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Case report

Rare E196K mutation in the *PRNP* gene of a patient exhibiting behavioral abnormalities

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ABSTRACT

Genetic transmissible spongiform encephalopathies (TSEs) account for approximately 10–15% of overall human prion diseases worldwide, but genotype–phenotype correlations remain incomplete. Here we report the case of an 80-year-old man who developed rapidly progressive behavioral abnormalities and myoclonus following a stroke. Repeated electroencephalography (EEG) revealed a general slowing of the basic activity, as well as several episodes of triphasic waves, with neither periodic activity nor recorded seizure. 14.3.3 protein was detected in cerebral cerebrospinal fluid, and direct sequencing of the PRNP gene showed an E196K mutation associated with homozygosity for methionine at codon 129. The patient was diagnosed with probable genetic prion disease with a Creutzfeldt-Jakob disease-like phenotype. The *PRNP* E196K mutation has only rarely been described in the literature, and generally patients exhibited an atypical initial phenotype, mainly involving abnormal behavioral features. Further observations are needed to confirm this particular clinical pattern associated with the mutation.

1. Introduction

Genetic transmissible spongiform encephalopathies (TSEs) account for approximately 10–15% of human prion diseases worldwide [1–2]. Historically, three different clinical phenotypes have been identified: Creutzfeldt-Jakob disease (CJD) [3], fatal familial insomnia (FFI) [4], and Gerstmann-Sträussler-Scheinker disease (GSS) [5]. However, since these first descriptions, numerous unusual phenotypes have been reported [6–8]. In 1985, the *PRNP* gene was isolated [9], and the first mutations were discovered a few years later [10,11]. This gene encodes the protein PrP, whose conformational conversion into an abnormal form called PrPsc is responsible for the development of the disease. More than 30 mutations have been identified as being involved in the development of genetic TSE, with a variety of geographical distributions and frequencies [1]. As a result, it now appears necessary to establish correlations between the genetic and clinical features of this disease.

We report here the case of a patient with probable genetic prion disease with a Creutzfeldt-Jakob disease-like phenotype associated with a rare *PRNP* E196K mutation who initially exhibited atypical clinical manifestations principally characterized by behavioral abnormalities.

2. Case report

An 80-year-old right-handed man was admitted to our stroke unit because he had exhibited a sudden loss of balance 6 h earlier. The patient had a history of treated hypertension, type-2 diabetes, myocardial infarction, and peripheral vascular disease, and asymptomatic left internal carotid artery stenosis. In contrast, he had no particular familial medical history. At admission, we noted a left cerebellar syndrome associated with dysarthria and dysphagia. Both muscular strength and sensation were normal, as were deep tendon reflexes. The left plantar reflex was extensor. Cerebral Magnetic Resonance Imaging (MRI) revealed multiple deep hyperintense lesions on T2-weighted sequences, compatible with lacunes, which were also found within the brainstem (Fig. 1). On diffusion-weighted MRI, two hyperintense lesions were noted in the right caudate nucleus and the left cerebellar hemisphere with a decreased attenuated apparent diffusion coefficient (ADC), which was suggestive of a recent infarction of these territories (Fig. 1). MR angiography showed stenosis of both the left internal carotid artery, and the initial portion of the left vertebral artery, while the right carotid artery was normal. These results were confirmed by conventional angiography. Trans-esophageal echo-cardiography and

