

CBN-19-93 Bartesaghi

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*†*

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31 **Running head:** Psychiatry of Presenilin-1 L226F Mutation
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38 **ABSTRACT**

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40 The presenilin-1 (*PSEN1*) L226F mutation has been linked to very early onset of prominent
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42 behavioral and psychiatric disturbances followed by cognitive decline within a few years. We
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44 report a novel case of early-onset Alzheimer disease that was originally diagnosed as
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46 psychotic depression in a patient with this gene mutation. We also compare our patient's
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48 clinical data to those of other cases of this mutation that have been described in the literature.
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51 Because atypical behavioral and psychiatric disturbances in young (<40 years) individuals
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53 can herald Alzheimer disease, a tight collaboration between psychiatrists and neurologists is
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55 crucial for an early diagnosis.
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1 **Key Words:** early-onset Alzheimer disease, *PSENI*, genetic, behavioral symptoms
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7 **AD** = Alzheimer disease. **ADAD** = autosomal dominant Alzheimer disease. ***PSENI*** =
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Genetic mutations in the presenilin-1 (*PSENI*) 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 *PSENI* L226F mutation. We
also review the only other three cases of ADAD with the *PSENI* L226F mutation that have
been reported thus far.

PSENI 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, *PSENI* 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 *PSENI* 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

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

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

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24 A 36-year-old, left-handed woman of South American origin was referred to the
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26 neurology department of the Aldo Ravelli Center for Neurotechnology and Experimental
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28 Neurotherapeutics in Milan, Italy, in the spring of 2018 with a history of behavioral changes
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30 and cognitive impairment that had begun 8 years earlier. The first manifestations of affective
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32 restriction were noticed by her family in 2010, but it was not until 2012, after her last child
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34 was born, that the woman consulted a psychiatrist. At that time, she was diagnosed with
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36 postpartum depression with psychotic symptoms and was treated with antipsychotic
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38 medication and antidepressants.
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44 Despite the treatment, the patient reported that she had never completely recovered
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46 from her psychotic symptoms; nevertheless, she spontaneously stopped taking her
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48 medications soon after 2012 until 2017. Her family members stated that during this time, the
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50 patient experienced vague cognitive manifestations, such as forgetfulness and anxiety, which
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52 they ascribed to her personality. The patient and her family moved abroad from 2015 to 2017
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54 to manage a new commercial activity but returned to Italy due to the patient's growing
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56 inability to manage money and activities of daily living. Her clinical picture consisted of
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58 severe anxiety with frequent bursts of tears, interpretative thinking toward her family
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1 members, disorganization, and forgetfulness. During the past year, she had become totally
2 incapable of taking care of herself and her three children. Moreover, her family members
3 reported at least one episode of spatial disorientation where the patient was unable to find her
4 way home. In the autumn of 2017, her family asked for a psychiatric re-evaluation.
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10 At the beginning of 2018, the patient met with a private psychiatrist who prescribed
11 aripiprazole and escitalopram for a “dissociative picture with depressive elements.” She was
12 admitted to the psychiatry ward of our hospital, where duloxetine was introduced to manage
13 her depression. Because of her extrapyramidal symptoms, aripiprazole was replaced with
14 olanzapine. These medications were effective in reducing the patient’s anxiety and akathisia
15 but had no beneficial effect on her cognition. In addition, during hospitalization, the
16 psychiatrist observed compulsive behavior and a lack of inhibition.
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27 In the spring of 2018, the patient was assessed by a neurologist, an expert in dementia,
28 who suspected that she had a neurologic, rather than a psychiatric, condition. The patient was
29 transferred to the neurology department of the Aldo Ravelli Center for Neurotechnology and
30 Experimental Neurotherapeutics in Milan, Italy, for further diagnostic tests and therapeutic
31 management.
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39 The patient’s family history was unknown because she had been adopted, but she stated
40 that she had experienced normal early development. However, the family reported that she
41 had a history of occasional drug and alcohol abuse during adolescence and young adulthood.
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49 ASSESSMENTS

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54 We performed complete neurologic and neuropsychological examinations using tests
55 that explore executive, attention, memory, and language functions. Blood tests were also
56 performed, complete with a screening for autoimmune and infective diseases; cerebrospinal
57 fluid dosage of beta-amyloid, tau, and phosphorylated tau; and a neuroradiological study with
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1 MRI, followed by ¹⁸F-FDG-PET and florbetaben-PET. To confirm our suspicion of a
2 neurodegenerative condition, we performed genetic testing using next-generation sequencing.
3 We administered quetiapine and pregabalin to manage the patient's behavioral symptoms and
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5 rivastigmine to manage her cognitive function. At the 6-month follow-up, we retested her
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10 with the same battery of neuropsychological tests.
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15 RESULTS

20 Neurologic and Neuropsychological Examinations

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

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48 The patient's blood tests were normal. Serological testing ruled out syphilis and viral
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50 infections, including HIV. Cerebrospinal fluid analysis was consistent for reduced levels of
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52 beta-amyloid (536 pg/ml, cutoff level >600 pg/ml) and for elevated levels of the tau (1603
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54 pg/ml, cutoff level <300 pg/ml) and phosphorylated tau proteins (133 pg/ml, cutoff level <61
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Radiologic Findings

