Journal of Neurology (2022) 269:4853–4862
https://doi.org/10.1007/s00415-022-11125-8

ORIGINAL COMMUNICATION

Progressive cognitive impairment and familial spastic paraparesis due to PRESENILIN 1 mutation: anatomoclinical characterization

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Received: 17 December 2021 / Revised: 1 April 2022 / Accepted: 4 April 2022 / Published online: 19 April 2022

Abstract

Introduction Autosomal dominant Alzheimer's disease (ADAD) due to presenilin 1 (PSEN1) mutation can induce atypical neurological symptoms such as movement disorders and epileptic seizures in the context of early-onset progressive cognitive impairment.

Methods This study includes the anatomoclinical description of three patients of two generations of the same family with movement disorders and progressive cognitive impairment. All were evaluated by trained neurologists, underwent protocolized neuropsychological evaluation, and were assessed by structural (magnetic resonance) and functional (SPECT, PET-18FDG, or PET-18F-Florbetapir) brain imaging tests. A molecular genetic study was performed for all patients, and post-mortem confirmatory anatomopathological evaluation for one of them.

Results The three female patients had an age of onset of symptoms of 38–51 years. All developed progressive multidomain cognitive impairment, paraparesis, and dysarthria, two with ophthalmoparesis and one with untriggered epileptic seizures since early stages. Bilateral cortical fronto-parietal atrophy and global cortical hypoperfusion or posterior bilateral hypometabolism were detected. PET-18F-Florbetapir, when performed, was positive for amyloid cortical deposit. The molecular genetic study confirmed the *PSEN1* mutation c.869-2 A>G. Postmortem study of one of them confirmed Alzheimer's disease anatomopathological features with classic cotton wool plaques (CWP), including coexistence of amyloid angiopathy and Lewy body co-pathology.

Discussion The phenotype of ADAD due to *PSEN1* mutations is very heterogeneous between and across the same family. Family history assessment should include information not only about cognitive decline, but also about movement disorders and untriggered epileptic seizures. Further studies are needed to identify genetic or epigenetic factors that determine phenotypic diversity in this disease.

Keywords Autosomal dominant Alzheimer's disease · Cognitive impairment · Presenilin 1 · Neuropathology · Paraparesis

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Introduction

Alzheimer's disease (AD) is the most common cause of both early-onset (before the age of 65 years) and late-onset dementia [1]. By the year 2050, it is estimated that 131.5 million people worldwide will be affected by AD [2]. Early-onset AD (EOAD) accounts for 2–10% of cases, while autosomal dominant AD (ADAD) accounts for only 0.5–1% of cases [3, 4]. Mutations of presenilin 1 (P*SEN1*) or presenilin 2 (*PSEN2*) and amyloid protein precursor protein (*APP*) have been described as responsible for the latter [2, 5]. Mutations of *PSEN1*, located on chromosome 14q24, account for 67% of cases of ADAD [6]. More than 215 pathogenic mutations have been described in the *PSEN1* gene; more than 70% are located in exons 5, 6, 7, and 8 [7–10]. *PSEN1* is implicated in the beta-amyloid (Aβ) pathway, the immune system, blood brain barrier integrity, synaptic plasticity, axonal guidance, cytoskeleton function, apoptosis, phagocytosis, and autophagy [11]. PSEN1 is an essential protein for the catalytic core of the γ-secretase complex, which catalyzes the cleavage of membrane proteins including APP [12, 13].

Diagnosis of both EOAD and ADAD is challenging, even within the set of *PSEN1* variants, because there is substantial heterogeneity in clinical presentation [14, 15]. In addition to multidomain cognitive impairment of amnesic predominance, *PSEN1* mutations are more frequently associated with atypical neurological symptoms than sporadic late-onset AD cases [16]. These atypical neurological symptoms include spastic paraparesis, cerebellar ataxia, myoclonus and epileptic seizures [9, 17, 18] and they are more frequent if the onset of symptoms occurs earlier than the age of 40 [16, 19]. In turn, fluent or non-fluent aphasia, apraxia, dyscalculia and visual agnosia tend to occur earlier compared with sporadic cases of AD and they could be the first symptoms in up to 25% of the cases [4, 16]. Spastic dysarthria has also been described, although infrequently, in this context [20]. Onset with severe neuropsychiatric symptoms that may lead to a differential diagnosis with the behavioral variant of frontotemporal dementia have been also described [16, 21]. The location of the point mutation, insertion, or deletion potentially can help to predict the accompanying symptomatology of cognitive impairment: If it occurs after codon 200, more frequent visuospatial involvement, spastic paraparesis, and greater association with amyloid angiopathy have been described [16, 22]. If it occurs prior to codon 200, a higher risk for developing epileptic seizures and myoclonus has been reported [23].

