AINO JOURNAL, Vol. 6, 2007, pp. 75 – 78

Case Report

"Probable" and "definitive" diagnosis of a formidable disease: Creutzfeldt-Jacob disease

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Abstract

A 75-year-old female with rapidly progressive dementia, pyramidal and extrapyramidal signs, myoclonus, and mutism received a diagnosis of probable sporadic Creutzfeldt-Jakob disease (sCJD) after eliminating other possible candidates, such as normal pressure hydrocephalus (NPH), some form of encephalopathy, and so on. However, postmortem brain biopsy revealed the case to be non-CJD. Facing the triad of progressive dementia, myoclonus, and pyramidal/extrapyramidal features, Alzheimer's disease (AD) should be retrospectively considered if the disease course is long and dementia with Lewy bodies (DLB) is the differential diagnosis if Parkinsonism is present. Findings on electroencephalogram (EEG) or in cerebrospinal fluid (CSF) typical of CJD do not exclude AD or DLB.

Key words: CJD, differential diagnosis

Introduction

Creutzfeldt-Jakob disease (CJD) is the main representative of transmissible fatal prion diseases of the brain, and may be sporadic in most cases (Prusiner SB, 1998). Clinical examination yields only a suspected diagnosis using the WHO criteria for probable or possible CJD (WHO Press release, 1998). A definite diagnosis relies upon neuropathology on autopsy and/or *in-vivo* invasive biopsy. The only one biochemical marker included in the diagnostic criteria for CJD approved by the WHO is an elevated level of 14–3–3 protein in the cerebrospinal fluid (CSF). The electroencephalography (EEG) patterns, such as the periodic sharp wave complexes (PSWCs) are also employed, but do not clearly emerge until the middle stage of CJD (Hung CI, 2007). Alzheimer's disease (AD) and Lewy body dementia (DLB) are the most frequent differential diagnoses in sporadic CJD (sCJD) in elderly patients, whereas chronic inflammatory disorders of the central nervous system must be considered in younger patients. To reduce transmission risks and avoid unnecessary treatments, a definite diagnosis in the early stage is imperative, although all differential diagnoses involve a very poor prognosis similar to CJD. We report a case in which an immunocytochemical assay via a postmortem brain biopsy denied the diagnosis of sCJD (false positive), and differential diagnoses were retrospectively outlined with an emphasis on recent progress in the diagnosis of CJD.

Case Presentation

A 75-year-old female developed rapid progression of cognitive dysfunction, pronounced speech disturbance, pyramidal/extrapyramidal signs, myoclonus, and ataxic gate disturbance over several months following an episode of the common cold. MRI findings of the brain were nonremarkable. Serological viral titers and tuberculosis were negative. There was no geographic clustering or occupational risk associated with this patient. The patient showed progressive dementia (MMSE 17/30), muscle weakness with cog-wheel rigidity, finger tremor, appetite loss, and persistent mild fever over 2–3 months

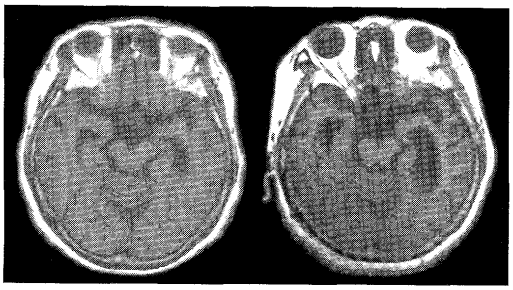

Figure 1 T1-weighted magnetic resonance images 2 and 7 months after onset. Rapid progression of diffuse cerebral atrophy occurred during the 5 months between images.

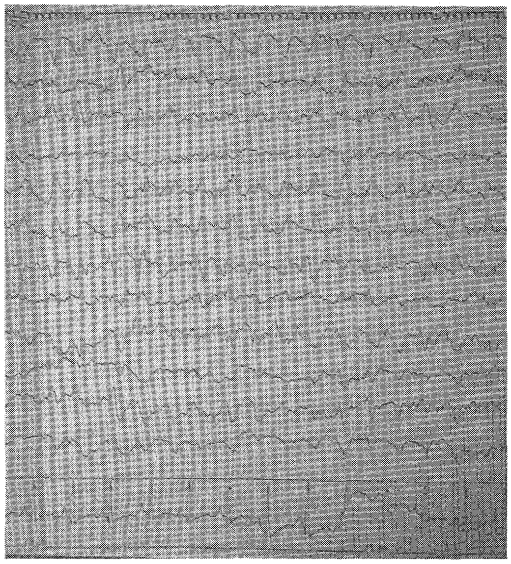

Figure 2 Electroencephalography (EEG) patterns show periodic sharp wave complexes (PSWCs) at middle stage, 5 months after onset.

following the onset. Parkinson disease and/or NPH were suspected because of progressive brain atrophy with marked ventricular enlargement and periventricular lucency (Fig. 1). However, the patient's condition worsened even after trials of anti-Parkinson drugs and/or ventriculo-peritoneal shunting. The first attack of general convulsions 5 months after the onset was investigated by EEG and CSF tap, showing positively for PSWCs (Fig. 2) and 14-3-3 protein. Finally, the patient fulfilled the diagnostic criteria for probable CJD (Fig. 3). After early and middle stages, the patient's condition remained stable in the appalic state, with non-akinetic mutism (JCS I-3), myoclonus, and occasional choleoathetoid movement for more than 2.5 years. The myoclonus

