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FIRST EUROPEAN CASE OF CREUTZFELDT-JAKOB DISEASE WITH A *PRNP* G114V MUTATION

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Abstract

Genetic Creutzfeldt-Jakob disease is due to mutations in the *PRNP* gene. Only two families with a *PRNP* G114V mutation have been described around the world. We report the first European case, who had no family history and initially presented with isolated deficit in hippocampus-dependent memory. Initial investigations were normal except for elevated total tau protein in the cerebrospinal fluid. He died 4 years after disease onset. This case highlights the diagnostic difficulties posed by genetic Creutzfeldt-Jakob disease, and shows that genetic analyses should be considered even in sporadic cases.

Keywords: Creutzfeldt-Jakob disease; genetic; PRNP; atypical presentation; 14.3.3

Abbreviations:

MRI: magnetic resonance imaging

CSF: cerebrospinal fluid

EEG: electroencephalogram

Introduction

Genetic prion diseases, including genetic Creutzfeldt-Jakob disease (CJD), are due to mutations in the *PRNP* gene, which encodes the prion protein (PrP). The phenotype of genetic CJD is pleomorphic, owing partly to the type of mutation. A rare missense mutation in *PRNP*, G114V, was described in an Uruguayan (Rodriguez et al., 2005) and a Chinese family (Liu et al., 2010). Here we report the first European case of genetic CJD with a *PRNP* G114V mutation.

Case presentation

A 39-year-old right-handed male with no medical history was referred to the Department of Neurology at the Pitié-Salpêtrière Hospital for the assessment of memory impairment. His brother died at 25 from a limb-girdle dystrophy; his parents, both 74 years old, and his maternal half-sister were healthy (Figure 1). For the last 3 years, he had attention deficit leading to difficulties in his work as a computer engineer. Memory loss and spatial and temporal disorientation appeared 6 months before admission and worsened rapidly: he forgot to pick up his daughter from school, did not remember the previous day's business meeting and forgot how to go to work.

The first clinical examination was normal. Neuropsychological evaluation (CH, Table 1) revealed dysexecutive syndrome and impaired episodic memory with spatial disorientation suggestive of hippocampal dysfunction. The first investigations were performed 3 and a half years after symptom-onset. Brain MRI was normal. In the cerebrospinal fluid (CSF), the 14-3-3 protein was negative but total tau protein was increased (1927pg/mL; normal range 100-450), with normal Aβ 1-42 (858pg/mL; normal range 500-1500) and phosphorylated tau (57pg/mL; normal value <60). Several EEG showed a diffuse theta activity, without periodic sharp wave complexes. There was no evidence of autoimmune encephalitis: anti-GAD, anti-

Yo, anti-Hu, anti-Ri, anti-CV2 and anti-Tr antibodies were negative in the serum; anti-NMDA receptor, anti-AMPA1 receptor, anti-AMPA2 receptor, anti-LGI1, anti-Caspr2, and anti-$GABA_{B1}$ receptor antibodies were negative in the CSF.

Over the following 6 months, cognitive functions declined significantly and the patient developed parkinsonian syndrome, myoclonus and hyperreflexia. Brain MRI performed 3 months after the first one showed hyperintensities of the parieto-occipital cortex on diffusion-weighted imaging associated with a reduced apparent diffusion coefficient (DG, Figure 2). EEG remained nonspecific. Sanger sequencing found a heterozygous c.341G>T/p.G114V mutation and MM genotype at 129 codon (rs1799990) in the *PRNP* gene.

The patient died 4 years after disease onset. Post-mortem histopathological study showed moderate spongiosis in most cortical areas, the caudate nucleus and the thalamus. The hippocampus was spared, contrasting with severe impairment of the entorhinal cortex. There was no confluence of the vacuoles, and gliosis was moderate. PrP immunohistochemistry showed diffuse synaptic labelling (DS, Figure 3).

