CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Case of Autosomal Dominant Alzheimer Disease With Negative Findings From PiB-PET Examination

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Neurol Genet 2024;10:e200119. doi:10.1212/NXG.0000000000200119

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Abstract

Background and Objectives

This study reports an uncommon case of autosomal dominant Alzheimer disease (AD) with negative PiB-PET findings.

Methods

A 55-year-old woman was admitted to the hospital due to a progressive cognitive decline for over 9 years, along with a possible dementia family history. The patient underwent routine laboratory tests, neuropsychological assessments, and neuroimaging examinations. Additionally, the cerebrospinal fluid sample was analyzed for AD biomarkers using the Single Molecular Array (Simoa) technique. A targeted Next-Generation-Sequencing (NGS) panel screening was also conducted.

Results

Routine blood and CSF laboratory tests, as well as CSF tap test, yielded negative results. Cranial MRI showed atrophy of the whole brain. PiB-PET scanning indicated that PiB was merely retained in her brain with an overall standard uptake value ratio (SUVR) <1.0. Simoa analysis showed an increase in the level of CSF t-tau and a decrease in that of CSF Aβ42. NGS panel screening detected a c.G2032A (p.D678N) heterozygous mutation in APP. Consequently, the patient was diagnosed with autosomal dominant AD.

Discussion

We have reported an uncommon case of autosomal dominant AD carrying p.D678N variant in APP with negative PiB-PET results. The diagnosis of AD should not be directly excluded solely based on the negative PiB-PET results.

Introduction

Alzheimer disease (AD) is a neurodegenerative disease characterized by progressive cognitive impairment. Senile plaques formed by β-amyloid (Aβ) deposition and neurofibrillary tangles consisting of tau protein aggregation were the 2 pathologic features of AD. PET imaging with the ^{11}C-labeled Pittsburgh compound B (PiB) can visualize Aβ aggregates in the brain of patients with AD[1] and has been widely used in the diagnosis of AD and the evaluation of Aβ clearance in clinical trials. We present here an uncommon case of autosomal dominant AD with negative PiB-PET findings, probably due to the specific genetic variant the patient carries.

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Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the Natural Science Foundation of Chongqing, China (2023NSCQ-MSX0204).

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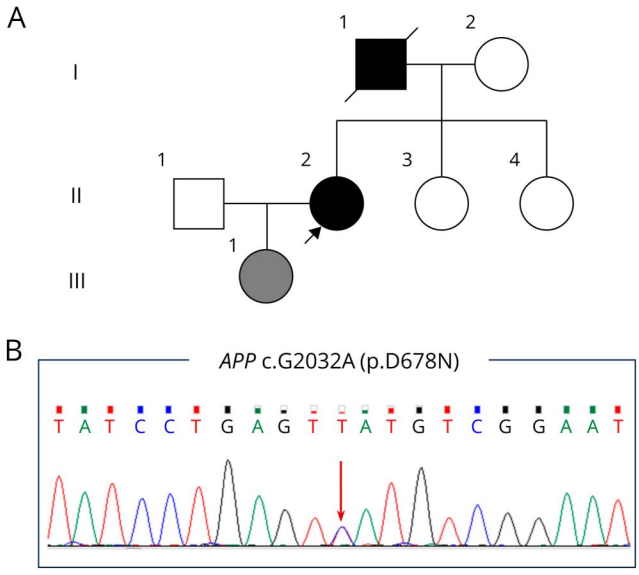
Figure 1 Pedigree Chart of the Patient (A) and the Sequencing Chromatogram (B) of the *APP* Variant (p.D678N)



(A) In the pedigree chart, the proband (II-2) was indicated with the black arrow. Her father (I-1) also experienced suspected dementia before death, and her daughter (III-1), who was indicated as the gray circle, has a 50% risk of carrying p.D678N variant. (B) Due to the use of reverse sequencing, the peak plot results showed c.C2032T variant instead of c.G2032A variant in the reverse complementary sequence.

Case Report

A 55-year-old woman was admitted to our hospital with a progressive cognitive decline for a period of over 9 years. The patient was initially found to be reluctant to engage in social activities, accompanied by diminished interest and impairment in recent memory. At that time, these symptoms were mild and did not affect her life, which led to no health-seeking behavior. Four years ago, her cognitive impairment significantly exacerbated, and she could not continue her former job. Besides, there were occasionally inappropriate behaviors in public places, such as the attempt to undress her skirt and underwear. Two years ago, she began to experience hypologia and difficulties in semantic understanding, finally resulting in an inability to take care of herself in daily life. The patient was previously diagnosed with "dementia" multiple times in other hospitals, but the cause remained unknown. And her symptoms continued to worsen after symptomatic treatment (not clearly defined). It was worth noting that her father also experienced "dementia" before death, but did not receive any treatment or examination in a hospital. Conversely, her mother and 2 younger sisters do not have similar clinical manifestations. Her spouse and the only daughter had no comparable symptoms at the present age (Figure 1A). No other special medical histories were found.

