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CASE REPORT

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A novel presenilin 1 L166H mutation in a pseudo-sporadic case of early-onset Alzheimer's disease

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Abstract We report a 44-year-old woman presenting at 33 years with memory loss, followed by progressive dementia. Her family history was negative for dominant genetic disorders at high penetrance. Analysis of presenilin-1 gene revealed a missense mutation at codon 166, leading to the substitution from leucine to histidine. The mutation occurs in the third transmembrane domain of presenilin-1, at the position of two different mutations previously described, associated with an atypical phenotype. The present case has two implications: (1) mutations of presenilin-1 have to be searched also in apparently sporadic cases of dementia beginning in the third decade of life; (2) as yet unidentified factors, besides the γ-secretase complex, influence the phenotype of presenilin-1 mutations.

Key words Familial Alzheimer's disease • presenilin-1 • Beta amyloid • Gene mutations

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Introduction

Mutations of the presenilin-1 (*PSEN1*) gene are the most common cause of familial early-onset Alzheimer's disease (AD) [1]. Presenilin-1 is an evolutionary conserved protein with 8 transmembrane domains, which, following association with other proteins and endoproteolysis of its third cytoplasmic loop, functions as the catalytic subunit of γ-secretase. More than 140 different mutations of *PSEN1*, spread all over its open reading frame, have been reported [1]. A common feature of the mutated *PSEN1* is the increased production of β-amyloid peptides ending at residue 42 (Aβ42) [2], which aggregate more easily than the Aβ40 species. We report a novel mutation of *PSEN1* in a patient expressing an early-onset form of AD lacking a positive familial history.

Case report

A woman, now aged 44, started to make errors in the execution of simple tasks at the age of 30. Her family history did not support a dominant transmission at high penetrance: the parents of the patient were not demented (her mother died at 83, her father at 63, neither of them affected by neurodegenerative disorders), nor were her older five siblings. A brother and a sister of her paternal grandparents were both affected by late-onset dementia, while her grandparents were not. At the age of 33, she began complaining of progressive memory deficits and disorientation in time and space, which caused significant impairment in her occupational functioning. At 35 years, she showed poor personal hygiene and irritability. At this stage of the disease the neuropsychological assessment demonstrated deficits in memory, attention, visuospatial orientation, slowing of visual reaction times and anomies. Neurological examination, performed when the patient was 36 years old, showed sporadic segmental myoclonus, postural tremor and persisting blinking. Later on the patient developed extrapyramidal hypertonus and hypokinesia. Polygraphic electroencephalogram revealed generalised paroxysmal abnormalities not correlat-

ed with myoclonic jerks. Magnetic resonance imaging demonstrated supratentorial cortical atrophy, especially in the insula and in the periinsular temporal lobe, and marked hippocampal atrophy, while SPECT imaging showed bilateral parietal lobes and middle frontal lobe hypometabolism.

Following informed consent, peripheral blood sampling was carried out in the patient, and genomic DNA was extracted with a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). *PSEN1* exons 3–12 were amplified by PCR, followed by DNA sequencing of forward and reverse strands. *APOE* genotyping was performed according to standard procedure.

Results

DNA sequencing showed a missense point mutation at nucleotide 745 of the mRNA of the I-467 *PSEN1* isoform (CTT to CAT), leading to the substitution of residue 166 from leucine to histidine. The single-strand conformation polymorphism aberrant pattern typical of the mutation was not detected in 95 healthy Italian adult subjects. The patient was homozygous for *APOE* allele ε3.

Discussion

The leucine to histidine substitution occurs in the third transmembrane domain of presenilin-1, at the codon 166, in which two other different pathogenic mutations were described, associated with an atypical phenotype, characterised by a very early-onset and the presence of paraparesis and seizures. The phenotype of the present case is instead typical of early-onset AD, which is expressed by mutations widely distributed within the *PSEN1* open reading frame (for review, see Ref. [3]). In light of the phenotypical homogeneity in spite of different sites of mutation, Berezovska et al. [4] proposed that presenilin-1 exists in metastable conformations different for the reciprocal position of the N-terminal and C-terminal domains, on which the cleavages leading to Aβ C-termini of different lengths depend. *PSEN1* mutations seem to facilitate a more open configuration which in turn favours the γ-cleavage at residue 42 of Aβ, leading to the increased Abeta42/Abeta40 ratio observed in the biological fluids of the affected patients. Conversely, the phenotypical heterogeneity expressed by different *PSEN1* mutations at the same codons [5] and by identical mutations, also within the same kindred [6], is still not explained. As it has been recently proposed [7], yet unidentified tissue-specific components probably regulate γ-secretase activity, influencing the rate and quality of Aβ species overproduction in the presence of *PSEN1* mutations. Usually *PSEN1* mutations are inherited in dominant fashion and exhibit high penetrance, while in the pedigree of our patient a history of dementia is lacking. The absence of a clear familial transmission suggests the occurrence of a mutation *de novo*, or an alternative paternity. However, our report confirms previous observations, indicating that *PSEN1* mutations have to be searched also in apparently sporadic cases of dementia beginning in the third decade of life.

Sommario *Una donna di 44 anni ha iniziato a presentare all'età di 33 anni turbe della memoria, seguite da demenza ingravescente. La storia familiare della paziente è negativa per malattie genetiche dominanti ad alta penetranza. L'analisi del gene della presenilina 1 ha rivelato una nuova mutazione al codone 166, costituita dalla sostituzione da leucina a istidina. La mutazione occupa il terzo dominio transmembrana della presenilina 1, nella posizione di due differenti mutazioni già descritte. Il caso descritto ha due implicazioni: (1) occorre cercare mutazioni della presenilina 1 anche in casi di demenza apparentemente sporadici, se l'esordio è nella terza decade di vita; (2) esistono fattori ancora ignoti, oltre al complesso della γ-secretasi, che influenzano il fenotipo delle mutazioni della presenilina 1.*

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