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Case Report
MS, 1 figure, 1 table

Psychiatric Disorders in Alzheimer Disease With the Presenilin-1 L226F Mutation

Francesca Bartesaghi, MD,† Chiara Emilia Rosci, MD,*† Cecilia Rassiga,*† Valentina Barbieri, MD,*‡ Orsola Gambini, MD,*‡ Stefano Floro, MD,*† Andrea Maria D'Arrigo, MD,*† Angelo Del Sole, MD,*§ Elio Angelo Scarpini, MD,‖¶ Daniela Galimberti, PhD,‖¶ and Alberto Priori, MD, PhD*†*

From the *Aldo Ravelli Center for Neurotechnology and Experimental Neurotherapeutics, University of Milan, Milan, Italy; †Clinical Neurology Unit I, ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, San Paolo University Hospital, Milan, Italy; ‡Clinical Psychiatry Unit, ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, San Paolo University Hospital, Milan, Italy; §Nuclear Medicine Unit, ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, San Paolo University Hospital, Milan, Italy; ‖University of Milan, Dino Ferrari Center, Milan, Italy; and ¶Neurodegenerative Diseases Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy.

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[Corresponding author: Alberto Priori, MD, Clinica Neurologica Università degli Studi di Milano, Polo Universitario San Paolo, Via Antonio di Rudinì 8, Milano 20100 Italy; Telephone number: 02 818 43 225. email address: alberto.priori@unimi.it]

The authors declare no conflicts of interest.

Correspondence: Alberto Priori, MD, PhD, Neurology Unit, University of Milan, San Paolo University Hospital, Antonio di Rudinì 8 Street, Milan 20100 Italy (email: alberto.priori@unimi.it).

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ABSTRACT

The presenilin-1 (*PSEN1*) L226F mutation has been linked to very early onset of prominent behavioral and psychiatric disturbances followed by cognitive decline within a few years. We report a novel case of early-onset Alzheimer disease that was originally diagnosed as psychotic depression in a patient with this gene mutation. We also compare our patient's clinical data to those of other cases of this mutation that have been described in the literature. Because atypical behavioral and psychiatric disturbances in young (<40 years) individuals can herald Alzheimer disease, a tight collaboration between psychiatrists and neurologists is crucial for an early diagnosis.

Key Words: early-onset Alzheimer disease, *PSEN1*, genetic, behavioral symptoms

AD = Alzheimer disease. **ADAD** = autosomal dominant Alzheimer disease. ***PSEN1*** = presenilin-1.

Genetic mutations in the presenilin-1 (*PSEN1*) gene are the most common cause of autosomal dominant Alzheimer disease (ADAD) (Lleò et al, 2004). The manifestation of ADAD may sometimes be difficult to recognize, particularly if the patient presents with early-onset psychiatric disturbances. A classical neurologic condition such as Alzheimer disease (AD) may present with initial psychiatric features such as depression or bipolar disorder; however, detection of a neurologic substrate underlying the early phases of ADAD, especially when psychiatric features are prominent in young (<40 years) individuals, remains unclear. In this report, we present a case of ADAD with the rare *PSEN1* L226F mutation. We also review the only other three cases of ADAD with the *PSEN1* L226F mutation that have been reported thus far.

PSEN1 L226F is a very rare gene mutation and has been reported in only three prior cases (Bagyinszky et al, 2016; Gómez-Tortosa et al, 2010; Zekanowski et al, 2006). First detected in 2006, *PSEN1* L226F is a missense point mutation on exon 7 of chromosome 14 (CTC→TTC) that results in the substitution of leucine with phenylalanine, which causes changes in the surface of a transmembrane domain of *PSEN1* by increasing hydrophobic interactions. The first case of an individual with this gene mutation was a man with prominent behavioral symptoms who had been clinically diagnosed with frontotemporal dementia at the age of 33 (Zekanowski et al, 2006). His autopsy revealed AD pathology. The second case was a 33-year-old woman who had developed depression followed by a speech

and memory deficit; she was clinically diagnosed with AD, which was confirmed at autopsy (Gómez-Tortosa et al, 2010). The third case was a 37-year-old woman who had developed paranoid ideation and anxiety, which progressed to nonfluent aphasia and cognitive and memory deficits; she was clinically diagnosed with AD, but no autopsy was performed (Bagyinszky et al, 2016).

These three cases, plus the one presented here, had a prodromal phase that was dominated by isolated psychiatric disturbances that occurred while the patients were in their early 30s; this phase was followed by rapid cognitive decline and dementia.

