**Objective:** To report the clinical and neuropathological features in the first patient seen, to our knowledge, with familial Creutzfeldt-Jakob disease and an R208H mutation associated with a Val/Val homozygosity at codon 129 in the prion protein gene (**PRNP**) and a type 2 protease-resistant prion protein.

**Patient and Results:** A 61-year-old man with a long-standing history of memory loss and emotional disorders had an obvious behavioral change. Then he developed cerebellar ataxia, followed by cognitive decline. He had no myoclonus. Electroencephalography showed slow activity, and 14-3-3 protein detection was negative. Finally, the patient developed akinetic mutism and died 7 months after the onset of ataxia. Neuropathological examination showed severe spongiform changes in the frontal cortex and striatum and gliosis in the striatum and thalamus. Kuru plaques were noted in the cerebellum, notably in the molecular layer. Immunohistochemical findings showed granular, synaptic, perineuronal, and perivacuolar staining with antiprion antibodies. Kuru plaques were also stained.

**Conclusion:** This study strengthens the linkage of the R208H mutation to Creutzfeldt-Jakob disease and points to some particular features such as Kuru plaques and long-standing psychiatric signs.

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**Inherited Prion Diseases Represent 5% to 10% of All Prion Diseases and Exhibit an Autosomal Dominant Transmission.** Three classic phenotypes have been described, including familial Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker syndrome, and fatal familial insomnia. They are linked to mutations in the prion protein gene (**PRNP**), which encodes the prion protein (PrP). Familial CJD shares some clinical features with sporadic CJD (sCJD) and the 2 forms extensively overlap at the histopathological level. In contrast to plaquelike deposits, which have been reported in some familial CJD, true amyloid plaques are rare, and to our knowledge, only 1 familial case has been reported to be associated with such plaques. As in sCJD, the type of protease-resistant PrP (PrPres) and the codon 129 genotype act as major determinants of the disease phenotype, and distinct familial CJD phenotypes can be observed in subjects carrying the same PRNP mutation. To date, more than 55 mutations associated with a CJD phenotype have been described. Among the rarer ones, R208H was reported in 2 patients associated with a met/met genotype at codon 129 and a type 1 proteinase K-resistant PrP. We report a third patient with the R208H mutation with another genotype at codon 129 and a different proteinase K-resistant PrP type. This patient was characterized by some particular histological and clinical features.

**Methods**

This 61-year-old man had no family history of dementia; he never underwent neurosurgery and never spent time in the United Kingdom. He was known to have diabetes mellitus with frequent hypoglycemia since age 11 years. He had not attended school and was living at home with a long-standing history of memory loss and emotional disorders. At the age of 58 years, his family noticed a progressive worsening of these complaints. Three years later, he had an obvious behavioral change with aggressiveness, eating disorder, and delirium. He pretended he was a dog and urinated in public. Two months later, he developed cerebellar ataxia. Five months after the behavioral changes, the patient was unable to walk and had cognitive decline with indifference and apathy. Neurological examination showed bilat-
eral grasping, a decrease in speech, bladder incontinence, pyramidal signs predominantly on the left side, vertical oculomotor palsy, and horizontal nystagmus in left gaze. A secondary motor and sensory demyelinating peripheral neuropathy was confirmed by electromyography. There was no myoclonus. Fasciculations with muscle atrophy were noted. Multiple electroencephalograms showed slow activity. Brain, fluid-attenuated inversion recovery, and T2-weighted magnetic resonance imaging did not show any hyperintensity. Cerebrospinal fluid analysis revealed a hyperproteinorachy (0.65 g/L), and 14-3-3 protein detection was negative. The patient developed akinetic mutism and died of septicemia following a pulmonary infection at the age of 61 years. Based on his first motor symptoms, the duration of his disease was estimated at 7 months.

Figure 1. Neuropathological hematoxylin-eosin staining (A-C) and immunohistochemical findings with anti-prion protein monoclonal antibody 12F10 (D-F). A, The striatum shows severe spongiform changes (original magnification ×250). B, The frontal cortex shows deep laminar spongiform changes (original magnification ×100). C, A Kuru plaque with fine spicules around a central core is seen in the molecular layer of the cerebellum (original magnification ×630). D, Immunolabeled plaquelike deposits in the frontal cortex (original magnification ×400). E, A 30-µm plaque surrounded by a rim of spongiform vacuoles looking like a flower in the frontal cortex (original magnification ×630). F, In the frontal cortex, there is a strong reaction around a neuronal perikarya and a diffuse synaptic pattern that comprises abundant, tiny immunolabeled dots occasionally accompanied by coarser and bigger deposits (original magnification ×250).
although behavioral symptoms began several years earlier. Because CJD was suspected, an autopsy restricted to the brain was requested.

