

LETTERS TO THE EDITOR

Age of onset in patients with Alzheimer's disease with different apoE genotypes

Alzheimer's disease is the most common form of dementia, affecting about 10% of the elderly population. Four genetic loci have so far been implicated in Alzheimer's disease, either in rare family pedigrees in which the defective gene (amyloid precursor protein, presenilin-1, presenilin-2) cosegregates with early onset Alzheimer's disease, or in late onset cases in which polymorphism of the apolipoprotein E (ApoE) gene on the chromosome 19 is identified as an important individual risk trait. Apolipoprotein E is a normal constituent of plasma lipoproteins and has an important role in the maintenance of the integrity of the neuronal membrane and myelin sheath, but is also deposited in senile plaques in Alzheimer's disease. Three allelic forms of the ApoE gene have been characterised—Apo ε2, Apo ε3, and Apo ε4. In a previous study, we found that the Apo ε4 allele constitutes a major risk factor for Alzheimer's disease in the Portuguese population,¹ similar to that described for other populations.² In the present study, we tested the hypothesis that different ApoE genotypes might be associated with distinct clinical phenotypes in Alzheimer's disease.

Consecutive patients with sporadic Alzheimer's disease from the dementia study group outpatient clinic were studied. The diagnosis of probable Alzheimer's disease was established according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association (NINCDS-ADRADA). All patients were submitted to neurological history and examination (including mental status examination), laboratory analytical tests, and brain CT according to the recommendations of the American Academy of Neurology to exclude other causes of dementia. For ApoE genotyping, genomic DNA was extracted from peripheral blood, and allelic variants identified by the polymerase chain reaction (PCR) amplification.¹ Relevant clinical characteristics were compared in the patients with Alzheimer's disease with different ApoE

genotypes. Age of onset was defined as the age at which the first symptoms required for the diagnosis of Alzheimer's disease were noticed. Information provided by the patient was always checked by questioning the spouse or a close relative. The interviewing neurologist was unaware of the ApoE genotype of the patient.

Sixty eight patients with sporadic probable Alzheimer's disease were studied. Twenty eight were Apo ε3/ε3, 31 ε3/ε4, and nine ε4/ε4. The age of onset of disease was significantly higher in the patients bearing the Apo ε4 allele (ε3/ε4 and ε4/ε4, 65.7 (7.1), n=40), compared with patients without the Apo ε4 allele (ε3/ε3, 61.6 (7.6), n=28, p<0.05, two tailed Student's *t* test). The time from the onset of the disease to the first outpatient interview, which may reflect the initial progression of the disorder, was not different between the two genotype groups. No significant differences in relation to the sex, education, disease installation, disease course, interference with professional or social life, arterial hypertension, diabetes mellitus, dyslipidaemia, and CT were found.

The main finding of the present study was that the age of onset in Alzheimer's disease was higher in patients bearing the Apo ε4 allele. The table shows data from different studies on the age of onset according to the ApoE genotype. Studies looking specifically at familial or early onset cases were not considered, as these might represent subsets of patients with particular forms of Alzheimer's disease. Various studies found that patients bearing the Apo ε4 allele were either younger or older at the onset, whereas others could detect no significant difference (table). It is noteworthy that the two studies that found a higher age of onset for patients bearing the Apo ε4 allele were those including relatively younger patients with Alzheimer's disease (Dal Forno, 1995 and the present study, table). Furthermore, analysis of the 10 studies in the table shows that the difference between the ages of onset in patients without and with the Apo ε4 allele significantly relates to the mean age of patients with Alzheimer's disease (linear regression, slope 0.46 (0.13), 95% confidence interval 0.16–0.77). A possible interpretation is that the presence of the Apo ε4 allele could represent a particularly high risk in the older patients of a relatively young Alzheimer's disease population, and the reverse would be true for a comparatively older Alzheimer's disease sample. This interpretation is consistent with the previously reported data showing that the Apo ε4 allele might exert its effect as a risk factor for Alzheimer's disease mainly in the 60–69 dec-

ade of life, and less so in the preceding and subsequent decades.³

In conclusion, the present study reinforces the idea that the importance of the Apo ε4 allele as a risk factor for Alzheimer's disease depends on the age of the person, although conclusive evidence can only result from large epidemiological studies.⁴

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Sudden bilateral deafness: lateral inferior pontine infarction

Sudden unilateral deafness usually suggests a cochlear impairment but a brainstem stroke should also be evoked especially when brainstem signs are associated. Deafness with brainstem infarct was described many years ago¹ but bilateral deafness has been very rarely reported²⁻⁴ and would have a poor prognosis.³ We report a case of lateral inferior pontine infarct disclosed by bilateral deafness with a favourable course.

