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A case of dementia with *PRNP* D178Ncis-129M and no insomnia

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Abstract

Objective—To describe a dementia case clinically diagnosed as Alzheimer’s disease with a *PRNP* genotype usually associated with Familial Fatal insomnia.

Methods—PCR amplification and subsequent direct sequencing of *PGRN*, *MAPT*, *PSEN1*, *PSEN2*, *APP* and *PRNP* genes.

Results—A point mutation (D178N) was found in the *PRNP* gene.

Conclusion—The mutation D178N in the *PRNP* gene associated with the M129 genotype is usually associated with Familial Fatal Insomnia. However, a few cases have been reported with different clinical phenotypes. Here we describe one of these cases and stress the importance of genetic screening of *PRNP* in early onset dementia cases.

Keywords

Dementia; prion gene; Familial fatal insomnia

Introduction

Alzheimer’s disease (AD) is the most common cause of dementia and is a progressive neurodegenerative disorder with an insidious onset. Familial cases with a defined inheritance pattern account for only 5 to 10% of AD cases with an early age at onset and are usually associated with mutations in three genes: *APP* (OMIM #104760), *PSEN1* (OMIM #104311) and *PSEN2* (OMIM #600759) ¹. Clinical phenotypes in dementia are variable. This, together with the lack of precise and explicit clinical or biochemical antemortem diagnostic markers, leads to the need for a regular differential diagnosis for early onset dementias ², such as frontotemporal dementias (associated with mutations in two genes: *MAPT*, OMIM #157140 and *PGRN*, OMIM #138945) and prion diseases (associated with mutations in the prion protein gene: *PRNP*, OMIM #176640) ³.

In hereditary prion diseases, clinical manifestations are also variable ⁴. In both AD and some prion diseases, neurodegeneration may be accompanied by cerebral deposits of amyloid and aggregated tau neurofibrils ^{3, 5, 6}. Creutzfeldt-Jakob disease (CJD) and Gerstmann-Straussler-

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Scheinker disease (GSSD) are the prion diseases in which dementia is an important part of the clinical syndrome. The clinical picture of CJD is typically characterized by a rapidly progressive dementia, associated with myoclonus, cerebellar, pyramidal and extrapyramidal signs⁷. In GSSD, the classical presentation is a cerebellar syndrome with dementia occurring later, and a mean duration of disease of five years⁸. Familial fatal insomnia (FFI) is an autosomal dominant disorder mainly characterized by neuronal degeneration limited to selected thalamic nuclei, together with progressive insomnia and dysautonomia. FFI is caused by a mutation at codon 178 of the *PRNP* gene that leads to a D178N substitution in the protein when the amino acid at codon 129 is a methionine on the mutated allele (in cis); the same mutation results in CJD when the amino acid at codon 129 is a valine (in cis)⁹.

Here we describe a dementia case with a genotype usually associated with FFI (D178N mutation in “cis” with a methionine in codon 129 in the *PRNP* gene) presenting without insomnia.

Methods

Informed consent for the participation in this study was obtained from the patient, who was diagnosed as a probable Alzheimer’s dementia case, according to the standard Diagnostic and Statistical Manual, revision 4 (DSM IV)¹⁰ criteria and the National Institute of Neurological Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) protocol guidelines¹¹.

Mutation analysis was performed on genomic DNA extracted from saliva, collected using Oragene Kits (DNA Genotek). The coding exons and the respective flanking intronic sequences of *PSEN1*, *PSEN2*, *PRNP* and *PGRN*, together with the non-coding exon 0 of the latter; exons 16 and 17 of *APP* and exons 1, 3, 9, 10, 11, 12 and 13 of *MAPT* gene were PCR amplified using primers (available on request) and Roche FastStart PCR Master Mix polymerase (Roche Diagnostics Corp., IN). Resulting PCR products were sequenced using the same forward and reverse primers with Applied Biosystems BigDye terminator v3.1 sequencing chemistry and run on an ABI3730xl genetic analyzer as per manufacturer’s instructions. The sequences were analyzed with Sequencher software, version 4.1.4 (Genecodes, VA). In our laboratories early-onset dementia cases are subject to genetic analysis for the *PSEN1*, *PSEN2* and *APP* genes. If this analysis is negative, other genes known to underlie early onset dementias are screened (*MAPT*, *PGRN* and *PRNP*).

