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CASE REPORT

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Young-onset Alzheimer's dementia mimicking progressive myoclonic epilepsy spectrum

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Abstract

Background Young-onset Alzheimer's dementia (YOAD) refers to the onset of disease before the age of 40 years. Classical AD typically presents with memory impairment with involvement of other cognitive domains like language, visuospatial orientation. On contrary, YOAD shows phenotypic heterogeneity in the form of predominant psychiatric disturbances apart from dementia and rarely seizures, cerebellar ataxia. We report a 36-year-old lady with dementia, myoclonus, seizures and cerebellar ataxia of 3 year duration mimicking progressive myoclonic epilepsy (PME) spectrum who had novel missense mutation in *PSEN1* gene (L226F) suggestive of YOAD.

Case presentation A 36-year-old lady presented with seizures in the form of generalized tonic–clonic seizures of 3 year duration followed by multifocal myoclonic jerks, cognitive decline of 2 year duration and imbalance while walking of 1 year duration. Montreal cognitive assessment (MOCA) score was 6/30. Addenbrooke's cognitive examination III (ACE-III) score was 16/100. The mental status examination showed diffuse impairment of lobar functions. Brain magnetic resonance imaging showed diffuse cerebral and cerebellar atrophy. Skin biopsy did not show Lafora bodies or dermal inclusions on electron microscopy. Whole exome sequencing showed pathogenic missense variant NM_000021.4(PSEN1):c.676C > T (p.Leu226Phe) in *PSEN1* gene suggestive of YOAD.

Conclusions YOAD due to *PSEN1* mutation has to be considered in patients with cerebellar ataxia, seizures, myoclonus, dementia with psychiatric disturbances. This case highlights the high index of suspicion for differential diagnosis of YOAD in patients with young-onset dementia with ataxia, seizures and myoclonus.

Background

Early onset Alzheimer's disease (EOAD) refers to the onset of AD before 65 years of age and young-onset AD (YOAD) before the age of 40 years. EOAD constitutes about 5–15% of AD cases. *PSEN1* gene mutations is one of the genes associated with EOAD/YOAD and are commonly inherited in an autosomal dominant manner, but de novo mutations also have been described [1]. There are more than 200 reported PSEN1 mutations. EOAD due to PSEN1 mutations show phenotypic heterogeneity [2]. Hereby, we report a 36-year-old lady with dementia, myoclonus, seizures and cerebellar ataxia of 3 year duration mimicking progressive myoclonic epilepsy (PME) spectrum. The other possibility was autoimmune epilepsy/ dementia. Whole exome sequencing showed a novel missense mutation in *PSEN1* gene (L226F). Alzheimer's disease (AD) is a progressive degenerative disease characterized by the progressive loss of memory and disturbance of additional cognitive functions namely word-finding, spatial cognition, reasoning, judgment, and problem solving. It is a common cause of dementia in elderly. There are three genes involved in EOAD/

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YOAD namely amyloid precursor protein (APP) on chromosome 21, presenilin 1 (PSEN1) on chromosome 14, and presenilin 2 (PSEN2) on chromosome 1. PSEN1 gene mutation constitute about 18–50% cases of EOAD. PSEN1 is a component of γ-secretase responsible for APP cleavage and the mutations alters the secretase activity of γ-secretase and increase the ratio of $A\beta_{42}$ to $A\beta_{40}$ [3]. Patients with PSEN1 mutation have phenotypic heterogeneity apart from the common presentation of dementia. These include psychiatric symptoms, such as apathy, depression, psychosis, and disinhibition, parkinsonism, myoclonus, seizures, spastic paraparesis and dystonia. Snider et al. reported three family members with young-onset dementia who had mutation (S170F) in exon 6 of the *PSEN1* gene. Patients had seizures with myoclonus along with dementia [3]. Similarly, Piccini A et al. reported a young male patient with *PSEN1* mutation (S170F) who presented with psychiatric disturbances, ataxia, myoclonus and dementia [4]. We describe a young female patient who had seizures, myoclonus, cerebellar ataxia and dementia. She had a novel mutation in *PSEN1* gene (L226F) with confirmation on Sanger sequencing. *PSEN1* L226F is a known pathogenic mutation discovered in European EOAD patients. The reported phenotype with this mutation is fronto-temporal dementia [5]. But ataxia, myoclonus, seizures have not been reported with *PSEN1* L226F mutation.

Case presentation

A 36-year-old lady presented with seizures of 3 year duration followed by myoclonic jerks, cognitive decline of 2 year duration and imbalance while walking of 1 year duration. The symptoms started with seizures which was of generalized tonic–clonic type. The frequency was 2–3 episodes per month. For the same, she was started on recommended dose of levetiracetam (1 g/day) and frequency reduced to 1 episode every 3–4 months. One year later, she started having intermittent, multifocal myoclonic jerks which was stimulus sensitive (auditory) and cognitive decline. The cognitive domain primarily involved was memory, execution, language. She had impairment in episodic and semantic memory, developed executive dysfunction requiring help for all her activities of daily living. Her speech output had reduced and difficulty in comprehension. One year later, she had difficulty in walking in the form of imbalance with no diurnal variation. She had mild upper limb incoordination. Her paternal aunt had history of psychiatric disturbances at the age of around 35 years. Systemic examination was unremarkable. Neurological examination showed poor orientation to time, place and person, lack of insight. Montreal cognitive assessment (MOCA) score of 6/30. Addenbrooke's cognitive examination III (ACE-III) score of 16/100. The mental status examination showed diffuse impairment of lobar functions. There was mild ataxic dysarthria. Fundus and cranial nerves examination was normal. Motor examination showed reduced tone, normal muscle power and brisk deep tendon reflexes. Sensory examination was normal. There were intermittent, multifocal myoclonic jerks. There was mild finger–nose incoordination with dysdiadochokinesia, impaired knee–heel coordination and wide-based ataxic gait. Plantar responses were mute. In view of seizures, myoclonic jerks and dementia, a possibility of progressive myoclonic epilepsy was considered. Complete hemogram, renal, hepatic and thyroid function tests were normal.

