


Case of early-onset Alzheimer's disease with atypical manifestation

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To cite: Zhu L, Sun L, Sun L, et al. Case of early-onset Alzheimer's disease with atypical manifestation. *General Psychiatry* 2021;**34**:e100283. doi:10.1136/gpsych-2020-100283

Received 16 May 2020
Revised 08 September 2020
Accepted 13 December 2020

ABSTRACT

Short-term memory decline is the typical clinical manifestation of Alzheimer's disease (AD). However, early-onset AD usually has atypical symptoms and may get misdiagnosed. In the present case study, we reported a patient who experienced symptoms of memory loss with progressive non-fluent aphasia accompanied by gradual social withdrawal. He did not meet the diagnostic criteria of AD based on the clinical manifestation and brain MRI. However, his cerebrospinal fluid examination showed a decreased level of beta-amyloid 42, and increased total tau and phosphorylated tau. Massive amyloid β -protein deposition by 11C-Pittsburgh positron emission tomography confirmed the diagnosis of frontal variant AD. This case indicated that early-onset AD may have progressive non-fluent aphasia as the core manifestation. The combination of individual and precision diagnosis would be beneficial for similar cases.

INTRODUCTION

CLINICAL REPORT AND METHODS

Early-onset Alzheimer's disease (EOAD), which comprises 5% of Alzheimer's disease (AD), shows a 1.6-year average delay in diagnosis compared with late-onset AD.^{1,2} The clinical phenotype of atypical EOAD is heterogeneous, and primary progressive aphasia (PPA) is rarely the initial manifestation of related dementia syndromes. Compared with the progressive non-fluent aphasia (PNFA) related to the language variant phenotype of frontotemporal lobar degeneration (FTLD), molecular imaging studies in patients with primary progressive aphasia suggest the pathological basis of AD.³ Neurodegeneration usually starts in a specific neural anatomic networks. The clinical phenotype of PPA can usually infer the type of protein degeneration, which can be used to infer gene mutation. With the development of biomarkers such as genetics, molecular biology, neuroimaging and positron emission tomography (PET), accurate diagnosis can be gradually achieved. In this case study, we describe an AD patient with PNFA as the first symptom.

The patient was a 63-year-old married man, a right-handed businessman, native of

Shanghai, with 12 years of school education. He has memory loss and non-fluent speech for 7 years combined with personality changes for 5 years. The patient recovered from hepatitis A 32 years ago and has well-controlled hypertension for 30 years.

The patient's caregiver described that the patient showed forgetfulness and developed poor pronunciation at the age of 56. His short-term memory has gradually declined as noticed that he repeatedly gave money to customers while selling clothes. He frequently forgot where he parked his bicycle, and it was hard for him to speak a full sentence; his language was vague and short. He was impatient when being asked to repeat a word. Over time, he could only say some single syllables. He evolved into fully aphasia gradually, and his personality also changed gradually. At the age of 59, he could not recognise himself in the mirror and he often hid his shoes because he was worried that they would be stolen. Therefore, his wife had accompanied him to see a neurologist. The physical and neurological examination revealed no remarkable signs. His brain MRI showed mild atrophy in the bilateral frontal lobe ([figure 1A](#) at the age of 59). Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed that glucose metabolism in the bilateral frontal and parietal lobe was declined, and the left side was significant ([figure 1B](#) at the age of 59). The Mini-Mental State Examination (MMSE) score was 18 out of 30 (18/30). At that point, he was diagnosed with cognitive impairment and treated with rivastigmine. After the treatment, his memory improved slightly. In 2017, the neurologist gave him quetiapine and donepezil due to developing visual hallucinations and irritability. The second brain MRI scan revealed increased frontal and temporal atrophy compared with the first one ([figure 1C](#) at the age of 61). The FDG-PET revealed that the cerebral cortical glucose metabolism was further reduced, especially the bilateral frontal and parietal lobes were obvious ([figure 1D](#) at the age of 61).