The neuropathological findings in EOAD and ADAD are characterized by non-cored plaques lacking associated neuritic dystrophy; they are called cotton wool plaques (CWP) [24]. The presence of CWP across the cortex seems to be more frequent in cases of mutations located in exons 8 and 9 of *PSEN1* [22, 24]. Specifically, additional frontotemporal loss in association with increased tau pathology has been described in cases with *PSEN1* mutations [25–27]. Different concomitant pathologies have also been described—vascular dysfunction and Lewy bodies—suggesting the hypothesis that, in some cases, the location and the extent of these pathologies explains the different phenotypes of *PSEN1* mutations [28]. The presence of amyloid angiopathy is also more frequent in cases of ADAD compared with sporadic AD [22, 29].

We aim to provide a detailed anatomic-clinical description of a rare *PSEN1* mutation (c.869-2 A>G) and correlate the anatomopathological findings with the clinical course. In turn, we emphasize the clinical and anatomopathological differences of ADAD with respect to sporadic AD. To this purpose, we present a series of three patients from two generations of the same family with this mutation, all of them with cognitive impairment with other atypical neurological features such as spastic paraparesis. A molecular genetic study was performed for all three patients, and the disease was confirmed by anatomopathological evaluation in one of them.

Materials and methods

Clinical records and results of neuroimaging of the three patients were assessed by experienced neurologists, following the ethical guidelines of our institution. Written informed consent was obtained from all participants or their relatives to perform genetic and pathological brain studies. The analysis of human brain samples was carried out by neuropathologists at the Navarra brain bank institution, according to current national legislation (Royal Decree ref.RD1716/2011).

Post-mortem study

Post-mortem study was limited to the brain. Immediately after removal from the skull, the left hemisphere was fixed in 10% neutral buffered formalin for 4 weeks. The right hemisphere was subsequently frozen and stored at −80 °C. A diagnosis was made following dissection and gross examination of the left hemisphere according to a previously described protocol [30]. Tissue blocks were selected and embedded in paraffin. Four-micrometer sections were cut and stained with hematoxylin and eosin and processed for immunohistochemistry.

Immunohistochemistry

Formalin-fixed 4-µm-thick sections were mounted on slides and de-waxed. After antigen retrieval, sections were incubated overnight with one of the following primary antibodies: Aβ-amyloid (1/50, Dako, Glostrup, Denmark), anti-AT8 (1/50, Inmunogenetics, Ghent, Belgium), anti-α-synuclein (1/500, Chemicon, Billerica, MA, United States), or anti-TDP-43 (1/200 Abcam, Cambridge, United Kingdom). The reaction product was visualized using an automated slide immunostainer (Leica Bond Max) with Bond Polymer Refine Detection (Leica Biosystems Newcastle Ltd, Newcastle upon Tyne, United Kingdom) and slight counterstaining with hematoxylin.

Molecular genetic study

Blood was collected from the studied patients and relatives after obtaining informed consent. DNA was extracted using a MagNa Pure Compact Nucleic Acid Isolation Kit I and MagNa Pure Compact Instrument (Roche Molecular Diagnostics, Pleasanton, CA, USA).

Amplification of all coding exons and adjacent areas of the PSEN1 gene and family segregation studies were performed by direct sequencing (ABI 3500 Genetic Analyzer, Applied Biosystems, Warrington, United Kingdom). The chromatograms were analyzed with Chromas 2.3 (Technelysium Pty Ltd.). Available databases were used to determine the complete sequence of the gene and to design the most appropriate primers for polymerase chain reaction (PCR): University of California Santa Cruz USCS Genome Browser (https//genome.ucs c.edu/) and Primer3plus (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3pllus.cgi/).