Discussion

Our patient and the 9 previously reported cases of *PRNP* G114V mutation are characterized by early onset (before 45 years of age), long disease duration (several months to several years) and polymorphic symptoms (mainly psychiatric in the Uruguayan family, whereas our patient had isolated hippocampal dysfunction initially) (Liu et al., 2010; Rodriguez et al., 2005) (Table 2). Investigations results were often negative: no patient had periodic sharp wave complexes on EEG, brain MRI only displayed diffuse atrophy in the Uruguayan family, and the 14-3-3 protein was negative in two patients (not performed in the other cases). The neuropathology findings are similar to those previously described (Liu et al., 2010; Rodriguez et al., 2005): spongiosis was predominant in the neocortex, whereas the hippocampus,

brainstem and cerebellum were relatively spared. However, we did not observe any extensive gliosis.

This case highlights several misleading features common to genetic CJD. In contrast to sporadic CJD, genetic CJD is known to manifest earlier and have slower progression. The clinical phenotype can be polymorphic, depending largely on the type of *PRNP* mutation (Capellari, Strammiello, Saverioni, Kretzschmar, & Parchi, 2011). Although inheritance is autosomal dominant, there is no family history in almost 50% of patients with genetic CJD, probably due to incomplete penetrance (Kovács et al., 2005). The occurrence of limb-girdle dystrophy in our patient's brother is probably coincidental, as we did not find any case of muscle disorder in patients with a *PRNP* mutation in the literature. In addition, genetic CJD patients have less frequent EEG, MRI and CSF abnormalities than sporadic CJD. First, classical periodic sharp wave complexes occur in only 10% of genetic CJD patients (Wieser, Schindler, & Zumsteg, 2006). Second, brain MRI is normal in 50% of patients (Kovács et al., 2005). Third, 14-3-3 protein could be less sensitive than total tau protein to diagnose genetic CJD, which underlines the importance of dosing CSF biomarkers if CJD is suspected (Coulthart et al., 2011). If negative, these investigations should be repeated, and *PRNP* genetic testing should be proposed even in the absence of familial history.

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Declaration of interest

Dr. Louis Cousyn reports no disclosures.

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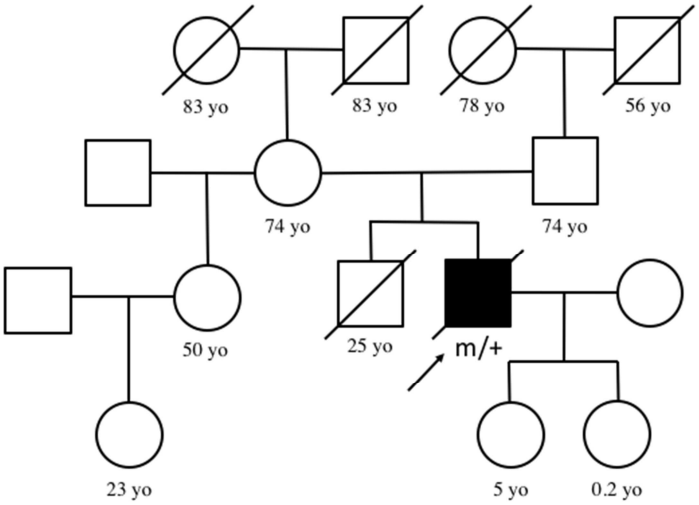
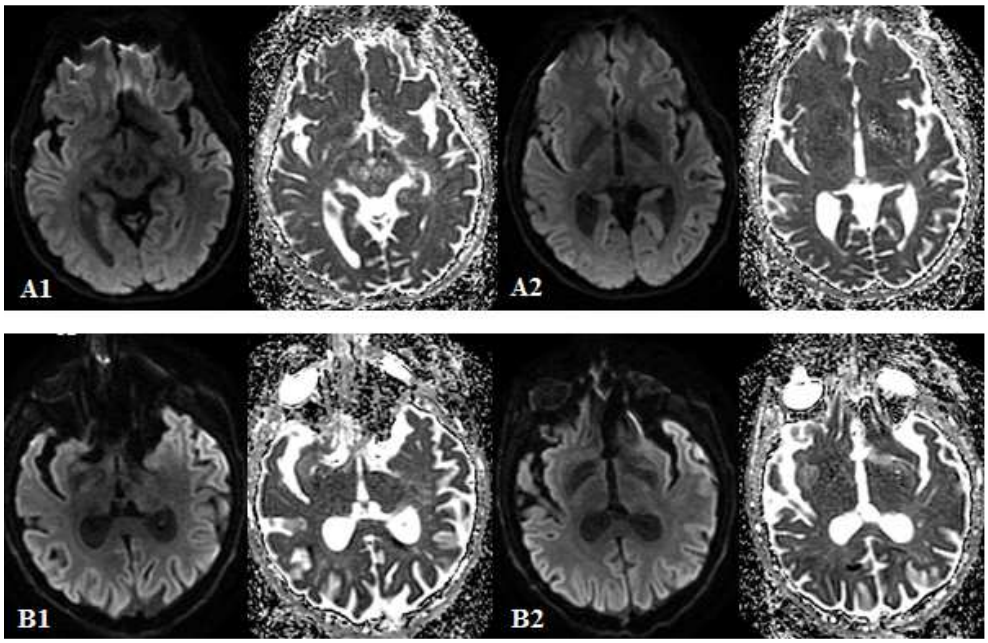
Figure 1. Pedigree of the family



