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Progressive Stroke-Like Symptoms in a Patient with Sporadic Creutzfeldt-Jakob Disease

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Key Words
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Abstract
Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare neurodegenerative disorder in which accumulation of a pathogenic isoform of prion protein (PrP^{Sc}) induces neuronal damage with distinct pathologic features. The prognosis of sCJD is devastating: rapid clinical decline is followed by death generally within months after onset of symptoms. The classic clinical manifestations of sCJD are rapidly progressing dementia, myoclonus, and ataxia. However, the spectrum of clinical features can vary considerably. We describe a definite, neuropathologically verified sCJD in a 67-year-old woman who initially presented with progressive stroke-like symptoms: left-sided hemiparesis and ataxia within a few days. The initial brain magnetic resonance imaging (MRI) showed bilateral cortical hyperintensity on diffusion-weighted sequences (DWI) resembling multiple ischemic lesions. Despite anticoagulation with low-molecular-weight heparin, the patient deteriorated rapidly, became dysphagic and bedridden with myoclonic jerks on her left side extremities correlating with intermittent high-amplitude epileptiform discharges on electroencephalography (EEG). Basal ganglia hyperintense signal changes in addition to cortical ribboning were seen in DWI images of a follow-up MRI. Repeated EEG recordings showed an evolution to periodic sharp wave complexes. Protein 14-3-3 was positive in her cerebrospinal fluid specimen, in addition to an abnormally high total tau level. In the terminal stage the patient was in an akinetic, mutistic state with deteriorating consciousness. She died 19 days after admission to the hospital. Neuropathologic investigation corroborated the clinical diagnosis of sCJD with spongiform degeneration and immunohistochemical demonstration of the deposition of pathologic PrP^{Sc}.

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Introduction

Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare and invariably fatal neurodegenerative disorder caused by accumulation of a misfolded, protease-resistant, and pathogenic form of prion protein (PrP^{Sc}), which possibly evolves from its normal cellular precursor (PrP^{C}) either through spontaneous post-translational conformational change (random misfolding) or due to mutation of the prion protein gene (PRNP) [1]. What seems to follow is a self-perpetuating conformational conversion and propagation of PrP^{Sc} infectivity throughout the brain, although the exact mechanisms of spreading remain unclear [2]. No inflammatory or immunologic reaction is evoked. The physiologic function of PrP^{C}, a membrane-bound sialoglycoprotein found predominantly in the brain, is unknown.

sCJD represents about 85% of human prion disease cases [3]. Other, less common types include familial (inherited) and acquired forms. PrP^{Sc} is able to replicate, is potentially transmissible, and can (like in the case of variant CJD) cross the species barrier [1]. Transmitted prion diseases are thought to have very long incubation periods of up to several decades.

The clinical presentation of sCJD can be highly variable and significant overlap exists with other central nervous system (CNS) disorders. We describe a neuropathologically verified sCJD in a patient who initially presented with progressive stroke-like symptoms.

Case Report

A 67-year-old woman had previously been healthy. She was a non-smoker and had normal plasma glucose and lipid levels. She had no history of substance abuse, blood transfusions, major surgical procedures, or symptoms suggesting cardiac or cerebrovascular disease. Her blood pressure (BP), however, had been abnormally high (up to 205/105 mm Hg) and had been followed on a regular basis during the previous 4 months. There was no family history of rapidly progressing dementia or movement disorders leading to death.

