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Variably Protease-Sensitive Prionopathy: Two New Cases With Motor Neuron-Dementia Syndrome

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ABSTRACT

We describe two patients with variably protease-sensitive prionopathy (VPSPr) who developed progressive upper motor neuron symptoms, insomnia, behavioral and cognitive decline, compatible with primary lateral sclerosis associated with frontotemporal dementia (FTD). Neuropathology revealed a spongiform encephalopathy with frontotemporal and pronounced thalamic involvement, associated with fine synaptic abnormal prion protein conformer (PrP^{Sc}) deposits, microplaques, and intraneuronal aggregates. Western blot analysis revealed a characteristic VPSPr proteolytic profile, lacking the diglycosylated band. Both patients were methionine homozygous at *PRNP* codon 129 and carried no pathogenic mutations. These cases illustrate that VPSPr can present with a prominent motor neuron syndrome and FTD features.

1 | Introduction

Variably protease-sensitive prionopathy (VPSPr) is the most recently described subtype of sporadic prion diseases [1, 2], first documented in 2008 [3], with nearly 90 cases [1] reported worldwide [4]. Its neuropathological and biochemical features are atypical for other sporadic prion diseases, such as Creutzfeldt-Jakob disease (sCJD) or fatal insomnia (sFI). VPSPr shows a distinct neuroanatomical distribution and immunohistochemical abnormal prion protein conformer (PrP^{Sc}) deposition pattern, together with a characteristic ladder-like Western blot (WB) profile of the proteinase K (PK)-resistant PrP (PrP^{res}), which is more susceptible to digestion than the aggregates found in other prionopathies [5, 6]. VPSPr do not fulfill established sCJD diagnostic criteria and remain underdiagnosed during life [2].

We describe the clinical, biochemical, and neuropathological findings of two patients with VPSPr presenting with a motor

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neuron/frontotemporal dementia (FTD) syndrome, providing insights for its early recognition.

2 | Patients and Methods

Human brain samples were used according to the current Spanish national legislation (Royal Decree RD1716/2011). Detailed protocols of neuropathological, genetic, and biochemical studies are provided in Supporting Informations and methods.

Both patients were residents of Navarre, a community in Northern Spain. A summary of the main clinical features is shown in Table 1.

Patient 1. A 57-year-old man presented with low mood and walking difficulties during the last 6 months. He had no history of psychiatric illness or relevant diseases, no family history of neuropsychiatric disorder. He reported apathy, asthenia, clinophilia, and insomnia. Emotional lability and intermittent eye contact were evident. He developed progressive gait disturbance with instability. Neurological examination 4 months later revealed normal speech, without hypophonia or dysarthria. Cranial nerves including ocular movements were normal. Generalized spasticity and hyperreflexia, clonus, and bilateral Babinski and Hoffmann signs were observed despite normal strength and no fasciculations. Sensibility was preserved. Mild generalized bradykinesia was observed, but resting tremor was absent. Gait was broad-based, but possible without support. Cranial and spinal magnetic resonance imaging (MRI) showed no relevant findings. In the following months, he lost significant weight. Signs of cognitive decline with inattention, bradyphrenia, and memory loss were also remarkable. Two years after symptom onset, gait disturbance worsened, leading to falls. He was disoriented, language was hypofluent and dysarthric, with occasional paraphasias. Ideomotor praxias and Luria sequence were impaired. Eye movements remained normal. He showed no lingual atrophy or fasciculations; the palmomental reflex was present bilaterally. A severe pyramidal syndrome and global bradykinesia persisted. Gait was very unstable. No myoclonus was observed.

New cranial MRI (Figure 1A,B), brain ^{18}Fluorodeoxyglucose (FDG)-positron emission tomography (PET) (Figure 1C) and other additional results are summarized in Table 1.

During the following year, the patient developed dysphagia and evolved to total dependency. He died of sepsis secondary to rectal abscess 46 months after symptom onset.

Patient 2. A 74-year-old man consulted for progressive gait disturbance for 9 months, with greater clumsiness of the right leg and instability. He lost 10 kg weight in the last year. He had no previous diseases and no family history of neuropsychiatric disease.

