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Probable Early-Onset Alzheimer's Disease in an Apolipoprotein E2 Homozygote

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Key Words
Alzheimer's disease · Apolipoprotein E2 · Homozygote · Positron emission tomography scan · Neuropsychological assessment · Cerebrospinal fluid analysis

Abstract
Objective: To describe a case of early-onset Alzheimer's disease (AD) in an apolipoprotein (Apo) ε2/ε2 homozygote. ***Background:*** Apo ε2/ε2 is the rarest of the ApoE genotypes, representing only 1.4% of the population. Cognitive decline in ApoE ε2 homozygotes has rarely been reported. ***Case Report/Methods:*** We report a 58-year-old Apo ε2/ε2 female who meets clinical criteria for probable AD as confirmed by neuropsychological testing, positron emission/computed tomography scan, CSF analysis and genetic screening for known mutations. ***Results:*** The clinical course is typical of AD, with progressive cognitive and functional decline. ***Conclusion:*** Clinically confirmed early-onset AD is atypical in ApoE2 homozygotes but can occur.

Introduction

Many studies have examined the role of the apolipoprotein E (ApoE) genotype associated with the risk of developing Alzheimer's disease (AD). Approximately 78% of the population possesses the ε3 allele making it the most commonly expressed. The ε4 allele is found in 22% of the US and European populations, and the ε2 allele in only 7% [1]. The ε4 allele has been associated with an increased risk of AD [2] and is widely considered a significant contributor to the pathogenesis of AD. Additionally, the ε4 allele has been linked to individuals with vascular disease. Of the 6 possible genotypes, ε2/ε2 is the rarest and is present in less than 1.4% of the general population.

The ε2 allele has been suggested to have the protective effect of delaying age of onset of AD [3]. Dementia subjects with the ApoE ε2ε2 allele have reduced β-amyloid pathology in the frontal and parietal cortices compared to patients with AD with the ε3/ε3 genotype [4]. In a recent case report, an ε2 homozygote was described as having minimal cognitive decline (MMSE 28/30 proximate to death) despite significant plaque and tangle burden found on autopsy, suggesting that ApoE ε2ε2 might protect against cognitive decline, even in the presence of sig-

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nificant neuropathology [5]. Previously, we reported the first case of an ApoE ε2/ε2 carrier with clinically confirmed AD [6]. Here, we describe a second case involving an ε2 homozygote with clinically confirmed AD but with presenile onset.

Case Report

The subject is a 58-year-old left-handed Caucasian female with 12 years of education. Memory loss was noted by a friend of 40 years who described significant personality and cognitive changes following an appendectomy in the summer of 2006. At the time she presented to our clinic, she was reported to have had a change in personality characterized by decreased anger and irritability in addition to an impaired sense of direction with a tendency to get lost. Professionally, she had experienced troubles over the previous few years which ultimately led to her retirement. She exhibited name-finding and word-finding difficulty. No hallucinations or delusions were reported.

The patient's medical history at the initial presentation included hypothyroidism, hypercholesterolemia, foot surgery, mastectomy and appendectomy. Her medications at the initial presentation included simvastatin, levothyroxine and aspirin. Her family history was unremarkable for degenerative brain conditions; it was specifically unremarkable for AD or frontotemporal dementia (FTD). She was reported to be a social drinker but may have been drinking more in the past although there was not a reliable quantification available. At the time of evaluation, she was not reported to be consuming alcohol. She did not smoke or use illegal drugs. Review of systems established a tendency to binge and purge. There was no bladder or bowel incontinence reported.

Physical examination at the initial evaluation was significant for normal vital signs including normotensive blood pressure and normal cardiac, carotid, pulmonary, abdominal and extremity examinations.