The patient presented at the Emergency Ward of a regional hospital due to progressing symptoms (day 1). She had experienced fatigue and loss of energy for approximately 3 months, and more recently (for 3–4 weeks) insomnia, memory impairment, sluggish speech, tinnitus, strange facial discomfort, progressing balance and gait difficulties and clumsiness of the left limbs with abnormal sensations and jerky movements in the left upper limb. There had been a rapid exacerbation of motor symptoms over a 3-day period prior to admission. Upon arrival, unsteady gait with gait apraxia was observed, and she was only able to walk with assistance. Left finger-nose ataxia and dysdiadochokinesis, as well as weakness of the lower part of the left face were observed, the knee reflex being slightly brisker ipsilaterally. Visual or positive motor symptoms were absent and there were no other relevant findings in neurologic exam. Brain computed tomography scan, chest X-ray, and the results of routine blood tests were unremarkable, and there were no clinically significant ECG findings. BP was high (165–205/95–105 mm Hg). On day 2 the patient was referred to the Emergency Department of Helsinki University Central Hospital for neurological evaluation. The attending neurologist observed mild dysartria with left upper motor neuron facial paresis, left hemiparesis and ataxia (upper limb predominating). BP was 190/90–95 mm Hg with a heart rate of 85/min. Brain magnetic resonance imaging (MRI) with MR angiography of the intracranial and cervical arteries was performed within 2 h of admission. T2-weighted images showed mild leucoaraiosis in the subcortical white matter. More distinctively, diffusion-weighted imaging (DWI) showed multiple parenchymal hyperintensities in both cerebral hemispheres (parietal, temporal, and occipital lobes bilaterally with the right side more affected). MR angiography images were technically suboptimal due to movement artifacts, but no obvious arterial pathology was observable. The initial working diagnosis was ischemic stroke based on clinical features (high BP, highly asymmetric, rapidly evolved motor symptoms) and imaging findings consistent with multifocal cerebral ischemia. Low-dose aspirin (100 mg) plus slow-release dipyridamole (200 mg twice daily) were initiated, the dosage of antihypertensive agent candesartan was increased (16 mg once daily) and the patient was transferred to a neurological ward. On days 3–5 the patient

remained stable and her BP was reduced to normal levels. Echocardiography (day 3) demonstrated left-sided cardiac hypertrophy consistent with chronic hypertensive heart disease, but there were no findings supporting a putative cerebral embolism with a cardiac source. A wide range of blood and urine tests were taken for hematologic, clinical chemistry, and serologic evaluation. Fasting plasma glucose (4.7–5.9 mM) and cholesterol (total 4.7 mM, LDL 2.4 mM) levels were in the normal range, and there were no other clinically relevant abnormal findings.

On day 6 the patient became rapidly less alert, dysphagic with exacerbation of motor symptoms (weakness and ataxia) on the left side extremities. With the initial working diagnosis, progressive ischemic stroke was assumed and the patient was anticoagulated using subcutaneous low-molecular-weight heparin (LMWH, dalteparin 7,000 IU twice daily) with anti-FXa activity monitoring. Antiplatelet therapy was discontinued. The first brain MRI re-scan was unsuccessful due to motor restlessness of the patient. At this point (day 8), mild intermittent myoclonic jerks in the left side limbs were observed with abnormal electroencephalography (EEG) showing diffuse slowing and sporadic, high-amplitude epileptiform discharges with partial periodicity, right-sided predominance, and clinical correlation with contralateral myoclonus. Clinical and EEG findings now evoked suspicion of a sCJD as a diagnostic alternative. The 1st MRI images (from day 2) were re-evaluated, leading to the conclusion that cortical hyperintense signal changes seen on DWIs (**fig. 1**) could also be explained by sCJD-related pathology. Myoclonic jerks were unresponsive to intravenous valproic acid (loading dose of 600 mg followed by 300 mg twice daily). On day 9 the patient had become bedridden and increasingly drowsy. Myoclonus was more frequent and of higher amplitude. Severe ataxia and motor paresis on the left side, paralysis of left conjugate gaze, and inattention of the left visual field (consistent with the right frontal and parietal lobe lesions, respectively) could be observed. DWI images of the 2nd MRI (day 10) showed widely distributed cortical signal hyperintensities (ribboning) in the right frontal (insular) cortex and parieto-occipital cortices bilaterally, the findings being less remarkable on the left side and less conspicuous than in the 1st MRI. DWI hyperintensities were detectable also in the basal ganglia, particularly in the caudate and the anterior parts of the lentiform nuclei, corroborating the neuroradiologic diagnosis of sCJD.

