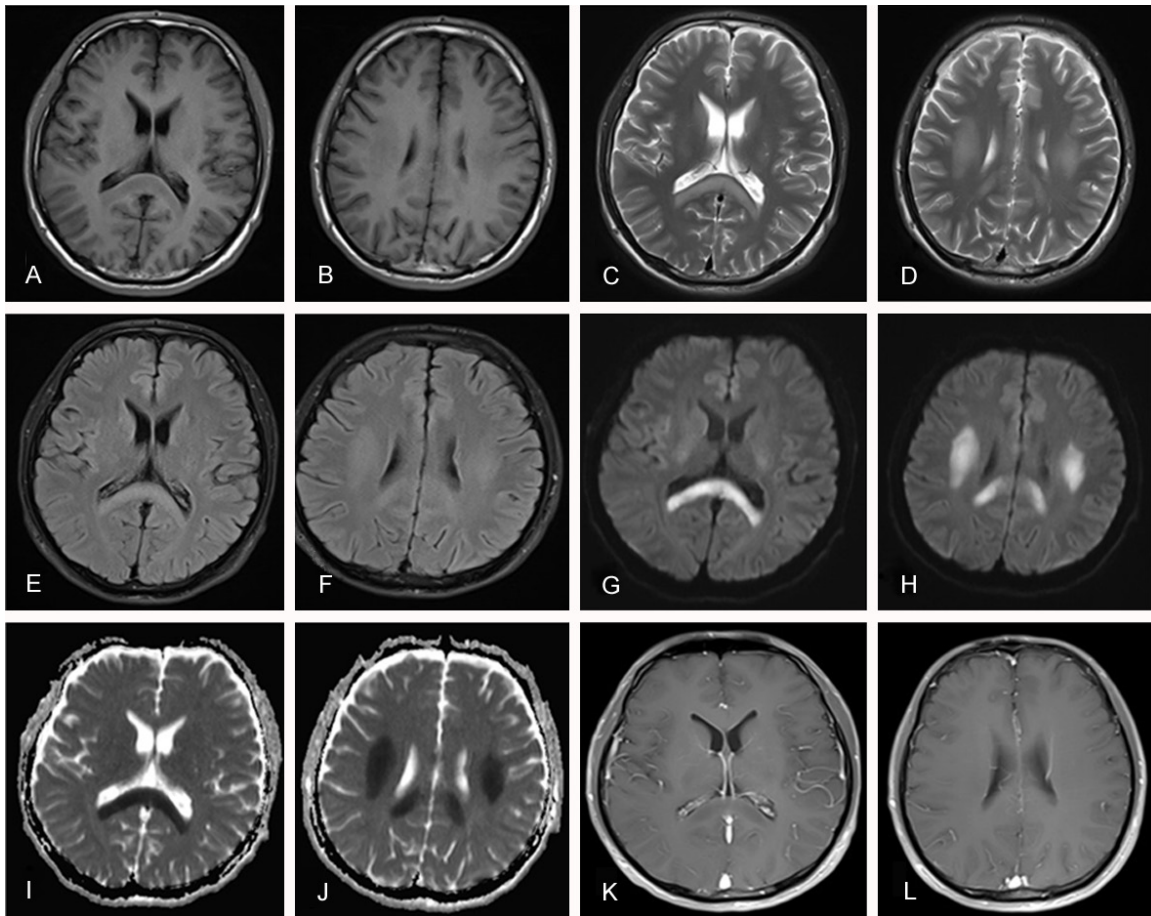


Figure 1. MRI lesions of the brain involved the splenium of corpus callosum and white matter of bilateral radial area. A, B. T1WI low signal; C, D. T2WI slight signal; E, F. FLAIR slightly higher signal; G, H. DWI high signal; I, J. ADC low signal; K, L. No change in enhancement. ADC, abnormal diffusion restriction; DWI, diffusion weighted imaging; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; WI, weighted image.

the symptoms lasted 4 h before complete remission. At 1 day before hospitalization, the patient's mouth askew and slurred speech reoccurred, accompanied by facial numbness, difficulty in breathing, wheezing, not supine, and inability in swallowing and chewing food. He was unable to speak for 3 h before hospitalization. He had no fever prior to the onset of symptoms and no history of vaccination. An examination of the patient at hospitalization showed that he was conscious, had dysarthria, had bilateral peripheral facial paralysis, had reduction in limb tendon reflexes, had unstable bilateral finger from the nose test and rapid rotation test, and had weak bilateral soft palate, resulting in difficulty in lifting. His pharyngeal reflex resolved, but an examination of other nervous systems showed that it was normal. His condition improved significantly after treatment with hormonal and gamma globulin.

