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FAMILIAL CREUTZFELD-JAKOB DISEASE, COMPATIBLE WITH PRNP C.532G>A (P.ASP178ASN) GENE MUTATION

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Abstract

Background: Prion disease is a rare entity, with an estimated prevalence ranging from 0.32 to 1.73 cases per million individuals. The familial form corresponds to 10% of all cases, with an age of onset between 40 and 50 years. To date, over forty germline mutations have been described, with the most frequent being the c.598G>Ap.Glu200Lys (E200K) mutation. **Case presentation**: A 41-year-old male presented in November 2021 with progressive memory impairment. By April 2022, he developed tremors and balance disturbances. Neurological examination revealed features consistent with dementia, pancerebellar and parkinsonian syndromes. Magnetic resonance imaging showed symmetrical and bilateral hyperintensities in the basal ganglia. Given these findings and familial factors, genetic sequencing of the PrP gene was performed, revealing a mutation in 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 possibility in individuals with rapidly progressing dementia. Although there are both clinical and paraclinical diagnostic criteria, DNA sequencing is essential for identifying de novo or autosomal dominant hereditary mutations.

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

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Background

Prion disease is a rare entity, with spongiform encephalopathy or Creutzfeldt-Jakob disease (CJD) being the most common; a prevalence of 0.32-1.73 per million people is estimated.[1] According to the latest classification by the World Health Organization (WHO), prion diseases are categorized based on their etiology into sporadic, familial, and iatrogenic forms. The familial variant (fCJD) constitutes approximately 10% of the total cases, with a predominant occurrence between the ages of 40 and 50.[1,2] The prion gene (PrP), located on the short arm of chromosome 20, has been considered to be the main cause, however, just over 40 germline mutations have been described, the most frequent being c.598G>Ap.Glu200Lys (E200K).[2]

Case presentation

A 41-year-old male from Minatitlan, Veracruz, with a family history of rapidly progressive dementia and tremors (Figure 1), initially presented in November 2021 with a gradual memory impairment, difficulty to recognize direct relatives, and visual and olfactory hallucinations. By April 2022, he manifested speech disorder, limbs tremors, and walking difficulties associated to balance issues.

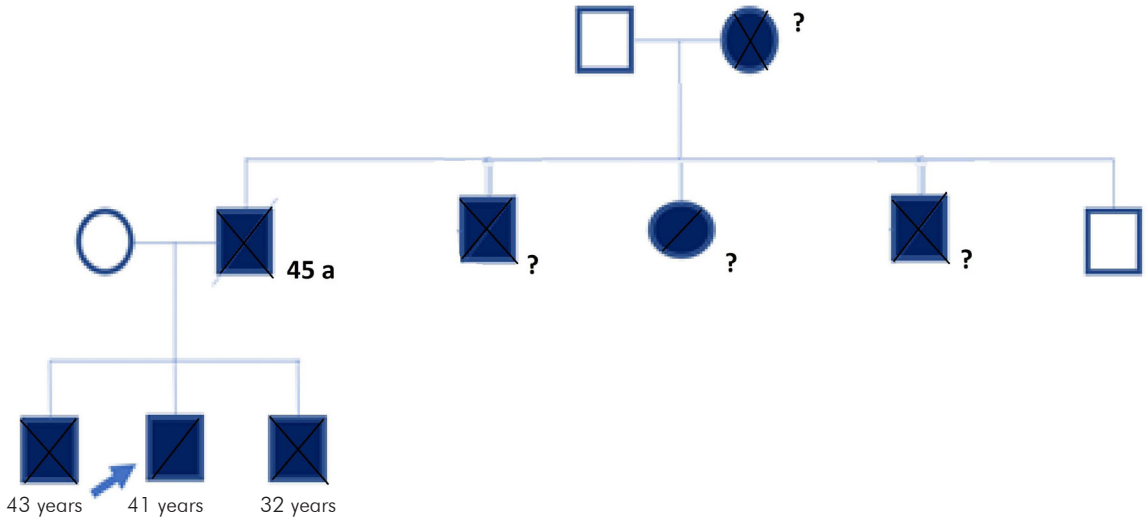


Figure 1. Family tree of the patient based on clinical history (data provided by mother). According to interrogation, the patient's father and two brothers of different ages exhibited a similar clinical pattern, with more pronounced and rapid progressive neurological deterioration, ultimately resulting in their deaths. This genealogical information suggests an autosomal-dominant mutation as the underlying cause of the disease, with the patient's grandmother identified as the first known carrier. Squares: males, circle: females, X: individuals affected by rapid progressive dementia.