Through physical examination, it was found that the patient's alertness was impaired. She could only speak monosyllabic words along with severe cognition decline, and she could not complete basic neuropsychological scale assessments (e.g., MMSE, MoCA, etc). She was slow in walking and turning, without any signs of parkinsonism, such as rigidity, bradykinesia, or tremor. There was no other notable abnormality of cranial nerves. Cranial MRI showed atrophy of the whole brain, especially in the cortex and hippocampus. The CSF tap test yielded negative results. The CSF level of t-tau was 526.79 pg/mL (cutoff value = 313 pg/mL),[2] and those of Aβ42 (cutoff value = 933 pg/mL)[2] and Aβ40 were 143.13 pg/mL and 5,290.35 pg/mL, respectively. Next-generation sequencing panel screening was performed because of the early onset age and potential family history of dementia, revealing a c.G2032A (p.D678N) heterozygous mutation in the *APP* gene (Figure 1B). The abovementioned evidence supported the diagnosis of autosomal dominant AD. Surprisingly, the PiB-PET scan indicated that PiB was merely retained in the bilateral frontal lobe, parietal lobe, temporal lobe, occipital lobe, and basal ganglia with an overall standard uptake value ratio (SUVR) < 1.0 (cerebral SUVmax 0.76–0.91, cerebellar SUVmax 1.10, cerebellum as the reference region, see Figure 2), which seemed to be inconsistent with common manifestations of familial AD showing obvious PiB retention in the striatum and cortex.[3] The PiB retention of the patient was further quantified using the Centiloid scale with CapAIBL.[4] And the PET quantification report also indicated a low amyloid burden, with 0.73 for global cerebral SUVR and −32.46 for the Centiloid.

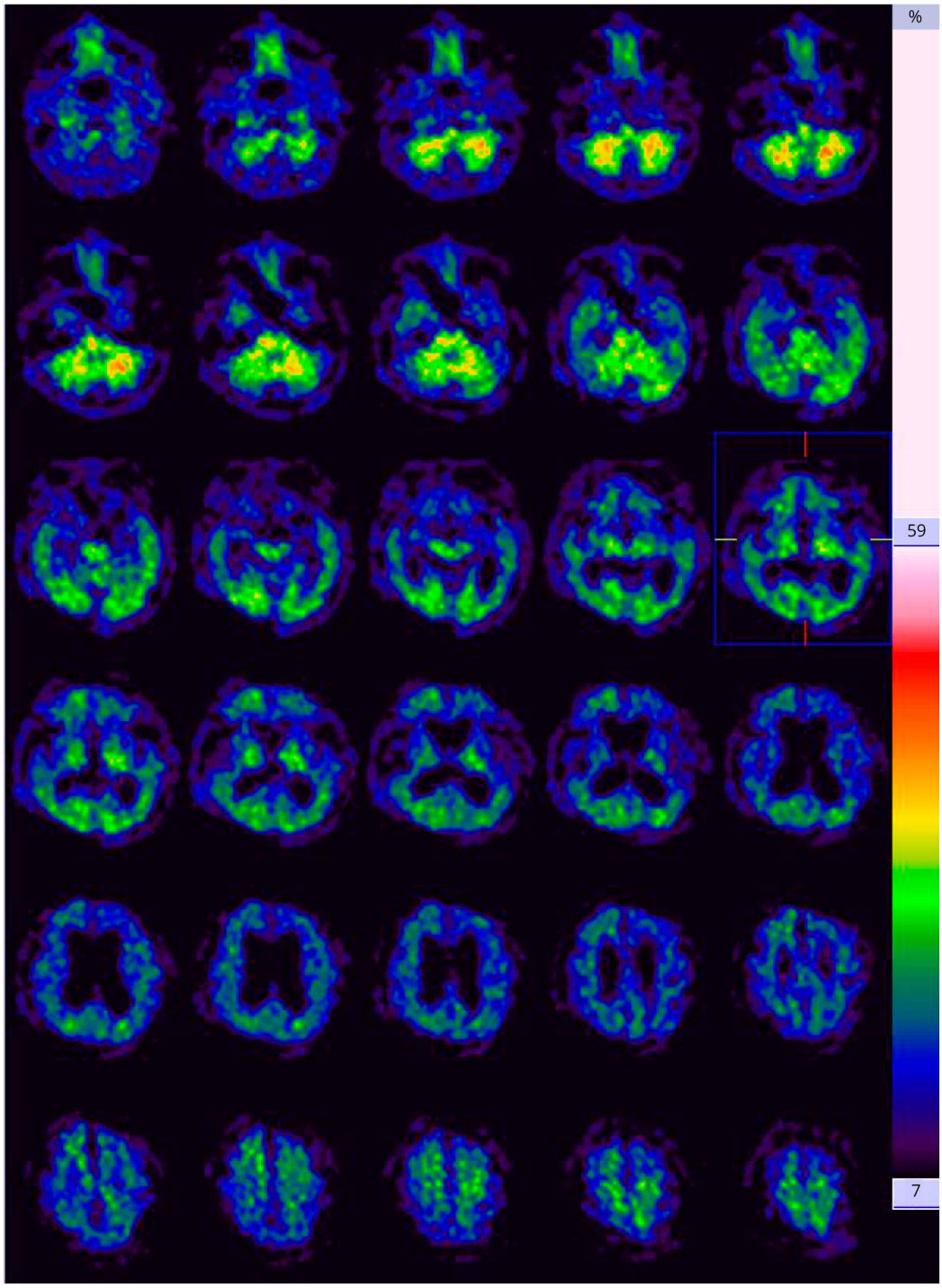
The patient was then treated with memantine, 10 mg qd, plus donepezil hydrochloride, 5 mg qn. She was only slightly improved in emotional state at discharge. Six months after discharge, a brief telephone follow-up was conducted with the patient's spouse. It was found that the patient's speech ability and cognitive function continued to decline.

