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Case Report

Differential diagnosis between Creutzfeldt-Jakob disease and limbic encephalitis: a case report

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Abstract: Creutzfeldt-Jakob disease (CJD) is a degenerative disease of the nervous system, which is transmissible and dominantly inherited, caused by prion protein. CJD was divided into sporadic, inherited or acquired by infection types, in which the sporadic CJD accounted for 90%. Limbic encephalitis (LE) is another inflammatory disease of central nerve system with acute or sub-acute onset and clinical manifestations of recent memory deficit, mental and behavioral abnormalities and epilepsy of marginal textures like hippocampus, amygdaloid nucleus, insular lobe and cortex of gyrus cinguli. These two diseases are both clinically rare, and they often have many similar symptoms, so the differential diagnosis is challenging, especially in the elderly patients. In this paper, we reported a patient of Creutzfeldt-Jakob disease with nontypical symptoms.

Keywords: Creutzfeldt-Jakob disease, limbic encephalitis, differential diagnosis

Case report

The patient and his family members had been informed and agreed to report this case and the related images, and the report had been approved by the Ethics Committee of Ethical Research under Zhujiang Hospital of Southern Medical University.

Male patient, 72 years old, admitted to hospital on June 30, 2015 for headache, fever and unconsciousness for over a month. The patient had headache for about a month, with paroxysmal exacerbation, especially on occipitalia. Then the patient gradually got a fever, with highest body temperature of 39.5°C, but had no symptoms like nausea, emesis or limb exercise disorder. In local hospital, it was regarded as encephalopathy. Therefore the patient was treated through anti-inflammatory and anti-infection treatment. The state of patient did not get better and still had a fever repeatedly, and symptom of gatism appeared and the level of consciousness gradually decreased, with regular myoclonus onset of the limbs at 2-3 times/minute. For further diagnosis and treatment, the outpatient service accepted the hospital admission for "intracranial infection". Physical examination of nervous system: state of lethargy, eyes opening for short time by pressing eye socket, pupil at both sides with equal size and the same circle with diameter of 2.0 mm, sensitive to light reflex, doll head test being positive, no nystagmus, symmetrical frontal striation and nasolabial groove at two sides, great rise of tension of limb muscles, buckling of limb under pain stimulation, symmetrical rise of limb tendon reflex, positive ankle clonus at two sides, kneecap clonus not being found, positive Babinski sign of both lower extremities, neck having no resistance, Brudzinski's sign and cruveilher sign not being found.

Blood routine examination and blood biochemistry were shown in **Table 1** after the hospital admission. On June 30, 2015, the tested brain pressure through lumbar puncture was 160 mmH_2O. Cerebrospinal fluid routine examination and cerebrospinal fluid biochemistry were shown in **Table 2**. Etiology tests of germs and fungus related to cerebrospinal fluid were all negative. Autoimmunity indicator and vasculitis indicators were all normal. Head MRI showed multiple patch on the right cerebellar hemi-

Table 1. Results of blood examination and biochemistry

	2015/7/1	2015/7/12
White blood cell	4.06 G/L	8.57 G/L
Neutrophil	2.65 G/L	5.00 G/L
Neutrophil percent	65.30%	58.30%
Lymphocyte	0.71 G/L	1.03 G/L
Lymphocyte percent	17.50%	12%
Monocyte	0.67 G/L	2.54 G/L
Monocyte percent	16.50%	29.60%
Red blood cell	3.23 T/L	2.88 T/L
Hemoglobin	100 g/L	90 g/L
Sodium	129.9 mmol/L	127.7 mmol/L
Chlorine	89.3 mmol/L	86.7 mmol/L
Albumin	36.3 g/L	32.9 g/L
Globulin	28.9 g/L	23.8 g/L
Cystatin C	0.81 mg/L	0.95 mg/L
Osmotic pressure	280 mOsm/L	283 mOsm/L
Simple virus IgM antibody	I+II<0.5 S/CO	N/A
Simple virus IgG antibody	I+II>30.0 S/CO	N/A
C reactive protein	8.06 mg/L	15.3 mg/L

