

## Sporadic Creutzfeldt-Jakob Disease: A Four-Year Evolution Case with Heterozygosity at Codon 129 and Kuru Plaques

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### Abstract

A 55-year-old man was first evaluated after a one-year evolution of rapidly progressive dementia. The neurological examination showed MMSE 23/30 with impairment of multiple cognitive domains (memory, executive function, praxis and visuospatial), frontal release signs and pyramidalism. EEG revealed mild generalised slowing without periodic discharges. CSF analysis was negative for 14-3-3 protein. MRI showed hyperintense signals involving the dorsofrontal and parieto-occipital cortices and both medial thalamus which were particularly evident on DWI sequence. The motor and sensory primary cortices remained unaffected. Genotyping of the prion protein gen identified heterozygosity methionine-valine at codon 129 and no mutations. The patient developed progressive worsening in the behavioural, cognitive and motor domains that left him in a state of akinetic mutism for a few months before death, which occurred four years after the clinical onset. A pathological study demonstrated spongiform changes, gliosis, neuronal loss and Kuru-type plaques. Immunohistochemistry exhibited a synaptic pattern with focal plaques. A western Blot analysis was not possible, but an atypical long-duration MV2 sporadic Creutzfeldt-Jakob was the most probable diagnosis.

**Keywords:** Sporadic Creutzfeldt-Jakob disease; Magnetic resonance imaging; Long- duration, Kuru-type plaques; Heterozygosity methionine-valine

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## Introduction

Sporadic Creutzfeldt-Jakob disease (sCJD) is characterised by rapidly progressing dementia, myoclonus and extrapyramidal and pyramidal involvement. Patients worsen weekly until reaching a state of akinetic mutism before death. The median survival is around 6 months and 90% of patients die within a year [1,2].

A small percentage of cases of sCJD have a longer survival [1-3]. This difference might be explained by the polymorphism at codon 129 of the prion protein gene and the type of prion strain [1-3].

We herein report the clinical, neuroimaging and pathological findings of a particularly long-duration case of sCJD.

## Case Study

A 55-year-old man with cognitive complaints was referred to our department.

Ten months before he had left his job due to anxiety, depression and conflicts at work, but his family had noticed he was also experiencing cognitive problems. He did not remember what he had just done or where he had left things. He repeated the same questions and became lost even at home. His speech became less fluent. He did not know how to handle his mobile phone. He was not able to find the knob in the shower. He made mistakes when counting and dressing. His gait was awkward with frequent tripping and some falls.

Neurological examination showed frontal release signs (palmomental and grasp). The muscle tone was spastic, and the tendon reflexes were brisk with clonus. His gait was spastic without ataxia. Myoclonus was not noted. The MMSE score was 23/30 and a detailed neuropsychological examination detected failures in multiple cognitive domains (memory, executive function, praxis and visuospatial tasks). The patient showed anosognosia and difficulties in visual tracking. He scored positively on various items of NPI (anxiety, apathy, indifference, irritability and lability).

Laboratory findings were within normal ranges, including tests for syphilis, thyroid function, vitamins (A and E), ceruloplasmin, urine copper and immunological study. CSF revealed normal biochemistry and was negative for 14-3-3 protein. An initial electroencephalogram (EEG) showed little beta activity in the frontal areas without periodic discharges.

MRI (1.5 TESLA) showed hyperintense signals involving the dorsofrontal and parieto-occipital cortices and both medial thalamus which were particularly evident on DWI sequence. The motor and sensory primary cortices remained unaffected (**Figure 1**).

Genotyping of the prion protein gene did not reveal mutations. Codon 129 was heterozygous for methionine-valine (MV).

