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Possible Alzheimer's Disease in an Apolipoprotein E2 Homozygote

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Abstract

The objective of this study was to describe a case of Alzheimer's disease in an ApoE $\epsilon 2/\epsilon 2$ homozygote. ApoE $\epsilon 2/\epsilon 2$ is the rarest of the apolipoprotein E genotypes, representing only 1.4% of the population. There is only one case reported in the literature of a nonagenarian with minimal cognitive changes whose brain showed AD pathology on postmortem study. Here we report an 87-year-old ApoE $\epsilon 2/\epsilon 2$ female who meets clinical criteria for Alzheimer's disease, with confirmation from neuropsychological testing and PET scan. Clinical course is typical for Alzheimer's disease with decline on the Mini-Mental Status Examination from a score of 25 to 19 over 3.5 years. The patient is currently treated with donepezil and memantine. In conclusion, a clinically confirmed case of Alzheimer's disease is rare in Apo E2 homozygotes but can occur.

Keywords

Alzheimer's disease; apolipoprotein E2; homozygote; PET scan

Introduction

Many studies have examined the role of the apolipoprotein E (ApoE) genotype in the risk of developing Alzheimer's disease (AD). There are 3 ApoE alleles ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$) that can occur as homozygous or heterozygous pairs. The most common allele is the $\epsilon 3$ allele, expressed in approximately 78% of the population. The $\epsilon 4$ allele is found in 22% of the US and European population, and the $\epsilon 2$ allele in only 7% [1]. The $\epsilon 4$ allele has been associated with an increased risk of AD [2], and is widely considered a significant contributor to the pathogenesis of AD. Of the 6 possible genotypes, $\epsilon 2/\epsilon 2$ is the rarest, occurring in less than 1.4 % of the general population.

The $\epsilon 2$ allele has been suggested to have a protective effect, to delay the age of onset of AD [3]. Dementia subjects with the ApoE $\epsilon 2$ allele have reduced β -amyloid pathology in the frontal and parietal cortices compared to patients with AD with the $\epsilon 3/\epsilon 3$ genotype [4]. In a recent case report, an $\epsilon 2$ homozygote was described as having minimal cognitive decline (MMSE 28/30 proximate to death) despite significant plaque and tangle burden found an autopsy, suggesting that ApoE $\epsilon 2$ might protect against cognitive decline, even in the presence of significant neuropathology [5]. A literature search revealed no cases of a well characterized dementia of the Alzheimer's type in an $\epsilon 2$ homozygote. Here, we describe a case involving an $\epsilon 2$ homozygote with clinically confirmed AD.

Report of a case

The subject is an 88-year-old right-handed Caucasian woman with 12 years of education. Memory loss was noted by family members dating back 10 years, when she began to have trouble remembering conversations. At the time she presented to our clinic, she was disoriented and confused, and was reported to have had a change in personality characterized by increased uncooperativeness. She was depressed. Family noted a functional decline manifested by less driving, less cooking, reduced maintenance of the home and reduced participation in pleasurable activities. No hallucinations or delusions were reported.

The patient's medical history at initial presentation included fibromyalgia, restless leg syndrome (RLS), breast cancer, depression, cutaneous herpes zoster, mastectomy and hysterectomy. Her medications included trazodone, levothyroxine, acetaminophen, sertraline, prednisone, ropinirole (for her RLS) and multivitamins. There was a family history of "senility" (mother) and ischemic stroke (sister). She was reported to be a social drinker, but did not smoke or use illicit drugs. Review of systems was significant for weight loss and poor sleep. There was no bladder or bowel incontinence reported.

Physical examination at initial evaluation was significant for normal vital signs including normotensive blood pressure and normal cardiac and pulmonary examinations. She exhibited thoracic kyphosis and a papular facial rash.

Her neurological examination revealed intact cranial nerves. Motor exam showed normal and symmetric strength in all extremities and absence of muscular atrophy. Gegenhalten was noted in upper extremities. Deep tendon normal and symmetric, plantar response was flexion bilaterally. Sensation was intact to light touch, pinprick, vibration and proprioception. Coordination showed normal finger-nose-finger, heel-to-shin, and rapid alternating movements. Gait showed normal base and stance, with normal toe, heel and tandem walking. Posture was stooped.

Cognitive exam at initial evaluation showed alert mentation with fluent speech. The patient was able to repeat, name, and follow commands. Mini-Mental State Exam score was 25 out of 30 with points off for recall and orientation[6]. The clock draw demonstrated stimulus pull. Registration for a name and address was 5/5 and 5-minute recall was 2/5. Functional Assessment Staging score was 4 [7].