Neurological examination revealed a spastic gait with an increase in the support base and an inability to walk in tandem but no dysmetria. Mild generalized bradykinesia and generalized hyperreflexia were detected with clonus and a right Babinski sign. No amyotrophy, fasciculations, or sensory alterations were observed. Cranial nerves, including ocular movements, were normal. No speech or cognitive impairments were present. A cranial and spinal MRI was unremarkable. During follow-up, no clinical or electrophysiological signs of lower motor neuron involvement were detected, but insomnia, emotional lability, and depressive syndrome emerged.

After 2 years of follow-up, behavioral alterations, apathy, and progressively reduced verbal fluency with paraphasia led to a

TABLE 1 | Clinical and paraclinical findings of the two patients with VPSPr.

	Patient 1	Patient 2
Sex/age at onset (years)	Male 57	Male 74
Blood count and biochemical profile, thyroid hormones, and Vitamin B12	Unremarkable	Unremarkable
UMN/LMN neurophysiological findings	Yes/no	Yes/no
EEG	Normal (at 34 months from clinical onset)	NP
MRI	Moderate diffuse cortical and subcortical atrophy. Slight left thalamic DWI hyperintensity	Moderate diffuse cortical and subcortical atrophy was found without changes in the DWI
DaTSCAN	Normal	NP
FDG-PET	Frontal dorsomedial cortical and thalamic hypometabolism	NP
CSF-14-3-3 protein	Negative (at 34 months from clinical onset)	NP
CSF RT-QuIC	NP	NP

Abbreviations: CSF, cerebrospinal fluid; DaTSCAN, single photon emission computed tomography with the dopamine transporter ligand ^{123}I-FP-CIT; DWI, diffusion weighted; EEG, electroencephalogram; FDG-PET, ^{18}Fluorodeoxyglucose—positron emission tomography; LMN, lower motor neuron; MRI, magnetic resonance imaging; NA, not assessed; NP, not performed; UMN, upper motor neuron.

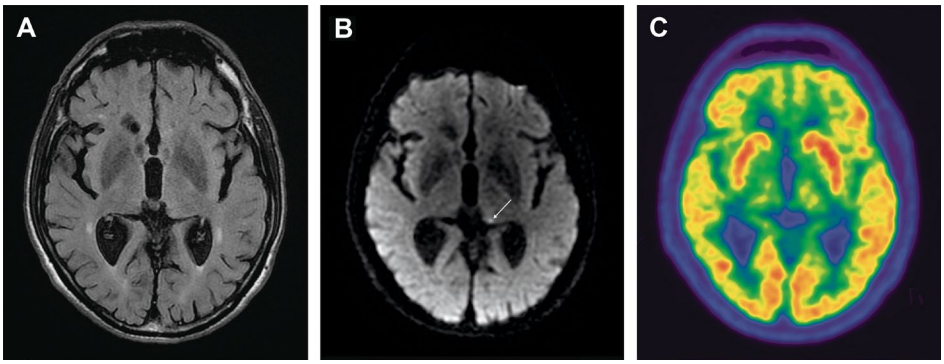

FIGURE 1 | Brain imaging of patient 1. (A) Brain magnetic resonance imaging (MRI), FLAIR sequence, axial section showing mild temporal atrophy and small hyperintense signals in white matter. (B) MRI-DWI sequence, axial section, showing slight hyperintensity in the left pulvinar (arrow). (C) ^{18}Fluorodeoxyglucose (FDG)-PET showing cortical hypometabolism of dorsomedial frontal cortex and thalamus.

diagnosis of dementia. He developed dysphagia and dysarthria and died after 67 months from clinical onset.

Written informed consent was obtained from both participants or their caregivers for brain and spinal cord donation to the Biobank of Navarra for neuropathological studies.