Cognitive screening at the initial evaluation showed alert mentation with fluent speech. The patient was able to repeat, name and follow commands. She demonstrated a Functional Assessment Staging score of 3 [7]. Her MMSE score was 23 out of 30 with points lost for repetition, 3-step command, praxis, naming and recall [8]. Normal clock drawing and intact generative speech were demonstrated. Registration for a name and address was 5/5, and 5-min recall was 4/5. Her neurological examination revealed intact cranial nerves. Motor examination confirmed normal tone, intact and symmetric strength in all extremities and absence of muscular atrophy. Deep tendon reflexes were 2+ at the biceps, triceps, brachioradialis and patella. Sensation to light touch, pinprick, vibration and proprioception was preserved. Coordination showed apraxia for finger-nose-finger and rapid alternating movements. Gait showed normal base and stance, with normal toe, heel and tandem walking.

The initial diagnostic impression was FTD mainly given the presenile onset and the presence of some personality change. Given her younger age, a complete evaluation including neuropsychological assessment, positron emission tomography scan with computed tomography (PET-CT) and CSF testing were undertaken.

Table 1. Test of Memory Malingering (TOMM), Blessed Orientation, Memory and Concentration Test (OMCT) and Clock-Drawing Test results

TOMM T1	raw = 44
TOMM T2	raw = 46
Blessed OMCT	raw = 14
Clock-Drawing Test	raw = 6/10

Table 2. Repeatable Battery for the Assessment of Neuropsychological Status A results

Immediate memory		0.1 percentile
Visuospatial		<0.1 percentile
Language		8th percentile
Attention		0.2 percentile
Delayed memory		0.2 percentile
List learning	raw = 17	z = –2.23
Story memory	raw = 6	z = –3.11
Figure copy	raw = 11	z = –5.11
Line orientation	raw = 2	z = –4.97
Picture naming	raw = 10	z = +0.67
Semantic fluency	raw = 11	z = –2.00
Digit span	raw = 8	z = –1.04
Coding	raw = 3	z = –4.87
List recall	raw = 2	z = –1.90
List recognition	raw = 17	z = –2.50
Story recall	raw = 4	z = –2.32
Figure recall	raw = 3	z = –3.81

Neuropsychological testing (tables 1–4) included Testing of Memory Malingering [9], Wechsler Abbreviated Scale of Intelligence [10], Repeatable Battery for the Assessment of Neuropsychological Status (RBANS A) [11], Trail-Making Tests A and B [12], Wechsler Adult Intelligence Scale, third edition (digit span) [13], Token Test [14, 15], Controlled Oral Word Association Test [16], Animal Fluency Test, Boston Naming Test [17], Judgment of Line Orientation [18], Stroop Test [19, 20], Test of Facial Recognition [21], 6-Item Cognitive Impairment Test [22] and the Clock-Drawing Task [23, 24].

The patient demonstrated impairment across measures with the exception of confrontation naming Boston Naming Test and attention (digit span). RBANS list learning was moderately impaired across 4 trials. List recall was mildly impaired with 2/10 words produced. Recognition memory was moderately impaired with 17 hits and 3 false-positive errors. RBANS immediate narrative recall was severely impaired (6/12 details recalled across 2 trials). Delayed narrative recall remained moderately impaired with 4/6 details recalled. She recalled 3 of 20 RBANS complex figure details after a delay (severe impairment). Language measures were moderately (animal fluency) to severely impaired (Controlled Oral Word Association Test, Token Test). Aspects of her