Results

Family history

The family is from Navarra, a region in Northern Spain with 638,213 inhabitants. The mother (I.2) of our first patient (II.6) showed cognitive decline with dementia without etiologic diagnosis of AD (Fig. 1). The fourth brother (II.4) of our first patient was affected by bipolar disorder, and the

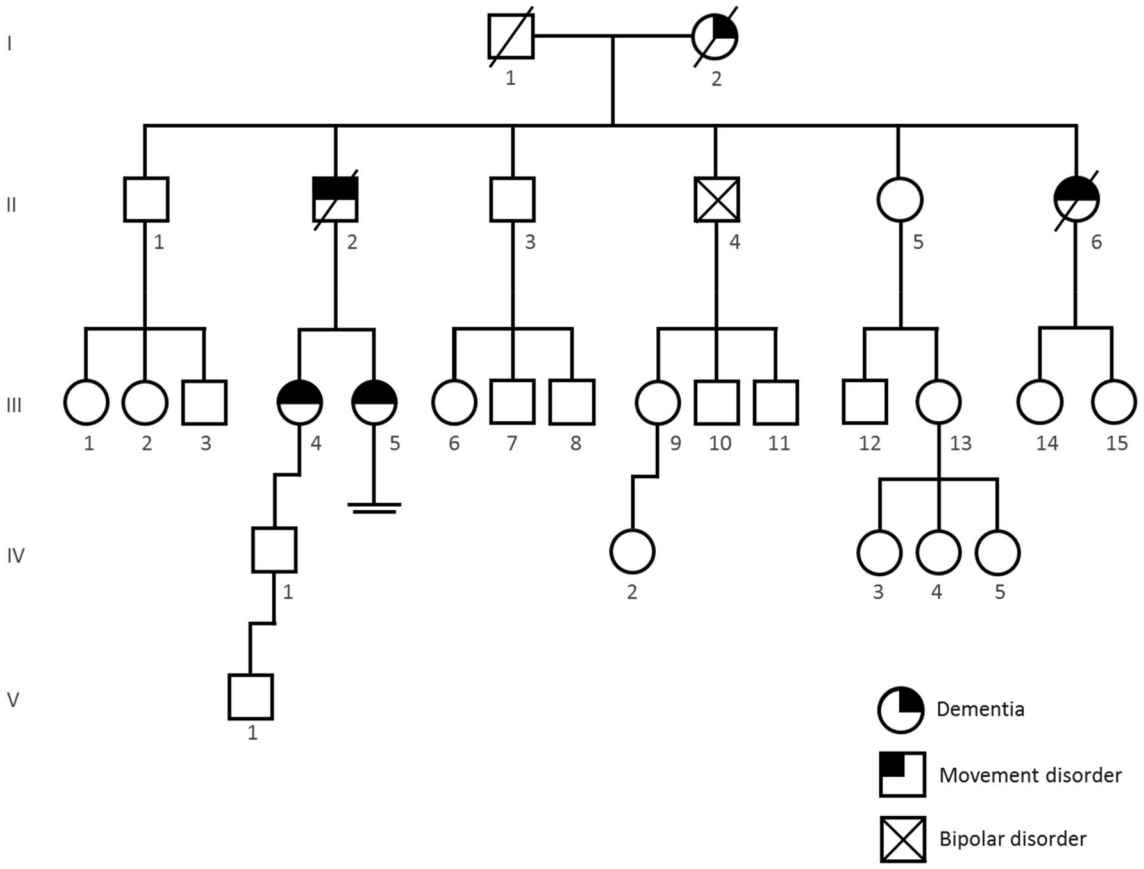

Fig. 1 Family pedigree illustrating dementia and movement disorders in different family members, including the three patients described in this study (II.6, III.4, and III.5). The four brothers and the sister of patient II.6 have not been analyzed for the presence of the *PSEN1* variant

second brother (II.2), who died at the age of 65 years, had presented a slow, progressive, unstudied gait disorder that had started in his fifties. Patients III.4 and III.5, nephews of our first patient and daughters of subject II.2, both of them experimented cognitive decline and progressive motor worsening on the late thirties or early forties.

