An ominous radiographic feature: cortical ribbon sign

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A 59-year-old woman presented with a 2-month history of headache, difficulty in finding words, and slow speech. Those symptoms were associated with intermittent bilateral jerky movements of the upper extremities. The patient had noted a memory decline over the prior 2 months. Her past medical history was significant for hypothyroidism, and her medications included levothyroxine. Her father was diagnosed with Alzheimer's disease at the age of 85. Physical examination did not reveal myoclonus, motor, or sensory deficits, hyper- or hyporeflexia, cerebellar signs, or ataxic gait. The patient had intermittent dysphonia, but her speech comprehension was intact. Results of laboratory studies, including a complete blood count, comprehensive metabolic profile, thyroid function tests, anti-thyroglobulin level, vitamin B₁₂ level, homocysteine level, erythrocyte sedimentation rate, antinuclear antibody, anti-double stranded antibody, anti-endomysial antibody, rapid plasma reagin test, Lyme antibody test, HIV-1/2 immunoassay, serum cryptococcal antigen, paraneoplastic panel, heavy metal screening, and drug toxicological tests, were normal.

The electroencephalography (EEG) study was normal. Magnetic resonance imaging (MRI) brain with and without intravenous gadolinium, including diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR), and apparent diffusion coefficient (ADC)

sequences, was performed. Cerebral MRI DWI demonstrated a ribbon-like signal hyperintensity of cerebral cortical gyri (cortical ribboning) of the right frontal, parietal, and occipital regions, known as the cortical ribbon sign (Fig. 1a–c). The corresponding FLAIR sequence showed less-intense cortical ribbon sign (Fig. 1), and ADC sequence illustrated hypointensity of the cortical ribbon areas (Fig. 1). Those MRI findings are highly suggestive of sporadic Creutzfeldt-Jakob disease (sCJD). The patient denied travel history to Europe, blood transfusion, hormonal injection, corneal transplant, or neurosurgical procedures. The patient underwent lumbar puncture, and cerebrospinal fluid (CSF) real-time quaking-induced conversion (RT-QuIC), 14-3-3 protein and total-tau protein analyses were sent to the reference laboratory (National Prion Disease Pathology Surveillance Center at Case Western Reserve University in Cleveland, Ohio, USA). They all were positive, confirming the diagnosis of sCJD. Since there has been no proven effective therapy for sCJD, the patient received intensive counselling on the natural history, supportive care options, and prognosis of the disease.

Creutzfeldt-Jakob disease (CJD) was first described separately by two German physicians—Hans Gerhard Creutzfeldt (neuropathologist) and Alfons Maria Jakob (neurologist) in the 1920s [1]. CJD is the most common form of human prion disease. CJD is a rare and fatal neurodegenerative disease, characterized by a rapidly progressive decline in memory, cognition, motor, and other brain functions [1]. It is caused by an infectious prion protein, defined as proteinaceous infectious particle without nucleic acid. CJD is divided into four subtypes and includes sporadic, variant, genetic/familial, and iatrogenic. Sporadic CJD (sCJD) comprises up to 95 % of cases, followed by familial (5–10 %), variant (<1 %), and iatrogenic (<1 %) forms

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Fig. 1 Brain MRI shows a signal hyperintensity of cortical gyri, characteristically known as the cortical ribbon sign. It involves the right parietal lobe (a), the right frontal and parietal lobes (b), and the right frontal, parietal, and occipital lobes (c). DWI (diffusion-weighted imaging) sequence is typically a more sensitive modality for identifying the cortical ribbon sign as compared to FLAIR (fluid-attenuated inversion recovery) sequence. The corresponding ADC (apparent diffusion coefficient) sequence demonstrates a classic cortical ribbon hypointensity as opposed to DWI

Table 1 Selected differential features of subtypes of Creutzfeldt-Jakob disease (CJD) [1–4]

Subtypes of CJD	Prevalence (%)	Mean age of onset (years, range)	Etiology	Typical MRI brain findings
sCJD	85–95	65 (57–75)	Spontaneous conversion of PrP ^c into PrP ^{Sc}	Cortical ribbon sign (more prominent on DWI)
vCJD (BSE, transfusion-related vCJD)	<1	26 (12–74)	Infection from bovine prions; blood and plasma transfusion	Pulvinar sign; Double hockey stick sign (more evident on FLAIR)
fCJD	5–10	Younger than sCJD patients	Germ-line mutations in <i>PRNP</i> gene (autosomal dominant)	The same as vCJD
iCJD	<1	Variable	Cadaveric human pituitary hormone injection (growth hormone, gonadotrophins), dural graft transplants, corneal transplant, liver transplant, use of contaminated neurosurgical instruments or stereotactic depth electrodes	Thalamic hyperintensity

