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Increased Apolipoprotein E ε4 in Epilepsy with Senile Plaques

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Inheritance of the apolipoprotein E (ApoE) ε4 allele is a risk factor for Alzheimer's disease (AD) and is associated with increased deposition of β-amyloid (Aβ) in AD, Down's syndrome, and normal aging. Aβ deposition in the form of senile plaques (SPs) has recently been described in patients with temporal lobe epilepsy (TLE). We studied the relationship between ApoE ε4 genotype and the deposition of Aβ in temporal lobe tissue from patients who underwent temporal lobectomy for intractable epilepsy. TLE patients with SPs had a 70% ApoE ε4 carrier frequency compared with a 27% carrier frequency among age-matched TLE controls without SPs. Our data suggest that the association between ApoE ε4 and intracerebral Aβ accumulation is not unique to the elderly or to those with dementia, and may be a feature of conditions in which there is both an ApoE ε4 allele and overproduction of Aβ precursor protein, and, presumably, Aβ.

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The deposition of β-amyloid (Aβ) in brain tissue is believed to play a central role in the pathogenesis of Alzheimer's disease (AD) [1]. Aβ accumulates in brain parenchyma and around cerebral vessels both in AD and in the related disorder, Down's syndrome (DS). The apolipoprotein E (ApoE) type ε4 allele predisposes to AD and appears to promote the parenchymal and cerebrovascular accumulation of Aβ in AD [2, 3], DS [4], and normal aging [3]. Head trauma, which leads to an increase in Aβ precursor protein (AβPP) expression, can also foster Aβ deposition especially when an ApoE ε4 allele is present [5, 6].

An association between Aβ deposition and temporal lobe epilepsy (TLE) has recently been described by one of us [7]. In that study, Aβ-immunoreactive senile plaques (SPs) were found in 11 of 114 (10%) temporal lobectomy specimens removed in the surgical treatment of intractable epilepsy from consecutive patients undergoing this procedure at the University of Western Ontario; those less than 30 years of age and those having obvious pathology that could account for the epilepsy (eg, brain tumor) were excluded from the study. Remarkably, SPs were present in some TLE patients of a surprisingly young age (<40 years). Most of the Aβ deposits were in the form of diffuse SPs, although 1 patient (age 59 years) had some neuritic plaques as well as amyloid angiopathy. Neurofibrillary tangles were rarely seen. None of the epileptics with SPs had evi-

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dence of dementia at the time of their preoperative neuropsychological assessment and none has shown evidence of cognitive decline on follow-up examination (mean follow-up now 5 years postoperative) [8]. There was no significant difference between TLE patients with SPs and those without, with regard to the severity of epilepsy, medication history, or head trauma [7]. It was concluded that Aβ deposition in these patients was directly related to seizure activity, an interpretation supported by an independent study demonstrating increased AβPP expression in human TLE foci [9]. It is of historical interest that the first histopathological description of SPs was made in 1892 by Blocq and Marinesco [10] in a pathological study of the brains of patients with a history of idiopathic epilepsy.

Considerable evidence links ApoE ε4 to Aβ deposition in AD [2, 3], DS [4], normal aging [3], cerebral amyloid angiopathy [6, 11, 12], and head injury [5, 6]. To investigate whether a similar relationship between the ApoE ε4 allele and Aβ deposition existed in TLE patients, we compared the ApoE genotypes of epileptic individuals with SPs in their temporal lobectomy specimens and epileptic controls without SPs. These patients are of particular interest to study, since their relatively young age removes much of the strong effect of aging on Aβ deposition [3].

Materials and Methods

ApoE genotypes were determined on archival formalin-fixed, paraffin-embedded temporal lobectomy tissue from 10 TLE patients with Aβ deposits (mean age, 47.5 ± 9.1 years) and 18 age-matched control TLE patients without Aβ deposits (mean age, 46.5 ± 5.9 years) using the primers of Wenham and colleagues [13]. One TLE specimen could not be accurately genotyped. Specimens were deparaffinized in xylene, washed with ethanol, and DNA was purified according to the manufacturer's protocol (QIAamp Tissue Kit, Qiagen). Polymerase chain reaction (PCR) was performed using the Perkin-Elmer thermal cycler and PCR reaction kit. After a 6-minute initial denaturation at 94°C, there were 40 cycles of 1-minute annealing at 65°C/1-minute extension at 70°C/2-minute denaturation at 94°C, followed by a final 10-minute extension at 70°C. After digestion with *Hha*I, products were separated by electrophoresis in a polyacrylamide gel. ApoE ε4 homozygotes were confirmed with another set of primers and PCR parameters, as recently described by Egensberger and co-workers [14].