Clinical features

Patient II.6

A 52-year-old woman sought consultation for clumsiness in her lower right limb over the last 8 months that had led to several falls. She also presented a change of character and affective symptoms with apathy, slowness, a tendency to mutism, memory loss, and difficulties in planning and carrying out activities of daily living. On neurological exploration, she was slow minded, partially oriented in time and space, had poor language, a positive snout reflex, normal strength, global osteo-tendinous hyperreflexia with predominance in lower limbs, bilateral Babinski sign, and gait with spastic paraparesis. Cerebellar maneuvers were normal, and she displayed neither amyotrophy nor fasciculations. Mini-Mental score was of 21/30 (Supplementary Table 1).

Neuropsychological assessment revealed multidomain cognitive impairment with clear predominance of executive function impairment. Speech was slow, with poor content and fluency. No alterations in sensoperception were found. She showed indifference to the tests, as well as marked anxiety and feelings of incapacity. Significant alterations in attention-concentration skills were evident as well as alterations of memory, both visual and verbal. Persistent dyspraxia for sequencing tasks and motor programs and difficulty in copying two- and three-dimensional drawings were found. Gnosias were preserved, and deterioration of the executive function was patent.

Blood tests including hematological, serological, and biochemical studies were normal. Basic autoimmunity profile, tumor markers, vitamin B12, and folic acid were normal as well. Negative for HIV and luetic serology. Biochemical cerebrospinal fluid (CSF) and cellular content were normal. Determination of core biomarkers of AD in the CSF was not performed.

Magnetic resonance imaging (MRI) of the cervical spine showed a mild degenerative cervical osteodiscal phenomena without signs of myelopathy. Cranial MRI showed signs of bilateral fronto-parietal cortical atrophy (Supplementary Fig. 1).

The syndromic diagnosis of a pyramidal syndrome with multidomain cognitive impairment of dysexecutive predominance with suspected neurodegenerative etiology was established.

Over the next years, the patient experienced a progressive worsening of motor and cognitive skills. She developed an asymmetric spastic tetraparesis predominantly in the right limbs that confined her to a wheelchair, a dystonic posture was seen in the upper right extremity (fisting posture with wrist and elbow flexion), language was impoverished to the point of mutism, facial hypomimia became more evident, and there was clear supranuclear ophthalmoparesis. Behavior disorders in the form of irritability appeared. She died 10 years after her first neurological consultation and post-mortem brain study was performed. In her death certification, the immediate or direct cause was considered aspiration pneumoniae and the essential cause the Alzheimer's Disease Dementia.

Patient III.4

A 43-year-old woman presented with progressive memory decline. According to the family's report, she had had moderate forgetfulness for about 4 years with daily living impairment, a tendency to daytime drowsiness, difficulty maintaining attention in conversations, and some change of character, namely irritability with neither delusional ideation nor hallucinations. Moreover, she had developed impaired gait with slowness and frequent stumbling as well as impaired speech. On neurological exploration, she was slow minded, with poor language, dysarthria, no oculomotor abnormalities, normal strength and sensation, global osteo-tendinous hyperreflexia, bilateral Babinski sign, spastic paraparesis, and ataxia. Neither amyotrophy nor fasciculations were present.

Her Mini-Mental State Examination (MMSE) score was 18/30, and neuropsychological exploration showed moderate to severe language impairment with marked anomia, as well as significant memory (both verbal and visual), executive function, and visuoconstructive declines (Supplementary Table 1).

Blood tests including hematological, serological (luetic and HIV), and biochemical studies (including thyroid function); basic autoimmunity profile; tumor markers; vitamin B12; and folic acid were normal. Non-pleocytosis or hyperproteinorrachia was found, and core biomarkers of AD in CSF were not evaluated.

Cranial MRI revealed signs of bilateral fronto-parietal cortical and cerebellar atrophy. Single-photon emission computerized tomography (SPECT) showed global cortical hypoperfusion of left parietal predominance (Supplemental Fig. 1).

The diagnosis of cognitive multidomain dementia associated with spastic paraparesis of probable neurodegenerative etiology was established.

In another visit, her mother revealed that the patient's aunt on her paternal side (Fig. 1, II.6) had presented with a

similar deterioration, and the patient's father (Fig. 1, II.2) had also developed a rapidly evolving process of gait disturbance in his fifties, a few years after suffering a traumatic brain injury, until he died. The patient has one sister, 8 years younger, who was asymptomatic at that time.