The filled square represents the proband case, empty symbols represent unaffected individuals, symbols with a diagonal line deceased individuals, squares are males and circles are females.

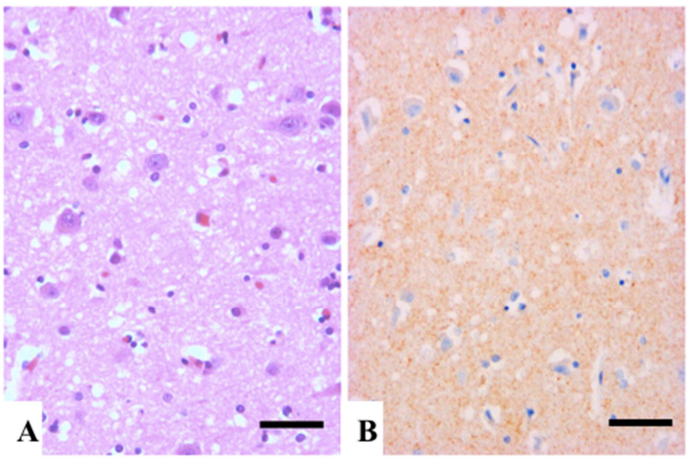
m: mutated allele, +: wild type allele, yo: years old.

Figure 2. Brain MRI (DG)



The first brain MRI (top row) was considered to be normal: diffusion-weighted (DW) sequence (left) and apparent diffusion coefficient (ADC) map (right) for each slice (A1 and A2). The MRI performed 3 months after (bottom row) showed DW hyperintensities (left) of the parieto-occipital cortex associated with a reduced ADC (right) in slices B1 and B2.

Figure 3. Neuropathology (DS)



A. Neuropathology of the frontal cortex (hematoxylin eosin) showing mild spongiosis and gliosis, spread all over the cortex. **B**. Anti-PrP immunohistochemistry (Spibio, 12F10 antibody, 1/200) showing diffuse synaptic staining. Tool bars are 50 µm.

Table 1: Neuropsychological assessment (CH)

Global cognitive efficiency		
MMSE (Folstein, 1975)	25/30	Mild impairment of the global cognitive efficiency
Mattis DRS (Mattis, 1988)	114/144	
Executive functions		
FAB (Dubois et al., 2000)	14/18	Mild executive impairment: - ineffective initiation - verbal incentive deficiency - decreased mental flexibility
TMT A (Reitan, 1958)	85s	
TMT B (Reitan, 1958)	Unachievable	
Verbal fluency	Literal: 7 words Categorical: 5 words	
Episodic memory		
Verbal Learning Test (Grober, 1987; Van der Linden et al., 2004)	- 5/4/16: Identification: 16/16 Immediate recall: 11/16 Free recall: 9/48 Total recall: 22/48 React to cueing: 33.33% Free delayed recall: 0/16 Total delayed recall: 0/16 - 5/18/16: Identification: 16/16 Immediate cued recall: 8/16	Encoding and storage deficits in verbal episodic memory with a rapid deterioration between the two assessments)
5 word-test (Dubois et al., 2002)	Identification: 5/5 Immediate recall (free + cued): 2/5 (2+0) Delayed recall: 0/5	
Working memory		
Direct span	3	Maintenance and manipulation deficits in working memory
Indirect span	3	
Instrumental functions		
Language: BECS-GRECO (Merck et al., 2011)	38/40	Normal
Praxic abilities: Mahieux's battery (Mahieux et al., 2009)	22/23	
The Modified Taylor Complex Figure (Hubley, 1996)	36/36	
Visuoperception: VOSP battery – Incomplete Letters (Warrington et al., 1991)	20/20	

