LETTERS

Apolipoprotein E and neurocognitive outcome from coronary artery surgery

The apolipoprotein E (apoE) gene (APOE) is polymorphic with three alleles, e2, e3, and e4, which give rise to three isoforms, E2, E3, and E4. Many reports have now described a strong association between the e4 allele and risk of developing late onset Alzheimer’s disease as the result of the E4 isoform binding to β-amyloid protein and accelerating the deposition of amyloid, which is the main constituent of senile plaques. The APOE e4 allele also appears to be associated with deposition of β-amyloid after traumatic brain injury, which is also accompanied by an increased APOE expression in the central and peripheral nervous systems.

Neurological and cognitive decrements are well documented complications of coronary artery bypass grafting (CABG) surgery. Given that APOE e4 is associated with deposition of β-amyloid after traumatic brain injury, and poor neurological outcome after subarachnoid haemorrhage and stroke, it may also adversely influence neurocognitive outcome after CABG surgery. In a preliminary report, Tardiff and colleagues found that the APOE e4 allele was associated with greater risk of cognitive impairment, especially in those patients with lower educational levels. More recently, Steed and colleagues were unable to replicate the findings in a larger study. However, both of these studies had low incidences of APOE e4 allele, and thus its role remains equivocal.

Previously, we have reported that palpable aortic atheroma and a preoperative neurological deficit are risk factors for a decline in cognitive test battery found that 52% of the test score variance before surgery on these six tests was explained by one component, validating the use of a General Cognitive Factor. The cognitive tests’ z scores were summed to obtain an overall General Cognitive Score, which was shown to have a very high correlation (r = 0.998) with the General Cognitive Factor.

Blood (2.7 ml) was collected into potassium/EDTA (1.2 mg/ml) at the three month follow up appointment, and DNA was extracted for APOE genotyping. Fifty-two patients were APOE e4 negative and 34 were APOE e4 positive. The allele frequencies for APOE e2, APOE e3, and APOE e4 were 0.07 (12/172), 0.62 (103/172), and 0.21 (37/172) respectively. The incidence of palpable aortic atheroma (χ² = 0.536, p = 0.464) and preoperative (χ² = 0.724) and postoperative (χ² = 2.44, p = 0.118) neurological deficits were not significantly affected by the APOE e4 allele.

We tested the hypothesis that people with one or more APOE e4 alleles would have a worse cognitive outcome after CABG surgery. Thus, analysis of covariance, follow up cognitive score was the outcome variable, preoperative cognitive score was controlled by entering it as a covariate, and APOE e4 status was a between subjects factor. With α set at 0.05 and the use of a two tailed test, the power of this study to detect different sized effects (in standard deviation units) in the primary outcome (General Cognitive Score) between the APOE e4 positive and APOE e4 negative groups was as follows: 61% at SD difference of 0.5; 76% at 0.6; 88% at 0.7; 94% at 0.8.

Verbal fluency was adversely affected after CABG surgery by the presence of the APOE e4 allele (F = 6.31, p = 0.014). However, possession of the APOE e4 allele had no significant influence of the General Cognitive Score (F = 0.261, p = 0.611) or any of the other cognitive tests (table 1). We have not shown any association between APOE e4 and general cognitive or neurological changes after CABG surgery. Verbal fluency was adversely affected by the presence of the APOE e4 allele, but this finding should be interpreted cautiously as it may be a type 1 statistical error.

Our findings neither fully support nor refute earlier reports. Reasons that may account for these contrasting findings are as follows.

The younger mean age of our study population (59 compared with 61 and 64 years) may limit the expression of APOE e4 and cognitive change but heighten the association of APOE e4 with coronary artery disease. This may account for our greater APOE e4 allele frequency (0.21 compared with 0.13 and 0.17) and failure to show an association with a decline in general cognitive ability.

Our cognitive test battery included verbal fluency, a measure of executive function, which was not specifically tested in the other studies. Deficits in executive functions influence a person’s ability to work, function appropriately at home, and maintain social relationships. These are often the changes that patients complain about after CABG surgery, and this cognitive domain has not been extensively investigated to date.

We assessed cognitive performance at 12 weeks as compared with six weeks in the other studies. The longer follow up time may unmask the interaction of APOE e4 and brain injury after CABG surgery in the cognitive domains related to executive function. Long term follow up at one or two years may show a greater affect of APOE e4 on general cognitive performance.

We found no association between APOE genotype and cognitive scores before surgery, which is in agreement with previous studies. In terms of recognised risk factors for cognitive decline, we found no association between APOE genotype and the presence of palpable aortic atheroma or neurological deficit before surgery.