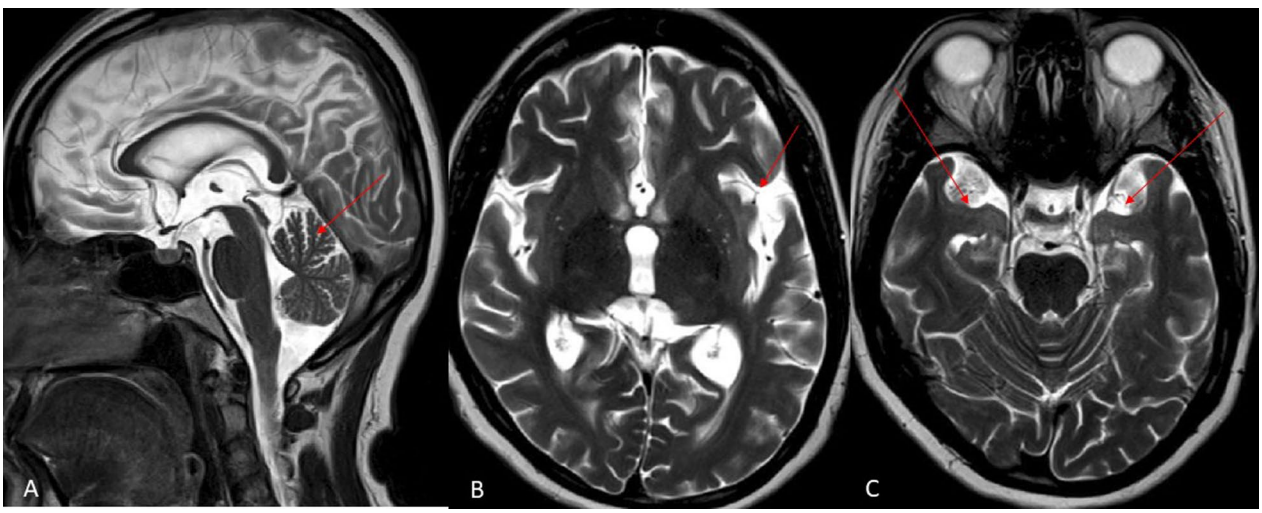

Fig. 1 Brain MRI (**A**) sagittal T2-weighted image shows cerebellar atrophy (red arrow); **B** axial T2-weighted image shows widening of sylvian fissure (red arrow); **C** axial T2-weighted image shows bilateral antero-medial temporal lobe atrophy (red arrows)

Serological test for human immunodeficiency virus and syphilis were negative. Serum and cerebrospinal fluid autoimmune antibodies profile (NMDA, AMPA, LGI1, CASPR2, GAD, GABA-A and B, amphiphysin, DPPX1, IGLON5, mGluR5) were negative. Electroencephalogram showing mild diffuse slowing of background rhythm in the theta range with no triphasic waves. Brain magnetic resonance imaging showed diffuse cerebral and cerebellar atrophy (Fig. 1). Skin biopsy did not show Lafora bodies or dermal inclusions on electron microscopy. Whole exome sequencing showed missense variant NM_000021.4(PSEN1):c.676C > T (p.Leu226Phe) in *PSEN1* gene. The gene *PSEN1* has a low rate of benign missense variation as indicated by a high missense variants Z-score of 2.16. It contains 79 pathogenic missense variants, indicating that missense variants are a common mechanism of disease in this gene. The p.Leu226Phe missense variant is predicted to be damaging by both SIFT and PolyPhen2. The clinical phenotype of the proband matched with that of the disorder caused by pathogenic variants in *PSEN1* gene. This variant was classified as Pathogenic. She was started on clonazepam (1 mg/day) with donepezil (10 mg/day) and continuation of levetiracetam. She was started on cognitive rehabilitative exercises and balance training.

Conclusion

YOAD due to *PSEN1* mutation have shown phenotypic heterogeneity. This has to be considered in patients who presents with cerebellar ataxia, seizures, myoclonus, dementia with psychiatric disturbances. This case highlights the high index of suspicion for differential diagnosis of YOAD in patients with young-onset dementia with ataxia, seizures and myoclonus.

Abbreviations

PSEN1	Presenilin 1
YOAD	Young-onset Alzheimer's dementia
EOAD	Early onset Alzheimer's dementia

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RRM: design of study, acquisition, analysis, interpretation of data, approval of final draft of manuscript. GA: genetic analysis, acquisition of data, writing of first draft of manuscript. DD, VC, HP: interpretation of data, approval of final draft of manuscript.

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There are no competing interests.

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