
Reading title: Familial Creutzfeldt-Jakob disease in a Mexican patient.

Yeiscimin Sánchez-Escobedo\textsuperscript{1}, María del Rosario López-Zapata\textsuperscript{2}, Julio César López Valdés\textsuperscript{3,4,5*}, Rafael Sánchez-Mata\textsuperscript{3}, Laura Mestre-Orozco\textsuperscript{6}, Ulises García-González\textsuperscript{3,4}

1. Hospital Regional de Poza Rica, PEMEX. Departamento de Medicina Interna. Poza Rica, Veracruz; México
2. Hospital Central Sur de Alta Especialidad (H.C.S.A.E.), PEMEX. Departamento de Neurología. Tlalpan, Ciudad de México.
3. Hospital Central Sur de Alta Especialidad (H.C.S.A.E.), PEMEX. Departamento de Neurocirugía. Tlalpan, Ciudad de México.
4. Universidad Nacional Autónoma de México (U.N.A.M.), División de estudios de Posgrado. Ciudad Universitaria, Ciudad de México; México
5. Universidad Autónoma de Tamaulipas (U.A.T.). Facultad de Medicina de Tampico “Dr. Alberto Romo Caballero”. Departamento de investigación. Tampico, Tamaulipas; México.
6. Centro Médico American British Cowdray, Departamento de Patología Cuajimalpa, Ciudad de México

*Correspondence:
Julio César López Valdés ORCID 0000-0001-6238-0027
Email: jc.lopz@live.com Phone number: +521 8332949489
Pedro José Méndez #811 Colonia Cascajal. Tampico, Tamaulipas; México ZIP: 89280

List of abbreviations:
CJD: Creutzfeldt-Jakob disease
WHO: World Health Organization
fCJD: familial Creutzfeldt-Jakob disease
PrP: prion gene
mg/dl: milligram per deciliter
pg/ml: picogram per deciliter
ng/ml: nanogram per milliliter

© Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez. Open access articles under the terms of the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) license, which permits use, distribution and reproduction in any medium, provided the original work is properly cited. No commercial re-use is allowed
mmol/L: millimol per liter
U/L: units per liter
VDRL: Venereal Disease Research Laboratory
IgM: Immunoglobulin M
anti-HIV: anti-human immunodeficiency virus test

Declarations

Ethics approval and consent to participate: Ethics committee approval was not considered necessary because it was a case report. Informed consent was obtained from the patient for this study.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Availability of data and materials: Not applicable.

Competing interests: The authors declare that they have no competing interests.

Funding: This report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: YSE & MRLZ—conceptualization, writing initial draft. RSM & LMO—data collection, editing, supervision. JCLV: supervision and editing. UGG: supervision. All authors read and approved the final manuscript.

Acknowledgements: Not applicable.

Coauthor Orcid List

Yeiscimin Sánchez-Escobedo: Not available
María del Rosario López-Zapata: Not available
Rafael Sánchez-Mata: Not available

© Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez. Open access articles under the terms of the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) license, which permits use, distribution and reproduction in any medium, provided the original work is properly cited. No commercial re-use is allowed
Laura Mestre-Orozco: Not available

Ulises García González: 0000-0002-6661-5409
TITLE: Familial Creutzfeld-Jakob disease, compatible with PRNP c.532G>A (p.Asp178Asn) gene mutation

ABSTRACT: **Background:** Prion disease is a rare entity; a prevalence between 0.32-1.73 per million people is estimated. The familial form corresponds to 10% of the total cases, with a peak of presentation between 40-50 years. Over forty known germline mutations have been described, the most frequent being c.598G>Ap.Glu200Lys (E200K). **Case presentation:** A 41-year-old man began in November 2021 with progressive memory impairment. In April 2022 he started to have tremors and balance disturbances. The neurological examination was compatible with dementia, pancerebellar and parkinsonian syndromes. Magnetic resonance imaging showed symmetrical and bilateral hyperintensities of the basal ganglia. Due to the findings and family history, a sequencing search for the PrP gene was performed, resulting in a mutation of the PrPSc gene c.532G>A (p. Asp178sn), compatible with a familial variant of Creutzfeldt Jacob Disease. **Conclusions:** Prionopathy should be considered as a diagnosis to rule out in people with rapidly progressive dementia. Although there are both clinical and paraclinical diagnostic criteria, diagnosis through DNA sequencing is necessary to determine de novo or autosomal dominant hereditary mutations.

**Key words:** Prion disease, familial variant, Creutzfeld-Jakob disease, prionopathies.

Background: Prion disease is a rare entity, spongiform encephalopathy or Creutzfeldt-Jakob disease (CJD) is the most common; a prevalence of 0.32-1.73 per million people is estimated. According to the latest World Health Organization (WHO) classification, it is divided according to its etiology into sporadic, familial, and iatrogenic varieties. The familial form (fCJD) makes up approximately 10% of the total cases, with a peak presentation between 40-50 years of age. The prion gene (PrP) which is in the short arm of chromosome 20 has been thought to be the main cause; however, just over 40 known germline mutations have been described, the most frequent being c.598G>Ap.Glu200Lys (E200K).

Case presentation: A 41-year-old man, from Minatitlan, Veracruz, with a family history of rapidly progressive dementia and tremors (Figure 1), debuted in November 2021 with progressive memory impairment, difficulty to recognize direct relatives, visual and olfactory hallucinations. In April 2022 he began with speech disorder, limbs tremors, and difficulty to walk associated to balance problems.

On admission, he was disoriented, with non-fluent and dysarthric language (slurred speech), mini-mental study test results were 9 points. On neurological examination, he presented difficulty to perform ocular movements; slow glottic movements plus inability to move upward the tongue, and tongue fasciculations were observed.