After treatment for 2 days, the symptoms of mouth askew and slurred speech improved, dyspnea resolved, and the patient was able to swallow and chew food on his own and move limbs freely. At 7 days after treatment, all the symptoms disappeared completely. The patient was transferred to the "Hospital for Infectious Diseases" for relevant examination due to pulmonary space-occupying lesions during hospitalization. *M. tuberculosis* was not found in the sputum culture. The serum was negative for *M. tuberculosis* antibody. Tuberculosis could not be ruled out from the imaging studies, and the tuberculosis with negative bacteria was considered. The imaging study showed that the symptoms significantly improved after 3 months of anti-tuberculosis therapy.

Laboratory tests

The lumbar cerebrospinal fluid pressure was 210 mmH₂O and was colorless and transpar-

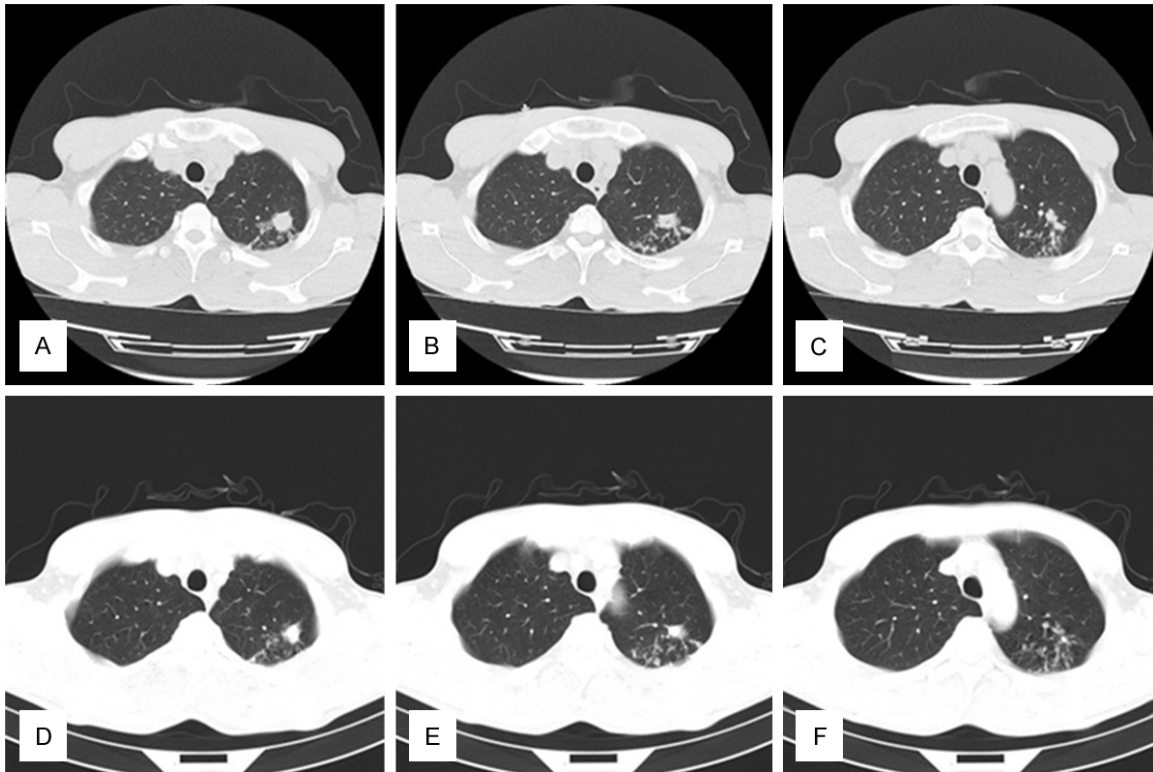


Figure 2. Visible slug high density in the left upper lobe backend and around patchy high-density shadow 3 days after pathogenesis (A-C); the slug high density became smaller and the surrounding patchy high-density shadow became larger when reviewed after 3 months (D, E); the high-density shadow in the left lung backend has got smaller than it was three months ago (D, F).

