LETTER TO THE EDITOR

Inherited prion disease with 4-octapeptide repeat insertion linked to valine at codon 129

Raquel Sánchez-Valle,1,2 Jordi Yagüe,1,3 Antoni Turón,4 Juan I. Aróstegui,3 Carlos Nos,5 Mª Jesús Rey,6 Isidro Ferrer7 and Ellen Gelpi1,6

1 CJD Unit, Department of Neurology, Hospital Clinic, 08036 Barcelona, Spain
2 Alzheimer’s Disease and Other Cognitive Disorders Unit, Department of Neurology, Hospital Clinic, 08036 Barcelona, Spain
3 Immunology Department, Hospital Clinic, 08036 Barcelona, Spain
4 Memory and Dementia Unit, Hospital Santa Caterina, Institut d’Assistència Sanitària, 17190 Girona, Spain
5 CJD Surveillance Unit, Health Department, Generalitat de Catalunya, 08005 Barcelona, Spain
6 Neurological Tissue Bank of the Biobanc-Hospital, Clínic-IDIBAPS, 08036 Barcelona, Spain
7 Institut de Neuropatologia, IDIBELL, Hospital Universitari de Bellvitge, University of Barcelona, 08907 Barcelona, Spain

Correspondence to: Raquel Sánchez-Valle, CJD Unit/Alzheimer’s Disease and Other Cognitive Disorders Unit, Hospital Clinic, C/Villarroel, 170 08036 Barcelona, Spain
E-mail: rsanchez@clinic.ub.es

Sir, We have read the article by Kaski et al. (2011) with great interest, where the authors describe the results of their investigations of patients from the UK with four extra octapeptide repeat insertions (OPRIs) in the prion protein gene (PRNP). Herein, we would like to present a case that we had the opportunity to study with four extra OPRIs in the PRNP gene, but associated with a different genetic background at codon 129.

Kaski et al. (2011) analysed 10 patients with four extra OPRIs. The predominant clinical syndrome was a rapidly progressive cortical dementia with myoclonus, motor and cerebellar signs resembling sporadic Creutzfeldt-Jakob disease (CJD). Age at onset and disease duration presented considerable variability; the mean age of onset was 60 years (range 39–85 years) with median disease duration of 414 days (range 59–2319 days). The 14-3-3 test was positive in all tested patients (n = 4). MRI showed hyperintensities typical of sporadic CJD only in one out of five patients studied. The genetic analysis revealed that all patients have additional four R2 repeats within the repetitive part of the PRNP gene located between positions 51 and 91, and all of them were homozygous for methionine (M) at codon 129. Only one patient presented with familial history of early-onset dementia suggesting that the 4-OPRI has a very low penetrance and that, perhaps, its presence is not enough to produce the disease.