Discussion

Families with *APP* mutations were first identified in 1911, and the amyloid hypothesis remains the dominant paradigm in autosomal dominant AD research.[5] It was reported that the *APP* variants account for 15%–20% of all known pathogenic variants for familial AD, and most of them are nonsynonymous within or flanking the Aβ sequence.[3,6] The pathogenic variant c.G2032A (p.D678N) in *APP* was first identified in a pedigree from Japan in 2004[7] and was recently reported in a pedigree from mainland China in 2020.[8] However, PiB-PET examinations were neither performed for the 2 probands nor their affected relatives.

There have been only 2 pathogenic variants of autosomal dominant AD that may cause negative PiB-PET results to date. Among them, patients carrying the variant p.E693G in *APP* may have cognitive impairment, decreased levels of Aβ42, and increased levels of p-tau in the CSF, without obvious PiB retention in the brain.[9] Meanwhile, the variant

Figure 2 PiB-PET Images of the Patient Showed Negative Results



The PiB-PET scan indicated that PiB was merely retained in the bilateral frontal lobe, parietal lobe, temporal lobe, occipital lobe, and basal ganglia (SUVmax 0.76–0.91, cerebellar SUVmax 1.10), with an overall SUVR <1.0. The color ranging from red (warm color) to purple (cold color) represents the standard uptake value ranging from high to low. The "%" in the color bar indicates the "brightness level" of the image. PiB = ^{11}C-labeled Pittsburgh compound B; SUV = standard uptake value; SUVR = standard uptake value ratio.

p.E693Δ in *APP* can also lead to excessive production of Aβ oligomers without causing significant PiB retention in the brain.[10] Therefore, this small group of patients with autosomal dominant AD carrying specific gene variants deserves attention due to the "false-negative" PiB-PET results.

The p.D678N variant leads to the change from aspartic acid (Asp) to asparagine (Asn) at the 7th position of the Aβ protein. Previous studies have demonstrated that synthetic Asn7-Aβ will affect Aβ fibril formation and initial α-helical structure formation,[7] without affecting Aβ overproduction in

vitro.[11] Therefore, we speculate that the variant may affect the conformation structure or deposition amount of the Aβ fibrils, leading to low PiB retention in the brain.

In summary, we have reported an uncommon case of autosomal dominant AD carrying the c.G2032A (p.D678N) variant in *APP* with negative PiB-PET results. The pattern of PiB retention may vary in patients with autosomal dominant AD carrying different pathogenic gene variants, and the diagnosis of AD should not be directly excluded solely based on the negative PiB-PET results, especially in a group of patients with autosomal dominant AD carrying p.E693G, p.E693Δ, or p.D678N in the *APP* gene.

Study Funding

Natural Science Foundation of Chongqing, China (2023NSCQ-MSX0204).

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* September 15, 2023. Accepted in final form October 25, 2023. Submitted and externally peer reviewed. The handling editor was Associate Editor Suman Jayadev, MD.

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Appendix (continued)

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Fan Zeng, PhD	Department of Neurology, Daping Hospital, Third Military Medical University, Chongqing, China	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data