ent. Result of routine biochemistry test showed that it was normal. The result of exfoliocyto-logical examination was normal. The cerebrospinal fluid tuberculosis antibody, cerebrospinal fluid tuberculosis virus antibody, cerebrospinal fluid herpes simplex virus antibody, cytomegalovirus antibody, and Coxsackie virus antibody were negative. The results of adenosine deaminase and ink stain were normal.

Imaging

The results of MRI lesions of the brain are shown in **Figure 1**. It was found that the lesions of the brain involved the splenium of corpus callosum and white matter of bilateral radial area (**Figure 1**), and visible slug high density in the left upper lobe backend and surrounding patchy high-density shadow appeared 3 days after pathogenesis (**Figure 2A-C**). The slug high density became smaller and the surrounding patchy high-density shadow became larger when reviewed after 3 months (**Figure 2D-F**). The MRI lesions of the brain involved only the corpus callosum 25 days after diagnosis, and

the results are presented in **Figure 3**. The MRI lesions of the brain involved only the corpus callosum 60 days after the diagnosis, and the results are shown in **Figure 4**. Compared with 25 days after the diagnosis, 60 days after the diagnosis showed smaller lesions and lower signals.

Discussion

The clinical MERS is characterized by the brain MRI findings of reversible lesions in the splenium of corpus callosum; sometimes white matter lesions of the bilateral symmetry are involved. The clinical features of the disease are nonspecific, and it usually represents the clinical syndrome of encephalitis or encephalopathy. The corpus callosum is located beneath the cortex in the eutherian brain at the longitudinal fissure. It comprises the fibers that connect the left and right hemisphere cortical. It is categorized into the mouth, knees, trunk, and splenium. The myelin sheath of the corpus callosum has higher water content with abnormal water electrolyte metabolism, abnormal

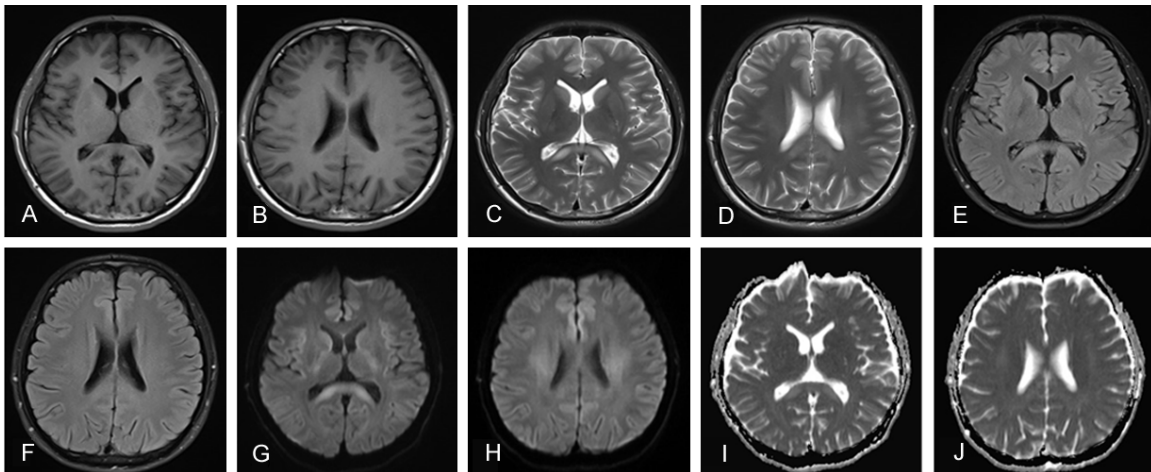


Figure 3. MRI lesions of the brain involved only the corpus callosum 25 days after diagnosis. A. T1WI low signal; B. Normal signal; C. T2WI high signal; D. Normal signal; E. FLAIR slightly higher signal; F. Normal signal; G, H. DWI high signal; I. ADC low signal; J. Normal signal. ADC, abnormal diffusion restriction; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; WI, weighted image.