Upon admission, the patient exhibited disorientation with non-fluent and dysarthric language (slurred speech), scoring 9 points on the mini-mental study test. During the neurological examination, he presented difficulty performing ocular movements, slow glottic movements, plus inability to elevate the tongue, and observable tongue fasciculations. He presented slightly increased tone in the upper limbs and left patellar hyperreflexia. The patient also showed bilateral dysmetria with decreased amplitude and speed observed in the finger tap test, slow supination movements of the arms, accompanied by a severe, low-frequency, low amplitude, posture-induced tremor. The bilateral heel-to shin test was not completed due to stiffness. His gait was plantigrade with slow steps, absent arm swinging, and difficulty in rotating on his 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 yielded normal results.

Laboratory blood tests including liver and kidney function, neoplastic markers and vitamins levels, were all within normal limits. HIV and hepatitis B and C antibody tests yielded negative results (Table 1).

Table 1. Laboratory profile results during hospitalization

Total leukocytes: 8,370 cells	Activated partial thromboplastin time: 32 seconds	Globulin: 2.9	Ca 19.9: >2.0 U/ml
Neutrophils: 4,730 cells	INR: 1.42	Calcium: 9.4 mg/ dl	CA125: 5.5 ng/ ml
Lymphocytes: 2,820 cells	Vitamin B12: 967 pg/ml	Phosphorus: 3.9 mg/dl	Total prostate specific antigen: 0.24 ng/ml
Hemoglobin: 13.62 mg/dl	Glutamic oxaloacetic transaminase: 21 U/L	Potassium: 4.2 mmol/L	Non-reactive anti-HIV type 1 and 2
Platelets: 194,000 cells	Glutamic pyruvic transaminase: 31 U/L	Sodium: 140.2 mmol/L	Non-reactive hepatitis A IgM
Glucose: 127 mg/dl	Lactic dehydrogenase: 85 U/L	Chlorine: 102 mmol/L	Non-reactive hepatitis B surface antigen
Urea: 37 mg/dl	Amylase: 62 U/L	Non-reactive viral profile	Non-reactive hepatitis C virus antibodies
Creatinine: 0.9 mg/dl	Total protein: 7.6 g/dl	Alpha fetoprotein: 2.75 ng/ml	Non-reactive VDRL
Prothrombin time: 18.8 seconds	Albumin: 4.7 g/dl	Carcinoembryonic antigen: 0.9 ng/ml	Lipase: 63 U/L

Magnetic resonance imaging revealed symmetrical and bilateral hyperintensities in the basal ganglia, while T2 diffusion-weighted imaging MRI displayed 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 but no triphasic waves.

It is noteworthy that the patient's father and two deceased brothers had previously undergone genetic sequencing for Huntington's disease, which yielded negative results, along with tests for other metabolic diseases.

Analysis of spinal fluid indicated normal cellularity and positivity for 14-3-3 protein. Considering these results and the family history of rapidly progressive dementia, genetic testing for Creutzfeldt-Jakob disease was requested. A sequencing search for the PrP gene was conducted, resulting in a positive finding for the PrPSc c.532G >A (p.Asp178Asn) gene mutation. Thus, a diagnosis of Creutzfeldt-Jakob disease was stablished.

The patient remains under ongoing medical care. During the most recent follow-up visit, he was found bedridden, with inability to speak, and exhibiting partial swallowing and sphincter control issues.