With sCJD as the most likely diagnosis, the decision not to resuscitate and to withhold life-sustaining treatment was made in good agreement with the patient's family members. The LMWH dosage was reduced to thromboprophylaxis level (5,000 IU once daily), clonazepam (0.5 mg twice daily) was initiated to suppress myoclonus, and a nasogastric tube was inserted to secure enteral drug delivery and nutrition. A transdermal fentanyl patch (up to 50 μg/72 h) was introduced to provide pain relief.

Cerebrospinal fluid (CSF, sampling on day 15) leukocyte and protein levels were in the normal range, as were the results of serologic tests for different microbial pathogens. Protein 14-3-3 was positive. CSF total tau level was markedly elevated (>1,200 pg/ml), whereas the concentration of phospho-tau (P-tau) was normal (38 pg/ml). The 2nd EEG (day 18) was typical for sCJD showing destruction of the background rhythms with distinctive periodic, synchronous, and generalized bi-/triphasic sharp-wave complexes (PSWCs) (**fig. 2**).

From day 11 onward the patient showed a rapid clinical deterioration into an akinetic mutistic state. Myoclonic phenomena were less remarkable, and there was a general increase in spasticity. The patient became febrile, comatose, and developed episodes of apnea. She died 19 days after admission.

Post-mortem neuropathologic examination was done. The CNS macroscopic findings were quite unremarkable and unspecific: there were no signs of cortical (hippocampal or other) atrophy or focal pathologic changes. Intracranial arteries were normal. However, the microscopic and immunohistochemical examinations were confirmatory for sCJD: spongiform degeneration with vacuolar change most prominent in the molecular layer of the cerebellum and, to a lesser extent, in neocortical areas, putamen, and thalamus. Neither florid (characteristic for variant CJD) nor Kuru plaques were detected. Immunohistochemistry showed protease-resistant PrP immunoreactivity, most clearly in the cerebellar cortex, but also in cortical and basal ganglia specimens.

Discussion

No therapeutic interventions exist that can alter the clinical course of sCJD [4]. Fortunately, this fatal disease is rare with an estimated worldwide incidence approximately one case per million per year [1, 2].

The diagnosis of sCJD is relatively straightforward when a patient with rapidly progressive dementia manifests myoclonus and PSWCs on EEG [3, 5]. Confusion and memory disturbance are the most common presenting features and practically all develop dementia at some stage [4]. Ataxia develops in up to 2 thirds [3]. The stroke-like symptoms in our patient (rapidly progressing hemiparesis and ataxia), however, substantiate the fact that sCJD can be a clinical chameleon [4] and the diagnosis challenging. Vague prodromal symptoms of fatigue, malaise, depression, decreased appetite, and sleep disturbances have been documented in about 1 third of the patients with sCJD [1, 6]. The disease may also present with focal cortical or lateralized syndromes [7] that mimic other CNS disorders (for example neurodegenerative, inflammatory, vascular, paraneoplastic, or metabolic) [4]. The classic features may be absent early on. Ataxia, for example, is the presenting symptom only in a minority [4]. In the later stages, however, characteristic symptoms usually become apparent, as they did in the present case.