Table 2. Results ofcerebrospinal fluid examination and biochemistry

	2015-06-30	2015-07-08
Glucose	2.5 mmol/L	4.0 mmol/L
Blood glucose at fingertip	10 mmol/L	8 mmol/L
Lactic acid	4.8 mmol/L	5.9 mmol/L
Adenosine deaminase	9.1 IU/L	6.9 IU/L
Protein	2452 mg/L	1442 mg/L
Chlorine	112.9 mmol/L	112.9 mmol/L
Red blood cell (microscopic examination)	0 M/L	0 M/L
Cerebrospinal fluid pressure	160 mmH_2O	100 mmH_2O

spheres and brainstem with abnormal signals of long flake T1 and T2, and obvious Flair image, and few abnormal signals of long flake T1 and T2 in basal ganglia region at both sides, corona radiata area and centrum semiovale, and obvious Flair image. No abnormality was seen in other brain parenchyma, cerebral cistern.Sulus slightly broadened, supratentorial ventricle extended, and median metathsis had no skewing (as shown in **Figure 1**). Electroencephalogram upon hospital admission showed a basic rhythm disassembly on bilateral hemisphere, waveform disorder, bad adjustment and amplitude, and dissymmetrical amplitude and wave rate. Too many 4-7 HZ and 20-50 μVθ activities and many 2.8-3.6 HZ and 30-50 μVδ activities widely appeared in each lead. Onset wave was not found in the whole process.

According to the medical history and relevant examination of the patient, diagnosis of viral, bacterial or fungoid encephalitis is nearly eliminated. The symptoms of the patient like progressive disturbance of consciousness and serious hyponatremia were similar with that of LE. Tumor indicators: glycogen antigen-72-415.1 KU/L (normal: 0-6.9), neuronspecific enolase-21.4 ug/L, and no other abnormality seen. CT of lung: inflammation on outside of the right and middle of lung and the double bottom lung, and tubercule under pleura at front end of the right up lung, being considered as benign lesion. The patient also presented pleural effusion on the right side, incrassation of pleura on both sides, and aortosclerosis. However, MR focused on brain of the patient did not distribute along the limbic system, but multiple patches and abnormal signals of long flake T1 and T2 were found in the right cerebellar hemispheres and brainstem. During the pathogenetic process, the patient had balderdash and disturbance of consciousness with progressive exacerbation (patient in slight comatose state on the third day upon hospital admission), and continuous and regular myoclonus appeared. Sporadic CJD could not be eliminated, but MR focus on brain of the patient had non-cortex variation in the form of “waistband or lace”, and no “three-phase wave” is seen in the electroencephalogram upon hospital admission. In order to differential the two diagnoses, we carried out lumbar puncture on July 8, 2015 again, and the tested brain pressure was 100 mmH_2O.

After hospital admission, treatment was conducted: hormone and gamma globulin impact therapy (0.4 g/Kg·d), continuously used for 3 d