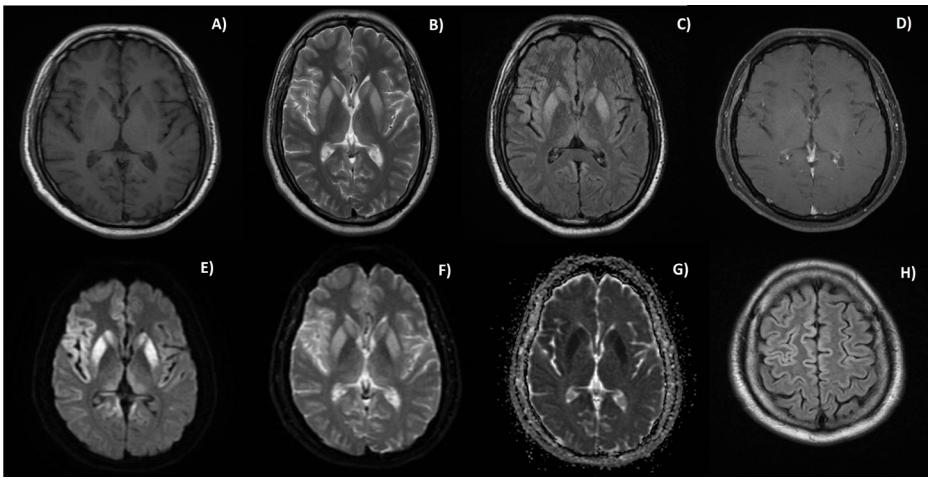
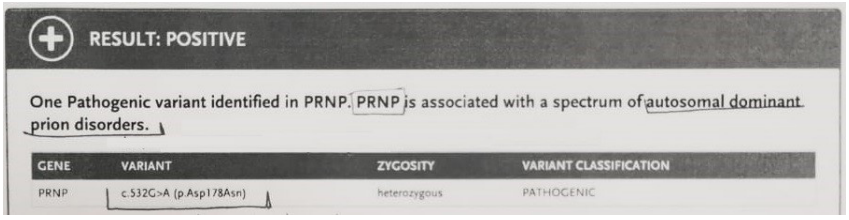


Figure 2. Simple and contrasted magnetic resonance imaging axial sections at the level of the third ventricle and lateral ventricles, where cortical lesions and basal nuclei are shown with their appearances across different imaging weightings. A) Axial slices in T1: lesions appear isointense to both gray and white matter. B) Axial slices in T2: lesions exhibit behavior similar to T1. C) FLAIR sequence: lesions are visible in the direction of the cortical grooves and appear hyperintense in the basal ganglia. D) Axial sections with Gadolinium application: without evidence of enhancement. E and F) DWI sequence: cortical and basal ganglia lesions appear hyperintense with the same restriction behavior. G) ADC sequence. H) Axial section, T2 sequence: ventral view reveals the 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, there are no signs of infarction, hemorrhage, mass, or focal intracranial abnormalities, and no features of normal pressure hydrocephalus.


RESULT: POSITIVE

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

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
PRNP	c.532G>A (p.Asp178Asn)	heterozygous	PATHOGENIC

Figure 3. Original image capture of genetic test results

Discussion

There are limited reports of prionopathies in Mexico and in medical literature in general, particularly concerning cases related to fCJD and genetic studies. In this described case, the presence of three direct-line relatives with a medical history of rapidly progressive dementia and tremors, the absence of a clear diagnosis and the exclusion of other genetic or metabolic pathologies, led to the consideration of familial Creutzfeldt-Jakob disease.

In addition, imaging studies revealed brain atrophy and hyperintensities in the caudate nuclei, which has been reported to have a sensitivity of 91% and a specificity of 93% in such cases.[4,5,6] Only 50% of cases initially present electroencephalographic manifestations, with up to 80% of patients showing these features in subsequent studies.[7] In this case, the observed tremor features align with the wing-beating tremor, a phenomenon previously described in only one other fCFD case.[11]

Isolated reports have shown the prion gene exhibiting amino acid substitutions in different codons, such as E196A, E200K 129 (M/M), 171 (N/S), 180 (V180I) and 219 (E/K).[8,9,10] Among PrP mutations, four (E200K, D178N, A117V, and P102L) demonstrate a generational pattern, while the rest may indicate an isolated de novo mutation if no familial association is stablished.[7]

Moreover, the PrPSc c.532G gene>A (p.Asp178Asn) mutation is related to a single nucleotide variant, associated to protein change D178N; ASP178ASN, located on 20p13.[12]

Conclusions

Despite their low incidence, prionopathies should be consider as a possible diagnosis, especially in cases with a family history of rapidly progressive dementia. It is crucial to recognize that the initial diagnosis of these diseases involves clinical and biochemical exclusion, followed by immunohistochemical and/or genetic confirmation.

Ethics approval and consent to participate

Ethics committee approval was not deemed necessary as this constitutes a case report. Informed consent was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report along with accompanying images.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author contribution

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

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