3 | Results

3.1 | Neuropathological Findings

Formalin-fixed brain weighted 1200 g in case 1 and 972 g in case 2. In both cases, the neuropathological study was similar. Gross diffuse brain atrophy with gyral narrowing and slightly enlarged sulci was observed. Histology (Figure 2A1–L1 for patient 1 and A2–M2 for patient 2) showed mild spongiform change in cortical areas (Figure 2A1,A2,B2), moderate in the motor cortex. Superficial spongiosis and shrunken motor neurons were seen. The temporal cortex showed pronounced neuronal loss and gliosis with small vacuoles distributed along all cortical layers. Immunohistochemistry for PrP (antibody 12F10) showed faint, fine-synaptic pathological PrP^{Sc} deposits associated with fleecy and freckled deposits in deep cortical layers (Figure 2A1,B1 inset, E2, I2). Occasional dots and microplaques were also identified (Figure 2B1 inset, F2, G2, J2). The hippocampus and striatum were mildly affected. In contrast, the thalamus showed marked spongiform change, neuronal loss and gliosis (Figure 2C1,C2). Faint extracellular synaptic and frequent fine-granular intraneuronal PrP^{Sc} aggregates were observed (Figure 2C1 inset, K2). The cerebellar molecular layer was moderately gliotic but lacked obvious spongiform alteration (Figure 2D1,D2). Irregular pathological PrP^{Sc} deposits were detected in the molecular layer (Figure 2D1 inset, H2), and at the cortico-subcortical boundary in the white matter (Figure 2D1 lower inset, M2) along with some microplaques (Figure 2L2). In the spinal cord, loss of motor neurons (Figure 2E1–G1) and degeneration of the lateral corticospinal tract (Figure 2H1) along with frequent intraneuronal PrP^{Sc} aggregates were observed (Figure 2I1–L1).

In case 2, mild age-related tau (AT8) positive neurofibrillary pathology with few tangles and neuropil threads was observed (Braak neurofibrillary stage II), without significant Aß pathology, or TDP-43 or α-synuclein deposits.

3.2 | Genetic Analysis

Sequencing of the complete *PRNP* gene revealed no pathogenic mutations or polymorphisms. Both patients were homozygous for methionine at codon 129 (Met/Met genotype).

3.3 | Biochemical Analysis

WB analysis was performed from both patients (Figure 3). The membrane was developed using 3F4 monoclonal antibody (1:4000 dilution), which showed two clear bands corresponding to the non-glycosylated and monoglycosylated PK-resistant fragments of PrP, identical in size to the corresponding bands of the sCJD VV2 isolate. No diglycosylated PrP-resistant fragment could be detected. All cases showed the same PrP^{res} profile after mild PK digestion (3 μg/mL): non-glycosylated and monoglycosylated bands (~19 and 22–25 kDa), identical to sCJD VV2, but lacking diglycosylated fragments.

PK titration confirmed the markedly lower resistance of VPSPr fragments compared to sCJD controls, with complete digestion at concentrations > 20 μg/mL (Figure S1). Comparison with previously reported VPSPr cases revealed indistinguishable fragment patterns, including a faint 8–10 kDa band detectable with C-terminal but not N-terminal antibodies (Figure S2).

4 | Discussion

We describe two patients with neuropathologically and biochemically confirmed VPSPr who presented clinically with primary lateral sclerosis (PLS) associated with FTD. Both patients suffered from a gait disorder related to upper motor neuron involvement and subsequently developed FTD and generalized bradykinesia justified by the pyramidal spasticity [7, 8], without oculomotor disorder, ataxia, or myoclonus, as would be expected for other sporadic prion diseases. EEG and 14-3-3 protein in cerebrospinal fluid (CSF) were also not