Brain MRI with DWI [8], assessment of 14-3-3 protein from CSF [9] and serial EEG recordings [10] should be integrated into the diagnostic workup of sCJD. DWI sequences demonstrate increased cortical and basal ganglia signal and are highly sensitive and specific for sCJD [8, 11]. PSWCs on EEG occur in about 2 thirds of patients with sCJD [10]. CSF protein 14-3-3 is a marker of neuronal death and can be detected in many CNS disorders, such as stroke, encephalitis, and paraneoplastic syndromes [1–3]. In sCJD it has been reported to have 80–90% sensitivity and 90% specificity for the diagnosis [12]. Characteristic MRI and EEG changes are commonly found only with repeated examination [1]. This was also the case in our patient whose EEG changed from unspecific to characteristic with pseudoperiodic paroxysms [4] in just 10 days. Our patient's DWI findings were typical with cortical ribbon hyperintensities, a highly sensitive finding in sCJD [13]. The patient's CSF protein 14-3-3 was positive, tau level was very high, whereas P-tau/total tau ratio was low. All these findings are in support of sCJD. There is class I evidence on dramatic increases in CSF total tau without similar increases in P-tau [12]. Finally, neuropathologic findings (essential for definite diagnosis) in the present case were typical for sCJD.

Clinically atypical forms of sCJD are well recognized in the literature. The phenotypic variation seems to be due to differences in both the molecular and physicochemical structure of prion strains and polymorphism of the PRNP [6, 14]. Six subtypes of sCJD with different clinicopathologic features based on codon 129 polymorphism (methionine/valine) and PrP type have been proposed [14]. Sporadic CJD has also been classified into 5 different phenotypes which differ by several characteristics, for example age at disease onset, survival time, and diagnostic test results [15]. Neither PrP^{Sc} phenotyping nor PRNP sequencing were done in the present case. The age at onset of our patient (67 years) was quite typical for sCJD [5].

There were subtle hints towards the diagnosis of sCJD and against the cerebrovascular diagnosis already at the beginning of the acute stroke-like presentation of the left-sided motor paresis and ataxia. Firstly, there was a lack of major cerebrovascular risk factors besides hypertension and age of 67 years. Secondly, there was a 3-month prodromal phase of unspecific symptoms of fatigue and loss of energy. Even more atypical for ischemic stroke, there was a subacute 3–4-week period with a broad range of other, mostly non-localizing symptoms. The symptoms of ischemic stroke usually evolve in minutes, more seldom do they progress over hours or days, with basilar artery thrombosis symptoms sometimes evolving over weeks with asymptomatic periods in between. Thirdly, even in the first head MRI, there were bilateral (although more prominent in the right

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hemisphere) hyperintense lesions affecting multiple vascular regions. However, such a finding could also be attributed to cardiac embolization, and the basal ganglia hyperintense lesions typical for sCJD were lacking at that point.

The stroke-like symptoms of the present case demonstrate the variability in the clinical presentation of sCJD. A high level of clinical suspicion may prove useful in obtaining early diagnosis and therefore avoiding costly and inefficient therapeutic strategies.

Fig. 1. The 1st brain diffusion-weighted images of the Creutzfeldt-Jakob disease patient showing hyperintensity of the right insular cortex (**a**; arrow) and occipital cortices bilaterally (**b**; arrows).

