Sensory compromise and peripheral polyneuropathy as intial manifestation of Creutzfeldt-Jakob disease. About a case.

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ABSTRACT

Creutzfeldt-Jakob disease is a rare neurodegenerative disease with a high incidence in Chile compared to the rest of the world. The condition is mainly characterized by the development of rapidly progressive dementia and various nonspecific neurological signs, the most common being myoclonus. The case that will be described below stands out for the atypical initial manifestations that the patient presented, such as sensory compromise in the cranio-cervico-dorsal region and peripheral polyneuropathy of the lower extremities, which meant a delay in the clinical diagnosis of the disease. It is important to know the different symptoms and signs that can be present in the clinical picture of CJD, both typical and those less frequent, in order to be able to diagnose the disease in earlier stages. Similarly, it is essential to have diagnostic tools such as the detection of 14-3-3 protein or Tau protein in health centers in our country. This would allow the health team to provide adequate and timely support management to these patients.

Key words: *Creutzfeldt-Jakob Disease, prion, peripheral polyneuropathy, Chile.*

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INTRODUCTION

Creutzfeldt-Jakob Disease is a fatal rare neurodegenerative disease belonging to the transmissible spongiform encephalopathies, also known as prionic diseases. These are infectious forms of a natural protein named PrP C which can be found mainly in lipid rafts of the external cellular membrane of neurons[1]. The infectious form of the prion protein, named PrP Sc, has the capacity of using PrP C as a substrate and transform it into an abnormal prion protein PrP Sc. Given the fact that prion proteins are found mainly in neurons, the diseases they produce are neurodegenerative, caused by the abnormal accumulation of PrP Sc, generating characteristic neuropathological lesions such as spongiform vacuolization, astrogliosis and neuronal loss in the central nervous system.

CJD is classified in sporadic, acquired or familial, the latter being caused by a mutation in the codifier gen of the prion protein denominated PRNP, located in the short arm of the chromosome 20.[2]

CJD affects one person in every one million per year globally and 10% of these corresponds to the familial form. Despite its low incidence worldwide, in Chile the incidence is about 3,5 cases in every million inhabitants, therefore it is a disease of mandatory notification in the country[3].

Regardless of the etiology, the disease acquires a rapid and fatal clinical course. The principal clinical features are rapidly progressive dementia and diverse non-specific neurological signs, myoclonus being the most frequent. Other signs commonly described are cortical blindness, ataxia and akinetic mutism at late stages of the disease. Clinical findings considered as atypical signs include sleep disturbances, chorea, psychiatric symptoms and peripheral neuropathy 4 . Usually within a year from the onset of the symptoms, the patients die.

The following case corresponds to an atypical presentation of CJD that had as initial manifestation sensory compromise in the cranio-cervico-dorsal region and peripheral polyneuropathy of the lower extremities, which added to other non-specific signs namely weight loss, insomnia, mood and personality disorders, made CJD not to be within the firsts diagnostic suspicions. The family background and the clinical course towards cerebellar involvement with myoclonus and rapidly progressive dementia helped to establish CJD as the main diagnostic.

PRESENTATION OF THE CASE

This is a 73 years old male patient, previously self-reliant with a medical history of hypertension and hypothyroidism in treatment, who initiated a clinical course of 1 month of pruritus in the cranio-cervico-dorsal region, followed by sensory abnormalities of the limbs, all of which motivated him to consult in a primary care center in March of 2017, being referred for study by dermatology and hematology, suspecting a possible monoclonal gammopathy; therefore, a protein electrophoresis and immunofixation on serum were performed, obtaining a monoclonal peak in gamma region of 1,60 g/dL (reference values: 0,60-2,10) and immunofixation of monoclonal IgG lambda. One month later, another protein electrophoresis was performed, obtaining a monoclonal peak in the gamma region of 1,30 g/dL. In addition, a 24-hour urine collection was analyzed, showing protein levels of 256 mg/day (0-150) with a negative result for Bence-Jones protein. A last urine protein electrophoresis was performed, showing only presence of albumin, with no monoclonal components.

Afterwards, the patient was referred for Neurological evaluation, 4 months after the symptoms initiated. A sensory polyneuropathy was suspected with these clinical features. In the interrogation, the family explained that after 2 months of the clinical course onset, the patient had insomnia, irritability, attentional disturbances, emotional lability, distress and low mood, associated with weight loss of 14 kg. approximately over 3 months and constant cramps.

In the physical examination they found as features, trigger fingers, abolished deep tendon reflexes

(DTR) in lower limbs, tacto-algesic hypoesthesia from the distal third of both legs, with no sensory involvement in upper limbs, discrete left dysdiadochokinesia, with ipsilateral dyssynergia, without dysmetria. Abnormal tandem gait, with prominent lateropulsion of his body to the right, simple Romberg test negative and retropulsion with sensibilized Romberg test.

