

An atypical phenotype of CJD associated with the E200K mutation in the prion protein gene

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Abstract E200K mutation of the prion protein gene (PRNP) presented with a variety of phenotypes. A 55-year-old woman complaining of slowly progressive walking difficulties came to our observation. She showed a severe progressive ataxo-spastic syndrome but a mild cognitive impairment only. Repeated EEGs showed a diffuse slowing of the rhythm without specificity. Brain MRI revealed by FLAIR showed widespread multiple hyperintensities in the whole cerebral cortex, caudate and putamen nuclei, and in the pulvinar and medial thalamus bilaterally. These signal abnormalities were best detected by DWI with restricted diffusion on ADC map. The clinical diagnosis of possible genetic Creutzfeldt-Jakob disease (CJD) has been confirmed by PRNP gene analysis which revealed the presence of a E200K mutation. This report confirms the heterogeneity of phenotypes in E200K mutated familial CJD with the occurrence of a new phenotype not previously described.

Keywords Creutzfeldt-Jakob disease (CJD) · PRNP E200K gene mutation · Brain-MRI/FLAIR/DWI · Phenotype heterogeneity

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Introduction

Genetic Creutzfeldt-Jakob disease (gCJD), which comprises about 10% of the human prion diseases, has been associated with several point mutations, insertions, and deletions in the prion protein gene (PRNP) [1].

The E200K mutation, the most common mutation linked to gCJD, has been frequently found in the Mediterranean area and it has been related to a sepharditic original source in the North African area, mainly among Lybian Jews [2]. The mutation has also been described in southern Italy in a small circumscribed and geographically isolated area of rural Calabria [3] and in Sicily.

Case study

In March 2009 a 55-year-old woman, right-handed, who worked as a primary school teacher complained of vertigo, slowly progressing difficulties in walking and weakness of the inferior limbs, that quickly progressed to involve the upper limbs. A month later, after her admission to a neurological clinic, she was diagnosed with cerebrovascular disease and treated with aspirin. On May 2009, when she came into our observation, she appeared alert and able to orient herself but not able to walk without assistance. She showed dysarthria, dysphonia, spastic tetraparesis (more severe on the left side), and bilateral dysmetria and incoordination (more evident on the right side). Neuropsychological evaluation showed a very mild cognitive impairment involving the executive cognitive domains only. In particular, there was no significant memory dysfunction and the MMSE was 29/30. One week after admission the patient showed parcellary myoclonic jerks in the trunk and upper extremities that resolved with clonazepam. On her relatives'

request she was discharged after 3 weeks of follow-up. During this time motor impairment steadily progressed, while cognitive functions remained unchanged.

Routine blood studies, including lactic acid, immunological, and paraneoplastic markers assessment gave normal results. Repeated EEG recordings showed a diffuse slowing down (theta rhythm). Brain MRI revealed widespread multiple hyperintensities in the whole cerebral cortex with relatively sparing of the frontal cortex of the left side, the caudate and putamen nuclei, more on the right side, and the pulvinar and medial thalamus bilaterally. These signal abnormalities were barely visible on T2, and better detected by DWI with restricted diffusion on ADC map (see Fig. 1). The MRI pictures turned out to be unchanged when compared with a previous exam performed 1 month before elsewhere; SPECT and DaT brain scan were normal.

The patient had a brother who had died at about 35 years of age after a rapidly progressing neurodegenerative disease that had lasted a few months, which raised the diagnostic suspicion of CJD. Interestingly, the family came from a small village in the south of Italy where a cluster of patients with CJD linked to the E200K mutation has been described [3]. The clinical suspect of a possible genetic CJD was confirmed by PRNP sequencing analysis which revealed the E200K mutation and homozygosity for methionine (MM) at codon 129.

Discussion

The interesting aspect of the present case lies in the atypical clinical phenotype either at the onset and during the clinical progression.

The patient showed a severe progressive ataxo-spastic syndrome but only a mild cognitive impairment. Repeated EEG recordings showed a diffuse slowing down of the rhythm in the absence of the pseudoperiodic triphasic bilateral and synchronous waves typically associated to CJD. The mild cognitive impairment involved the

executive cognitive domains without significantly affecting other cognitive functions including memory performances. The suspect of a possible gCJD was made on the basis of the familial clinical history and the MRI abnormalities, which were already visible 1 month after the onset of symptoms.