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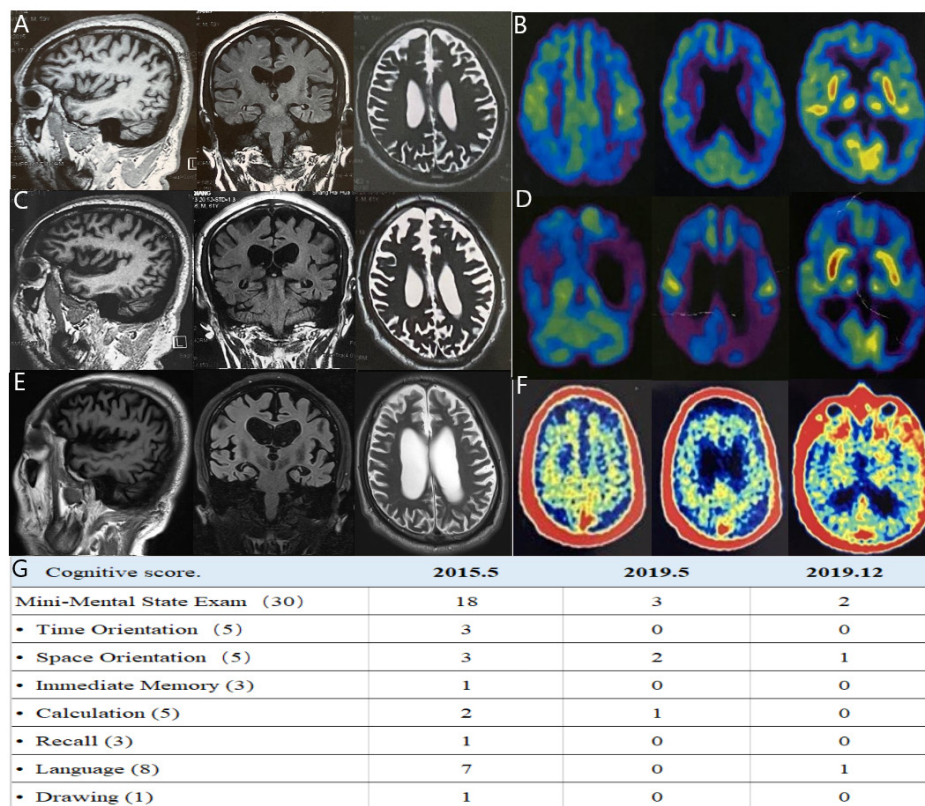


Figure 1 Brain imaging and cognitive score of the patient. (A) The patient's MRI in May 2015 revealed mild atrophy of the bilateral frontal lobe (at the age of 59). (B) The patient's FDG-PET in May 2015 revealed that glucose metabolism in the bilateral frontal and parietal lobe was reduced, and the left side was significant (at the age of 59). (C) The patient's MRI in July 2017 (2 years after the first scan), revealed more atrophy of the bilateral frontal lobe and temporal lobe atrophy occurred (at the age of 61). (D) The patient's FDG-PET in August 2017 revealed that the cerebral cortical glucose metabolism was reduced more, bilateral frontal and parietal lobes obvious in particular (at the age of 61). (E) The patient's third MRI in May 2019 (2 years after the second scan) revealed atrophy of the whole cerebral cortex with bilateral frontal lobes, temporal lobe and hippocampus more affected (at the age of 63). (F) The patient's 11C-PIB PET in May 2019 revealed saliently amyloid deposition in diffuse cortical areas, particularly in the bilateral frontal, parietal, temporal cortices and posterior cingulated gyrus (at the age of 63). (G) Mini-Mental State Examination (MMSE) of the patient. MMSE in May 2015 revealed a total score was 18/30 (at the age of 59). MMSE in May and December 2019 revealed a total score were 3/30 and 2/30; the results showed severe impairments in language and other cognitive areas (at the age of 63). 11C-PIB PET, 11C-Pittsburgh compound B positron emission tomography; FDG-PET, fluorodeoxyglucose positron emission tomography.

In May 2019, the patient's symptoms aggravated further, which included bad temper, crying often and being more difficult to be looked after. His wife brought him to seek help from a psychiatrist, and he was admitted into the Department of Geriatric Psychiatry of Shanghai Mental Health Center. He underwent routine laboratory tests to exclude non-neurodegenerative and dementia. His neurological examination showed gait abnormality, negative Babinski's sign, muscular tension hyperactivity, knee jerk reflex hyperactivity and a weak positive right palmar jaw reflex. The MMSE score was 3/30. The patient exhibited severe impairments in orientation (2/10), attention and calculation (1/5), recall (0/6), language (0/8) and visual construction (0/1). The Montreal Cognitive Assessment score was 0 (0/30), which was significantly lower than it was in 2015 (figure 1G). The third brain MRI demonstrated atrophy of the cerebral cortex, especially in the bilateral frontal lobes and hippocampus. The medial temporal lobe atrophy scale was at grade 3 (figure 1E at the age of 63).

In addition, we tested three pathogenic genes for early-onset AD including amyloid precursor protein, presenilin-1, presenilin-2 genes related to neurocognitive disorders, but no mutation was found. Apolipoprotein E (APOE) genotyping showed APOE $\epsilon 3/\epsilon 3$ type. In order to reach a definite diagnosis, the patient underwent 11C-Pittsburgh compound B positron emission tomography (11C-PIB PET) and cerebrospinal fluid (CSF) examination. 11C-PIB PET revealed noticeable amyloid deposition in diffuse cortical areas, particularly in the bilateral frontal, parietal, temporal cortices and posterior cingulated gyrus (figure 1F at the age of 63). The measured CSF biomarkers showed decreased amyloid β -protein ($A\beta$) 42 (462 pg/ml; cut-off >562 pg/ml), increased total tau (754 pg/ml; cut-off <370 pg/ml) and increased phosphorylated tau (87.40 pg/ml; cut-off <66.26 pg/ml). Eventually, the diagnosis of frontal variant EOAD was reconfirmed considering the early onset of dementia, the slow progression of symptoms, the absence of focal

neurological damage signs and the exclusion of other systemic or brain diseases that could cause dementia. Due to the gastrointestinal adverse reactions of the patient, rivastigmine was suspended. We used memantine 10 mg b.i.d. and donepezil 5 mg q.d. to improve cognition and to control psychobehavioural symptoms and vortioxetine 10 mg q.d. to improve mood. After the treatment and follow-up for 7 months, the patient's behaviour and mood was improved significantly, and his language expression improved slightly (figure 1G at the age of 63).

