LETTERS TO THE EDITOR

Age of onset in patients with Alzheimer’s disease according to 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, similar to that described for other populations. 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 were determined by PCR amplification. 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 decades of life, and less so in the preceding and subsequent decades.

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 could only result from large epidemiological studies.

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Sudden bilateral deafness: lateral inferior pontine infarction

Sudden unilateral deafness usually suggests a cochlear impairment but a brainstorm stroke should also be evoked especially when brainstem signs are associated. Deafness with brainstem infarct was described many years ago but bilateral deafness has been very rarely reported and would have a poor prognosis. 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 normalised 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.

<table>
<thead>
<tr>
<th>First author</th>
<th>Reference</th>
<th>n</th>
<th>Age</th>
<th>Age of onset 1 or 2 ε4</th>
<th>No ε4</th>
<th>Comparison*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potier</td>
<td>Lancet 1993;342:697</td>
<td>91</td>
<td>75.1 (10.3)</td>
<td>73.6†</td>
<td>71.6</td>
<td>Younger</td>
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<tr>
<td>Corder</td>
<td>Neurology 1995;45:1323</td>
<td>972</td>
<td>79.4‡</td>
<td>71.1†</td>
<td>71.4 (7.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Frisoni</td>
<td>Ann Neurol 1995;37:956</td>
<td>62</td>
<td>79.8‡</td>
<td>74.3†</td>
<td>76.9 (4.6)</td>
<td>Younger</td>
</tr>
<tr>
<td>Leiters</td>
<td>Neurology 1995;47:55</td>
<td>26</td>
<td>68.9§</td>
<td>67.2†</td>
<td>66.2 (9.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Gomez-Isla</td>
<td>Ann Neurol 1996;39:62</td>
<td>329</td>
<td>77.8 (9.6)</td>
<td>70.8†</td>
<td>73.8§</td>
<td>Younger</td>
</tr>
<tr>
<td>Käkki</td>
<td>J Clin Epidemiol 1996;49:1143</td>
<td>234</td>
<td>80.2 (8.6)</td>
<td>76.1†</td>
<td>77.5</td>
<td>Younger</td>
</tr>
<tr>
<td>Holmes</td>
<td>J Neurol Neurosurg Psychiatry 1996;61:580</td>
<td>164</td>
<td>81.9 (6.6)</td>
<td>75.5 (5.9)</td>
<td>78.7 (7.9)</td>
<td>Younger</td>
</tr>
<tr>
<td>Mak</td>
<td>Neurology 1996:46:14</td>
<td>65</td>
<td>76.5 (8.3)</td>
<td>71.7§</td>
<td>73.7 (8.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Dal Forno</td>
<td>Arch Neurol 1996;53:345</td>
<td>101</td>
<td>69.6†</td>
<td>66.8†</td>
<td>62.4 (8.8)</td>
<td>Older</td>
</tr>
<tr>
<td>Simões de Couro</td>
<td>This study</td>
<td>68</td>
<td>68.8 (7.9)</td>
<td>65.7 (7.1)</td>
<td>61.6 (7.6)</td>
<td>Older</td>
</tr>
</tbody>
</table>

* 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.

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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. 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 paroxysmal 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 tumour extending from the left inferior colliculus to the controlateral brachium conjunctivum, was removed through a supracerebellar subtemporal approach. Histological examination confirmed the diagnosis of a lipoma. Since then there are 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 centroencephalic epilepsy induced by the mesencephalic lesion. Maizurri et al. in a review of over 200 cases, found that epileptic seizures were the most common feature in symptomatic cases. They are usually ascribed to interhemispheric disconnections in cases of callosal lipomas, or to the tenacious adherences 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.17 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. 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 synchronously 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.
with midbrain tumours have also been documented. The role of the pineal gland in modulating the EEG is also well documented in both experimental and clinical studies. In our patient, the complete restoration of normal EEG patterns and the subsidence of seizures after surgery suggest a close relation between symptoms and tumour.

Behavioural disturbances tending towards aggressiveness, similar to those we describe, have also been described in patients with lesions in the midbrain-forebrain area. The direct invasion of the upper midbrain may lead to severe behavioural disturbances through involvement of the midbrain-limbic system of Nauta. This system includes several structures located at the upper dorsal midbrain which, we suggest, may be encased by tumours of the pineal region. Weber reviewed clinical studies which disclosed changes in mental outlook and behavioural disorders in patients with tumours in the midbrain and pineal region; to explain these disturbances he suggested the direct involvement of the mesencephalic reticular system, the periventricular grey matter, and the midbrain-limbic system. Piatt and Campbell, in a more recent report, reviewing 37 pineal region meningiomas, identified 13 patients (37%) with dementia, emotional disturbances, or personality changes. Sano et al described 51 patients with violent, aggressive behaviour who significantly benefited from a selective postero medial hypothalamicotomy, with a pronounced calming effect in 95% of the cases.