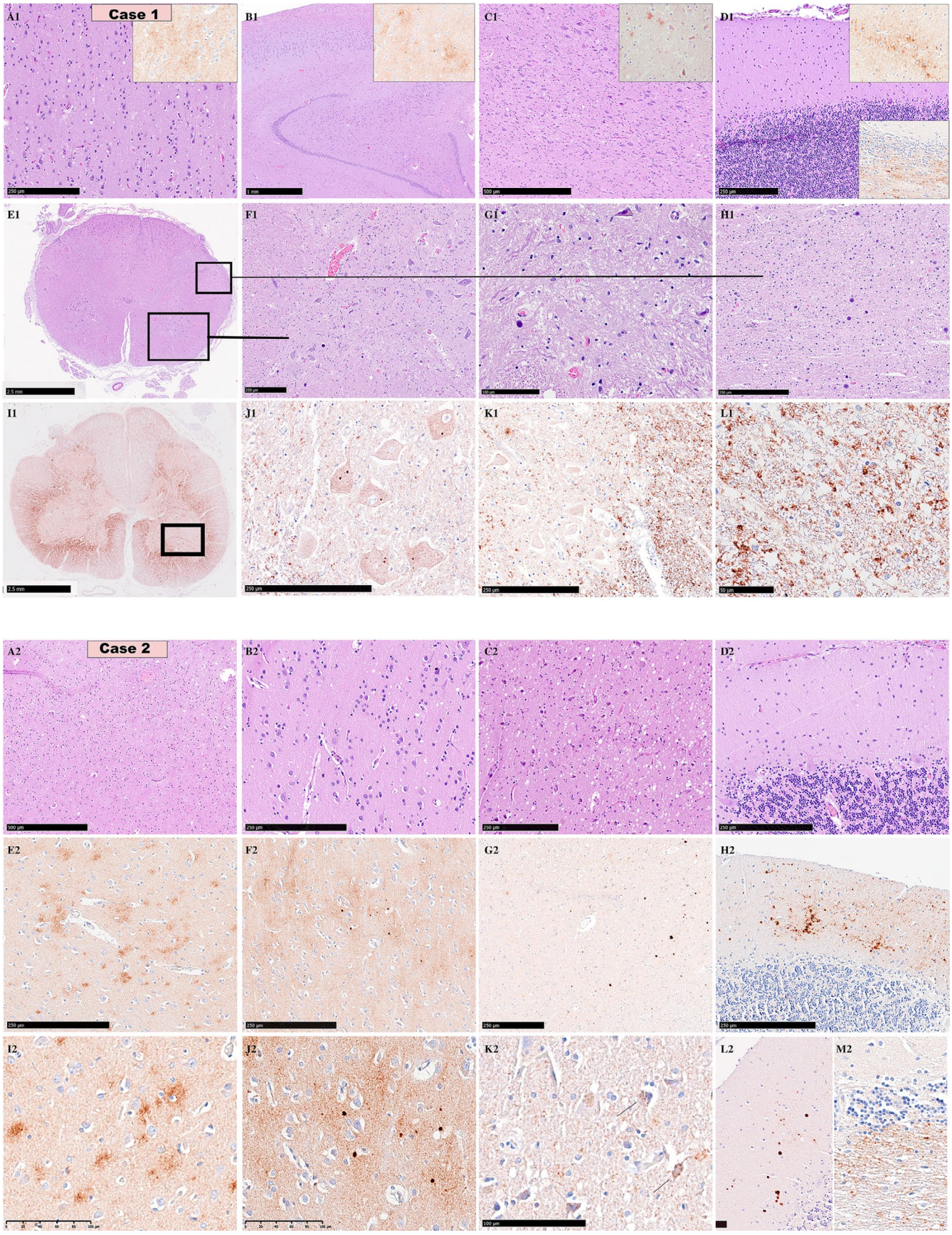

FIGURE 2 | Legend on next page.

FIGURE 2 | Neuropathological features. Case 1 (A1–L1). A1: Motor cortex with mild spongiform change. B1: The hippocampus is relatively well preserved. C1: The thalamus shows prominent gliosis and moderate spongiform change, while the cerebellum is only mildly affected (D1) (A1–D1: HE stained sections). The insets for each region depict immunohistochemical detection of pathological PrP^{Sc} deposits in a discrete synaptic and freckled (A1) or fleecy (B1) pattern, intraneuronal aggregates in thalamic neurons (C1), and irregular deposits in the molecular layer of the cerebellum (D1 upper inset) and white matter junction (D1 lower inset). E1–H1: Cross section through the spinal cord (E1) reveals a loss of motor neurons of the anterior horn (F1) with shrunken residual neurons and axonal spheroids (G1, arrow), as well as degeneration of the lateral corticospinal tract with gliosis, macrophages, and increased corpora amylacea (H1). I1–L1: Immunohistochemistry for PrP (antibody 12F10) reveals an immunostaining of the fasciculi proprii of the spinal cord (I1, L1), the white matter bordering the anterior and posterior horns (central gray matter) that contain the axons of the propriospinal neurons (K1 higher magnification of the transition gray-white matter). Case 2: (A2–M2). A2–D2. Motor cortex with diffuse microstructural alteration (A1) with mild to moderate spongiform change and gliosis (B2), which is much more pronounced in the thalamus (C2). The cerebellum is only mildly affected (D2) (A2–D2: HE stained sections). E2–M2: Different pathological PrP^{D} deposits as observed by immunohistochemistry (antibody 12F10) in different brain regions: Fleecy or freckled deposits in cortical areas on a faint synaptic background (E2, I2) with occasional coarse dots (F2, J2) or microplaques (G2), which were more obvious in the cerebellar granular layer (H2, L2). Intraneuronal fine-granular deposits were frequently observed in large thalamic neurons (K2). In the cerebellum, besides cortical deposits in the molecular layer (H2, L2), diffuse deposits were also observed in the white matter, at the cortico-subcortical boundary (M2). HE, hematoxylin and eosin; PrP^{D}, disease-related PrP deposits.