Results

Clinical presentation

The patient, a 51 year old female born in Macedonia, finished 12 years of education and worked as a nurse. She came into our clinic (Neurological Clinic, Clinical Center, Skopje, Macedonia) at the age of 50 years, reporting a progressive memory loss, depression, mild speech and language difficulties and dyspraxia. The patient was aware of her situation and was fearful. On neuropsychological testing, the patient was time disoriented, her verbal fluency was reduced (2 words for 1 minute) and comprehension was altered, but she was able to write. Her ability for new learning was limited, and she was not able to recall words that she had learned 20 minutes before, but she was able to partially recognize them.

Semantic memory was relatively spared, but episodic memory was much compromised. She could draw a clock. Her SLUMS score (Saint Louis University Mental Status- 30 point screening questionnaire that tests orientation, memory, attention and executive function/Saint Louis University Department of Veterans Affairs)¹² was 8/30. Four months later, she was disoriented with respect to time and place; and she could not draw a clock.

Comprehension was very limited and she could still write, but now with major difficulties. She could copy figures, but was unable to finish the neuropsychological testing. One year after the first examination, neuropsychological testing was attempted, but the patient was not testable. The SLUMS score at this time was 3/30. The EEG revealed slow brain activity, with theta and delta waves in frontotemporal regions. The CT presented a frontoparietal cortical atrophy and the MRI showed hyperintense hippocampus, basal ganglia and temporoparietal cortex signals on T2-weighted images. By that time the patient was diagnosed as probable Alzheimer's disease.

Three months after, according to information obtained from a caregiver, the patient had global aphasia, could not walk or perform any activities without help (eating, washing, dressing). She spent all days playing with a doll, and could only recognize family members. The patient never had any sleep disturbances.

According to the last information given by a caregiver, the patient is presently bedridden, has major difficulties with swallowing and can not recognize any relatives, she can not speak.

It is worth noting that the proband's brother presented very similar clinical signs, at a similar age as the proband. By family report his first symptom was depression, followed by complains of memory loss. He died at the age of 52, with clinical signs of dementia (progressive memory loss, aphasia, inability to walk and eating difficulties), approximately two years after his first visit to the clinic. He was not formally diagnosed with a neurological disorder.

It is also worth mentioning that the proband's mother was diagnosed with Pick dementia, and she died at the age of 60.

Sequence analysis

The D178N (c.532G>A) mutation was found in the *PRNP* gene. The patient is homozygous for methionine in the 129 codon, thus presenting the D178Nc129M genotype, mainly associated with FFI phenotype. No mutations were found in *PSEN1*, *PSEN2*, *APP*, *PGRN* or *MAPT*.

Discussion

The mutation D178N in the *PRNP* gene is associated with Fatal Familial Insomnia (FFI) and with Creutzfeldt-Jakob disease (CJD). It was first reported in Finnish kindreds¹³ and in 1992 a haplotypic relation between codons 129 and 178 in the *PRNP* gene was established: the D178N mutation associated with the 129M genotype was related to FFI while the same mutation associated with the 129V genotype was linked to familial CJD¹⁴. However, recent studies have reported some pedigrees segregating both with FFI and CJD phenotypes^{15, 16}. A Japanese family was reported with the D178N-129M genotype and a clinical presentation of cerebellar ataxia without overt insomnia¹⁷. Additionally, sleep disturbances may accompany other *PRNP* mutations¹⁸. Thus, the association between the two haplotypes and phenotypes is not as linear as first believed. The median age of onset associated with the D178N mutation (including both codons 129V and M) is 50 years and the median duration of the disease, 11 months¹⁹.

Clinically, patients present memory impairment as the initial symptom and the progression of the disease is similar to the sporadic forms of CJD, with a high frequency of cerebellar, myoclonus, extrapyramidal and pyramidal signs²⁰. However, the distinction between AD and CJD cannot always be made based on clinical and electrophysiological arguments, as emphasized before by numerous reports^{21–23}. The clinical phenotype of genetic prion diseases (including age of onset and duration of the disease) may be very variable even between

members of a family with the same mutation. The present case illustrates two main issues: 1) that genetic prion diseases may not be easy to diagnosis and may be erroneously clinically classified as other dementias, including Alzheimer disease and 2) although the current picture is that the mutations are the direct cause requiring no other external factors for the manifestation of the disease, this frequent phenotypic variability may be associated with other genetic and/or environmental factors, apart from the polymorphism in codon 129, still to be identified^{24, 25}. In fact, Zarranz et al claim that FFI and CJD may be the extremes of a spectrum rather than two discrete and separate entities²⁴. Thus, an early and specific diagnosis of early onset dementia is indispensable in order to be able to perform a correct clinical assessment, genetic counselling and, eventually, to apply efficient specific treatments. In summary, these data show that, particularly in cases with a rapid progression, screening of *PRNP* is warranted in suspected AD cases.

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