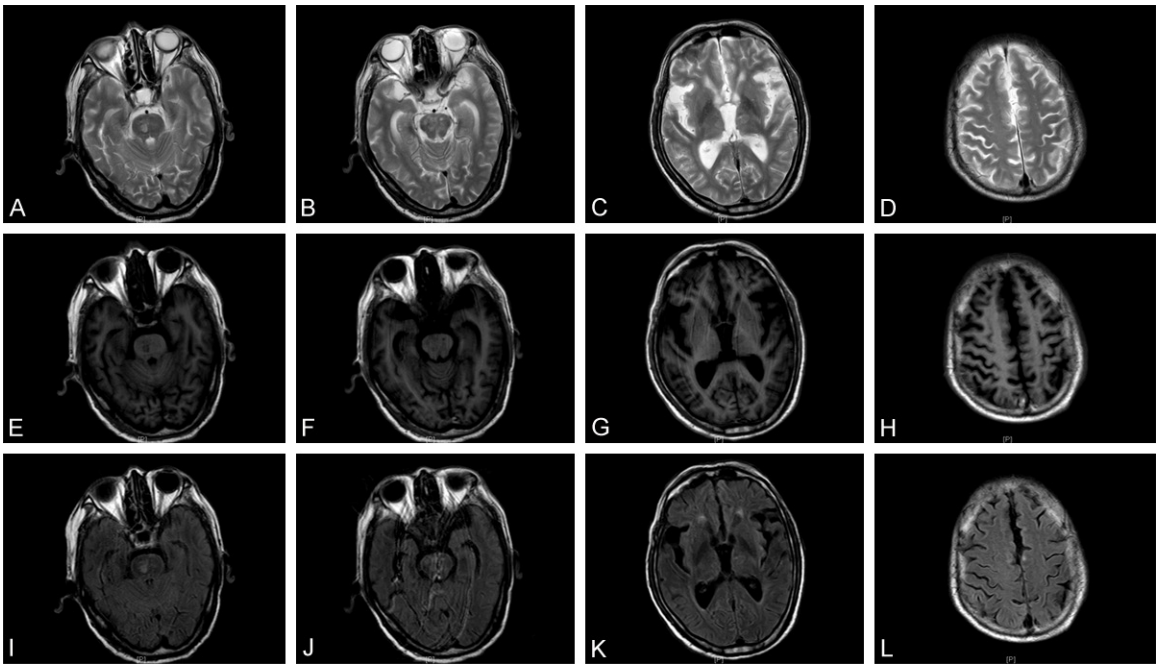

Figure 1. The MRI of cranium shows that there are multiple patching or dot abnormal signals of long T1 (E-H) and T2 (A-D) of the right cerebellar hemisphere and the brain stem, especially in Flair (I-L). And there are small amounts of patching abnormal signals of long T1 and T2 of bilateral basal ganglia, corona radiate and centrum ovale, especially in Flair. The rest parenchyma shows no abnormal signal, while the cistern and the sulcus widen and the cerebral ventricles over the tentorium enlarge. The median structure doesn't deflect.

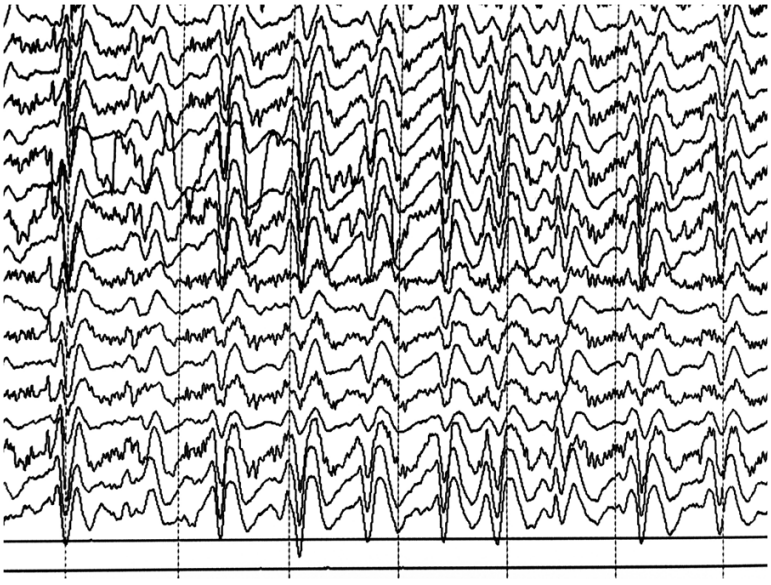

Figure 2. This EEG shows typical compounds of paroxysmal and large amplitude waves.