It was proposed as a possible etiology a paraneoplastic syndrome, already in study from the other specialties for suspicion of a monoclonal gammopathy. A study with magnetic resonance imaging (MRI) of the brain was performed, showing only signs of microangiopathy, electromyography with nerve conduction velocity that concluded the existence of a large-fiber demyelinating sensorimotor polyneuropathy (PNP). Blood tests showed hypovitaminosis B12, antinuclear antibodies discretely altered with speckled pattern and cytoplasmic immunofluorescence titer 1/80. Other tests, including immunological, infectious and blood work, were normal.

In the second neurological evaluation, 6 weeks after, the patient presented significant speech and gait disturbance, hypersomnia, 4 limbs clumsiness, maintained weight loss with normal appetite, nocturia and constipation. In the physical examination he had moderate hypokinetic dysarthria, discrete buccolingual dyskinesia, abolished lower limbs DTR, non reflective spontaneous myoclonus and chorea movements. In upper limbs bradyhypokinesia, with no extrapyramidal rigidity, dysmetria, dysdiadochokinesia and dyssynergia. Gait with double support and trembling of limbs when standing up. Flexed posture, marche a petit pas with wide-based gait. Evident titubation of trunk. During all this time, he presented distal hypoesthesia in lower limbs, with significant proprioceptive compromise. His family afterward said that the patient´s father had CJD, as well as his paternal uncle and 3 cousins, sons of that uncle. Given the family history, CJD was proposed as a possible diagnosis and paraneoplastic syndrome as a differential diagnosis, being subsequently admitted into the Internal Medicine Service of "Hospital doctor Hernán Henríquez Aravena" for study. At the admission, blood work was performed, which was normal. Once hospitalized, a computerized tomography (CT) scan of brain, thorax, abdomen and pelvis was performed, without pathological findings. After paraneoplastic syndrome was ruled out, the study continued with a quick stroke MRI protocol, showing a restricted diffusion pattern compatible with CJD, with bilateral basal ganglia hyperintensity, associated with cortical hyperintensities.

During hospitalization, his cognitive functions deteriorated, developing a rapidly progressive dementia, with temporo-spatial disorientation and lethargy, cerebellar involvement with increased ataxic gait, increased myoclonus frequency and nocturnal psychomotor agitation.

Anti-thyroid antibodies were analyzed to rule out autoimmune encephalitis, resulting slightly elevated for anti-thyroid peroxidase (TPO) antibodies 34,60 IU/mL (<5,61 IU/mL) and thryro-globulin antibodies (TGA) 83,43 IU/mL (<4,11 IU/mL), therefore empirical treatment with corticosteroids was initiated, without clinical improvement. Thereafter an electroencephalogram (EEG) was performed, showing diffuse theta slowing of 4-6 cycles per second on average. Once concluded the study, the patient was discharged and home palliative care services were provided, developing more neurological deterioration, presenting akinetic mutism at the final stages, dying nearly 7 months after the first symptoms initiated. Soon after his death, the genetic sequences of codon 129 and 200 of the PRNP gene concluded, being methionine/methionine homozygous and glutamate/lysine heterozygous respectively. The post-mortem histopathological study could not be performed on this patient, because there are no institutions in our region able to do the procedure.

DISCUSSION

The presentation of this case was complex, due to the unspecificity of his initial symptoms, being

necessary an approach from different specialties before getting to the definitive neurological study. The CJD in the family background made possible the approach to that diagnosis, nevertheless the classical clinical features like rapidly progressive dementia was not present from the beginning, turning this case into a challenge at the moment of approach to differential diagnoses, such as paraneoplastic syndrome or autoimmune encephalitis.

Considering the accentuated weight loss, it was necessary to rule out a systemic disorder associated, which was ruled out with the imaging study and blood tests.

About the autoimmune encephalitis, the presence of positive TPO antibodies made necessary to rule out Hashimoto's encephalopathy, thus the MRI features and corticosteroids treatment failure helped to establish CJD as the most probable diagnosis.