He presented slightly increased tone in the upper limbs and left patellar hyperreflexia. He showed bilateral dysmetria, the finger tap test showed amplitude and speed decreased; the supination movement for arms was slow accompanied with a severe, low-frequency, low
amplitude, posture-induced tremor. The bilateral heel-to-shin test was not achieved due to stiffness. The gait was plantigrade and slow steps, without arm swinging, and difficulty to rotate on its own axis. A dermatosis was identified on the left arm characterized by an irregular psoriatic plaque measuring approximately 10 x 15 centimeters. Other items of the neurological examination had normal results. The laboratory blood tests were normal, also the liver, and kidney functions were normal, as well as levels neoplastic markers and vitamins. Tests for HIV and antibodies for hepatitis B and C had negative results. (Table 1).

Magnetic resonance imaging showed symmetrical and bilateral hyperintensities of the basal ganglia, in T2 diffusion-weighted imaging MRI showing an asymmetrical cortical ribbon sign on both frontoparietal regions, predominantly on the right hemisphere (figure 2). In addition, an electroencephalogram was performed, which showed moderate alterations, with left frontal cortex irritability and without the presence of triphasic waves.

It is worth mentioning that the father of the patient and two deceased brothers had already been studied time before by genetic sequencing for Huntington's disease which were negative and other metabolic diseases.

The analysis of the spinal fluid revealed normal cellularity and positivity for 14-3-3 protein. Owing to these results and the medical family history related to rapid progressive dementia, a genetic study for Creutzfeldt-Jakob disease was requested. A sequencing search for the PrP gene was carried out, with a positive result for mutation of the PrPSc c.532G gene. >A(p.Asp178Asn). Creutzfeldt-Jakob disease was diagnosed based on this finding.

To date, the patient continues to be followed up. On his last visit, was found bedridden, with inability to speak, partial swallowing and sphincter control.
Discussion: There are few cases of prionopathies in Mexico and in literature, not to mention that cases related to fCJD and genetic study are limited. In the case described here, the presence of three direct-line relatives with a medical history of rapidly progressive dementia and tremors, with no clear diagnosis and having excluded the possibility of other genetic or metabolic pathologies led to the consideration of familial Creutzfeldt-Jakob disease.

In addition, the imaging studies showed brain atrophy and hyperintensities in the caudate nuclei, which has been described as having a sensitivity of 91% and a specificity of 93%.5, 6. Only 50% of the cases present initial electroencephalographic manifestations, and up to 80% of the patients in the subsequent studies 7. In this case, the tremor features are concordant with wing-beating tremor, only once time before described in a case of fCFD.11

In isolated reports, the prion gene has been proven to show amino acid substitutions in different codons, such as E196A, E200K 129 (M/M), 171 (N/S), 180 (V180I) and 219 (E/K)8-10. Likewise, within the PrP mutations, four mutations have been described (E200K, D178N, A117V and P102L) where a generational condition is evidenced, the rest may correspond to an isolated de novo mutation term if no familial association was found.7

In the other hand, the PrPSc c.532G gene>A (p.Asp178Asn) is related to a single nucleotide variant, associated to th protein change D178N; ASP178ASN and located in 20p13.12

Conclusions: Despite its low incidence, we must consider prionopathies as a possible diagnosis, especially in those patients with a family history of rapidly progressive dementia. We must remember that the diagnosis of this group of diseases is initially through clinical and biochemical ruling out with subsequent immunohistochemical and/or genetic confirmation.
References.


FIGURE NOTES.

Figure 1. Family tree of the patient according to clinical history (data provided by mother).

According to interrogation, the father died due to the same clinical pattern with greater and rapidly progressive neurological deterioration, as well as two brothers of different ages. This person's genealogy proves the disease with an autosomal-dominant mutation, where the first known carrier was the patient's grandmother.

Squares = man, circle = woman, X= rapid progressive dementia

Figure 2: Simple and contrasted magnetic resonance imaging, axial sections at the level of the third ventricle and lateral ventricles, where cortical lesions and basal nuclei can be seen with their image behavior according to the different weightings. A) Axial slices in T1, isointense lesions to the gray and white matter. B) Axial slices in T2, behavior similar to T1. C) FLAIR sequence, showing lesions in the direction of the grooves at the cortical level and hyperintense basal ganglia. D) Axial sections with application of Gadolinium, without evidence of enhancement. E and F) DWI sequence, hyperintense cortical and basal ganglia lesions with the same behavior on restriction. G) ADC sequence. H) Axial section, T2 sequence, towards ventral with presence of cortical lesions in both white and gray matter in frontal and right parietal gyri, as well as left parietal lesions and in the interhemispheric region. In addition, it is possible to observe the absence of infarction, hemorrhage, mass, or focal intracranial abnormality. There are no features of normal pressure hydrocephalus.
**Figure 3:** Original image capture of the results for genetic test

<table>
<thead>
<tr>
<th>Table 1: Laboratory profile results during hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total leukocytes</strong></td>
</tr>
<tr>
<td><strong>Neutrophils</strong></td>
</tr>
<tr>
<td><strong>Lymphocytes</strong></td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
</tr>
<tr>
<td><strong>Urea</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Creatinine 0.9 mg/dl</td>
</tr>
<tr>
<td>Prothrombin time 18.8 s</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
RESULT: POSITIVE

One Pathogenic variant identified in PRNP. PRNP is associated with a spectrum of autosomal dominant prion disorders.

<table>
<thead>
<tr>
<th>GENE</th>
<th>VARIANT</th>
<th>ZYGOSITY</th>
<th>VARIANT CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRNP</td>
<td>c.532G&gt;A (p.Asp178Asn)</td>
<td>heterozygous</td>
<td>PATHOGENIC</td>
</tr>
</tbody>
</table>