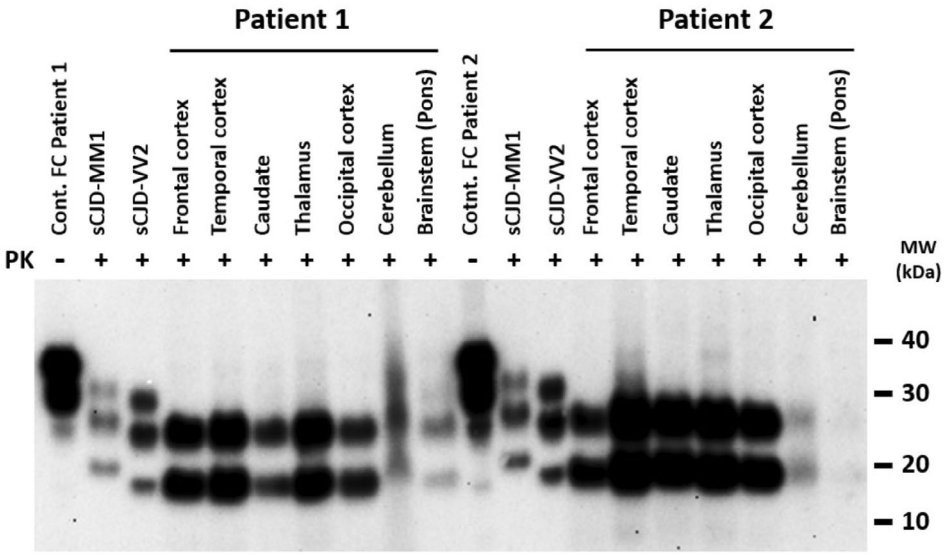

FIGURE 3 | Biochemical analysis of proteinase K resistant PrP in different brain areas from two VPSPr cases. Western blot analysis of brain homogenates (10% w/v in PBS) from two VPSPr patients. Seven brain areas [frontal cortex, temporal cortex, caudate nucleus, thalamus, occipital cortex, cerebellum, and brainstem (pons)] were homogenized at 10% in PBS and digested with 3 μg/mL of PK for 1 h at 42°C. Undigested frontal cortex (FC) samples (PK-) from each patient were included as controls, to assess potential alterations on the glycosylation pattern of the PrP. Additionally, two isolates from subtypes MM1 and VV2 sCJD patients, digested at 85 μg/mL were also included in the gel as a rapid reference for the size of the proteolytic fragments from the two patients under analysis. However, the different PK concentrations used precludes comparison of the amount of PK-resistant PrP in sCJD cases versus the amount detectable in VPSPr cases, significantly lower as illustrated in Figure S1. The same amount of VPSPr patients' brain homogenates was used in all cases for digestion and loading, signal intensity differences reflecting differences in the PK-resistant PrP amount in each area. Despite intense sonication, the sample from the cerebellum from Patient 1 did not migrate correctly in the gel due to high genomic DNA content in the sample. The membrane was developed with 3F4 mAb (1:4000 dilution), that showed two clear bands corresponding to the non-glycosylated and monoglycosylated PK-resistant fragments of the PrP, identical in size to the corresponding bands of the sCJD VV2 isolate. As expected, no di-glycosylated PrP resistant fragment could be detected, in agreement with previously published cases.

supportive in the first patient, and were not performed in the second patient. Both patients developed insomnia, from the early disease stages in patient 1, who displayed slight diffusion weighted (DWI) hyperintensity in the thalamus and a glucose hypometabolism on PET.