A 74 year old man with diabetes mellitus and auricular fibrillation regularised for two years, suddenly experienced a right deafness associated with vertigo and gait disorder. Three days later, deafness became bilateral. Clinical examination showed a major bilateral cerebellar ataxia and dysmetria without tinnitus, facial palsy, lateral gaze paresis, Horner syndrome, tactile, or motor disorder. Hearing loss was severe and prominent in the right ear. Neuropsychological examination was normal, especially oral expression,

Age of onset in Alzheimer's disease according to the apoE genotype

First author	Reference	n	Age	Age of onset		Comparison*
				1 or 2 ε4	No ε4	
Poirier	<i>Lancet</i> 1993;342:697	91	75.1 (10.3)	73.6†	77.6	Younger
Corder	<i>Neurology</i> 1995;45:1323	97‡	79.4†	71.1†	71.4 (7.4)	NS
Frisoni	<i>Ann Neurol</i> 1995;37:596	62	79.8†	74.3†	76.9 (4.6)	Younger
Lehtovirta	<i>Neuroscience</i> 1995;67:65	26	68.9†	67.2†	66.2 (9.0)	NS
Gomez-Isla	<i>Ann Neurol</i> 1996;39:62	329	77.8 (9.6)	70.8†	73.8†	Younger
Kukull	<i>J Clin Epidemiol</i> 1996;49:1143	234	80.2 (6.8)	76.1†	77.5	Younger
Holmes	<i>J Neurol Neurosurg Psychiatry</i> 1996;61:580	164	81.9 (6.6)	75.5 (5.9)	78.7 (7.9)	Younger
Mak	<i>Neurology</i> 1996;46:146	65	76.5 (8.3)	71.7†	73.7 (8.5)	NS
Dal Forno	<i>Arch Neurol</i> 1996;53:345	101	69.6†	66.8†	62.4 (8.8)	Older
Simões do Couto	This study	68	68.8 (7.9)	65.7 (7.1)	61.6 (7.6)	Older

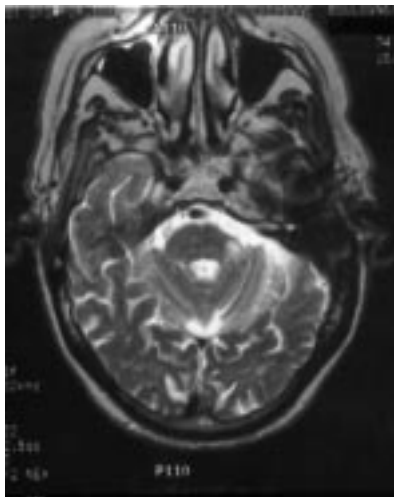
*Patients with ε4 allele younger or older than patients without ε4 allele, or non-significant difference (NS).

†Calculated from the results in the cited paper.

‡Only sporadic cases considered.

naming, and lecture. Tonal audiometry showed a sensory deafness on the left (60 to 80 dB loss) and a mixed deafness on the right (80 to 120 dB loss) with a prominent sensory component. Brain MRI disclosed a left inferior pontine infarction extending to the territory of the left anterior inferior cerebellar artery (AICA, figure). No lesion was found on the right side. Brainstem auditory evoked potentials (BAEPs) showed poorly synchronised responses with mildly delayed latencies of waves I (right 1.92 ms; left 1.96 ms); waves II to V were not recorded. Middle latency auditory evoked potentials were normal (right Na 19.4 ms, Pa 31 ms; left Na 20.1 ms, Pa 29.8 ms) demonstrating the sparing of higher auditory pathways. This pattern indicated a bilateral retrocochlear impairment. Echocardiography, ECG, and Holter-ECG were normal. Doppler sonography showed a stenosis of the left carotid artery of about 60%. Medical history, clinical picture, and the infarct location suggested that atherosclerosis of the basilar artery was the cause of stroke. The long term course showed a clear improvement and 10 months later, an important right hearing loss (50 to 70 dB) and a mild left hearing loss (10 to 30 dB) still persisted but allowed good intelligibility. Word repetition and environmental noise recognition were quite good. Nevertheless, some difficulties to localise sound persisted with systematic search to the left side.

According to Adams,⁵ deafness characterises the lateral form of inferior pontine infarct and is usually due to an infarction of the cochlear nucleus or auditory nerve. In the present case, the delayed latency of wave I supports the sparing of the distal part of the auditory nerves and the absence of waves II to V shows that deafness resulted from a bilateral cochlear nuclei or proximal auditory nerve impairment.⁶ The finding of a left inferior pontine infarct clearly supports this interpretation for the left deafness. On the right side, no lesion was found but the BAEP pattern strongly suggests a lesion within the same area. The right deafness is likely to be due to a lesion of the radicular portion of the auditory nerve, which is supplied by the auditory artery (branch of the anterior inferior cerebellar artery), or by a small pontine infarct even if it was not visualised on MRI.⁷



Spin echo T2 weighted axial MRI. Left sided infarction in the lateral inferior pons and in the middle cerebellar peduncle.