It has been recently reported that the characteristic high signal detected by FLAIR and even more by DWI, mainly in caudate and putamen and, in descending order in thalamus, cingulate gyrus, and cerebral cortex allows up to 87% of gCJD to be correctly identified [4].

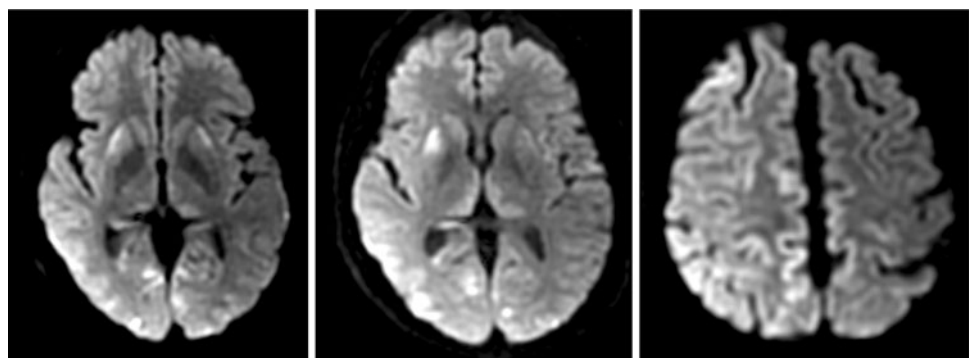
In particular the DWI hyperintensity in the caudate nucleus seems to have a sensitivity of 73% and a specificity of 100%. An hyperintense signal in the pulvinar, although more characteristic of vCJD, has also been reported in fCJD. However, as it was in this case, the intensity of the signal was, at variance with vCJD, equal or lower than in basal ganglia [4].

The MRI features in our patient could alternatively suggest an atypical vascular disease with stroke-like episodes such as MELAS. However, the ADC map is more frequently increased in this pathology [5]; furthermore the serum lactic acid in our case was normal.

The glutamate to lysine change at codon 200 (E200K) is a dominant mutation with a highly variable expressivity and incomplete penetrance.

This mutation was first reported by Goldfarb et al. [6] in a cluster of CJD patients in Slovakia. Another large cluster of E200K genetic CJD has been described among Jews of Lybian origin. Haplotype analysis carried out in 62 CJD families [7] suggested that the E200K mutation possibly originated from a single mutational event that had occurred in Spain. However, some Slovakian families and a family of Polish origin showed another unique haplotype, and even the haplotypes found in families from Germany, Sicily, Austria, and Japan resulted different from those occurring in Mediterranean or Eastern European familial clusters. Therefore, both founder effects and independent mutational events may explain the current geographical distribution of E200K mutation.

Fig. 1 Brain MRI: diffusion-weighted imaging (DWI) shows hyperintensities in the caudate and putamen nuclei, more on the right side, in the pulvinar and medial thalamus bilaterally and in the cerebral cortex



With regard to this, it is likely that the present case might belong to the Calabrian cluster [7].

Interestingly, the estimated cumulative penetrance in this cluster was about 60% and therefore, lower than among Lybian Jews in Israel but similar to that calculated for the Slovakian carriers.

It is noteworthy that among the more than 20 different point or insert mutations of PRNP that have been so far linked to genetic prion disease, only the E200K mutation is found in population clusters of different ethnic origin.

There are not definite explanations for this uncommon observation but it is likely that other genetic or environmental factors may play a role as additional risk determinants.

It has already been showed that some PRNP gene mutations influence the disease phenotype (clinical duration and neuropathology) of some familial forms of CJD [8].

Furthermore, the genotype at the polymorphic PRNP codon 129 in both mutated and wild type allele influences the disease duration and possibly even the clinical phenotype [6, 9].

The typical clinical presentation of this genetic CJD linked to the E200K mutation is a subacute progressive dementia with myoclonus, which is often indistinguishable from that of typical sporadic CJD (i.e., the MM1 subtype) [10].

This clinical picture is often associated to the development of pyramidal, cerebellar or extrapyramidal signs. Median age of onset is 58–60 years and the mean duration of the disease is 5–7 months [1].

Atypical clinical features, however, have also been reported including an early onset without myoclonus or the typical EEG pattern, supranuclear gaze palsy, demyelinating peripheral neuropathy, insomnia, focal upper limb dystonia, hemichorea, and superficial and deep sensory disturbances. These different phenotypes have been recently reviewed [11].

In this context our observation further expands the spectrum of the clinical phenotypes associated with the E200K mutation.

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