In the following years, she experienced a progressive worsening both in cognition as well as in motor skills and behavior. Besides, she lost the ability to walk about 8 years after the onset of symptoms. The last neurological examination carried out showed mutism, spastic tetraparesis predominantly in the lower and left limbs with a dystonic hand (fisting posture with wrist flexion), stereotypical movements with upper limbs, axial rigidity, and supranuclear ophthalmoparesis.

Currently, she is institutionalized in a bedridden situation with advanced dementia (GDS score 7).

Patient III.5

Patient III.4's sister consulted neurology at the age of 44 for memory difficulties. Her mother said that she often repeated questions, forgot details, and needed a shopping list for a year, although she was independent in her daily activities and took care of her sister with dementia.

Neurologic exam revealed mild dysarthria, normal cranial nerves, no oculomotor abnormalities, normal strength and sensation, and normal gait. Neither amyotrophy nor fasciculations were present.

Her MMSE score was 21 of 30 (Supplementary Table 1). Neuropsychological evaluation revealed generalized cognitive difficulties of moderate severity (compatible with a mild dementia state); memory dysfunction was the most prominent feature, with impairment in learning and retaining new information. Language, problem-solving skills, and visuospatial function were also affected. MRI of the brain showed global cortical atrophy. No white matter lesions were found (Supplemental Fig. 1).

A PET-18FDG that revealed a metabolism deficit in the posterior association cortex affecting the temporo-parietal region, including the angular gyrus, of predominantly the left hemisphere, with posterior cingulate cortex involvement. PET-18F-Florbetapir showed elevated amyloid presence in the bilateral frontal, temporal, and parietal cortices; the posterior cingulum; as well as in occipital cortex and caudates.

The patient's cognitive and functional state progressively worsened, with impoverished language, greater dysarthria, and gait unsteadiness. She also developed generalized tonic–clonic seizures 3 years after the onset of symptoms. When she was evaluated last time at 46 years of age, she had prominent dysarthria, non-fluent and anomic aphasia, spastic and wide-based gait and brisk reflexes. In addition, irritability and sleep disturbances had appeared.

Table 1 shows a summary of the patients' characteristics and the clinical findings.

Genetic study

We found the heterozygous c.869–2 A>G substitution in the *PSEN1* gene (NM 000,021.4) in the three patients. This variant is located in the splice acceptor site of exon 9; it causes the exclusion of exon 9 and results in the introduction of a missense change (p.Ser290Cys) at the aberrant exon 8–10 junction [31].

Neuropathological findings

The weight of patient II.6's brain was 997 g. It showed generalized atrophy with moderate ventricular dilatation. A macroscopic infarct was found in the basal side of the temporal lobe with extension to the amygdala and hippocampus. Mild arteriosclerosis was present in the posterior cerebral artery.

Microscopic examination showed that neuronal loss was widespread in the neocortex, with mild superficial spongiosis and frequent large, round, non-cored plaques consistent with CWP. With hematoxylin and eosin staining, they were densely packed throughout all the cortical layers, extending even into subcortical areas like the basal ganglia and brain stem (mesencephalon and pons) (Fig. 2A). From primitive types of AB deposits to neuritic plaques were also observed.

Severe astrogliosis proliferation was found in the frontal cortex and intermixed with macrophages corresponding with the infarct in the temporal lobe.

Amyloid angiopathy affecting meningeal and cortical arterioles were also present in the neocortex, amygdala, and hippocampus. The substantia nigra and locus coeruleus showed loss of neurons and depigmentation. Immunostaining against AB protein was demostrated in CWP, vessels and classic neuritic plaques (Fig. 2B). With Gallyas staining, the CWP were weakly argyrophilic and contain few dystrophic neurites (Fig. 2C). Tau immunostaining showed neuropil threads and neurofibrillary tangles in all the regions studied.

The patient's final neuropathological diagnosis met the criteria for EOAD, based on the actual consensus criteria [32]. The "ABC Score" was A3B3C3: Amyloid plaques were found in brain stem structures (Thal phase 4). Neurofibrillary tangles with p-Tau protein deposits were at Braak VI stage (B3), and according to the CERAD score, the density of plaques were frequent (C3). Cerebral amyloid angiopathy was type 2 (affecting large vessels and capillaries) and stage 2 according to reference criteria [33].

