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Clinical Picture of a Patient With a Novel *PSEN1* Mutation (L424V)

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Young onset dementia raises concern about familial and non degenerative dementias. We describe a patient with early dementia. At the age of 26, a woman developed symptoms of anorexia nervosa, at 30 a memory and attention deficit, and at 34 abnormal behavior with impulsivity, aggression, and dysexecutive disorder. At 36 she showed aphasia, stereotyped behavior, hyperreflexia, grasping reflex, urinary incontinence, myoclonus, and seizures. Blood and cerebrospinal fluid were normal. Brain computed tomography and single photon emission computed tomography showed diffuse cortico-subcortical atrophy and frontotemporoparietal hypoperfusion. A Leu424Val mutation was present in *PSEN1* gene. *PSEN1* mutations can produce Alzheimer's disease, frontotemporal dementia, and dementia with Lewy bodies phenotypes, or a combination of them. It has been proposed that the mutation type and location may influence the molecular pathogenesis and thus *PSEN1* would represent a molecular connexion between these entities. This case shows a novel *PSEN1* mutation with outstanding amnesic and frontal symptoms.

Keywords: Alzheimer's disease; anorexia nervosa; fontotemporal dementia; mutation; presenilin 1

Introduction

When dementia begins at young age (before 40 years according to NINCDS-ADRDA criteria for Alzheimer's disease, AD) etiologies different from those which are usual at more advanced ages have to be considered in the differential diagnosis. Amongst the possible causes are secondary nonvascular dementias, vascular dementias of cardioembolic, inflammatory and genetic origin as well as many familial neurodegenerative disorders. Occasionally the etiology remains unclarified. We present the case of a young patient who developed a dementing syndrome with atypical features, without a history of familial dementia and without evidence of a secondary dementia cause upon extensive workup.

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Case Report

Our case concerns a woman born from a normal delivery who suffered meningitis at age 7 without apparent sequels. She finished high school. Family history was only significant for dementia in her maternal grandfather, which started when he was over 80 years old. The proband is an only child, and her father and mother are alive and healthy. At the age of 26 the patient developed symptoms of anorexia nervosa, she put herself on a restrictive diet and laxatives, she had dysmorphophobia, weight loss, and amenorrhoea. When she was 30 years old she began to show attentional deficit and forgetfulness (she would not refill her car's gas tank, she could not find her keys, handbag, etc) as well as symptoms with a probable dysexecutive component (she would not drive correctly at roundabouts, she would tie her shoes up wrong, would not peel fruits properly, etc), all of which interfered with activities of daily living while maintaining a normal social behavior. At 34 she started to show irritability, despair, heteroaggressive behavior with verbal bursts, and sporadic suicide threats, developing within a few months into an overall inappropriate and impulsive behavior while

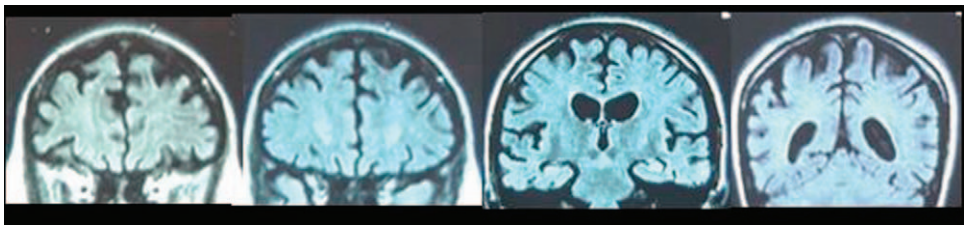

Figure 1. Coronal slices of magnetic resonance (anterior to posterior) performed when patient was 35 years old.