Seven months later the patient's condition had worsened. He was suffering from agitation, visual hallucinations and false

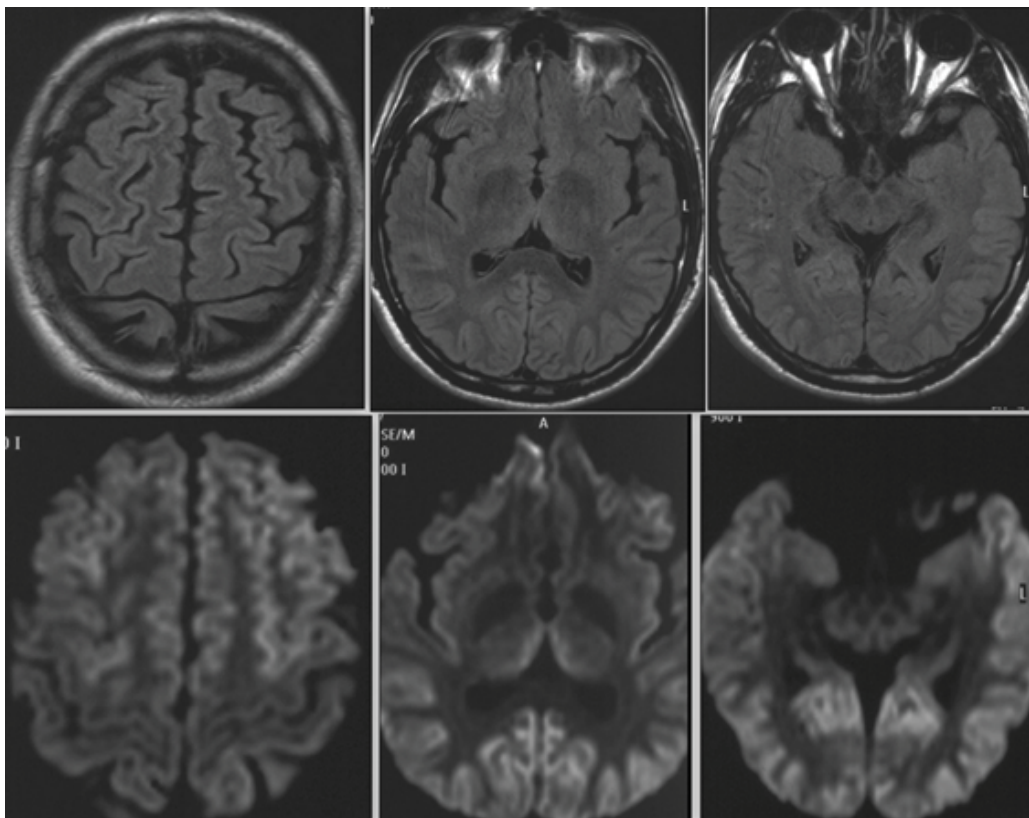
recognition delusions and was started on quetiapine up to 200 mg every day.

One year after the first evaluation the patient had double incontinence and his gait had worsened. On neurological examination, new signs had appeared such as supranuclear downgaze palsy, optic ataxia, facial hypomimia and rigidity. A new EEG showed generalised slowing without epileptiform discharges or periodic complexes.