CASE REPORT

A 36-year-old, left-handed woman of South American origin was referred to the neurology department of the Aldo Ravelli Center for Neurotechnology and Experimental Neurotherapeutics in Milan, Italy, in the spring of 2018 with a history of behavioral changes and cognitive impairment that had begun 8 years earlier. The first manifestations of affective restriction were noticed by her family in 2010, but it was not until 2012, after her last child was born, that the woman consulted a psychiatrist. At that time, she was diagnosed with postpartum depression with psychotic symptoms and was treated with antipsychotic medication and antidepressants.

Despite the treatment, the patient reported that she had never completely recovered from her psychotic symptoms; nevertheless, she spontaneously stopped taking her medications soon after 2012 until 2017. Her family members stated that during this time, the patient experienced vague cognitive manifestations, such as forgetfulness and anxiety, which they ascribed to her personality. The patient and her family moved abroad from 2015 to 2017 to manage a new commercial activity but returned to Italy due to the patient's growing inability to manage money and activities of daily living. Her clinical picture consisted of severe anxiety with frequent bursts of tears, interpretative thinking toward her family

members, disorganization, and forgetfulness. During the past year, she had become totally incapable of taking care of herself and her three children. Moreover, her family members reported at least one episode of spatial disorientation where the patient was unable to find her way home. In the autumn of 2017, her family asked for a psychiatric re-evaluation.

At the beginning of 2018, the patient met with a private psychiatrist who prescribed aripiprazole and escitalopram for a "dissociative picture with depressive elements." She was admitted to the psychiatry ward of our hospital, where duloxetine was introduced to manage her depression. Because of her extrapyramidal symptoms, aripiprazole was replaced with olanzapine. These medications were effective in reducing the patient's anxiety and akathisia but had no beneficial effect on her cognition. In addition, during hospitalization, the psychiatrist observed compulsive behavior and a lack of inhibition.

In the spring of 2018, the patient was assessed by a neurologist, an expert in dementia, who suspected that she had a neurologic, rather than a psychiatric, condition. The patient was transferred to the neurology department of the Aldo Ravelli Center for Neurotechnology and Experimental Neurotherapeutics in Milan, Italy, for further diagnostic tests and therapeutic management.

The patient's family history was unknown because she had been adopted, but she stated that she had experienced normal early development. However, the family reported that she had a history of occasional drug and alcohol abuse during adolescence and young adulthood.

ASSESSMENTS

We performed complete neurologic and neuropsychological examinations using tests that explore executive, attention, memory, and language functions. Blood tests were also performed, complete with a screening for autoimmune and infective diseases; cerebrospinal fluid dosage of beta-amyloid, tau, and phosphorilated tau; and a neuroradiological study with

MRI, followed by ^{18}F-FDG-PET and florbetaben-PET. To confirm our suspicion of a neurodegenerative condition, we performed genetic testing using next-generation sequencing. We administered quetiapine and pregabalin to manage the patient's behavioral symptoms and rivastigmine to manage her cognitive function. At the 6-month follow-up, we retested her with the same battery of neuropsychological tests.

RESULTS

Neurologic and Neuropsychological Examinations

Cognitive functions aside, the patient's neurologic examination was unremarkable. Quetiapine and pregabalin were effective in reducing her anxiety and her psychotic symptoms. The neuropsychological assessment, however, showed severe, multidomain cognitive impairment characterized by temporospatial disorientation, recent and remote memory impairment, attention deficit, naming deficit with anomia and semantic errors, reduced semantic and phonemic verbal fluency, visuospatial impairment (constructional apraxia with closing in), and symmetric ideomotor apraxia. She scored 12 out of 30 on the Mini-Mental State Examination, indicating severe cognitive impairment (Measso et al, 1993. Overall, the patient's neuropsychological data were compatible with AD.

Blood Tests

The patient's blood tests were normal. Serological testing ruled out syphilis and viral infections, including HIV. Cerebrospinal fluid analysis was consistent for reduced levels of beta-amyloid (536 pg/ml, cutoff level >600 pg/ml) and for elevated levels of the tau (1603 pg/ml, cutoff level <300 pg/ml) and phosphorilated tau proteins (133 pg/ml, cutoff level <61 pg/ml). Her anti-NMDA antibodies were negative.