Semiquantitative evaluation of spongiosis, neuronal loss, and gliosis was performed using hematoxylin-eosin–stained sections on 12 regions. The PrP immunohistochemical testing was performed on the frontal and occipital cortices and on the cerebellum using 3F4 (Senetek, Maryland Heights, Md) and 12F10 mouse antihuman PrP monoclonal antibodies using standard techniques.7 As previously described, Western blot analysis of proteinase K–resistant PrP was performed using the 3F4 monoclonal antibody.8 Genomic DNA was extracted from a fragment of frozen brain after receiving informed consent from the patient's family. The coding sequence of the PRNP gene was amplified and sequenced according to Peoc'h et al.9

RESULTS

Neuropathological examination of hematoxylin-eosin–stained sections showed intensive microvacuolar spongiform lesions in the frontal cortex and striatum (Figure 1A). Moderate microvacuolar changes were observed in the parahippocampal gyrus and the thalamus. Mild microvacuolar changes were also present in the parietal cortex, substantia nigra, medulla, and cerebellum. The temporal and occipital cortices and the hippocampus were spared. The pattern of spongiform changes was diffuse in the striatum and thalamus; deep laminar in the frontal (Figure 1B), parietal, and parahippocampal gyrus cortices; and focal in the substantia nigra and cerebellum. Severe gliosis was noted in the striatum and thalamus. Mild gliosis was observed in the frontal cortex, parahippocampal gyrus, and cerebellum and was associated with a discrete neuronal loss in the cerebellum. Lesion intensity for the 12 brain areas examined is displayed in Figure 2 using the lesional scoring described by Parchi and colleagues.4 Some Kuru plaques were noted in the cerebellum, notably in the molecular layer (Figure 1C). Immunohistochemical findings showed some plaques in the cerebellum and frontal cortex (Figure 1D). The largest plaques measured 30 µm. In the frontal cortex, a few plaques were surrounded by spongiotic vacuoles and looked like flowers (Figure 1E). In the frontal and occipital cortices and the cerebellum, granular, synaptic, perineuronal (Figure 1F), and perivacuolar staining were also present. In the frontal cortex, the plaques were more numerous in the deep cortical layers, and immunohistochemical findings were positive exclusively in these layers.

A Western blot analysis of PrP using the anti-PrP monoclonal antibody 3F4 showed 3 bands and disclosed a type 2 pattern according to Parchi et al4 with a nonglycosylated form migrating at 19 kDa. The monoglycosylated and diglycosylated band had almost the same intensity (Figure 3).

DNA sequencing of the PRNP gene revealed an adenine substitution for guanine at the second position of codon 208, which results in the substitution of a histidine for an arginine (R208H). The polymorphic codon 129 was homozygous for valine.

COMMENT

The clinicopathological presentation of this patient is very close to that reported by Parchi et al4 of patients with sCJD with type 2 PrPres and valine homozygosity.4 In both
cases, the disease onset was around 60 years of age with early ataxic symptoms and subsequent cognitive deterioration. Myoclonus was absent as well as periodic sharp waves on electroencephalogram. The neuropathological features were also very similar. There was a deep laminar pattern of spongiosis. Lesions were maximal in the striatum and thalamus, severe in the frontal cortex, and mild to moderate in the parahippocampal gyrus and substantia nigra. As described in sCJD with val/val at codon 129 and a type 2 migration pattern with rapid course, the degree of involvement of the neocortex was relatively spared. These data confirm the strong influence of PRNP codon 129 polymorphism and PrP type on the disease phenotype. They also support the hypothesis that the R208H mutation influences disease susceptibility without significantly affecting the disease phenotype. However, some particular features were noted in our patient. Psychiatric signs at onset are rare in groups with sCJD with type 2 PrPres and valine homozygosity but not with type 2 PrPres and methionine homozygosity subtypes. When present, they are confined to the granular cell layer of the cerebellar cortex, and localization in the molecular layer is unusual. They have been observed in the molecular layer of some other familial prion diseases such as Gerstmann-Straussler-Scheinker syndrome and variant CJD. As reported for a previous patient with methionine homozygosity with type 1 PrPres and an R208H mutation, years before the onset of the disease there was a "prodromic" syndrome, which corresponded to a worsening of emotional disorder in the present case and to a cortical sensory disturbance in the previous case. In both cases, the duration of the disease approximated 7 months but a 3-year duration could be discussed. Because of the presence of behavioral disturbance since childhood, we could also consider a lifelong duration in our case.

This observation emphasizes the physiopathological link between R208H and familial CJD. This new combination of R208H mutation, codon 129 val/val, and type 2 proteinase K–resistant PrP was associated with features shared by the group with sCJD with valine homozygosity and type 2 PrPres, but with the unusual presence of amyloid PrP plaques.

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Correspondence: Céline Basset-Leobon, MD, Department of Pathology, Rangueil Hospital, TSA 50032, 31059 Toulouse CEDEX 9, France (celine.basset@libertysurf.fr).

Author Contributions: Study concept and design: Basset-Leobon, Uro-Coste, and Delisle. Acquisition of data: Basset-Leobon, Uro-Coste, Peoc’h, Haik, Szadovitch, Rigal, Andreoletti, Hauw, and Delisle. Analysis and interpretation of data: Basset-Leobon, Uro-Coste, Rigal, and Delisle. Drafting of the manuscript: Basset-Leobon and Rigal. Critical revision of the manuscript for important intellectual content: Basset-Leobon, Uro-Coste, Peoc’h, Haik, Szadovitch, Rigal, Andreoletti, Hauw, and Delisle. Obtained funding: Uro-Coste, Rigal, and Delisle. Administrative, technical, and material support: Uro-Coste, Rigal, Andreoletti, and Delisle. Study supervision: Basset-Leobon, Uro-Coste, and Delisle.

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