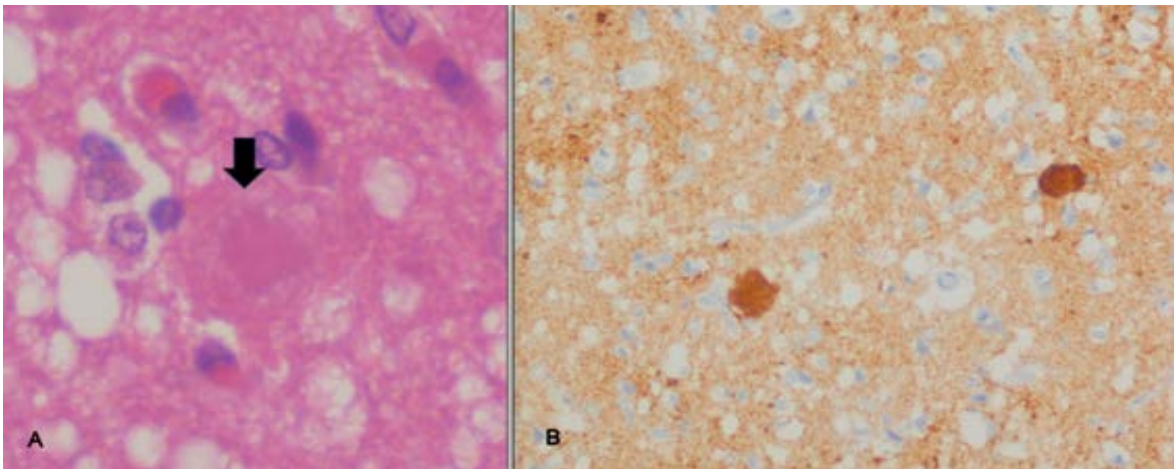
Two years after the initial assessment the patient was no longer able to speak or move by himself. He had occasional irregular jerking in his limbs.

He died due to a respiratory infection in a state of akinetic mutism three years after the initial assessment and at least four years after the clinical onset.

Postmortem samples were taken from the cortical regions to confirm the diagnosis. Microscopic examination revealed typical diffuse spongiform changes with small vacuoles uniformly distributed all over the cortical layers, marked astrocytosis and severe neuronal loss. Characteristic Kuru-type plaques with dense PAS-positive centres were frequently identified (**Figure 2A**). An immunohistochemistry study showed an extensive accumulation of prion protein in a synaptic pattern with focal plaques (**Figure 2B**). Frozen tissue was not available for western blot analysis.



**Figure 1** MRI findings: (A) Upper row, axial Flair from left to right, shows subtle symmetric hyperintense signal in the frontal cortex, medial thalamus, and the parieto-occipital and calcarine sulcus. (B) In lower row, axial DWI shows restricted diffusion in the frontal cortex, medial thalamus and visual primary occipital cortex. There is no involvement of the sensory and motor primary cortex.



**Figure 2** Neuropathological findings: (A) HE: Cortical spongiform changes and a Kuru-type plaque (black arrow). (B) Immunohistochemistry (Prion protein): a synaptic pattern with focal plaques.

## Discussion

This patient was difficult to diagnose in life as sCJD because of the slow course of the disease (MMSE 23/30 a year after the disease onset, three years to reach a state of akinetic mutism and four years until death), the absence of periodic complexes on the EEG and the negativity for 14-3-3 protein on CSF. The diagnosis was based on the MRI findings until pathological samples could be obtained.

Within the spectrum of CJD there are some subtypes characterized by long-duration and negative EEG and 14-3-3 protein: variant Creutzfeldt-Jakob disease (vCJD) [4], some hereditary forms of CJD [5] and the more recently described “protease-sensitive prionopathy” [6]. The absence of pulvinar sign on MRI, the MV heterozygosis and the pathological study without amyloid florid plaques do not support vCJD. The prion protein gene analysis did not show mutations. The striking changes on DWI sequence and the neuropathological findings also discard “protease-sensitive prionopathy”.

Western-blot analysis to determine which type of prion strain the patient had was not available and this was the main limitation of our study. Nevertheless, the case shares a number of characteristics with previously described MV2 sCJD patients [1,3,7]: long-duration (average duration of 17.1 months with a range from 5 to 72 months), negative EEG and 14-3-3 protein, medial thalamic hyperintensity on DWI sequence, Kuru-type plaques and synaptic patterns plus focal plaques on immunohistochemistry. However, some observations were atypical for MV2: absence of early ataxia, neuroimaging without involving striatum and uniform vacuolisation in all layers on neuropathology. The case may be classified as an atypical form of MV2 with severe cortical involvement, mimicking MM2-cortical-type sCJD, which has been described in other two cases up to now [8,9].

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## Conflicts of Interest

There are no conflicts.

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