CASE REPORT

First case of V180I rare mutation in a Brazilian patient with Creutzfeldt-Jakob disease

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ABSTRACT. Here, we report the first case of V180I rare mutation in a Brazilian woman whose clinical condition started with memory impairment for recent events and insomnia with 2 months of evolution, without any other alterations in neurological examination. Both the electroencephalogram (EEG) and the routine biochemical examination of cerebrospinal fluid (CSF) were normal. CSF 14-3-3 protein search was positive. Magnetic resonance imaging (MRI) of the encephalon showed findings suggestive of Creutzfeldt-Jakob disease, confirmed by sequencing of \textit{PRNP} gene that reveal V180I mutation also homozygosity for methionine at codon 129 (M129M).

KEYWORDS. Creutzfeldt-Jakob disease, V180I mutation, V180I/129M haplotype

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a rare and fatal neurodegenerative disorder caused by a pathological prion protein (PrP), encoded by \textit{PRPN} gene (20p13). Some mutations in the \textit{PRPN} gene are related to the heritable/genetic type of CJD (gCJD) and account for 5–15%
amongst all the cases of CJD. The point mutation c.538G>A that replaces valine for isoleucine at 180 (V180I) is one of the major causes of gCJD in Japan and extremely rare in other populations. Clinical features of gCJD with V180I mutation include late-onset; slower progression; lower odds of developing myoclonus; cerebellar and pyramidal signs compared with classical sporadic CJD (sCJD) symptoms. To our knowledge, we reported the first Brazilian case of gCJD with V180I mutation.

**CASE REPORT**

The patient was a 57-year-old Brazilian woman, Italian ancestry and higher education (13 y). Her clinical condition began with memory impairment for recent events and insomnia with 2 months of evolution, without any other alterations in neurological examination. The patient was submitted to cognitive examination by Montreal Cognitive Assessment (MoCA) and obtained 16/30 points. She had neither previously health issues nor cases of dementia in the family history.

Laboratory tests such as renal, hepatic, electrolyte, vitamin B12, folic acid, thyroid function and serological tests for human immunodeficiency virus (HIV) and Venereal Disease Research Laboratory (VDRL) were normal. The electroencephalogram (EEG) in sleep and wakefulness was normal as well as the routine biochemical examination of cerebrospinal fluid (CSF). CSF 14-3-3 protein search was positive. Magnetic resonance imaging (MRI) of the encephalon showed findings suggestive of sCJD (Fig. 2). The genomic sequencing of PRNP gene revealed, besides V180I mutation, homozygosity for allele A which encodes for methionine at codon 129 (M129M) (Fig. 1). After 16 months of clinical onset, the patient presented akinetic mutism, pyramidal signs such as hypertonia and hyperreflexia, as well as myoclonus. The patient died due to pulmonary infection, with 22 months of evolution.

**DISCUSSION**

It is known that the gCJD V180I mutation is extremely rare in populations outside of Japan; our case aroused interest because it is the first case described in Brazil and South America. The patient described had the onset of the symptoms at 57 y old and survival for 22 months, differing of clinical features expected for V180I gCJD, that include late-onset and slower progression. Moreover, there were not any neurological alterations in the initial phase, only the rapidly progressive dementia.

The main pattern of brain MRI in patients with the V180I mutation are the involvement of the cerebral cortex, sparing medial occipital and cerebellar cortices, agreeing with our findings, but in our case the basal ganglia was impairment, more compatible with sCJD diagnostic. The patient had EEG normal and positive for 14.3.3 protein, consistent with the description of the Japanese study with carriers of V180I mutation. On the other hand, the patient showed myoclonus and pyramidal signs only at the final stage of the disease. Although these signs are less frequent for carriers of this mutation, when observed, they are usually early in the disease’s course.

Homozygous for methionine at codon 129 (M129M) is a well-established risk factor for sCJD, although this association has not been shown in any previous study using a Brazilian sCJD cohort. Our patient presented the haplotype V180I/129M, and once the polymorphism at the codon 129 has a modifying effect on the phenotype and interferes with the susceptibility to all prion
diseases,9 this may explain the overlapping of symptoms between gCJD and sCJD presented in this patient.

Other relevant aspect to be considered is that penetrance and pathogenicity of V180I are still under discussion for other populations.10 Therefore, it is important to take into account the ethnical background to better understand the effects that this variant may have on the phenotype and susceptibility to CJD. In Brazilian population this kind of analysis will only be possible as other cases are described.

The V180I mutation still needs to be better understood, since it can present several variations in its clinical presentation. Also, it should be noted that the diagnostic criteria deserve to be reviewed, considering that strongly suggestive MRI, early onset, and the presence of rapidly progressive dementia in a patient without alterations in neurological examination do not allow the diagnosis of gCJD. Maybe patients with V180I/129M haplotype might show an atypical disease course, besides racial and/or environmental factors.

In conclusion, this mutation has not been reported so far in Brazil and more cases need to be described so that we can understand the differences between clinical manifestations.

**AUTHOR CONTRIBUTIONS**

Ricardo K. M. de Souza, diagnosis of the patient, acquisition of data, study concept and study supervision.

Nalini D. Josviak, interpretation of genetics data, study concept and design, critical revision of manuscript for intellectual content.

Meire S. Batistela, interpretation of genetics data, study concept and design, critical revision of manuscript for intellectual content.

Paulo S. F. Santos, acquisition of data, critical revision of manuscript for intellectual content.

Michele C. Landemberger, analysis of genetics data, study concept.

Ricardo Ramina, critical revision of manuscript for intellectual content.

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