DEFINITE CJD
Neuropathologically and/or immunocytochemically confirmed
PROBABLE CJD
I + 2 of II + III or Possible + positive 14-3-3
POSSIBLE CJD
I + 2 of II + duration <2 years

I	Rapidly progressive dementia
II	A Myoclonus
	B Visual or cerebellar problems
	C Pyramidal or extrapyramidal features
	D Akinetic mutism
III	Typical EEG (periodic sharp wave complexes (PSWCs))

Figure 3 World Health Organization diagnostic classification criteria for CJD. New diagnostic criteria recommended for sporadic Creutzfeldt-Jakob disease (sCJD). Press release WHO/22, 13 February, 1998.

slightly regressed following treatment with benzodiazepines. Complications were decubital ulcers and infections of the urinary tract. The patient died from pneumonia 3 years after disease onset, and a subcortical brain biopsy of the right frontal lobe was taken via a very tiny burr hole. The removed tissues were rapidly deep-frozen (−80℃) and immunocytochemically gave a definite diagnosis of non-CJD.

Discussion

The early symptoms of CJD are unspecific. A rapid deteriorative course and typical changes of CSF markers and EEG may support the diagnosis of CJD despite incomplete clinical criteria (e. g., lack of akinetic mutism). The detection of 14-3-3 protein is highly diagnostic in patients with CJD. The 14-3-3 protein can be detected early when clinical manifestations do not allow the diagnosis of clinically definite CJD. However, testing for the 14-3-3 protein is only modestly sensitive to sCJD, and caution is stressed against ruling out a diagnosis of the disease on the basis of a negative 14-3-3 result (Geschwind MD, 2003). Even in probable cases, further detection of mutations by molecular genetic analysis is of importance to further support the diagnosis of CJD. Tauprotein and neuron-specific enolase are also promising candidates for CSF markers. Tau was reportedly increased 58-fold in CJD and 3.5-fold in AD patients compared with controls, whereas A-beta42 was decreased 0.5-

fold in both CJD and AD (Kapaki E, 2001). The tau protein concentration in the CSF is probably a useful additional marker in differentiating CJD from AD. A point mutation at codon 196 (E196K) of the prion protein gene itself is also diagnostic. In addition, codon 129 was found to be homozygous for valine (Kovacs GG, 2000).

Other diagnostic evidence of typical EEG patterns, such as PSWCs, does not clearly emerge until the middle stage of CJD (Hung CI, 2007). Our patient showed PSWCs on EEG only just after epileptic events over the entire period of illness, which might represent an unreliable and nonspecific postictal change. The effectiveness of PSWCs and the detection of 14-3-3 protein in the CSF remain controversial as diagnostic criteria for CJD (Satoh K, 2007). Diffusion weighted images (DWIs) on magnetic resonance imaging (MRI) are useful and valuable tools with reasonable sensitivity (67%) and high-level specificity (93%), and should be considered as an additional cornerstone in the clinical diagnosis of CJD (Schröter A, 2000, Kallenberg, 2001). DWI is more sensitive to detect an abnormal cortical signal intensity in the early stage of CJD undetected by T_2WI (Xin L, 2006). Diffusion-weighted magnetic resonance imaging (DWI) and the detection of total tau protein in the CSF may be a more sensitive diagnostic procedure (Satoh K, 2007). In patients with rapidly progressive dementia and focal neurological signs, CJD should be the first diagnosis to be considered. Facing the triad of dementia, myoclonus, and rigidity, AD should be considered if the disease course is longer, and DLB is the differential diagnosis if Parkinsonism is present. Findings on EEG or in the CSF typical of CJD do not exclude AD or DLB. AD and DLB are the most frequent differential diagnoses in sCJD in elderly patients, whereas chronic inflammatory disorders of the central nervous system must be considered in younger patients (Zerr I, 2002). In addition, some treatable dementias among the most common diseases such as herpes encephalitis, multiple sclerosis, and Hashimoto's encephalitis should be ruled out in the early stage of illness, particularly in younger age groups (Poser S, 2000).

Although the true risk of transmitting classical and variant CJD (vCJD) from human to human is likely to be very minimal, patient nursing and care are highly complex because of the diagnosis of CJD. In Cutting-edge medicine for CJD, there are no effective treatment modalities. In spite of these facts, there is no clinical disadvantage even after the confirmation of non-CJD since all other differential diagnoses involve a very poor prognosis similar to CJD. Only patient frustration and wasted effort regarding antitransmission care result. Further studies on the physiopathological mechanisms of prion diseases may help facilitate the development of treatment to cure or delay the progression on this disease.

Acknowledgments

The authors are grateful to the patient for giving permission to publish her medical data. We are grateful to Prof. Tetsuyuki Kitamoto, Department of Prion Protein Research, Division of CJD Science and Technology, Tohoku University School of Medicine, for conducting the immunocytochemical assay of the patient's brain tissue. We also thank Mrs. Reiko Sakai, Aino Institute for Aging Research, for her skillful research assistance.

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