DISCUSSION

The initial clinical manifestations of the patient included short-term memory decline, poor pronunciation and personality changes at an early stage, followed by behavioural and psychological symptoms of dementia, including hallucinations, delusions of theft, gradual decline in self-care as well as depression. The patient's brain MRI initially showed mild atrophy of the bilateral frontal lobe. With the progress of the disease, more severe atrophy of the cerebral cortex, temporal lobe and hippocampus appeared besides the further atrophy of the bilateral frontal lobe. The atypical manifestation such as early aphasia, frontal lobe atrophy and personality changes can mislead clinicians in diagnosing frontotemporal lobar degeneration. This is the main reason leading to the misdiagnosis of this patient, which should be taken as a lesson or future reference for clinicians.

According to the current classification schemes, the clinical symptoms were in line with PNFA, which are halting speech by speech sound errors with spared content word comprehension and atrophy of the left frontal lobe.⁴ PNFA is one of the primary progressive aphasia.⁴ This patient met the diagnostic criteria of frontotemporal dementia, consistent with the early personality changes and cognitive abnormalities.⁵ In the past 7 years, the patient's speech fluency and cognitive function decreased continuously and rapidly. The clinical manifestations could not be explained by typical AD. The CSF phosphorylated tau was slightly higher, and no gene mutations associated with AD were found, which further made it harder to reach the diagnosis. However, the 11C-PIB PET showed heavy and extensive A β -amyloid depositions and provided definite pathological evidence of AD. A retrospective study found PNFA with 13%–31% of cases might have the pathology of AD.⁶ The patient met the research diagnostic AT(N) framework of AD, with A: (11C-PIB PET revealed amyloid depositions, CSF A β 42 decreased), T: (CSF phosphorylated microtubule-associated protein tau increased) and N: (cortical atrophy on MRI, glucose hypometabolism in the bilateral frontal parietal lobe and CSF total microtubule-associated protein tau increased).⁷ We use the AD pathological markers as the gold standard to exclude other types of dementia and reach an earlier and more accurate diagnosis. It's worth pointing out that the patient might have mixed neuropathology. Santos-Santos⁶ found that 75% of PNFA or PPA cases may have mixed pathological changes of FTLN and

AD. This poses a new challenge for clinicians, suggesting that verified, reliable and accessible biomarkers for diagnosis of FTLN should be developed urgently. Otherwise, the comorbid pathological cases would only be accurately diagnosed after autopsy.

After reaching a clear diagnosis, and according to the China guidelines for the diagnosis and treatment of dementia and cognitive impairment in 2018 and the guidelines for the diagnosis and treatment of AD,⁸ the patient was treated with cholinesterase inhibitors and excitatory amino acid receptor antagonists to enhance cognition, and antidepressants were given to relieve his mood. After the treatment, the patient's symptoms were improved, and his mood was stable. Additionally, the biopsychosocial medical model has become more and more accepted. We should treat the patients with medication and non-drug intervention for patients and their caregivers. Spouses and caregivers of patients with early-onset dementia bear a greater burden and higher depression rates.⁹ The speech impairments of this patient appeared early. He was emotionally unstable, grumpy and easy to be tearful, which was alleviated when his wife comforted him. Two weeks later, he was released from the hospital and continued to receive comprehensive rehabilitation treatments. Anyway, providing individualised psychosocial support for patients and their caregivers is very important for improving symptoms and quality of life.¹⁰

CONCLUSION

Some of PNFA are due to the underlying pathology of AD, which is more common in EOAD. In the present case, neither clinical examination nor MRI could definitively differentiate FTLN from EOAD. According to AT(N) research framework, we could eventually confirm the neuropathology diagnosis of AD or frontal-variant AD (fvAD), but the previous misdiagnoses were significant. FvAD can lead to social withdrawal and depression. These patients should benefit from accurate diagnosis, medication treatment and individualised psychosocial intervention.

Contributors LZ drafted the case report and manuscript; LMS performed the literature search; LS and SX supervised and revised the manuscript. All authors approved the final manuscript.

Funding This study was supported by a grant of Clinical Research Centre Project of Shanghai Mental Health Centre (CRC2017ZD02) and Scientific Research Program of Shanghai Jing an District Health Committee (2020MS16).

Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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