Alpha-synuclein staining revealed numerous neurites and Lewy bodies in mesencephalic structures, abundant in the amygdala and anterior cingulate cortex and to a lesser degree in the frontal and parietal regions (Fig. 2D). This

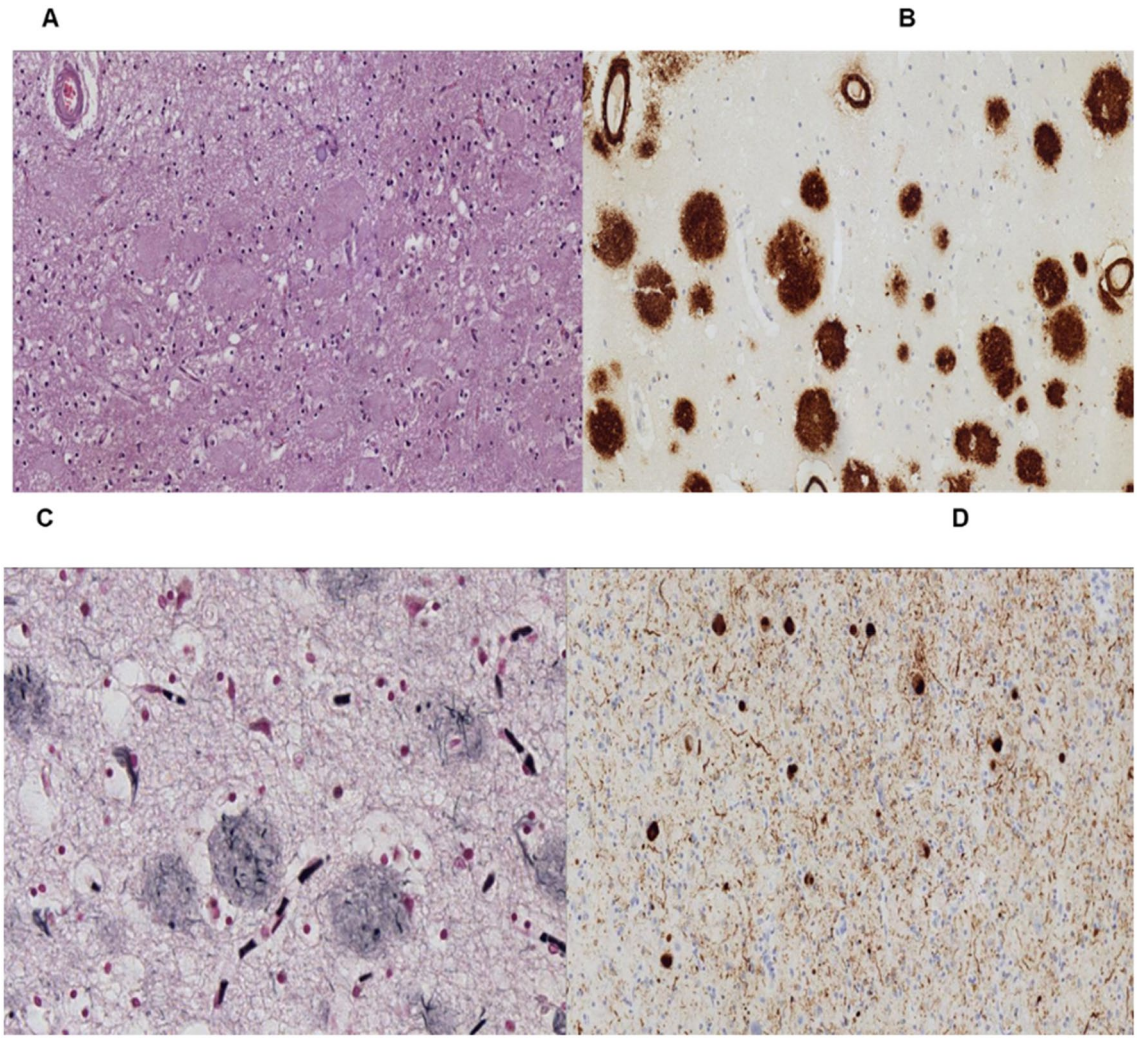

Fig. 2 **A** Wide ball-like parenchymal plaques devoid of a central beta-amyloid (Aβ) core, known as cotton wool plaques (CWP) (hematoxylin and eosin staining, 400×total magnification). **B** Aβ deposits in CWP and vessels (anti-Aβ staining, 400×total magnification). **C** CWP with sparse dystrophic neurites (Gallyas staining, 400×total magnification). **D** Neurites and Lewy bodies in the amygdala (anti-alpha-synuclein staining, 400×total magnification)

concomitant protein deposit met the diagnostic criteria for the diffuse neocortical McKeith category of Lewy body disease [34]. No particular findings were found in the cerebellum, Purkinje cell neurons were preserved, as well as vermis structure and dentate nucleus.

