A novel presenilin-1 mutation associated with a case of familial early onset Alzheimer's Disease

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Introduction

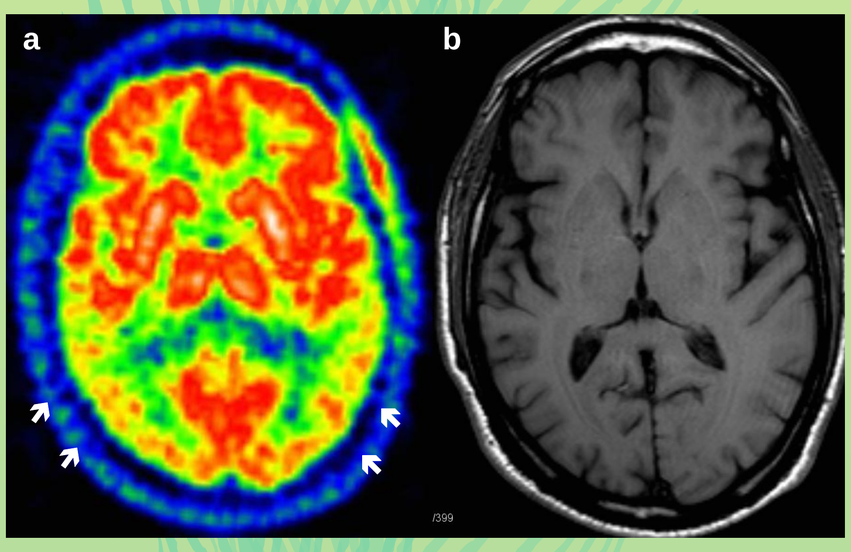
Alzheimer's Disease (AD), the most common form of dementia, can be due to a genetic mutation in up to 5% of cases. The most frequently associated genes, with an autosomal dominant pattern of inheritance, are Amyloid Precursor Protein (*APP)*, Presenilin-1 (*PSEN1)* and Presenilin-2 (*PSEN2)*[1]. Familial AD (fAD) has more frequently an early (<60 years) onset than sporadic and some atypical clinical features (e.g. movement disorders, oculomotor signs or more widespread pattern of cognitive deterioration).

Case report

A 48-year-old man was admitted to our Department complaining short-term memory deficits insidiously started one year before. He was the second born from non-consanguineous parents by normal full term delivery. Psycho-motor developmental milestones were normal and he grew healthy. Five patient's relatives (his father and four paternal aunts) also displayed cognitive deficits beginning between the 6th and the 7th decade. Medical History was unremarkable.
Neurological examination disclosed: diffuse hyperreflexia, mild oculomotor and ideo-motor apraxia, right hemineglect, anosognosia and Epstein sign. His neuropsychological profile was mainly characterized by executive dysfunction, working memory and episodic memory impairment. MMSE score was 21/30 and FAB score was 12/18. The interview disclosed important ideo-motor slowing and depressive symptoms .

Laboratories and Instrumental examinations

Blood and urine analyses were normal except for total cholesterol (232 mg/dL) and LDL-cholesterol (156 mg/dL). Thyroid function was normal; T.P.H.A. was negative; thrombophilic polymorphisms were uncontributing.
Homocysteine was mildly increased 13.47 mmol/L (n.v.: 3.5-11.2).
Biochemical CSF examination was normal.
CSF Aβ1-42 was significantly low (383 pg/ml) whereas total TAU and P181-TAU were not remarkable (336 pg/ml and 61 pg/ml respectively).