In a case report of CJD in which Hashimoto's encephalitis was proposed as a differential diagnosis, cerebrospinal fluid (CSF) 14-3-3 protein detection was performed to support CJD diagnosis[5]. This was not possible to perform due to unavailability in our clinical center. Detection of 14-3-3 and Tau protein are tests which, associated with an adequate clinical context, are of great utility to support CJD diagnosis[6]. Sensory peripheral compromise was the reason for consultation and initial symptom of this patient. Besides not being described among the typical clinical features of CJD, there have been reported cases associated with peripheral neuropathy, either being part of the clinical features or preceding them. The importance of this association remains undetermined and it is believed that the frequency of this symptom is underestimated[7]. Other atypical symptoms reported in this disease are insomnia and psychiatric symptoms. There have been reported cases in which insomnia with psychomotor agitation or mood and personality disorders, were initial symptoms of CJD, preceding typical features such as cognitive deterioration or cerebellar syndromes[8,9]. In a retrospective review of 126 CJD cases they found that 80% had psychiatric symptoms (depression, anxiety, psychosis, behavior change, sleep disturbance) among the first 100 days of the disease and 26% at the moment of consultation.[10]

As the disease progressed, the cerebellar compromise and myoclonus accentuated, developing subsequently a rapidly progressive dementia. With these clinical features suggesting CJD, it was indispensable to perform an MRI and EEG, both being necessary tools to establish CJD as a probable diagnosis, which can only be confirmed by neuropathological and/or immunocytochemistry analysis. Diffusion MRI showed alteration of basal ganglia, pulvinar nuclei and dorsomedial nucleus of the thalamus, being this an infrequent pattern that can be present in sporadic CJD[11] . It is noteworthy that imaging findings found in sporadic CJD, match those found in familial CJD[12] **(Figure 1)**. As other etiologies were ruled out and considering the clinical course

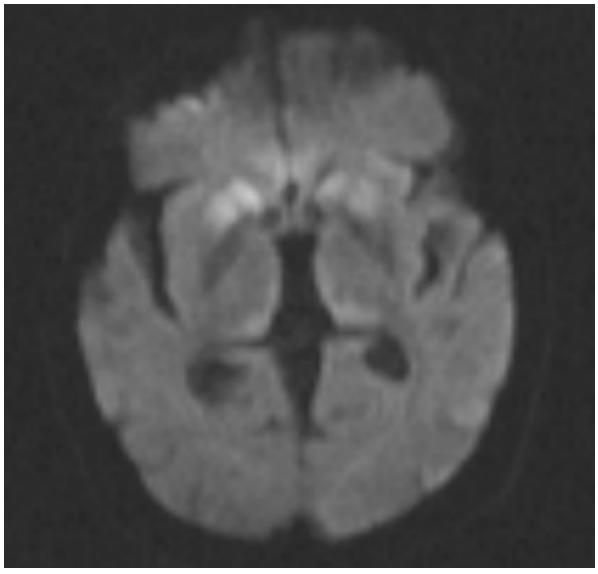

Figure 1. The following brain MRI shows compromise of putamen and caudate nucleus bilaterally, associated with hyperintensity of the anterior cingulate cortex and pulvinar and dorsomedial nucleus of the thalamus bilaterally. This corresponds to an infrequent pattern found in CJD and it is differentiated from the classical "double hockey stick" sign, present in the new variant CJD, by its lower hyperintensity compared with the caudate nucleus and putamen.[15]

associated with the imaging findings, it is possible to establish CJD as the most probable diagnosis, coinciding with the outcome of this disease with akinetic mutism.

Considering the important family health history, is reasonable to propose familial CJD with a punctual mutation such as E200K, for chilean clinical-epidemiological and genetic studies have proved a significant prevalence of familial forms of CJD surpassing the 30%, of which all of them have been linked to codon 200 heterogeneity.[13]

Mutation E200K can be associated with both methionine/valine and methionine/methionine genotypes. These are often associated with ataxic syndrome and can include in occasions peripheral neuropathies, which concurs with our case.[3]

It is important to maintain a line of study about CJD, due to the variety of clinical features that can present and the lethality that this disease entails. It is necessary to have the clinical suspicion when facing a CJD case, for which is important to consider both typical and atypical presentations.

Besides the high incidence in Chile, there are numerous institutions in which it is not possible to perform diagnostic studies such as 14-3-3 and Tau protein detection in CSF. Additionally, in our region there are no centers that perform post-mortem studies, making it necessary to implement these diagnostic tools and enable centers, thus contributing solidly to the approach and diagnosis of CJD along the country.

Amongst the most promising tests, there is the real time quaking induced conversion (RTQuIC) assay for the detection of PrP Sc aggregates. Although more investigation is required to determine its potential, there are studies in which it had almost 100% sensibility and specificity, in less than 24 hours, to diagnose sporadic CJD.[14]

Early stage diagnosis of CJD will not allow it to change its clinical course, but it will make it possible to approach it in a better manner and propose, with the patient's family, actions to relieve psychological burden and improve quality of life during the disease, thus an optimal healthcare can be provided to the particular necessities of each patient, resources can be optimized and the comprehension of this disease can be improved.

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