memory impairment persisted. At 35 she was admitted to the acute inpatient psychiatric ward and was diagnosed with a cognitive-behavioral disorder with prominent frontal dysfunction. She had aberrant behavior, bradylalia, dysnomia, mixed dysphasia, acalculia, and ideatory apraxia. She showed fluctuating postural distonia (Pisa syndrome) without being on neuroleptics. This clinical situation progressed into a catatonic state. She received electroconvulsive therapy, which improved her ability to walk and feed herself while cognitive deterioration and affective instability persisted. Upon starting treatment with trazodone, shortly after the electroconvulsive therapy, the patient developed a *status epilepticus*, which was promptly resolved and she subsequently remained on clonazepam and gabapentin. No abnormalities were detected upon extensive workup including thyroid hormones, B12 vitamin, folic acid, iron and cupper metabolism, antinuclear and antithyroglobulin, and antiperoxidase antibodies. Cerebrospinal fluid examination was also normal, including 14.3.3 protein and workup for Lyme disease, syphilis, herpes virus, cytomegalovirus, HIV-1, HIV-2, and other infectious encephalitis. Genetic testing requested for Huntington's disease was negative (16/17 CAG repeats). Electrocardiogram and chest radiograph were normal. Electroencephalogram on admission showed diffuse slowing without other specific features. Brain computed tomography (CT) and magnetic resonance imaging (MRI) disclosed generalized cortico-subcortical atrophy more pronounced in dorsal prefrontal, posterior parietal, and anterior temporal regions; hippocampus was proportional to the rest of the temporal lobe (Figure 1).

After discharge, at the age of 36, she was followed in the Neurology outpatient clinic. Communication difficulties with stereotyped vocalizations and laughing stood out. She had bilateral mydriatic, hyporeactive pupils and seemed to neglect her left upper limb. Deep tendon reflexes were brisk, plantar responses were indifferent, and grasping reflex was present. She did not show muscular atrophy, fasciculations, or bulbar signs. She walked with slight trunk flexion, she had urine incontinence and on occasions also fecal incontinence. A brain single photon emission computed tomography (SPECT) showed extensive hypoperfusion affecting frontal, temporal, and parietal lobes (Figure 2). She had sporadic myoclonic jerks and, after clonazepam discontinuation, she suffered three generalized motor seizures. One day after the seizures a new brain CT scan was performed in which broadening of cerebral ventricles and Silvian fissures was evident compared to the brain CT done 17 months before. Genetic analysis of the *MAPT* gene disclosed no abnormality. Mutation screening of the presenilin 1 gene (*PSEN1*, in chromosome 14) showed a cytosine to guanine transversion in exon 12 leading to a predicted missense mutation (Leu424Val; Figure 3). This change was not found in 178 people from a control sample.

Discussion

We report a case of dementia in the fourth decade associated to a missense *PSEN1* mutation. Although other missense mutations have been described affecting the same codon, we did not find previous reference to this specific mutation. From a clinical standpoint it is noticeable that the patient had presented with anorexia nervosa, 4 years prior to onset of the first cognitive symptoms. In fact the first behavioral and cognitive symptoms, as well as the mild cerebral atrophy seen on the first neuroimages, could be attributable to the prolonged anorexia, and we might expect them to be reversible if anorexia were successfully resolved and normal weight recovered.[1-6] Laboratory workup ruled out other causes sometimes associated with anorexia nervosa, such as Lyme disease,[7,8] HIV infection,[9,10] Wilson's disease,[11] or tumors in the hypothalamic-hypophyseal region.[12]

The progressive clinical picture developed after the age of 30 comprises outstanding early behavioral symptoms as well as attention, memory, lenguage,