We highlighted a hippocampal dysfunction in episodic memory with a rapid deterioration, some dysexecutive signs and normal instrumental functions. MMSE: Mini-Mental State Examination; Mattis DRS: Mattis Dementia Rating Scale; FAB: Frontal Assessment Battery; TMT: Trail Making Test; BECS-GECO: The GRECO neuropsychological semantic battery

Table 2. Main features of the 9 previously reported cases of *PRNP* G114V mutation in the literature

	(Rodriguez et al., 2005) Case III-14	(Rodriguez et al., 2005) Case III-16	(Rodriguez et al., 2005) Case III-19	(Rodriguez et al., 2005) Case IV-2	(Rodriguez et al., 2005) Case II-1	(Ye et al., 2008; Liu et al., 2010) Case III-4	(Liu et al., 2010) Case III-2	(Liu et al., 2010) Case III-3	(Liu et al., 2010) Case IV-2
Age at onset	27	18	22	22	28	45	45	35	32
Time from onset to death (y)	2	1	2	4	2	NA	2	2.5	NA
Summary general symptoms	Hallucinations, generalized tonic-clonic seizures, insomnia, hyperreflexia, extrapyramidal syndrome, myoclonus, incontinence	Akinetic mutism, insomnia, generalized tonic-clonic seizures, extrapyramidal syndrome, myoclonus, incontinence	Hallucinations, pyramidal syndrome extrapyramidal syndrome, mild cerebellar signs, myoclonus, incontinence	Mutism, gait disturbance, extrapyramidal syndrome, myoclonus, insomnia, incontinence	NA	Polyphagia, hallucinations, hyperreflexia, extrapyramidal syndrome	Generalized tonic-clonic seizures, rigidity, incontinence	Insomnia, short and slow steps, incontinence	Insomnia, extrapyramidal syndrome
Neuropsy-chological deficits	Behaviour disorder, frontal signs, apathy	Behaviour disorder, cognitive impairment	Behaviour disorder, dementia, asomatognosia, apathy	Behaviour disorder, cognitive impairment, apraxia	Behaviour disorder, dementia	Behaviour disorder, generalized dementia	Cognitive impairment, apathy	Behaviour disorder, dementia	Dementia (MMSE score: 17/30)
Brain MRI	NA	NA	Moderate diffuse encephalic atrophy	Diffuse cerebral atrophy	NA	Moderate diffuse cerebral atrophy, DWI hyperintensities (caudate nuclei, putamen, insular cortices)	Moderate diffuse cerebral atrophy	NA	Normal
14.3.3 protein	NA	NA	NA	NA	NA	Negative	NA	NA	NA

EEG	Diffuse cerebral damage	Diffuse encephalic damage	Background activity at 5-6 cycles per second; bilateral, sporadic, medium amplitude spike discharges	Background activity with a theta rhythm at 6-7 cycles per second	NA	Background activity at 5-6 cycles per second	Diffuse intermittent non-specific slow waves	NA	NA
Neuropatho-logy (frontal biopsy)	Moderate spongiform change, neuronal loss, gliosis, absence of amyloid plaque deposits, synaptic staining in PrP immunohistoch emistry	Spongiosis, gliosis, neuronal loss, absence of amyloid plaque deposits	NA	NA	NA	Neuronal loss, spongiform change, synaptic staining in PrP immunohistoche mistry	NA	NA	NA
Genetic analysis	PRNP G114V mutation	NA	PRNP G114V mutation	PRNP G114V mutation	NA	PRNP G114V mutation	NA	NA	PRNP G114V mutation

NA: not applicable; y: years