PrP^c normal form of human prion protein, PrP^{Sc} disease-forming isoform of human prion protein, sCJD sporadic CJD, vCJD variant CJD, BSE bovine spongiform encephalopathy, fCJD familial CJD, iCJD iatrogenic CJD, MRI magnetic resonance imaging, DWI diffusion-weighted imaging, FLAIR fluid-attenuated inversion recovery

(Table 1) [1–4]. The most characteristic clinical manifestation of sCJD is a rapidity of deterioration in neurological functions, typically over a period of a few weeks to months [1]. Clinical features of sCJD include myoclonic jerks, memory deficits, cerebellar signs (ataxia, nystagmus, tremors), pyramidal/corticospinal tract dysfunctions (spasticity, hyperreflexia, extensor plantar responses), extrapyramidal manifestations (bradykinesia, rigidity, tremors), visual disturbances (visual field cuts, cortical blindness, visual agnosia), and akinetic mutism [1, 2].

A brain MRI is the most useful imaging tool in assisting the ante-mortem diagnosis of sCJD, and also helps to differentiate variant CJD (vCJD) [1, 2]. In sCJD, hyperintense signal on the cortical gyri in MRI DWI is the most striking feature, and is known as the cortical ribbon sign. This feature is more easily evident on DWI than FLAIR with typical ADC cortical ribbon hypointensity [2, 3]. MRI sensitivity and specificity of sCJD are 98 and 93 %, respectively [1, 3]. A brain MRI in patients with vCJD typically demonstrates signal hyperintensity in the posterior pulvinar thalamic nuclei (pulvinar sign) or in bilateral posterior (pulvinar) and dorsomedial thalamic nuclei (double hockey stick sign), which are more pronouncedly seen on the FLAIR sequence [2, 3].

Lumbar puncture with CSF study is strongly recommended in patients with rapidly progressive dementia to rule out alternative etiologies before making a diagnosis of CJD. CSF 14-3-3 protein (a marker of neuronal death) and total-tau protein (a marker of neuronal degeneration) are surrogate markers of neuronal degeneration, and are measured in patients with suspected sCJD. Both proteins are usually elevated in CSF of sCJD patients with an approximate 75 % specificity [2]. Recently, a newer prion protein conversion assay has been developed, the real-time quaking-induced conversion (RT-QuIC) [1, 5]. The technique measures in vitro conversion of normal prion protein (PrP^c) to disease-forming isoform of prion protein (PrP^{Sc}) [5]. CSF RT-QuIC analysis is a more disease-specific marker test, has much higher sensitivity (89–91 %) and specificity (98–100 %), and significantly increases the premortem diagnostic accuracy of sCJD [5]. These CSF studies are recommended to be tested at a reference center with expertise on CJD. In the United States, the National Prion Disease Pathology Surveillance Center at Case Western Reserve University in Cleveland, Ohio, is one of the nation reference laboratories. Electroencephalography (EEG) is another important diagnostic tool for sCJD. Characteristic EEG features of sCJD are 1 Hz biphasic or triphasic periodic sharp wave complexes (PSWCs), but these EEG findings are typically not present in the early phase of vCJD [1, 2]. The gold standard of diagnosis of sCJD is still a brain biopsy, which is an invasive procedure, and is rarely required in cases and only if the other tests are nondiagnostic [2].

A diagnosis of sCJD requires a set of combined criteria based on the epidemiologic, clinical, EEG, and neuropathologic findings [1]. A modified set of criteria, recently proposed by the University of California San Francisco, incorporates MRI findings in the diagnostic criteria [2, 3]. Other treatable causes of rapidly progressive dementia should be excluded. These include important differential diagnoses such as autoimmune diseases, Hashimoto's encephalopathy, paraneoplastic encephalopathies, celiac disease, HIV/AIDS, neurosyphilis, or heavy metal toxicity [1, 2]. Unfortunately, there is no effective therapy for sCJD, and it invariably leads to death in 7–9 months from the onset of symptoms [1].

In conclusion, the diagnosis of CJD is highly complex, and is based on the constellation of a detailed clinical history and thorough neurologic examination, EEG features, MRI findings, and exclusion of other potential causes of rapidly progressive dementia, in conjunction with CSF analyses.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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