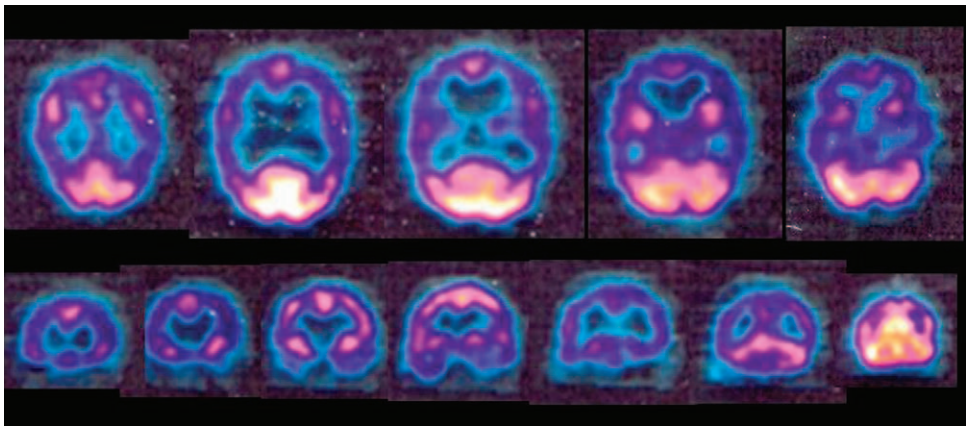

Figure 2. Brain ^{99m}Tc-ECD-SPECT showing severe hypoperfusion affecting frontal, temporal, and parietal lobes in both hemispheres.

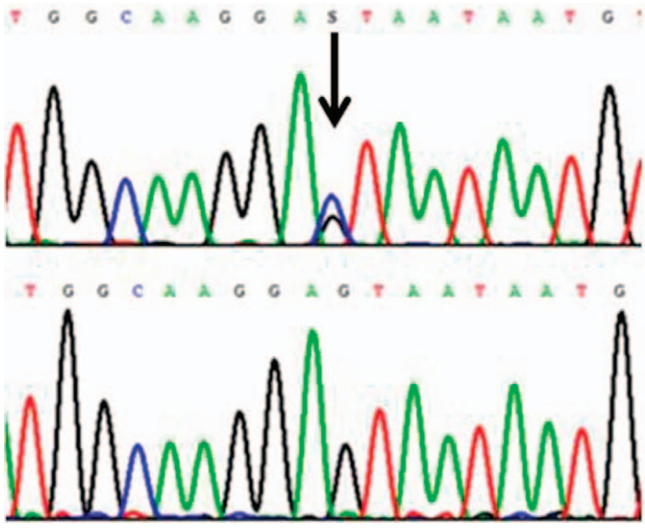

Figure 3. Electropherogram showing the c.1270 C > G mutation in exon 12 (arrow). The sequence is shown on the reverse strand. Upper lane: patient; lower lane: control.

praxis, executive, and movement disorder. It did not fit standard criteria for a typical degenerative dementia, but it shows the clinical profile of an extensive cerebral alteration, in keeping with the neuroimage findings (Figure 2). The early age of onset and the lack of a family history of dementia led to investigate as many potentially reversible causes as possible, as well as Creutzfeldt-Jakob disease. The negative results and the evolution made us suspect a degenerative dementia.

In spite of the lack of a significant family history of dementia (evidence of only a second-degree relative with dementia of late onset and no first-degree relatives with premature death of neurologic or other conditions), we considered the possibility of a genetically determined disorder with a spontaneous mutation in the patient. Screening of the tau gene was first undertaken because the leading syndrome was a frontal dysfunction (abnormal behavior, executive dysfunction, nonfluent dysphasia, cortical disinhibition signs, frontal type urinary incontinence) and there was abnormal body posturing, all of it reminiscent of *frontotemporal dementia and parkinsonism linked to chromosome 17* (FTDP-17).[13] The lack of tau mutations, together with the young onset age and early affected amnesic performance, led us to consider genetic causes of AD and to the finding of a Leu424Val mutation in *PSEN1* which very likely is the cause of the disorder in our patient.