Radiologic Findings

MRI showed temporoparietal and bilateral hippocampal atrophy (1.4 cm^3 bilaterally) (Figure 1A). FDG-PET revealed bilateral hypometabolism of the precuneus, posterior cingulate, temporoparietal, and frontal areas (Figure 1B). Florbetaben-PET demonstrated diffuse increase of cortical uptake and an intense uptake in the basal ganglia (Figure 1C).

< Insert Figure 1 here >

Genetic Testing

Despite the relatively young age of our patient at symptom onset, her neuropsychological test results, supported by her FDG-PET and florbetaben-PET results, prompted us to test for genetic mutations linked to dementia. Genetic screening revealed the presence of the *PSEN1* L226F mutation. The patient's apolipoprotein E genotype was E3/E3. At this point, we made the diagnosis of ADAD.

We administered rivastigmine, which is the first-line therapy choice for such cases (up to 9.5 mh/24h), but after a transient improvement in attention and orientation, the patient's cognitive function worsened, as repetition of the neuropsychological tests demonstrated at the 6-month follow-up, with a loss of function in everyday activities. At the 18-month follow-up, the patient's cognitive decline had further progressed to complete dependency in all daily activities in addition to insomnia and language and comprehension deterioration. Seizures appeared at about the same time, requiring the introduction of lamotrigine. We observed no further motor or sensory impairment.

At the end of 2019, the patient was institutionalized in a health care facility, where she died at the beginning of 2020. An autopsy was not performed.

DISCUSSION

Our case involved a young woman with behavioral abnormalities followed by a clinical picture mimicking postpartum psychiatric disturbances, who, within 5 years of the first behavioral symptoms, demonstrated progressive cognitive impairment that eventually led to complete dependency. To date, this is the most extensively studied individual carrying the *PSEN1* L226F mutation.

The clinical presentation of ADAD caused by *PSEN1* mutations can be similar to that of the sporadic form of AD, with the amnestic presentation being the most frequent. Neurologic features such as myoclonus, seizures, and extrapyramidal and cerebellar signs are more frequent in the autosomal dominant form of AD than in the sporadic form (Ringman et al, 2014). Atypical language and behavioral presentations can occur in a minority of both autosomal dominant and sporadic cases (Bateman et al, 2011). Spastic paraparesis and pyramidal signs can also occur in individuals with *PSEN1* mutations (Karlstrom et al, 2008).

Evidence of the association between *PSEN1* mutations and frontotemporal dementia-like phenotypes has been reported (Blauwendraat et al, 2018), but very few reports exist (Raux et al, 2000; Riudavets et al, 2013). The main consideration arising from our case and the three previously reported cases is that the *PSEN1* L226F mutation was heralded by atypical psychiatric disturbances followed by cognitive decline within a few years. All four individuals were diagnosed in their 30s, and their cognitive decline caused language impairment and behavioral changes. No extrapyramidal signs were present in our patient, but parkinsonism may be a late feature of ADAD related to the *PSEN1* L226F mutation (Table 1).

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Most of the variance between different *PSEN1* mutations in age at symptom onset seems to be accounted for by ADAD mutation, even if some clinical variability remains within many families with the same mutation. This finding suggests that other factors may have a role in modifying the onset of symptoms (Ryman et al, 2014). Nonetheless, age at symptom onset, clinical presentation, and disease progression seem to present a consistent picture of *PSEN1* L226F mutation, regardless of the ethnic or environmental background of the individuals.

Even though our patient started developing the first symptoms of AD in her late 20s, many years passed between the time when she experienced the first behavioral changes and the time at which she lost her autonomy due to cognitive impairment. A long initial phase during which psychiatric disturbances dominate the clinical picture appears to be a shared feature of our case and the other three cases of *PSEN1* L226F mutation.

The core diagnostic criteria for AD remain clinical; however, the recently revised criteria recognize the importance of other diagnostic methods beyond genetic testing, such as using neuroimaging (MRI, FDG-PET, amyloid-PET) and cerebrospinal fluid (beta-amyloid, tau, and phosphorylated tau) biomarkers, which can increase or decrease the level of certainty that AD pathology underlies the dementia (Jack et al, 2011).

Our patient's brain MRI and FDG-PET are in line with the data that have been reported in the literature. For example, in an MRI volumetric study, Gosche et al (2002) showed hippocampal atrophy, and Um et al (2017) demonstrated severe, diffuse cortical hypometabolism on FDG-PET. An amyloid-PET scan is indicated in individuals with progressive mild cognitive impairment with an uncertain etiology, individuals with atypical presentations and clinical course, and individuals with early-onset progressive dementias (Johnson et al, 2013).