for diagnostic treatment, and other supplement treatment. Cerebrospinal fluid routine examination and cerebrospinal fluid biochemistry were shown in **Table 2**. On July 14, 2015, Guangzhou Jinyu Testing Center reported: autoimmunity encephalitis antibody and the antibodies related to tumour syndrome were all negative, and limbic encephalitis could be almost eliminated. Through the treatment above, the patient did not get better obviously. On July 16, 2015, Electroencephalogram in reexamination indicated: typical paroxysmal compound with large amplitude wave could be seen (as indicated in **Figure 2**). And the patient died on July 20, 2015. On August 3, 2015, Guangdong Center for Disease Control reported that the cerebrospinal fluid 14-3-3 protein was positive, PRNP gene detection indicated the polymorphism of 129 amino acid was M/M type, and that of 219 amino acid was E/E type, and no mutation related to genotype CJD was found. So it was suspiciously sporadic CJD.

Discussion

Creutzfeldt-Jakob disease (CJD) is a fatal neurodegenerative disease characterized by rapidly progressive dementia caused by prion protein propagation [1, 2]. In 1979, Hadlow *et al.* [3] reported that the infectious agent was found in non-neural tissue, e.g., stomach, intestine, and the lymphatic system, even prior to clinical symptoms. The major symptoms of LE [4, 5] includes acute or subacute onset, and presents serious short-term dysmnesia, anterograde amnesia, and mostly complex partial or secondary onset of general epileptic seizure and mental symptoms like anxiety, depression, irritability, personality changes, acute insanity and hallucination. Some patients may have symptoms involving the limbic system and external brain tissue, such as cerebellum and brainstem.

The diagnosis of CJD shall conform to the following standards issued in 2009 [6]. (1) Progressive dementia; (2) At least 2 kinds of the clinical symptoms below: myoclonus, visual or cerebellum disorder, pyramid sign or dysfunction of extrapyramidal system and akinetic-mutism; (3) At least 1 positive result in the examinations below: 1) Typical presentation of electroencephalogram, namely, 1-2 times of typical three-phase wave per second; 2) Positive14-3-3 protein in cerebrospinal fluid examination, and course of disease clinically less than 2 years; 3) Signal of abnormally high caudate nucleus and (or) putamen on DWI image or FLAIR image through MRI examination. If 3 items are diagnosed and no other diagnosis is proposed in the routine examination, it can be probably diagnosed as "CJD"; if only the first 2 items are diagnosed, and no typical variation is found in electroencephalogram, and course of disease is less than 2 years, it can be possibly diagnosed as "CJD". According to the family members of the patient, he got solitary in the last one year, memory got worse, and after attack, the disturbance of consciousness of the patient got more serious and covered up the clinical symptoms of dementia. The patient had regular and continuous myoclonus and pyramid sign, and typical paroxysmal compound with large amplitude wave were found in electroencephalogram in the reexamination before leaving hospital, and 14-3-3 was positive in cerebrospinal fluid examination, and the clinical course of disease was less than 2 years, so the definite diagnosis of sporadic CJD reached the standards of diagnosis. The patient's death within a short period after leaving hospital has further proved it, and diagnosis in pathology has not been made because the patients' family did not allow the brain biopsy.

The case indicated that the focus of CJD in brain could similarly appear in brainstem. The patient had symptoms including progressive disturbance of consciousness based on dementia, and symptoms similar to intracranial infection like fever and headache. At the early period, the electroencephalogram might present diffuse slow wave, and turn into "three-phase wave" at the terminal stage due to the influence on brainstem.

In conclusion, considering this case, the understanding about sporadic CJD must be enhanced in clinic, so as to thicken the diagnosis of this disease for the patient with progressive disturbance of consciousness, and continuous and regular myoclonic seizure who has no effective results to immune regulation therapy.

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Disclosure of conflict of interest

None.

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