Known pathogenic *PSEN1* mutations—166 to this date[14]—are responsible for 2/3 of familial AD of presenile onset,[15] while *PSEN2* (chromosome 1) and *APP* (chromosome 21) mutations are much less frequent and the cause of about 18% of familial AD (FAD) remains unknown.[15]

The diversity of *PSEN1* mutations may at least in part explain the phenotypic heterogeneity of FAD. The first publications reported clinical manifestations similar to those of sporadic AD, associated with spastic paraparesis in some kindreds.[16,17] However further cases were described with *PSEN1* mutations and frontotemporal dementia (FTD)[18-25] or combined AD-FTD manifestations.[26-31] Autopsy studies, when available, showed some cases with AD pathology,[19,22,23,27-29,31] FTD[20] or both.[26,32] In all these cases there is variable presence of myoclonus[21,23-25,27,29,31] and seizures,[23,25-30] manifestations both of which present in our patient.

Ishikawa et al described in 2005 a Japanese patient with dementia and parkinsonism starting at

age 34 and family history of similar symptoms in the father and grandfather. They found a deletion of exon 12 of *PSEN1* gene and, on pathologic examination, beta amyloid (βA) deposits as well as Lewy bodies in the cerebral cortex and substantia nigra (dementia with Lewy bodies).[33] This same clinicopathologic combination has also been observed in other cases of familial dementia due to different *PSEN1* mutations.[34-36]

Although, to our knowledge, the mutation identified in our patient has not previously been reported, other mutations are known affecting the same codon, Leu424His[19] and Leu424Arg.[37,38] The case reported by Żekanowski et al[19] with a Leu424His missense mutation was 39 years old and showed a symptomatic combination akin to that of the patient reported here with personality changes, disinhibition, stereotyped behavior, mood disorder, executive dysfunction, memory and attention deficits, as well as rigid-akinetic movement disorder and cortical disinhibition signs. Their patient had diffuse atrophy on MRI and diffuse hypoperfusion on brain SPECT and no histopathology data were available. No clinical details are reported on the cases with the Leu424Arg mutation other than the age of onset which was at 30-31, like our patient's.[37,38] If the position of the mutation within the gene influences onset age, as has been proposed,[39] onset in the fourth decade could be attributable to mutations in exon 12. However, it is likely that other genetic (e.g. *APOE*) and/or environmental factors contribute to the clinical onset age as well.

PSEN1 mutations variably affect βA and tau pathology. Some cases show predominant cortical βA deposits[40] with increase in the $\beta A_{42}/\beta A_{40}$ ratio associated to a decrease in γ-secretase activity.[41] These cases have variable density of diffuse and neuritic plaques in the frontal cortex depending on the specific mutation.[41] The degree of amyloid angiopathy is also variable and appears to be greater when the mutation is located beyond codon 200.[42] Furthermore, specific mutations influence the degree of tau phosphorylation, with variable tau pathology and increase of insoluble tau.[43] One potential mechanism influencing tau hyperphosphorylation is the activation of glycogen-synthase kinase 3-beta (GSK3β) observed in some *PSEN1* mutations.[44-48] It is plausible that variable *PSEN1* mutations may lead to heterogeneous pathology and clinical pictures. Although βA deposits may be the leading histological consequence in some cases, more prominent tau pathology may be present in other cases (neurofibrillary tangles, Pick bodies, or τ dysfunction without inclusion bodies). Although the lack of histopathological examination of the brain in the case discussed here does not allow adding new data to the pathologic scenario, it is remarkable that the patient showed early amnesic disorder, as AD patients, and later outstanding frontal symptoms, common in tauopathies, as well as progressive frontotemporal and parietal atrophy and hypoactivity in neuroimage (CT, MRI, SPECT). These features might reflect either a mixed pathologic substrate or a frontal variant of AD.[49,50] Given the information concerning *PSEN1* mutations, we may hypothesize that presenilin 1 plays a complex and diverse role with implications in AD, FTD, dementia with Lewy bodies, and cerebral amyloid angiopathy. Finally, this report enhances the advisability of suspecting a genetic etiology whenever we face a case of early onset progressive dementia of unknown cause, even though a familial pattern is not evident.

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