In conclusion, epilepsy and behavioural abnormalities in patients with tumours involving the quadrigeminal plate area, although rarely reported, are probably more specific than was previously thought. We suggest that surgery may be curative when limited to symptomatic lipomas in which a relation between tumour location and symptoms has been recognised.

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Lambert-Eaton myasthenic syndrome and non-pulmonary small cell carcinoma

It is generally accepted that Lambert-Eaton myasthenic syndrome (LEMS) is associated with cancer in 50% to 60% of cases, the overwhelming majority of these cancers being small cell carcinomas of the lung. O’Neill et al stated that in cases in which the cancer is not small cell carcinoma of the lung the association may be fortuitous. However, small cell carcinomas can sometimes arise in other organ systems. They are considered, like small cell carcinomas of the lung, to be of neuroendocrine origin and presumably have the same antigenic potential. Posner stated that occasional cases of LEMS can be seen in association with non-pulmonary small cell carcinoma, particularly of the prostate and cervix, although reference to these occurrences in the literature is scant. We present a case of LEMS clearly causally related to extrapoluminal small cell carcinoma.

A 70 year old housewife presented in April 1996 with a three month history of leg weakness and dryness of the mouth. She was otherwise well. Examination disclosed quite pronounced weakness of hip flexion and mild weakness of knee extension and arm abduction. Deep tendon reflexes were all intact and did not become brisker after exercise. Her creatine phosphokinase was normal. Electrical studies disclosed a compound muscle action potential of 3.5 mV in abductor digiti minimi on supramaximal stimulation of the right ulnar nerve at the wrist, increasing in amplitude by 40% after 20 seconds of isometric exercise. A voltage gated calcium channel antibody
remains to be seen whether this is only a noma has resulted in complete clinical and carcinomas of the lung. Standard chemo-case as in cases associated with small cell that the immunological stimulus for the identical to those of LEMS associated with electrical, and immunological findings were causally related to non-pulmonary small cell presenting tumour represents metastasis seems unlikely in view of her negative primary source for our patient's small cell carcinoma was found. It is unlikely that this was normal. Her deep tendon reflexes were all very brisk, certainly brisker than when she first presented six months previ- but there was some residual weakness of hip flexion. Ten months after her initial presentation, her voltage gated calcium channel antibody assay was negative. Fifteen months after presentation there was no clini- cal or radiological evidence of recurrent tumour. The only abnormal finding on electromyography was persisting mild weakness of hip flexion. Electrical studies disclosed a compound muscle action potential of 6.7 mV in Abductor digiti minimi on supramaxi- mal stimulation of the right ulnar nerve at the wrist, with no significant increment in amplitude following 20 seconds of isometric contraction.

Despite intensive investigations, no primary source for our patient’s small cell carcinoma was found. It is unlikely that this patient has primary lung cancer; she is a lifelong non-smoker, the chest investigations were all negative, and inguinal nodes would be a most unusual site for metastatic lung disease to first appear. Small cell carcinoma of the cervix, probably the next most common primary small cell carcinoma, also seems unlikely in view of her negative gynaecological findings. It is possible that her presenting tumour represents metastasis from an occult primary abdominal neoplasia of gastric or colonic origin. We think that this patient had LEMS causally related to non-pulmonary small cell carcinoma of unknown origin. The clinical, electrical, and immunological findings were identical to those of LEMS associated with small cell carcinomas of the lung. It is likely that the immunological stimulus for the development of LEMS is the same in this case as in cases associated with small cell carcinomas of the lung. Standard chemo- therapeutic treatment for small cell carci-

We thank the Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, for performing the volt-

tage gated calcium channel antibody assays. CLARE GALTON Department of Neurology DAMIEN THOMSON Department of Oncology RICHARD BOYLE Department of Neurology, Princess Alexandra Hospital, Brisbane, Australia

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Untreated hepatitis C may provoke myasthenia gravis

Recent reports have suggested a causative link between the use of interferon (IFN) treatment in chronic hepatitis C virus (HCV) infections and the development of myasthenia gravis.1 This presents something of a conundrum given that low dose IFN has been advocated as a treatment for myasthenia and seems to be well tolerated in those with established disease. Further confusion arises from the well established finding that untreated HCV infection itself leads to a markedly increased risk of developing various autoimmune conditions including rheumatoid arthritis, autoimmune thyroid disease, systemic lupus erythematosus, and polymyositis.1 A recent retrospective study examined the prevalence of HCV markers in a population of 83 French myasthenic patients and found evidence for previous infection in 4.8%.1 The expected prevalence in a control French population would be only about 1%. However, because patients exposed to plas- maphoresis or intravenous immunoglobulin are known to have increased concentrations of HCV markers, the authors concluded that their result reflected the treatment histories of their patients. Nevertheless, in the absence of any subgroup analysis, it is equally possible that HCV infection itself is able to trigger the development of myasthenia.