MRI showed temporoparietal and bilateral hippocampal atrophy (1.4 cm³ 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 mg/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

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3 Our case involved a young woman with behavioral abnormalities followed by a clinical
4 picture mimicking postpartum psychiatric disturbances, who, within 5 years of the first
5 behavioral symptoms, demonstrated progressive cognitive impairment that eventually led to
6 complete dependency. To date, this is the most extensively studied individual carrying the
7 *PSENI* L226F mutation.
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12 The clinical presentation of ADAD caused by *PSENI* mutations can be similar to that
13 of the sporadic form of AD, with the amnesic presentation being the most frequent.
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15 Neurologic features such as myoclonus, seizures, and extrapyramidal and cerebellar signs are
16 more frequent in the autosomal dominant form of AD than in the sporadic form (Ringman et
17 al, 2014). Atypical language and behavioral presentations can occur in a minority of both
18 autosomal dominant and sporadic cases (Bateman et al, 2011). Spastic paraparesis and
19 pyramidal signs can also occur in individuals with *PSENI* mutations (Karlstrom et al, 2008).
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24 Evidence of the association between *PSENI* mutations and frontotemporal dementia-
25 like phenotypes has been reported (Blauwendraat et al, 2018), but very few reports exist
26 (Raux et al, 2000; Riudavets et al, 2013). The main consideration arising from our case and
27 the three previously reported cases is that the *PSENI* L226F mutation was heralded by
28 atypical psychiatric disturbances followed by cognitive decline within a few years. All four
29 individuals were diagnosed in their 30s, and their cognitive decline caused language
30 impairment and behavioral changes. No extrapyramidal signs were present in our patient, but
31 parkinsonism may be a late feature of ADAD related to the *PSENI* L226F mutation (Table
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< Insert Table 1 here >

1 Most of the variance between different *PSENI* mutations in age at symptom onset
2 seems to be accounted for by ADAD mutation, even if some clinical variability remains
3 within many families with the same mutation. This finding suggests that other factors may
4 have a role in modifying the onset of symptoms (Ryman et al, 2014). Nonetheless, age at
5 symptom onset, clinical presentation, and disease progression seem to present a consistent
6 picture of *PSENI* L226F mutation, regardless of the ethnic or environmental background of
7 the individuals.
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17 Even though our patient started developing the first symptoms of AD in her late 20s,
18 many years passed between the time when she experienced the first behavioral changes and
19 the time at which she lost her autonomy due to cognitive impairment. A long initial phase
20 during which psychiatric disturbances dominate the clinical picture appears to be a shared
21 feature of our case and the other three cases of *PSENI* L226F mutation.
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30 The core diagnostic criteria for AD remain clinical; however, the recently revised
31 criteria recognize the importance of other diagnostic methods beyond genetic testing, such as
32 using neuroimaging (MRI, FDG-PET, amyloid-PET) and cerebrospinal fluid (beta-amyloid,
33 tau, and phosphorylated tau) biomarkers, which can increase or decrease the level of certainty
34 that AD pathology underlies the dementia (Jack et al, 2011).
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42 Our patient's brain MRI and FDG-PET are in line with the data that have been reported
43 in the literature. For example, in an MRI volumetric study, Gosche et al (2002) showed
44 hippocampal atrophy, and Um et al (2017) demonstrated severe, diffuse cortical
45 hypometabolism on FDG-PET. An amyloid-PET scan is indicated in individuals with
46 progressive mild cognitive impairment with an uncertain etiology, individuals with atypical
47 presentations and clinical course, and individuals with early-onset progressive dementias
48 (Johnson et al, 2013).
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59 Individuals with early-onset AD may have a different topography of amyloid
60 deposition compared to those with late-onset AD. For example, individuals with early-onset
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1 AD retain higher levels of PiB (Pittsburgh B compound) in the bilateral basal ganglia,
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3 bilateral thalamus, left superior temporal cortex, and left cuneus compared to those with late-
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5 onset AD (Cho et al, 2013). More specifically, amyloid deposition appears to begin in the
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7 striatum of *PSENI* mutation carriers, whereas the earliest deposition in individuals with
8
9 sporadic AD appears to be in the frontal cortex and the precuneus/posterior cingulate region
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11 (Klunk et al, 2007). Florbetaben-PET in our patient demonstrated a diffuse cortical uptake
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13 and, despite the absence of extrapyramidal motor disturbances, an intense uptake in the basal
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15 ganglia, as described in individuals with early-onset AD (Cho et al, 2013; Um et al, 2017).
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22 CONCLUSION