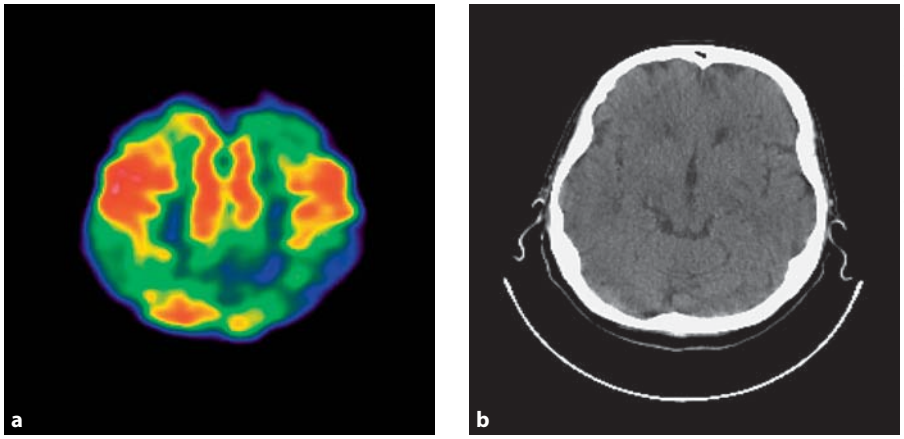

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Fig. 1. a Axial PET showing hypometabolism of parietal and posterior cingulate gyrus. **b** Axial CT showing no significant ischemic changes and no regional/focal atrophy.

Table 3. Digit span results

Forwards	total/span = 11/7	+0.45
Backwards	total/span = 3/3	z = –0.99
Total	raw = 14	ScS = 9
Token	raw = 23	severe impairment
COWAT (CFL)	raw = 8	ScS ≤ 2
Animal fluency	raw = 10	z = –2.06
Boston Naming Test	raw = 56	ScS = 10
JLO	raw = unable to acquire task	
Facial recognition	raw = 37 converted long	moderate impairment
Trials A	222″; 0 error	ScS ≤ 2
Trials B	unable to do	impaired

COWAT = Controlled Oral Word Association Test; ScS = scaled score; JLO = Judgment of Line Orientation Test.

token performance were believed to be due to ideomotor apraxia impairment. Visuospatial processing skills were moderately (facial recognition) to severely impaired (RBANS Judgment of Line Orientation and figure copy, Benton Judgment of Line Orientation). Processing speed was significantly reduced (Stroop word reading/color naming, Trail-Making Test A, RBANS coding). Executive functions were severely impaired (Trail-Making Test B, Stroop interference). The preponderance of frontal, visuospatial and language deficits noted were equal to or greater than memory impairments, which raised the question of a possible FTD. However, memory deficits were apparent and demonstrable with early onset and rapid progression. A possible AD variant with greater visuospatial and frontal involvement was hypothesized.

A PET scan with CT fusion of the brain showed mild symmetric cerebral atrophy without focality. Her ventricles and sulci were prominent for age. There were no masses, hemorrhages, white matter rarefaction, midline shift or CT evidence of acute infarcts detected. Marked hypometabolism associated with the frontal, temporal and parietal lobes was observed as well as hypometabolism of the posterior cingulate gyrus. The motor cortex, basal nuclei, occipital lobes and cerebellum appeared to be spared of the hypometabolism. These findings are consistent with advanced AD and not consistent with FTD. There were no masses, hemorrhages, midline shift or CT evidence of acute infarcts.

Table 4. Stroop results

W – 53	ScS ≤ 2
C – 20	ScS ≤ 2
CW – 5	ScS ≤≤ 2

ScS = Scaled score.

ApoE genotyping was performed by restriction endonuclease digestion of PCR-amplified genomic DNA by Athena Diagnostics. The patient did not possess an ApoE ε4 allele. The result – ApoE genotype: 2 and 2. This analysis performed at Athena Diagnostics is greater than 99% accurate. Analysis of the patient's profile did not identify abnormal DNA sequence variants in the coding region and intron/exon junctions for the *PSEN1, PSEN2* and *APP* genes. Furthermore, no duplication of the *APP* gene was detected.

