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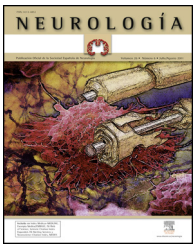

ORIGINAL ARTICLE

Clinical and neuroimaging characteristics of 14 patients with prionopathy: a descriptive study☆,☆☆

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Prion;
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Diagnosis

Abstract
Introduction: Prionopathy is the cause of 62% of the rapidly progressive dementias (RPD) in which a definitive diagnosis is reached. The variability of symptoms and signs exhibited by the patients, as well as its different presentation, sometimes makes an early diagnosis difficult.
Methods: Patients with diagnosis of definite or probable prionopathy during the period 1999—2012 at our hospital were retrospectively reviewed. The clinical features and the results of the complementary tests (14-3-3 protein, EEG, MRI, FDG-PET, and genetic analysis) were evaluated in order to identify some factors that may enable an earlier diagnosis to be made.
Results: A total of 14 patients are described: 6 with definite sporadic Creutzfeldt-Jakob (sCJD) disease, 3 with probable sCJD, 4 with fatal familial insomnia, and 1 with the new variant. The median age at diagnosis was 54 years old. The mean survival was 9.5 months. Mood disorder was the most common feature, followed by instability and cognitive impairment. 14-3-3 protein content in the cerebrospinal fluid was positive in 7 of 11 patients, and the EEG showed typical signs in 2 of 12 patients. Neuroimaging (FDG-PET, MRI) studies suggested the diagnosis in 13 of the 14 patients included.
Conclusions: Most patients presenting with RPD suffer from a prion disease. In our series the most useful complementary tests were MRI and FDG-PET, being positive in 13 of the 14 patients studied.

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PALABRAS CLAVE
Prión;
Creutzfeldt-Jakob;
Demencia rápidamente progresiva;
Resonancia magnética;
Tomografía por emisión de positrones;
Diagnóstico

Descripción de una serie de pacientes con diagnóstico de enfermedad priónica

Resumen
Introducción: Las prionopatías representan hasta el 62% de los casos de demencia rápidamente progresiva (DRP) en los que se alcanza un diagnóstico definitivo. La variabilidad de los síntomas y signos iniciales y las diferencias en su evolución dificultan el diagnóstico precoz.
Métodos: Estudio retrospectivo en el que se incluye a pacientes con prionopatía probable o definitiva, que acudieron a la consulta de Neurología de nuestro centro durante el periodo 1999—2012. Se describen las características clínicas y los resultados de las exploraciones complementarias (proteína 14-3-3, EEG, RM, PET-FDG y análisis genético), con la finalidad de identificar qué marcadores permiten un diagnóstico precoz.
Resultados: Se describe a 14 pacientes: 6 con enfermedad de Creutzfeldt-Jakob esporádica (ECJe) definitiva, 3 con ECJe probable, 4 con insomnio familiar fatal y uno con la nueva variante de la enfermedad de Creutzfeldt-Jakob. La mediana de edad al diagnóstico fue de 54 años y la mediana de supervivencia de 9,5 meses. El trastorno del ánimo fue el síntoma inicial más frecuente, seguido de inestabilidad de la marcha y deterioro cognitivo. La proteína 14-3-3 fue positiva en el líquido cefalorraquídeo en 7 de 11 pacientes y el EEG mostró signos típicos en 2 de 12 pacientes explorados. El estudio de neuroimagen mostró alteraciones en 13 de los 14 pacientes.
Conclusiones: Además de la DRP, el trastorno conductual y de la marcha son síntomas iniciales frecuentes en las prionopatías. En nuestra serie, las pruebas complementarias más útiles para apoyar el diagnóstico fueron la RM y la PET-FDG.

Introduction

Prion diseases constitute a group of neurodegenerative disorders caused by accumulation of PrP^{Sc}, an abnormal isoform of the cellular prion protein (PrP^{C}).[1] This cell-surface glycoprotein is made up of 209 amino acids and a disulphide bond.[1] The abnormal isoform is infectious in the absence of nucleic acids.[2] It is encoded by *PRNP* on chromosome 20, which presents a methionine (M)—valine (V) polymorphism at codon 129. Methionine homozygosity is a risk factor for developing prion diseases. They can be classified into acquired, hereditary, or sporadic forms.[1] The annual incidence rate of prion diseases is approximately 1 case per million people.[3] One of the most common clinical manifestations of these diseases is rapidly progressive dementia (RPD). In fact, up to 62% of patients with a form of RPD that can be conclusively diagnosed[4] have some type of prion disease. However, since the first signs and symptoms vary greatly,[5] only 18% of cases are diagnosed in the first assessment,[6] and the correct diagnosis is usually assigned an average of 8 months after symptom onset.

The purpose of this study is to describe the clinical features of prion diseases and how certain supplementary tests can contribute to the diagnostic process. To this end, we have retrospectively studied the cases of prion disease registered at Clínica Universidad de Navarra (Navarre, Spain).

Patients and methods

We conducted a retrospective study including all patients with either a probable or a definite diagnosis of prion disease, according to validated diagnostic criteria,[7,8] who had been examined in the neurology department at Clínica Universidad de Navarra between 1999 and 2012. Clinical signs and symptoms and results from additional tests were collected from medical histories. As supplementary diagnostic tests, we used 14-3-3 protein in CSF, analysis of *PRNP* (study of known mutations and assessment of polymorphism at codon 129), and findings from electroencephalography and structural and functional neuroimaging studies. We visually analysed the presence or absence and the location of hyperintense regions in both diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences on MRI. We visually determined the presence or absence and the location of hypometabolic and/or hypoperfused areas in cerebral metabolism studies using PET with F-18 fluorodeoxyglucose (FDG-PET) in 13 patients, and using SPECT with Tc^{99m}-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO SPECT) in another patient. For each additional test, each patient was assigned a pattern of impairment according to the presence and location of hyperintense, hypometabolic, and/or hypoperfused areas.[7–9] We therefore established 3 different patterns: a cortical pattern showing hyperintensity, hypometabolism, and/or hypoperfusion in the cortex; a subcortical pattern characterised by hyperintensity, hypometabolism, and/or hypoperfusion in the basal ganglia and/or thalamus; and a cortical-subcortical pattern showing hyperintensity, hypometabolism, and/or hypoperfusion in the cortical and subcortical regions. MRI and FDG-PET findings were compared in order to assess the sensitivity of these 2 techniques. For all cases, we investigated whether a neuropathology study had been performed and checked those results.