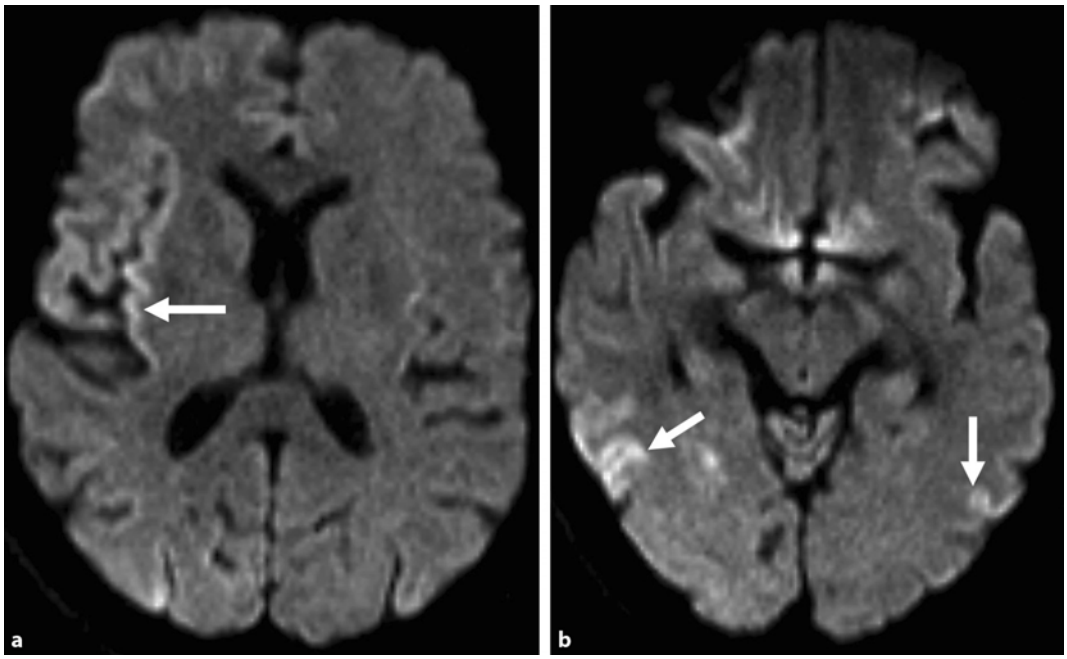

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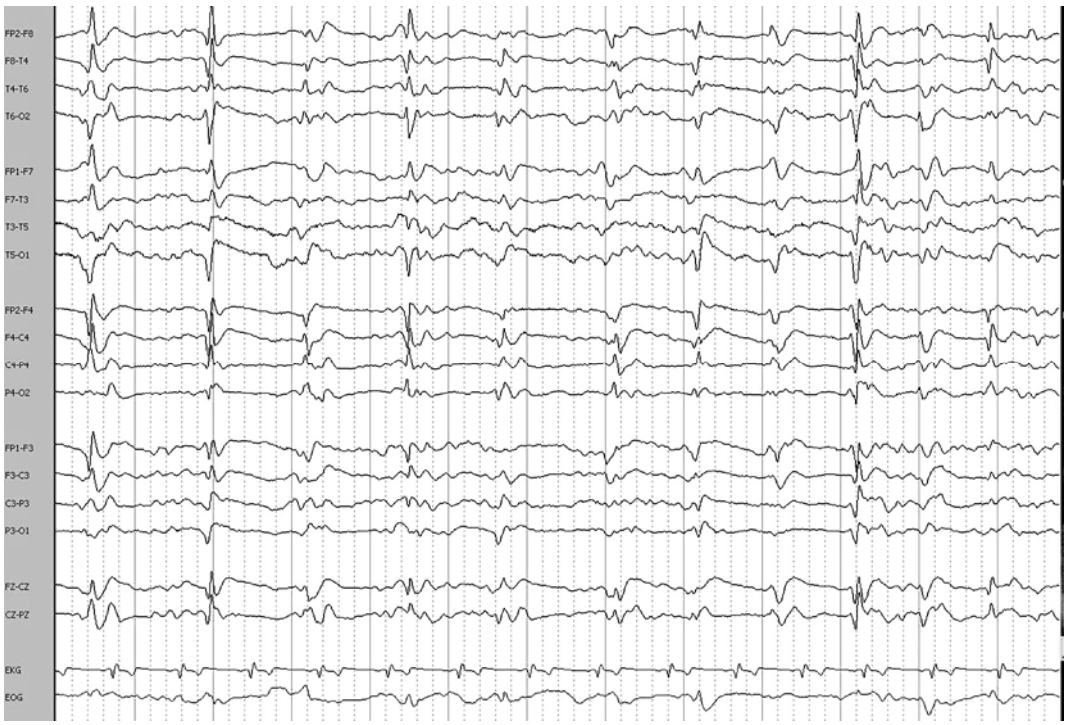
Fig. 2. The repeated 2nd electroencephalography of the present case demonstrates periodic generalized bi/triphasic complexes typical for sporadic Creutzfeldt-Jakob disease.



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