Sudden deafness due to a brainstem infarct could be underdiagnosed and we should look for this possibility using MRI and BAEP examination, especially in patients with risk factors for stroke and presenting with other neurological signs. This case also suggests that the deafness outcome may be favourable.

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Surgical treatment of quadrigeminal plate lipoma presenting with seizures and behavioural disorders

Intracranial lipomas are uncommon, rarely symptomatic, lesions. Those located in the quadrigeminal plate and ambient cistern account for 13% to 43% of cases and are less symptomatic. Of 37 quadrigeminal plate and ambient cistern lipomas reported in the literature, 15 were diagnosed during life, seven in children.¹ We had the opportunity to study an additional case of quadrigeminal plate lipoma in a four year old child, who presented with epilepsy and developed behavioural changes tending towards aggressiveness, which both subsided after surgery.

In 1986 the patient presented two episodes of tonic-clonic generalised epileptic seizures associated with fever; the EEG was normal. One year later, although he had benefited from therapy with phenobarbitone, he presented episodes of hypotonia, ataxia, motor incoordination, and confusion. A new EEG study disclosed bilateral paroxysmic abnormalities, such as sharp slow waves (figure A). The MRI disclosed a well defined lesion at the level of the left inferior colliculus, which showed a high signal in T1 and low in T2 sequence (figure B). Three months before admission, after the reduction of phenobarbitone dose, the child presented a new tonic-clonic generalised seizure. During the previous two years, his parents had noted

behavioural changes tending towards aggressiveness and hyperactivity. In 1988, the persistence of epileptic seizures, more than behavioural changes, led to the decision to remove the lesion surgically. In a semisitting position, a median suboccipital craniotomy was performed and a tumour, which extended from the left inferior colliculus to the contralateral brachium conjunctivum, was removed through a supracerebellar subtentorial approach. Histological examination confirmed the diagnosis of lipoma. The postoperative course was uneventful. The EEG disclosed only mild abnormalities. The child presented a few seizures after surgery, which were probably secondary to hypodose of the phenobarbitone. Since 1991 he has had no more seizures and since 1992 the EEG has been normal. The antiepileptic treatment was discontinued in 1994 and he remained seizure free without treatment. Concurrently, he became less aggressive and his social behaviour dramatically improved after surgery. At present he is attending school and performing well. Sequential CT and MR studies confirmed the total removal of the tumour.

We report a case of quadrigeminal plate lipoma in a child who presented initially with seizure disturbances. EEG disclosed diffuse symmetric abnormalities which were probably the expression of a centro-encephalic epilepsy induced by the mesencephalic lesion. Maiuri *et al*, in a review of over 200 cases, found that epileptic seizures were the most common feature in symptomatic cases.¹ These are usually ascribed to interhemispheric disconnections in cases of callosal lipomas, or to the tenacious adhesions of the tumour to the brain cortex. Lipomas, although they do not compress or displace the adjacent neural tissue, very often encase nerves and vessels involving the surrounding structures in regressive change within the tumour tissue. Alternatively, epileptic seizures are regarded as epiphenomena of coexisting congenital malformations such as callosal agenesis, microgyria, or hemispheric atrophy. These explanations, however, are unsatisfactory for small lesions located in the quadrigeminal plate, especially when neither hydrocephalus nor congenital abnormalities are associated.

Furthermore, a subcortical or brainstem induced epilepsy has been shown in animal models and found in patients with lesions in those areas.^{2,3} Browning *et al* found that brainstem epilepsy is independent of forebrain seizures and can be elicited even in the complete absence of connections between these two areas.⁴ Other authors have described convulsive fits elicited in cats and rats after stimulation of special points in the brainstem. EEG patterns were specific and significantly different from those of cortical epilepsy. So called tonic cerebellar fits have also been described as resulting from brainstem stimulation, and in laboratory studies controlled brainstem lesions facilitated or inhibited seizure activity. Other studies confirmed the possibility of inducing convulsive seizures by the stimulation of the brainstem, localising a low threshold convulsive area in the mesencephalic reticular formation. EEGs with generalised changes, predominantly synchronous theta waves, have been described in patients with tumours in the region of the aqueduct and with pineal region tumours, and pronounced EEG changes in more than 50% of patients