The patient was referred for neuropsychological testing. The test battery included the WASI [8], CVLT-II Short Form [9], portions of the WMS-R (LM, VR, Digit Span) [10], Trail Making Tests A and B (TMT A & B) [11], Boston Naming Test [12], MMSE, Executive Interview (EXIT) [13], 6-Item Cognitive Impairment Test (6-CIT) [14], and the Clock Drawing Task. On the CVLT-II Short Form, the patient had low average to mildly impaired learning across 4 trials. She was able to recall 6 of 9 words on the 4th learning trial (low average), but only 2 words at Short-Delay Free Recall (moderate impairment). Long-Delay Free Recall also was moderately impaired with 1 word recalled. Recognition memory was severely impaired with 5 hits and 2 false positive errors. She demonstrated a similar pattern of rapid forgetting on a narrative recall task (WMS-R Logical Memory). Initial learning of paragraph-length material was average; however, after a delay, she was unable to recall any narrative information. Visual memory for complex figures was relatively better, with initial learning in the average range; delayed visual recall was in the low end of the average range. Consistent with an early stage dementia of the Alzheimer's type, the patient's primary impairment was in the domain of memory encoding. Other domains, including attention, visuospatial construction, simple visual scanning, verbal and nonverbal reasoning, word knowledge, and confrontation naming were grossly normal. There was a trend toward frontal dysfunction on measures sensitive to early

Alzheimer's disease (TMT B, low average), the EXIT, and Clock Drawing. The findings were typical for Alzheimer's disease.

MRI of the brain showed mild atrophy and small vessel disease without evidence of infarction, intracranial hemorrhage, or mass. PET scan showed a moderate degree of parietal and temporal hypometabolism bilaterally, with decreased uptake in the area of the cingulate gyrus bilaterally (figure).

ApoE genotyping was performed by Serial Invasive Signal Amplification Reaction (SISAR) using genomic DNA through Athena Diagnostics (Worcester, MA). The result - Apolipoprotein E genotype: 2 and 2. This analysis performed at Athena diagnostics is greater than 99% accurate.

The patient was treated with donepezil starting after presentation. Memantine was added 3 years later. The patient tolerated both medications without problems. In follow-up visits over the next 3 ½ years, the patient had a steady cognitive decline, as reflected by MMSE scores shown in the table. At the time of this writing, she lives in a supervised care setting.

Discussion

This is the first reported case of clinical manifestations of AD in an ApoE $\epsilon 2/\epsilon 2$ homozygote. Clinical findings were supported by results of neuropsychological testing, MRI and PET scan. The pattern of progression for this patient is typical for AD. We have called this possible AD [15] because of advanced age; white matter changes; history of hypothyroidism; history of depression; and lack of autopsy confirmation.

It has been speculated that the $\epsilon 2$ allele is protective in AD. In fact, not only is there evidence of delay of disease onset,³ but there appears to be reduced frequency of sporadic cases with ApoE $\epsilon 2/\epsilon 2$. To our knowledge, there has not been a report of an $\epsilon 2$ homozygote with pathologically confirmed AD. Prior to our report, Berlau et al [5] had a case report of ApoE $\epsilon 2/\epsilon 2$ subject with advanced age who showed minimal cognitive changes prior to death, but significant neuropathologic changes on post-mortem examination consistent with AD.

The interaction between ApoE and neuropathologic changes has been investigated extensively. Many have found that the presence of ApoE $\epsilon 4$ is associated with an increased burden of pathological change associated with AD [16]. Alternative mechanisms for interaction between ApoE and neuropathological changes have been explored [17,18].

This case has not yet gone to autopsy to confirm the diagnosis. Given the profile of neuropsychological testing, progressive clinical decline, and confirming PET scan, however, a diagnosis of AD seems likely [19]. This case might be useful to track trajectory of cognitive changes in AD subject that are ApoE $\epsilon 2$ homozygotes. Without pathological confirmation, the critical link of APOE $\epsilon 2$ to AD pathology cannot be made. Because of that, it is unclear whether this case will have only AD pathology at autopsy [20]

Clinical care and monitoring of the progress of this patient is ongoing, and provisions have been made for post-mortem examination. When other centers with patients who appear to have AD and are ApoE $\epsilon 2$ homozygotes publish reports, it will be possible to establish a database to determine whether in fact the rate of progression is slower in this population, as this case suggests. In addition, efforts to explain the mechanism(s) by which neuroprotection or slowing of disease progression occur are needed.

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1a

1b

1c

1d

Figure 1. (PET/CT)

- 1a. Axial view showing hypometabolism of parietal (and parafalcine) regions
- 1b. Axial view showing hypometabolism of temporal (and frontal) lobes
- 1c. Coronal section showing temporal hypometabolism
- 1d. Sagittal view showing hypometabolism in temporal and parietal lobes

Table

MMSE scores

10/2004	06/2005	10/2005	04/2006	11/2006	05/2007	08/2007	02/2008
25	24	27	25	26	22	20	19