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

- 1
2
3
4
5
6 Bagyinszky E, Park SA, Kim HJ, et al. 2016. *PSEN1* L226F mutation in a patient with early-
7 onset Alzheimer's disease in Korea. *Clin Interv Aging*. 11:1433–1440.
8
9 doi:10.2147/CIA.S111821
10
11
12
13 Bateman RJ, Aisen PS, De Strooper B, et al. 2011. Autosomal-dominant Alzheimer's disease:
14 a review and proposal for the prevention of Alzheimer's disease. *Alzheimers Res Ther*.
15 3:1. doi:10.1186/alzrt59
16
17
18
19
20
21 Blauwendraat C, Wilke C, Simón-Sánchez J, et al. 2018. The wide genetic landscape of
22 clinical frontotemporal dementia: systematic combined sequencing of 121 consecutive
23 subjects. *Genet Med*. 20:240–249. doi:10.1038/gim.2017.102
24
25
26
27
28 Cho H, Seo SW, Kim J-H, et al. 2013. Amyloid deposition in early onset versus late onset
29 Alzheimer's disease. *J Alzheimers Dis*. 35:813–821. doi:10.3233/JAD-121927
30
31
32
33 Gómez-Tortosa E, Barquero S, Barón M, et al. 2010. Clinical–genetic correlations in familial
34 Alzheimer's disease caused by presenilin 1 mutations. *J Alzheimers Dis*. 19:873–884.
35
36
37
38
39
40
41 Gosche KM, Mortimer JA, Smith CD, et al. 2002. Hippocampal volume as an index of
42 Alzheimer neuropathology: findings from the Nun study. *Neurology*. 58:1476–1482.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
- Jack CR Jr, Albert M, Knopman DS, et al. 2011. Introduction to Revised Criteria for the
Diagnosis of Alzheimer's Disease: National Institute on Aging and the Alzheimer
Association Workgroups. *Alzheimers Dement*. 7:257–262.
doi:10.1016/j.jalz.2011.03.004
- Johnson KA, Minoshima S, Bohnen NI, et al. 2013. Appropriate use criteria for amyloid
PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine

1 and Molecular Imaging, and the Alzheimer's Association. *J Nucl Med.* 54:476–490.
2
3 doi:10.2967/jnumed.113.120618
4

5 Karlstrom H, Brooks WS, Kwok JB, et al. 2008. Variable phenotype of Alzheimer's disease
6
7 with spastic paraparesis. *J Neurochem.* 104:573–583. doi:10.1111/j.1471-
8
9 4159.2007.05038.x
10

11 Klunk WE, Price JC, Mathis CA, et al. 2007. Amyloid deposition begins in the striatum of
12
13 presenilin-1 mutation carriers from two unrelated pedigrees. *J Neurosci.* 27:6174–
14
15 6184. doi:10.1523/JNEUROSCI.0730-07.2007
16
17

18 Lleò A, Berezovska O, Growdon JH, et al. 2004. Clinical, pathological, and biochemical
19
20 spectrum of Alzheimer disease associated with PS-1 mutations. *Am J Geriatr*
21
22 *Psychiatry.* 12:146–156.
23
24

25 Measso G, Cavarzeran F, Zappalà G, et al. 1993. The Mini-Mental State Examination:
26
27 normative study of an Italian random sample. *Dev Neuropsychol.* 9:77–85.
28
29
30 doi:10.1080/87565649109540545
31
32

33 Raux G, Gantier R, Thomas-Anterion C, et al. 2000. Dementia with prominent
34
35 frontotemporal features associated with L113P presenilin 1 mutation.
36
37 *Neurology.* 55:1577–1578. doi:10.1212/wnl.55.10.1577
38
39

40 Ringman JM, Goate A, Masters CL, et al. 2014. Genetic heterogeneity in Alzheimer disease
41
42 and implications for treatment strategies. *Curr Neurol Neurosci Rep.* 14:499.
43
44
45 doi:10.1007/s11910-014-0499-8
46
47

48 Riudavets MA, Bartoloni L, Troncoso JC, et al. 2013. Familial dementia with frontotemporal
49
50 features associated with M146V presenilin-1 mutation. *Brain Pathol.* 23:595–600.
51
52
53 doi:10.1111/bpa.12051
54
55

56 Ryman DC, Acosta-Baena N, Aisen PS, et al. 2014. Symptom onset in autosomal dominant
57
58 Alzheimer disease: a systematic review and meta-analysis. *Neurology.* 83:253–260.
59
60
61 doi:10.1212/WNL.0000000000000596
62
63
64
65

1 Um YH, Choi WH, Jung WS, et al. 2017. A case report of a 37-year-old Alzheimer's disease
2 patient with prominent striatum amyloid retention. *Psychiatry Investig.* 14:521–524.

3
4
5 doi:10.4306/pi.2017.14.4.521
6

7 Zekanowski C, Golan MP, Krzyśko KA, et al. 2006. Two novel presenilin 1 gene mutations
8 connected with frontotemporal dementia-like clinical phenotype: genetic and
9
10 bioinformatic assessment. *Exp Neurol.* 200:82–88.

11
12
13 doi:10.1016/j.expneurol.2006.01.022
14
15
16
17
18
19
20
21
22
23
24
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Figure Legend

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