CSF testing for 42-amino-acid β-amyloid (Aβ42), tau and phosphorylated (phospho) tau was done by Athena Diagnostics. Determination of Aβ(1–42) peptide, total tau and phospho-tau concentrations in CSF was performed by ELISA methodology as provided by Innogenetics NV [Innotest™ β-Amyloid(1–42), Innotest hTAU Ag and Innotest Phospho-tau]. Concentrations were determined from standard curves using synthetic Aβ(1–42) peptide, recombinant human total tau protein and a synthetic 34-amino-acid peptide phosphorylated at the position equivalent to threonine-181 in the tau protein. An Aβ(1–42) tau index was calculated as ATI = [Aβ(1–42)]/(240 + 1.18 total tau) and represents a ratio normalized by the discrimination line Aβ(1–42) = 240 + 1.18 total tau. This line represents a sensitivity of 85–94% and specificity of 83–89% for distinguishing AD from non-AD populations with an ATI value of 1.0 being on the line. An ATI of less than 1.0 typically designates individuals with AD as compared to an ATI of greater than 1.0, found to correlate with non-AD individuals. The phospho-tau level provides an analytical tool for differentiating AD from other forms of dementia. A phospho-tau >61 pg/ml typically distinguishes AD from FTD and dementia with Lewy bodies as indicated by phospho-tau levels <61 pg/ml with sensitivities of 72–85% and specificities of 74–85%. Consistent with a diagnosis of AD, the patient possessed reduced levels of cerebrospinal Aβ(1–42) of 288.75 pg/ml, a total tau of 1,082.05 pg/ml and an elevated phospho-tau protein concentration of 123.5 pg/ml. These levels resulted in an ATI of 0.19.

The patient returned for follow-up 9 months later. Her MMSE had declined to 18/30 despite treatment with a cholinesterase inhibitor and memantine. She continued to live alone but financial matters were handled by power of attorney.

Discussion

This is the second reported case of a clinically confirmed patient with probable AD with an ApoE ε2/ε2 homozygote. Clinical findings of dementia are supported by neuropsychological testing, PET/CT scan and CSF. While the presenile onset for this patient favors the diagnosis of FTD, the CSF markers, specifically the ATI as well as the PET scan favor a diagnosis of AD.

As determined by the total tau concentration and reduced CSF levels of Aβ(1–42) peptide, an ATI of less than 1.0 typically indicates a diagnosis of AD while a value >1.0 is typical of control populations representing normal aging, alcohol dementia, depression, psychological and other neurological disorders. A phospho-tau level of >61 pg/ml has been found to discriminate AD from FTD and dementia with Lewy bodies with sensitivities ranging from 72–85% and specificities of 74–85% [25, 26]. Most studies have found normal to mildly increased CSF total tau levels in other dementias such as FTD and dementia with Lewy bodies [27].

It is possible that the PET/CT and CSF markers give false-positive results. However, Silverman et al. [28] reported a 93% positive predictive value with PET for AD. Further CSF testing for Aβ42/tau in AD is 89% sensitive and 90.2% specific [27].

It has been speculated that the ε2 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 ε2/ε2. In view of the presenile onset of AD experienced by this patient, this case directly challenges the concept that the ε2 allele has a protective effect against early-onset AD. To our knowledge, there has not been a report of an ε2 homozygote with pathologically confirmed AD. Prior to our report, Berlau et al. [5] had a case report of an ApoE ε2/ε2 subject with advanced age who showed minimal cognitive changes prior to death, but significant neuropathological changes on postmortem examination consistent with AD. In fact, a presenile onset would typically favor an ApoE ε4 homozygote or an autosomal dominant form of AD.

The interaction between ApoE and neuropathological changes has been investigated extensively. Many have found that the presence of ApoE ε4 is associated with an increased burden of pathological change associated with AD [29]. Alternative mechanisms for interaction between ApoE and neuropathological changes have been explored [30, 31].

This case has not yet gone to autopsy to confirm diagnosis. Consequently, the presence of AD pathology is unknown [32]. It is possible that the subject has the Testing of Memory Malingering 40 Poly T repeat [33] but this was not assessed as the test is not commercially available. Given the combined results of the neuropsychological testing, the ATI, phospho-tau concentration and corroborative PET/CT scan, a diagnosis of AD seems likely [28].

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