We would like to report a new case with four extra OPRIs (R2R2R2R3) that, in contrast to those cases described by Kaski et al. (2011), was heterozygous valine/methionine (V/M) at codon 129. The patient was a 38-year-old male, who developed rapid progressive cognitive decline with memory impairment, inattention and spatial disorientation. The EEG registers presented slow baseline rhythm but failed to show periodic sharp wave complexes. The 14-3-3 test was positive in CSF. The first MRI performed 7 months after clinical onset revealed normal T1-weighted images with cortical hyperintensities in frontal and occipital cortices in fluid-attenuated inversion recovery and diffusion-weighted sequences, associated with restricted diffusion (apparent diffusion coefficient map). A second MRI performed 7 months later, showed, in addition to cortical lesions, hyperintensities in basal ganglia such as those previously described as typical of sporadic CJD. At this point, a diagnosis of probable CJD was established. The patient had no epidemiological risk factors for iatrogenic or variant CJD. There was no known family history of neurodegenerative disease. His father had died due to a heart attack, cognitively intact at the age of 71 years, and his mother was alive and healthy at the age of 70 years. He was the fourth sibling of a five-member kindred. One of his siblings had suffered from Down syndrome and died in the first decade of life. The other three
siblings were alive and asymptomatic in their forties. Despite absent family history of disease, genetic study was performed following experts' recommendations. The PRNP analysis revealed a heterozygous insertion of 96 nucleotides grouped in four octapeptide repeats within the normal octapeptide repeat region (R1R2R3R4). No point mutations were detected. The patient was heterozygous, M/V at codon 129. Valine and the 4-OPRI were located at the same allele. After this unexpected result, a genetic analysis of the patient's mother was performed, with previous written informed consent. Genetic analysis showed that she carried the same 4-OPRI mutation, but in this case with the homozygous V/V genotype at codon 129. Her parents had died at 93 and 76 years, respectively, without symptoms suggestive of neurodegenerative disease, and she had four siblings, three of whom had already died, and none had presented symptoms of dementia. No other family members participated in the study. During evolution, the patient presented frequent myoclonus and visual hallucinations and his neurological state deteriorated rapidly to become mute and bedridden. He died 17 months after the onset of symptoms. Brain was donated for research purposes to the Neurological Tissue Bank of the Biobanc-Hospital Clinic-IDIBAPS. Unfixed brain weight was 1265 g. Macroscopic examination showed mild frontal lobe and cerebellar vermis atrophy. Histologically, extensive spongiform change with middle-sized vacuoles, accentuated in deep cortical layers and basal ganglia was observed. In addition, neuronal loss, astrogial and microglial proliferation were detected. Frequent ballooned neurons were observed in frontal, temporal and cingular cortices. There was also severe involvement of subiculum and parahippocampal gyrus, and abundant, partly bizarre appearing Hirano bodies were observed in the CA1 sector (Martinez-Saez et al., 2011). In cerebellum, mild spongiform changes in the molecular layer associated with moderate loss of granule cells was detected, with relative preservation of Purkinje cells. Immunohistochemistry showed a diffuse synaptic PrPSc deposition pattern in all affected brain areas, although deposits were relatively faint in relation to spongiform change. Additional coarser granular deposits were detected in subiculum, transentorhinal cortex and focally in the molecular layer of cerebellar cortex. No tigroid pattern was detected. No prion protein amyloid plaques were visible (Fig. 1). Additionally, frequent neuritic profiles immunoreactive for hyperphosphorylated tau were detected in the neuropil in areas with marked spongiform change. No β-amyloid deposits, abnormal α-synuclein or TDP-43 protein aggregates were observed. Western blot analysis performed from frozen brain tissue (frontal lobe) using anti-prion protein monoclonal antibody 3F4 showed the presence of PrPSc type 1 after protease K digestion. The patient's mother has been followed-up on an annual basis. In November 2011, she was 74 years of age and continues to be asymptomatic with normal cognition in formal cognitive examination and presents a normal MRI. In their article, Kaski et al. (2011) discuss that, due to the observed low penetrance of the disease, other factors different from the 4-OPRI mutation could interact to produce the disease (Kaski et al., 2011). In this sense, prion disease susceptibility is thought to be conferred on a molecular level by homotypic protein–protein interactions, especially the degree to which the wild-type and mutant prion proteins can adopt the same pathogenic conformations. Individuals with 4-OPRI and homozygous at codon 129 would then be more prone to develop the disease than heterozygous individuals. Given that 4-OPRI with 129 M/M has an older mean age of clinical onset than many other inherited prion diseases, Kaski et al. (2011) consider that it would be reasonable to predict that the age of onset of 4-OPRI with 129 M/V genotype might lie beyond the average human lifespan. This hypothesis will be supported by the absence of patients with 129 M/V genotype in their cohort or in the literature. In contrast, our patient presented a 4-OPRI on a 129 M/V genotype, being the mutation linked to valine. This finding suggests that the presence of valine in the affected chromosome does not prevent the pathological effect of the mutation. The presence of 129-M in the normal allele would confer less homotypic protein–protein interaction than in the homozygous M/M state, but contrary to what would be expected, it is still able to produce the disease at an age below the range of age of 4-OPRI 129-M, or at least, not at an older age than 4-OPRI 129M. The patient’s mother, who present the same 4-OPRI linked to homozygous V/V genotype at 129, has not developed the disease. Kaski et al. (2011) also hypothesize that the presence of valine in the healthy chromosome could prevent or delay the disease. We believe that this possibility will fit much better with our findings, but in this case, OPRI cases will contradict the effect of homotypic protein–protein interactions that have been demonstrated in animal models and in sporadic, acquired and even some other inherited forms of prion diseases. In this sense, a meta-analysis performed to examine the relation between the number of inserted octapeptide repeats in PRNP, polymorphism at codon 129 and age at disease onset found that patients with genotype M/M tended to have an earlier onset and carriers of V/V genotype a later onset, compared with carriers of genotype M/V (Croes et al., 2004). Our patient presented at 38 years of age. Age of onset in different PRNP mutations presents considerable variability even within a family. In fact, in the article by Kaski et al. (2011), the 10 subjects with 4-OPRI presented a wide range of age of disease onset (39–85 years) even if all of them were homozygous M/M and rs1029273CC (Kaski et al., 2011). In this sense, and due to the fact that the age of our patient (38 years) is just below the range of ages of disease onset published for 4-OPRI, we prefer to be cautious concerning the younger age of onset in this patient. We do not have a convincing explanation for a younger age of onset in 4-OPRI V/M relative to M/M or V/V other than that the 4-OPRI-129V haplotype could create a distinct strain conformation that could be joined by wild-type 129-M protein or epistasis. We have not...
analysed the rs1029273 genotype that would be of interest to evaluate if this polymorphism could influence the age of onset in our patient or the lack of symptoms in his mother. Finally, the presence of valine at codon 129 in our patient suggests a different ancestral origin relative to the British cases.

Concerning neuropathological findings, our patient showed morphological changes reminiscent of those described for VV1 (Parchi et al., 2009, 2010), associated with faint diffuse synaptic PrPSc deposits with unusual focal granular deposits in subiculum, transentorhinal cortex and cerebellar molecular layer. No prion protein amyloid deposits or tigroid pattern, as described by Kaski et al. (2011), were detected by immunohistochemistry. PrPRes was type 1 on western blot. The British patients presented different patterns of PrPSc type 1, 2 and 3. Only one patient presented a type 1 PrPRes, which the authors related to shorter disease duration (79 days), and was not the case in our patient. We also observed abundant hyperphosphorylated tau-immunoreactive neuritic profiles surrounding spongiform change, but this is also observed in cases with sporadic CJD.

In conclusion, although less frequently, 4-OPRI linked to valine at codon 129 can also produce the disease. The effect of polymorphism M/V at codon 129 on the non-mutated chromosome on the phenotypic expression of the disease in OPRI carriers needs further investigation.

Acknowledgements

The authors acknowledge brain donors and their relatives for generous brain donation to the NTB-Biobanc-HC-IDIBAPS. The authors also thank Carina Antiga for helpful support in the Brain Donor Program and Rosa Rivera, Sara Charif and Verónica Santiago, Abel Muñoz and Leire Echarri for skilful technical and laboratory work.

Funding

Instituto de Salud Carlos III (FIS 080036 to R.S.V.).

References