We report on a 35 year old male patient with established chronic HCV infection who devel-

oped myasthenia gravis in the absence of any treatment for his liver disease. The patient had acquired hepatitis C through intravenous drug misuse several years earlier and had a positive polymerase chain reaction for HCV RNA (104 copies/ml) in the absence of overtly deranged liver function. He presented to the neurology clinic with a short history of ptosis, bulbar dys-

function, and proximal weakness, all of which were fatiguable. A clinical diagnosis of myasthenia was supported by a positive edrophonium test and electrophysiological investigations including single fibre EMG. An assay for acetylcholine receptor autoantibodies was negative, however, as was the remainder of an autoantibody screen. Routine blood tests were all normal with the exception of a mild hypergammaglobulinaemia (IgG concentrations 21.6 g/l). Thorax CT was normal and liver biopsy disclosed mild portal tract lymphocytic infiltration in the absence of cirrhosis. His symptoms improved markedly with pyri-

doostigmine therapy and a course of intravenous immunoglobulin before an un-

expected thymectomy.

The response to HCV infection can lead to a plethora of immune and autoimmune disturbances.2 The development of myas- thenia, however, has not previously been directly linked to HCV infection. Rather, in the two cases of myasthenia and HCV infection reported to date,1 IFN treatment for hep-

titis is implicated as the important causative factor. Our case shows the possibility that HCV infection alone can trig-

ger generalised myasthenia. This scenario presents a potential therapeutic dilemma as immunosuppressive therapy for myasthenia, especially corticosteroids, may be expected to exacerbate the liver damage caused by hepatitis C and hasten the development of cirrho-

sis. Furthermore, many alternative immunosuppressants are hepatotoxic. If our patient were to develop worsening myasthenic symp-
toms, cyclosporin may represent the treat-

ment modality of choice.

BOOK REVIEWS


The Colour Guide series covers many specialties, and takes the form of 50-60 of page openings with illustrations on one side and explanatory text on the other. The illustrations of this second edition covering neurology are excellent, and the text clear and concise.

The “blurb” on the back of this short, well presented neurological picture book de-
scribes its format as user friendly, ideal for examination preparation, and reviewing a wide selection of clinical material. I agree!

This book is a comprehensive account of the current state of knowledge and practice of spinal cord disease. It is a multiauthor book, is well illustrated and referenced, and the bibliography is comprehensive. By their very nature, multiauthor books run the risk of repetition but editorial control has clearly kept this to a minimum. Nevertheless the inquisitive reader may find that he has to consult several chapters to extract all available information on a particular topic.

The book has chapters on anatomy, neuropathology, spinal electrophysiology, and clinical features of spinal cord disease but they are scattered throughout the first half of the book, which runs, in total, to 600 pages. By preference I would have put these chapters at the beginning, to set the scene for the numerous and comprehensive accounts of spinal cord disease which follow. In all, there are 32 chapters covering such diverse problems as decompression sickness, spinal cord repair after injury, and psychosexual aspects of spinal cord disease. The “bread and butter” of neurological practice, spinal cord compression in all its guises, is well dealt with. I found some of the chapters rather short—perhaps the five page chapter on hazards of lumbar puncture could, for example, have been incorporated into a larger chapter on the investigation of spinal cord disease. I particularly enjoyed the chapters on spinal tumours and degenerative disease. The chapter on clinical features of spinal cord disease was, in general, a good account although I am not sure that I would agree with the assertion that astereognosis and graphaesthesia are signs of posterior column disease.

As well as exercising control over errors of duplication, editors of multiauthor books need to police contributions for errors of omission, which in some ways is a more difficult task. For the most part the authors are to be congratulated on their success in this regard although there are some topics which I would have liked to see covered more fully. Radiation myelopathy, for example, is dealt with under pathology but not any of the clinical chapters and more discussion on interneuronitis and its aetiology would have been useful. In fact, given the breadth of topics this book deals with, I am a little surprised that neuroimmunology does not have a chapter to itself.

My criticisms are minor. This is a useful book for the practising clinical neurologist and would be a welcome addition to any departmental library.

DAVID DICK


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