Individuals with early-onset AD may have a different topography of amyloid deposition compared to those with late-onset AD. For example, individuals with early-onset

AD retain higher levels of PiB (Pittsburgh B compound) in the bilateral basal ganglia, bilateral thalamus, left superior temporal cortex, and left cuneus compared to those with late-onset AD (Cho et al, 2013). More specifically, amyloid deposition appears to begin in the striatum of *PSEN1* mutation carriers, whereas the earliest deposition in individuals with sporadic AD appears to be in the frontal cortex and the precuneus/posterior cingulate region (Klunk et al, 2007). Florbetaben-PET in our patient demonstrated a diffuse cortical uptake and, despite the absence of extrapyramidal motor disturbances, an intense uptake in the basal ganglia, as described in individuals with early-onset AD (Cho et al, 2013; Um et al, 2017).

CONCLUSION

Our report describes a rare case of *PSEN1* L226F mutation and early-onset ADAD. Our case aligns with the distinctive phenotype of the mutation—young prodromal psychiatric presentation followed by cognitive decline—similarly to the other three cases available in the literature. ADAD can hide behind insidious atypical psychiatric disturbances, which should be diagnostically assessed in tight collaboration between psychiatrists and neurologists. The behavioral and psychiatric disturbances exhibited by individuals with ADAD are the same as those often found in individuals with the prefrontal syndromes. A careful neurologic assessment should search for other subtle signs of frontal lobe and cognitive dysfunction that will lead to a diagnosis of ADAD.

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Figure Legend

FIGURE 1. A. MRI of the brain, FLAIR sequences: (1) coronal section; (2) axial section: note the temporoparietal and hippocampal atrophy (arrows). **B.** FDG-PET of the brain, 3D reconstruction of transaxial sections, qualitative study: (1) right hemisphere, lateral view; (2) left hemisphere, lateral view; (3) right hemisphere, medial view; (4) left hemisphere, medial view; note the bilateral hypometabolism (green-blue) of the precuneus, posterior cingulate, temporoparietal, and frontal areas (arrows). **C.** Florbetaben-PET of the brain, 3D reconstruction of transaxial sections, qualitative study: (1) right hemisphere, lateral view; (2) left hemisphere, lateral view; (3) anterior view; (4) posterior view; (5, 6) axial sections; note the diffuse increase of cortical uptake of the tracer (red), demonstrating cortical deposition of beta-amyloid and an intense uptake in the basal ganglia. Our case is the first where an amyloid-PET scan was performed, further confirming that the *PSEN1* L226F mutation is associated with the particular deposition pattern (arrows).

TABLE 1. Clinical Features of Individuals With the Presenilin-1 L226F Mutation

Feature	Zekanowski et al, 2006	Gómez-Tortosa et al, 2010	Bagyinszky et al, 2016	Our Case
Gender	Male	Female	Female	Female
Age at diagnosis (years)	33	33	37	36
Family history	Mother, early dementia (33 years)	Father, early dementia (36 years)	None	Unknown
Clinical diagnosis	FTD	AD	AD	AD
Symptoms	Behavioral changes, frontal signs, subsequent severe memory impairment, parkinsonism, and mutism	Depression, dysarthria and nonfluent aphasia, cognitive impairment, and parkinsonism	Paranoid ideation and anxiety, cognitive decline, frontal signs, nonfluent aphasia, mutism, and parkinsonism	Psychotic depression, cognitive decline with marked memory and language deficit, and seizures
Neuropsychological examination	Impairment in planning, problem solving, and attention	Deficit in verbal memory and in executive and visuoconstructive functions	Deficit in calculation, praxis, visuoconstructive function, and memory	Attention deficit, language deficit with anomia and reduced semantic and verbal fluency, constructional apraxia with closing in, and ideomotor apraxia
Neuroimaging	CT: frontal atrophy SPECT: frontal areas hypoperfusion	MRI: mainly biparietal atrophy	MRI: bilateral hippocampal and parietal cortical atrophy FDG-PET: mainly biparietal hypometabolism	FDG-PET: temporoparietal and frontal hypometabolism Amyloid-PET: diffuse cortical uptake, in particular in the basal ganglia
Age at death	38	42	44	38
Autopsy	AD pathology	AD pathology	Not done	Not done

AD = Alzheimer disease. **FTD** = frontotemporal dementia. **SPECT** = single-photon emission computed tomography.

Figure