In neither patient was the diagnosis of prion disease suspected during life, which represents the diagnostic challenge posed by VPSPr. Neuropathological examination remains the gold standard for diagnosing VPSPr, given the low sensitivity of both CSF- and skin-based RT-QuIC assays in detecting VPSPr [9].

In Spain, four other cases of VPSPr have been previously reported [10–12]. Those described here feature similarities with the two cases reported by Vicente-Pascual et al. [12], which showed signs of motor neuron disease.

It is known that the genotype of codon 129 influences phenotypic diversity in VPSPr cases [13]. VPSPr cases with valine homozygosity present more frequently with psychiatric, language and cognitive symptoms [14] while in the only eight methionine homozygotes VPSPr cases published so far, motor manifestations are frequent and survival is longer [4, 5, 12, 15–18].

The neuropathological phenotype of our two cases is comparable to that reported in the literature. Variable spongiform change in frontotemporal regions, prominent involvement of the thalamus, degeneration of upper and lower motor neurons, and better preservation of the striatum and cerebellum are salient features. The immunohistochemical PrP^{Sc} deposition pattern shows a combination of faint synaptic deposits, fleecy or freckled deposits, coarser dots, microplaques, and intraneuronal PrP^{Sc} accumulations.

The electrophoretic profile of PK-resistant PrP fragments from these two patients aligns with previously reported VPSPr cases carrying the 129MM genotype [15], particularly in their markedly lower PK resistance compared to sCJD prions and the absence of the diglycosylated band. This absence has been previously studied in depth, and although it is poorly understood yet, it has been proposed to result from the impeded conversion of the diglycosylated and monoglycosylated (at position 181) PrP^{C} due to a dominant-negative effect or the involvement of alternative co-factors [19]. Additional ~17 and ~23 kDa fragments reported previously were not detected, possibly due to methodological differences. In fact, despite the 3F4 antibody used here being sufficient to confirm the neuropathological diagnosis, not all the proteolytic fragments characterizing VPSPr prions could be detected with this antibody and the digestion conditions used, as proven by the detection of additional faint bands upon milder PK digestion (Figure S1) or when using alternative antibodies (Figure S2), a panel of antibodies covering both N and C-terminals being the preferable option for the complete characterization of the ladder-like biochemical pattern of VPSPr, as shown before [20].

Our findings highlight the utility of low-concentration PK digestion protocols, complementary to the use of antibody panels, in revealing this distinctive PrP^{Sc} profile, which may be crucial for confirming diagnosis in cases where conventional biochemical assays fail to detect PrP^{Sc}.

In conclusion, we suggest that the presence of an early and severe pyramidal syndrome with or without cognitive or thalamic involvement should raise suspicions of VPSPr, especially when observed in individuals homozygous for methionine at *PRNP* codon 129. Potential biomarkers to support the diagnosis could include FDG-PET to detect early thalamic dysfunction.

Author Contributions

M.E.E. contributed to analysis and interpretation of data, acquisition of image data, and writing the manuscript. M.V.Z. contributed to coordination of experimental assessment and manuscript revising. H.E. contributed to experimental execution and image acquisition. J.S.R.G. contributed to acquisition of clinical data and manuscript revising. F.G.-A. contributed to genetic assessment and manuscript revising. A.S.-S., M.C.C., and I.F. contributed to anatomopathological assessment and manuscript revising. E.G., I.J., and J.C. contributed to drafting/revising the manuscript for content, interpretation of data, acquisition of image data, and study supervision.

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Conflicts of Interest

The author H.E. is employed by the commercial company ATLAS Molecular Pharma SL. This does not alter our adherence to the Journal's policies on sharing data and materials and did not influence in any way the work reported in this manuscript, given that the company had no role in study design, funding, and data analysis. The rest of the authors declare no conflicts of interest.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** acn370294-sup-0001-supinfo.docx. **Data S2:** acn370294-sup-0002-Figures.docx.