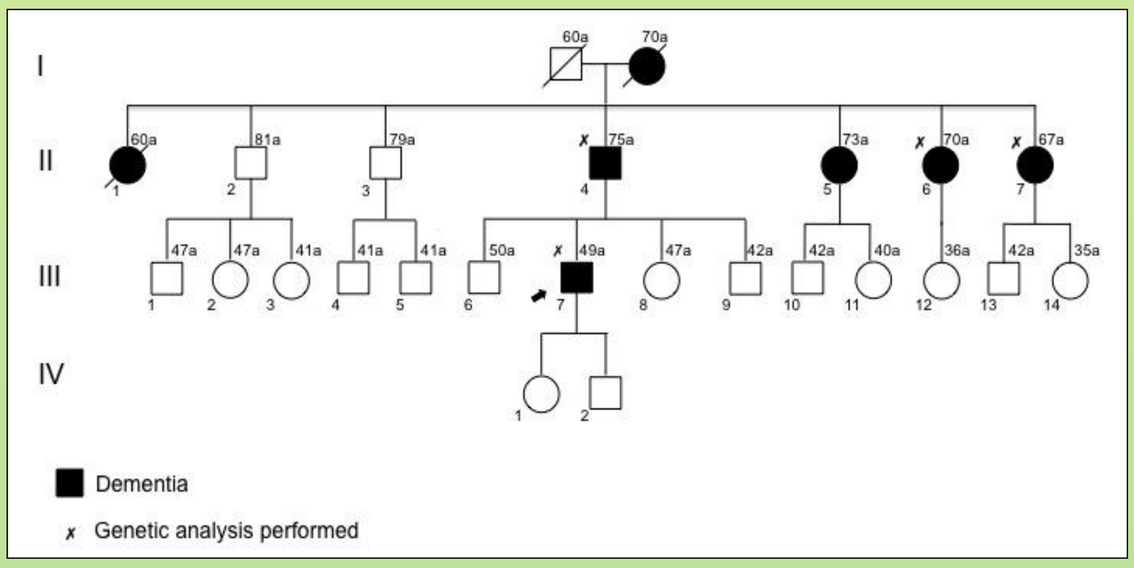
a. Cerebral PET with ^{18}FDG revealed hypometabolism in posterior cingulate cortex, bilateral parietal (arrows), temporo-parietal, temporal cortex and precuneus (right>left).

b. Brain nuclear MRI showed mild increase in subarachnoid spaces to the parietal convexity.

Neuropsychological tests	Raw scores	Corrected scores	Equivalent scores
Screening tests			
Mini Mental State Examination (MMSE)	**21/30**	**20.62**	**≥ 23,8**
Frontal Assessment Battery (FAB)	**12/18**	**11.7**	**0**
Attention and Executive Functions			
Attentional matrices	**28/60**	**19.25**	**0**
Phonological fluency	**16**	**17.1**	**0**
Verbal Memory			
BSRT - Immediate recall	5/8	4.8	2
BSRT - Delayed recall	5/8	4.8	2
RAVLT - Immediate recall	**15/75**	**12.8**	**0**
RAVLT - Delayed recall	**1/15**	**0.2**	**0**
Constructional apraxia			
Constructional apraxia test (from MODA battery)	**5/14**	**4**	**0**
Abstract Reasoning			
Raven's progressive matrices	**-/36**	**-**	**0**

Neuropsychological evaluation

Access and retrieval of stored verbal information appears impaired for single phonemes. Verbal memory is within normal limits for both immediate and delayed recall in structured material (Babcock Short story Reminding Test – BSRT) but impaired for unstructured information (Rey's Auditory Verbal Learning Test - RAVLT). Among executive functions, both phonological fluency and FAB are altered. Selective attention (Attentional matrices) is impaired too. Logical abilities and abstract reasoning are impaired at Raven's progressive matrices test. Constructional apraxia test (from Milan Overall Dementia Assessment – MODA – battery) is positive for constructional apraxia, perseverations and closing-in phenomenon.



Family pedigree revealed the presence of dementia in the grand-mother, the father (II.4) and four aunts (II.1,5,6,7) of the proband.
Genetic analysis disclosed *PSEN1* V379G missense mutation on hexon 11. The same mutation was found in the patient's father and two aunts.

Discussion

More than 200 *PSEN1* mutations have been reported, usually associated with early onset and discrete heterogeneity in clinical features and progression rate. The index case and his family strongly suggest a novel disease-causing *PSEN1* mutation because of the early onset with specific clinical phenotype, the *in vivo* evidence of AD pathology (decreased CSF Aβ1–42) and the presence of the same symptoms in four affected members of two different generations [2].However its definite pathogenic role has still to be demonstrated, by means of complete genetic analyses in affected and unaffected relatives and, most of all, by *in vitro* pathogenicity assays [3].

[1] AD & FTD Mutation Database at www.molgen.ua.ac.be/Admutations/
[2] Dubois B, Feldman HH, Jacova C et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13(6):614-629.
[3] Cruz de Sousa L, Lamari F, Belliard S et al. Cerebrospinal fluid biomarkers in the differential diagnosis of Alzheimer's disease from other cortical dementias. J Neurol Neurosurg Psychiatry 2011
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