Discussion

We have presented three cases of two generations of the same family with early-onset dementia (38–51 years), with dysarthria and early spastic paraparesis in all of them, and ocular motility involvement in two of them. There is a positive family history in at least a third generation, although it was not possible to obtain genetic confirmation in the latter. The diagnosis of probable ADAD with atypical neurological signs and symptoms was established in all cases based on anamnesis, physical examination, neuropsychological assessment, and structural and functional neuroimaging findings. Diagnosis of ADAD was confirmed by detection of mutation in splice acceptor site of exon 9 of *PSEN1 (*c.869-2 A>G substitution). There is a well-known c.869–1 G>T substitution whose pathological effects on Aβ42 production have been described [35] as well as in other *PSEN1* mutations that lead to the loss of exon 9 [36, 37].

It should be noted that among patients with a *PSEN1* mutation, the most frequent clinical form is isolated progressive amnestic-predominant multidomain cognitive impairment [16]. However, atypical neurological symptoms may be associated, as in the cases presented here, such as spastic paraparesis (asymmetric onset and course as reported in our series is uncommon) [16], myoclonus, cerebellar

Table 1 Summary of main clinical characteristics of the patients

	II.6	III.4	III.5
Sex	Female	Female	Female
Age at symptom onset	51 years	38 years	43 years
First symptom	Leg clumsiness	Amnesic cognitive decline	Amnestic cognitive decline
Follow-up period	10 years	12 years to the present	5 years to the present
Asymmetric paraparesis	Yes	Yes	Yes
Dysarthria	Yes	Yes	Yes
Ophthalmoparesis	Yes	Yes	No
Ataxia	Yes	Yes	No
Dystonia	Yes	Yes	No
Untriggered seizures	No	No	Yes
Brain magnetic resonance	Fronto-parietal cortical atrophy	Fronto-parietal cortical atrophy	Global cortical atrophy
Brain SPECT	Normal	Global cortical hypoperfusion of left parietal predominance	
Brain PET 18FDG			Hypometabolism of the posterior association cortex with posterior cingulate cortex involvement
Brain PET-18F-Florbetapir			Amyloid deposition in frontal, temporal, parietal cortex and posterior cingulum as well as in the occipital cortex and caudates

involvement (cerebellar ataxia), and/or parkinsonism or dystonia [38]. At the time of presentation of spastic paraparesis most, but not all, have previous multidomain cognitive impairment. More infrequently, isolated progressive spastic paraparesis has been reported to exist for more than a decade before the onset of cognitive impairment [39, 40], as may be the case of the of the father of the patients III.4 and III.5. However, the prevalence of spastic paraparesis in ADAD due to *PSEN1* mutations is estimated to be 1–2%, although in mutations that directly affect exon 9 or its splice acceptor site, such as the mutation we describe, the prevalence would be higher, up to 5–6% cases [16, 39]. Nevertheless, the presentation of dysarthria [20] and supranuclear ophthalmoparesis from early stages of the disease, although described, is much rarer, broadening the presenting phenotype of *PSEN1* mutations.

It is not uncommon to have a family history of cognitive impairment and/or movement disorders not studied or of unknown etiology and with an undetermined age of onset. In the consultation for the study of cognitive impairment, it is common to collect information on family history of neurodegenerative dementias and their age of onset, but it is less common to ask for detailed information regarding atypical features in the clinical course (late-onset seizures, motor disorders, etc.). The presented case series not only reflects the frequency of atypical symptoms, but also the variability in the clinical presentation of a mutation in the same family. ADAD is clearly an underdiagnosed entity. If the anamnesis of the family history were to be extended, it is likely that more cases would be detected that suggest a diagnosis of ADAD with atypical features, and a genetic diagnosis could be made during life. In addition, advances in the neuropathological phenotyping of each mutation are crucial to understand the variability of clinical presentation and to deepen the knowledge about the pathophysiology of the disease.