Results

The ApoE ε4 allele was markedly overrepresented among TLE patients with SPs (Table); 70% of epileptics with SPs had at least one ε4 allele compared with only 27% in epileptics without SPs. Epileptics with temporal lobe SPs had a 45.0% ApoE ε4 allele frequency, compared with a 13.9% ApoE ε4 allele frequency in age-matched epileptics without SPs (χ^2 = 6.637, p = 0.01). The ε4 frequency in the control epileptic subjects approximates the ApoE ε4 allele frequency in a general Canadian population (15.2%). As in AD, a dose effect of ApoE ε4 alleles was apparent in epileptic temporal lobes; SPs were present in both ApoE ε4 homozygotes but in only 50% of ApoE ε4 heterozygotes (5 of 10) (see Table). There was also an increased maximum plaque density in the two ε4 homozygotes (25.5 ± 2.1 SP/mm^2; mean age, 42.5 years) compared with the five ε4 heterozygotes (16.4 ± 3.0 SP/mm^2; mean age, 53.0 years) (Student's t = 0.013).

Aβ Status, ApoE Genotypes, and Age/Gender of TLE Patients

	Genotypes				
	ε2/ε3	ε3/ε3	ε2/ε4	ε3/ε4	ε4/ε4
No Aβ (n = 18)	41/M 44/F 46/F 57/M	36/F 39/M 44/M 46/M 47/F 48/M 49/M 51/F 56/F	51/F	44/F 44/F 46/M 47/M	None
% of total	22	50	5	22	0
With Aβ (n = 10)	51/F	36/M 38/M	None	43/M 48/F 54/F 59/M 61/F	36/M 49/F
% of total	10	20	0	50	20

Age is given in years.
Aβ = β-amyloid; ApoE = apolipoprotein E; TLE = temporal lobe epilepsy.

As in other conditions of ApoE ε4-associated Aβ-amyloidosis, the ApoE ε2 allele tended toward underrepresentation in TLE patients with SPs (10%) compared with those without (27%; NS). Mesial temporal sclerosis (MTS) was present in some epileptic temporal lobes, but its presence did not correlate with Aβ pathology. However, there was no statistically significant difference in the frequency of ApoE ε4 alleles among those epileptics with MTS (32%) compared with those without (17%).

Discussion

Keeping in mind our relatively small sample size, our results suggest that the ApoE ε4 genotype is associated with Aβ deposition in epilepsy. The local induction of AβPP within a seizure focus in the brain of an ApoE ε4 homozygote may be sufficient to cause focal cerebral Aβ accumulation. These data, like those from head injury–related Aβ deposition associated with ApoE ε4 [5, 6, 15], extend the spectrum of ApoE ε4-related Aβ deposition to include individuals of earlier ages than

have been previously described and includes individuals without dementia. Periodic reevaluation of their cognitive status will be required to determine the natural history of TLE patients with ApoE ε4 alleles and Aβ deposits.

The apparent emergence of a robust association involving the promotion of Aβ accumulation in ApoE ε4 carriers who are likely to have elevated AβPP levels (and presumably elevated Aβ generation) is noteworthy. These situations may be either genetic (eg, DS [4]) or acquired, secondary to injury (eg, head injury [5, 6, 15]) or abnormal electrical activity (ie, epilepsy [7–10], this study). This robust association of Aβ accumulation with ApoE ε4 and elevated AβPP/Aβ may be particularly useful in modeling of amyloid pathology in experimental animals. The investigation of such a strategy is now in progress.

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Use of Desferrioxamine in the Treatment of Aceruloplasminemia

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Aceruloplasminemia is a newly recognized autosomal recessive disorder of iron metabolism resulting in neurodegeneration of the retina and basal ganglia. We report here on the treatment of a patient who developed progressive extrapyramidal symptoms that included blepharospasm, grimacing, and rigidity associated with increased iron deposition in the brain and visceral organs. Treatment for 10 months with the iron chelator desferrioxamine decreased brain iron stores, prevented progression of the neurological symptoms, and reduced plasma lipid peroxidation. These data suggest that early treatment with this chelator may be useful in such patients to diminish central nervous system iron accumulation and to prevent or ameliorate neurological symptoms associated with neurodegeneration.

Miyajima H, Takahashi Y, Kamata T, Shimizu H, Sakai N, Gitlin JD. Use of desferrioxamine in the treatment of aceruloplasminemia. Ann Neurol 1997;41:404–407

Ceruloplasmin is an abundant α_2 serum glycoprotein that contains more than 95% of the copper present in human plasma [1]. Aceruloplasminemia is an autosomal recessive disorder affecting iron metabolism through a complete deficiency of ceruloplasmin ferroxidase activity due to mutations in the ceruloplasmin

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