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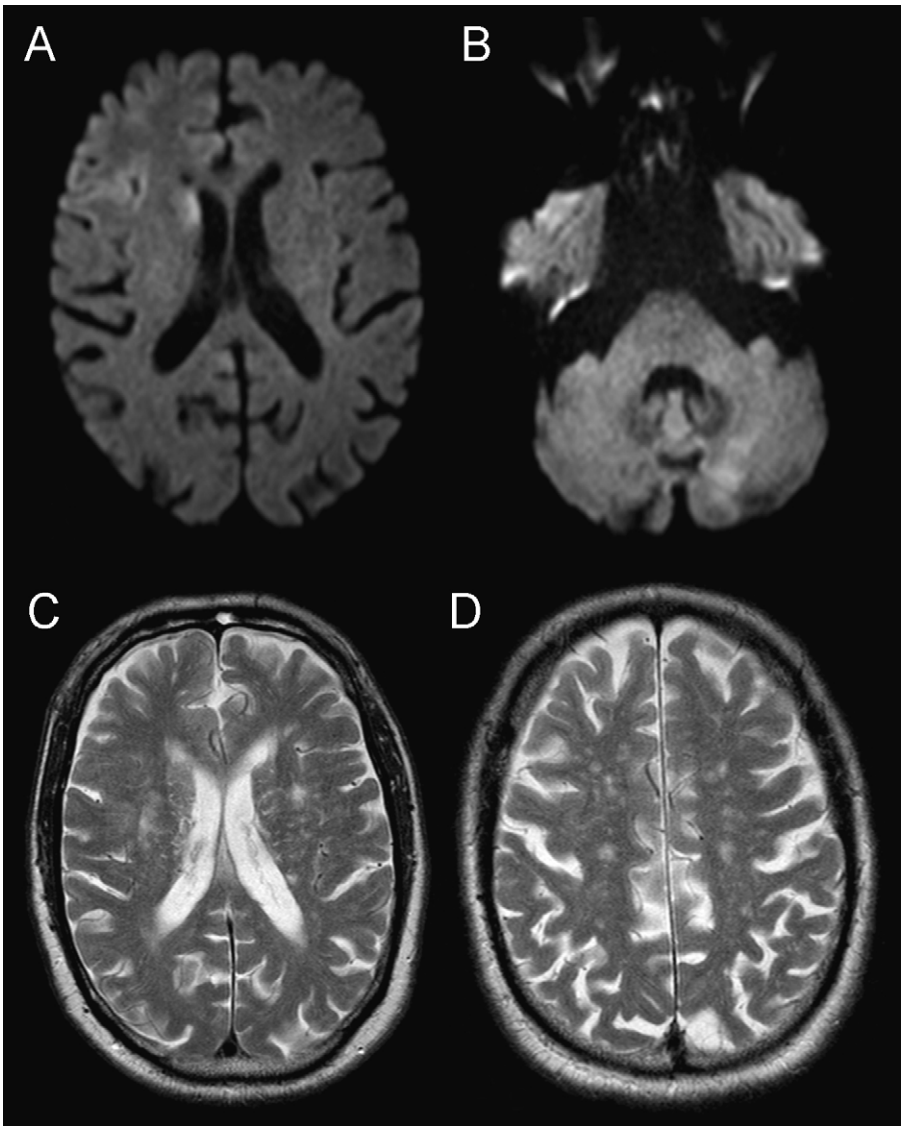

Fig. 1. Initial cerebral magnetic resonance imaging (MRI). On diffusion-weighted sequences (A and B), two hyperintense lesions were noted in the right caudate nucleus (A) and the left cerebellar hemisphere (B) with a decreased attenuated apparent diffusion coefficient. On T2-weighted sequences, multiple bilateral deep hyperintense lesions were found (C and D).

routine laboratory exams were normal. Therefore, the initial diagnosis was cerebellar and cerebral infarcts. Conventional treatment of stroke was performed. Unfortunately, during the 2 weeks following his admission, the patient exhibited progressively worsening abnormal behavior characterized by hallucinations and intense agitation interspersed with periods of severe apathy. In addition, several episodes of clonic jerk affecting the right upper limb were observed. His relatives mentioned that he had recently (3 months) experienced difficulties in using his computer keyboard, and sleep disorders characterized by repeated periods of severe insomnia. The neurological examination revealed ideomotor apraxia, which was not searched for during the first examination. Cerebral MRI was repeated, but revealed no additional lesions. Repeated electroencephalography (EEG) showed a general slowing of the basic activity, as well as several episodes of triphasic waves, with neither periodic activity nor recorded seizure. The cerebral spinal fluid (CSF) was normal for cell count and blood-CSF-barrier function but 14.3.3 protein was detected. Direct sequencing of the *PRNP* gene open reading frame revealed an E196K mutation associated with homozygosity for methionine at codon 129. The patient was diagnosed with probable genetic prion disease with a Creutzfeldt-Jakob phenotype. The patient rapidly developed severe akinetic mutism and coma, and died 3 months after his admission. No autopsy was performed.

3. Discussion

The clinical presentation of our patient, which justified his admission to hospital, i.e. cerebellar syndrome associated with dysarthria and dysphagia, was highly suggestive of an acute stroke. The hyperintense lesion in the left cerebellar hemisphere on the diffusion-weighted MRI associated with the stenosis of the initial portion of the left vertebral artery on the MR angiography was compatible with a left cerebellar hemisphere infarct. However, another lesion was found in the right caudate nucleus without stenosis of the arteries supplying this territory. This lesion was initially considered an infarct, but the clinical progression of our patient and the subsequent findings went against this assumption. Actually, several cases of CJD with stroke-like onset have been described in the literature [12,13], and in a systematic review [14], this atypical clinical presentation accounted for 5.6% of 532 database patients with definite or probable CJD. In their CJD patient with an onset