The *PSEN1* c.869-2 A>G mutation was first described in a 46-year-old female with EOAD without a family history, and then in a 48-year-old German patient with a clinical presentation similar to frontotemporal dementia [31]. In both cases, prominent and early aphasia with agrammatism and visuoconstructive disturbance and dyscalculia were described in addition to significant amnesic affectation. In other cases reported in China for this specific mutation, there was no association with asymmetric paraparesis and ophthalmoparesis or higher risk of epileptic seizures during either the early stages or progression of the disease [41]. Hence, we believe we have presented an infrequent mutation with a different phenotype relative to previously published cases for this specific mutation. In our knowledge, we have made the first anatomopathological description of this mutation.

Structural neuroimaging (MRI) findings with mild cerebellar atrophy [8] present from the early stages are also congruent with what has been previously described. The presence of cerebellar atrophy is not necessarily associated with cerebellar ataxia, as has occurred in our cases. In the case of our patients the MRI wasn't able to detect

the expected hippocampal atrophy, the most frequent radiological sign in ADAD as well as in late-onset sporadic AD [42]. In our patients, the MRI findings showed a relatively symmetrical diffuse atrophy with comparatively less involvement of the occipital cortex at the time of MRI. Perhaps this can be explained, at least partially, by the fact that in our patients the visuospatial symptomatology was less relevant than in other cases of *PSEN1* mutations and the obtention of the images in late stages of the disease (diffuse symmetrical cortico-subcortical atrophy reflecting congruent with multidomain dementia). In turn, the PET-18FDG and PET-18F-Florbetapir findings had already been reported in other cases of *PSEN1* mutation, with frequent amyloid deposition predominantly in the occipital region and in the striatum [20].

Neuropathological studies in ADAD have also described greater levels of amyloid angiopathy compared with sporadic AD [26, 29] and higher frequency of Lewy body pathology (LBD) [26, 28], like in patient II.6. Except for a higher proportion of amyloid angiopathy in *PSEN1* mutations beyond codon 200, as in patient II.6, there do not seem to be major variations between different mutations affecting *PSEN1* [26]. In addition LBD co-pathology in EOAD seems to be more frequent in *PSEN1* mutations, especially in limbic regions [28, 43, 44], but also has been described in neocortical regions and brainstem [19]. It has been suggested that the coexistence of LBD could be related, as in our case, to a higher probability of presenting extrapyramidal symptoms [45, 46]. A variable distribution of alpha-synuclein, but mainly cortical diffuse stages, could have an impact on the duration of the disease [28, 46, 47]. The coexistence of amyloid angiopathy and LBD might not only influence the duration of the disease; it might also affect the speed of progression and the probability of developing atypical symptoms. It has been suggested that a large deposit of CWPs at basal ganglia and a rarefaction, a significant loss of neurons and depigmentation of substantia nigra could be more frequent in those patients with *PSEN1* mutations with extrapyramidal symptoms [16] such as our case with focal upper limb dystonia. On the other hand, it should be noted that in the autopsy of the patient II.6 with gait ataxia at last stages of the disease, no significant damage to Purkinje cells or to the vermian structure or to dentate nucleus was detected, unlike what was reported in other *PSEN1* mutations that occur with ataxia [16].

Conclusions

PSEN1 mutations are the leading cause of ADAD. Their clinical phenotype is extremely variable even in the case of a specific mutation and within the same family. Atypical neurological features can appear even before the cognitive decline. Hence, a proper and extensive familial anamnesis is also essential for the improvement of the capacity of an early and accurate diagnosis of these patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-022-11125-8.

Funding MA declares funding from the Instituto Carlos III of the Spanish government through the Río Hortega grant (CM19/00066). The rest of the authors do not declare any source of funding relevant to this work. All the authors declare not to have financial or non-financial interests that are directly or indirectly related to this work.

Declarations

Conflicts of interest None of the authors declare any conflict of interest.

Ethical standards The patients included in this study signed the corresponding informed consent form approved by the ethics committee of the University Hospital of Navarra. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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