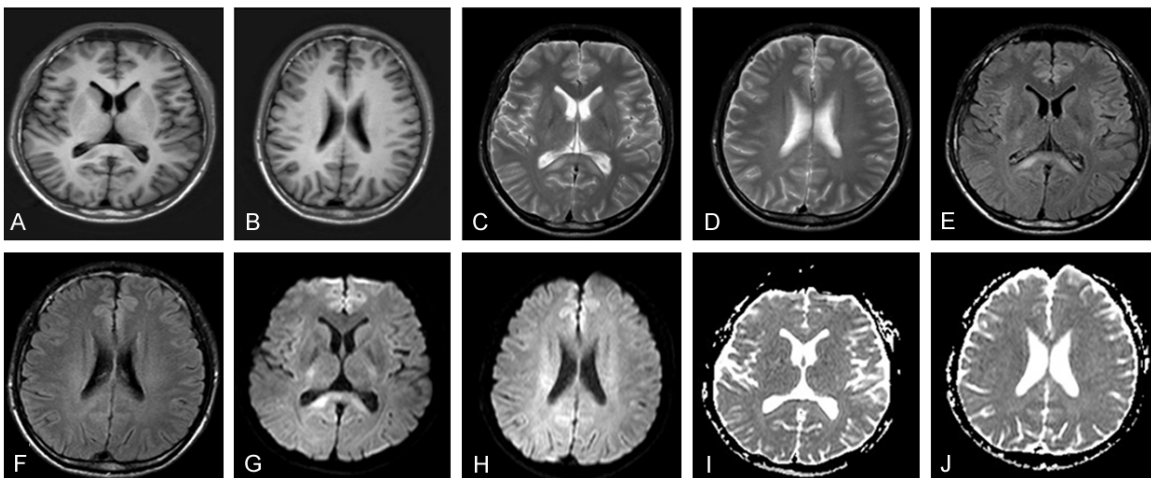


Figure 4. MRI lesions of the brain involved only the corpus callosum 60 days after the diagnosis. A. T1WI lower signal; B. Normal signal; C. T2WI slightly higher signal; D. Normal signal; E. FLAIR high signal; F. Normal signal; G. DWI high signal; H. Normal signal; I. ADC signals; J. Normal signal. ADC, abnormal diffusion restriction; DWI, diffusion weighted imaging; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; WI, weighted image.

ion transport, and insufficient self-regulation and protection, which limits diffusion of moisture. Thus, it is more likely for this site to have cytotoxic edema and vasogenic edema, compared with other sites [3]. In this study, the MRI scan of the brain found that there were long strip T1 signal, long T2 signal, high FLAIR signal, high diffusion-weighted imaging (DWI) signal, and low abnormal diffusion restriction (ADC) signal, which were consistent with the lesions of the patient. And the cytotoxic edema was considered as a secondary lesion.

Vasogenic edema exhibits high diffusion, increased ADC value, and high DWI signal due to the increase in extracellular water [4]. To investigate why MERS lesions were reversible, Kerstin [5] et al. used diffusion tensor imaging and functional MRI imaging technology in patients with epilepsy and showed that cytotoxic edema isolated from the corpus callosum belonged to glial cells (myelin sheath) without destroying the nerve fibers; Hence the disease is reversible. The pathogenesis of MERS is not yet clear. At present, a number of studies have

shown that the manifestation of the nervous system for MERS is induced by pro-inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor- α (TNF- α), 5, soluble TNF receptor-1 (sTNFR-1), and other causes [6].

Tuberculosis is a chronic infectious disease caused by human-type or *Bacillus tuberculosis bovis*. The formation of void is the common evolution, and it furthermore shows the progress of the lesions and activities of tuberculosis. After the formation of void, *M. tuberculosis* is excreted through the sputum, and a number of *M. tuberculosis* enter into the blood vessels within the lesion and participate in the circulation of blood. Cytokines form complex networks during the immune response and have specific biological effects that play important roles in the immune response. It can not only help to limit and exclude pathogens, but also may cause pathological damage to the immune system. IL-6, produced by the Th2 cells, has multiple immune functions, takes part in the early inflammatory response, and has significantly higher levels in the peripheral blood inpatients with tuberculosis [7].

After lung injury, the macrophages release large amounts of TNF- α , which not only increase the inflammatory response, but also promote the proliferation of fibroblasts and secretion of collagen [8]. The biological process of TNF must be mediated by its receptor, TNFR. TNFR, which consists of TNFR1 and TNFR2 types, is distributed on the surface of a variety of tumor and normal cells. sTNFR-1, derived from the surface of TNFR cells, is the fragment from the outer segment of TNFR-1 cells after proteolysis. Its main function is to compete with TNFR for TNF with high affinity and specificity, thus limiting the binding between TNF and TNFR, inhibiting the activity of TNF, and resulting in TNF lose its cytotoxicity for its target organs [9]. All these results indicate that inpatients with cavitary pulmonary tuberculosis, the IL-6, TNF- α , and soluble TNFR-1 are present abundantly in the blood, and later enter the brain tissue through the blood-brain barrier, leading to inflammation and a series of clinical symptoms and imaging changes.

Some studies have categorized MERS into I and II types based on the MRI imaging. The lesions of type I involve only the splenium of the corpus callosum, while type II not only involve the splenium of the corpus callosum, but also other

sites of cerebral white matter. And compared with the lesions of the splenium of the corpus callosum, the white matter lesions are absorbed earlier. After short-term treatment, type II converted into type I, and finally the lesions completely disappear. The patient in this study had type II, and the lesions were in the splenium of the corpus callosum and white matter in the bilateral radial area. The lesions of the white matter in the bilateral radial area disappear 25 days after treatment, while the lesions of the splenium of the corpus callosum were still present 60 days after treatment. However, ADC sequence completely disappeared and DWI sequence partly disappeared, indicating that the cytotoxic edema gradually fades away.

Ni and Cheng [10] measured the serum antibody level of tuberculosis in 304 patients with tuberculosis, and the positive rate was 74.0% for patients with tuberculosis, which signifies that the serum antibody of tuberculosis has limitation in diagnosing tuberculosis. Even if the sputum smear is currently the most important approach for diagnosing tuberculosis, the positive rate is low ranging from 25 to 35%, and there were still about 65-75% negative smear or culture-negative suspected TB diagnostic problem [11]. All these imply although both the serum and sputum *M. tuberculosis* antibody were negative, the patient was still diagnosed to have tuberculosis, i.e. negative bacteria Tuberculosis. In this study, the patient had negative serum antibody and sputum *M. tuberculosis*, which belongs to negative bacteria Tuberculosis. After standardized treatment of tuberculosis, the lesions became smaller and the surrounding satellite lesions appeared. Hence the diagnosis of tuberculosis was established, which is negative bacteria Tuberculosis.

No specific treatment is available. Studies from other countries have reported that methylprednisolone shock therapy, dexamethasone therapy, anti-epileptic drugs for short-term therapy, antiviral therapy, or injection of gamma globulin can have good prognosis, with complete disappearance of neurological symptoms and without any sequelae. The prognosis is good even without special medical treatment. The symptoms of the patient in this study have obviously improved after treatment with dexamethasone and gamma globulin, which is consistent with the previous studies.

The factors caused by mild encephalitis/encephalopathy

In summary, MERS is a new imaging and clinical syndrome with unique clinical features and good prognosis. Its etiology is basically clear, while its pathogenesis is still unknown. A number of relevant studies have been performed in other countries, especially Japan. In China, MERS has not attracted enough attention. It is hoped that clinicians especially neurologists have sufficient knowledge about MERS to avoid unnecessary examinations and improper treatment.

Acknowledgements

This study was funded by Medical Foundation of Shanghai Jiao Tong University.

Disclosure of conflict of interest

None.

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