In conclusion, this study does not support the hypothesis that the APOE e4 allele confers additional risk of general cognitive or neurological decline after CABG surgery. Rather, it implies a specific effect on long term outcome of verbal fluency that warrants further investigation.

Acknowledgement

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Table 1: Influence of APOE e4 on individual cognitive tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-score mean (SD)</th>
<th>Post-score mean (SD)</th>
<th>Mean difference (95% CI) e4 (+) - e4 (−)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVLT</td>
<td>e4 (−)</td>
<td>74 (11)</td>
<td>79 (9)</td>
<td>0.71 (2.7 to 4.1)</td>
<td>0.176</td>
</tr>
<tr>
<td></td>
<td>e4 (+)</td>
<td>73 (14)</td>
<td>78 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASAT</td>
<td>e4 (−)</td>
<td>80 (20)</td>
<td>86 (18)</td>
<td>0.78 (−3.3 to 4.8)</td>
<td>0.147</td>
</tr>
<tr>
<td></td>
<td>e4 (+)</td>
<td>78 (18)</td>
<td>83 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail making</td>
<td>e4 (−)</td>
<td>126 (52)</td>
<td>123 (43)</td>
<td>0.73 (−1.8 to 19.6)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>e4 (+)</td>
<td>127 (56)</td>
<td>123 (66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>e4 (−)</td>
<td>55 (14)</td>
<td>55 (15)</td>
<td>5.2 (1.1 to 9.4)</td>
<td>6.310</td>
</tr>
<tr>
<td></td>
<td>e4 (+)</td>
<td>58 (15)</td>
<td>52 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegboard</td>
<td>e4 (−)</td>
<td>170 (32)</td>
<td>171 (35)</td>
<td>6.9 (−5.5 to 19.1)</td>
<td>1.270</td>
</tr>
<tr>
<td></td>
<td>e4 (+)</td>
<td>178 (40)</td>
<td>169 (47)</td>
<td></td>
<td></td>
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<tr>
<td>WAIS</td>
<td>e4 (−)</td>
<td>112 (20)</td>
<td>117 (21)</td>
<td>−0.393 (−4.7 to 3.9)</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>e4 (+)</td>
<td>108 (20)</td>
<td>113 (23)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APOE e4 (+), Apolipoprotein epsilon 4 allele present; APOE e4 (−), apolipoprotein epsilon 4 allele absent; AVLT, auditory verbal learning test; PASAT, paced auditory serial addition task; Pegboard, grooved peg board; Trail making, trail making parts A and B; WAIS, Wechsler adult intelligence scale revised.

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Interferon β-1a treatment of corticosteroid sensitive polymyositis

Inflammatory myopathies may occur with malignancies or collagenosis (lupus erythematosus, rheumatoid arthritis, overlap syndromes) or be associated with retroviral disease.

Muscle biopsy and corticosteroid treatment

Necrotising myositis was diagnosed based on CK from approximately 3000 U/l to 1000 U/l, the reduction was not sustained. During the course of the disease, two hospitals performed biopsies 3 and 11 years after the onset of symptoms.

Beta interferon was given in the treatment of inflammatory myopathies.

ACKNOWLEDGEMENT

Japanese cases of familial hemiplegic migraine with cerebellar ataxia carrying a T666M mutation in the CACNA1A gene

Familial hemiplegic migraine (FHM) is an autosomal dominantly inherited disorder characterised by migraine attacks preceded by transient hemiparesis. In 1993, Joutel et al. mapped the locus for FHM to chromosome 1p13 by linkage analysis, and the causative gene was subsequently identified as CACNA1A, encoding a P/Q-type calcium channel α1A subunit. Cases involving the CACNA1A gene have been found in approximately 50% of FHM cases, and linkage to chromosome 1 has been shown in some of the other families.

FHM with progressive cerebellar ataxia (FHM/PCA) has been described, in cases carrying CACNA1A mutations. Other clinical phenotypes associated with ataxia may also be caused by mutations in the CACNA1A gene, which includes episodic ataxia type 2 (EA-2) and spinocerebellar ataxia type 6 (SCA6). EA-2 is characterised by recurrent episodes of attacks of cerebellar ataxia accompanied by interictal nystagmus. In SCA6, expansion of a CAG trinucleotide repeat coding for a polyglutamine stretch at the C-terminus of the CACNA1A has been identified as the causative mutation.

These data suggest that mutations in the CACNA1A gene can lead to a broad spectrum of clinical presentations, and the relation...
between clinical phenotypes and genotypes in FHM has been discussed in recent reports. Here we describe a Japanese family with FHM/PCA, and discuss implications for genotype–phenotype correlations.

Case 1
A 67 year old woman was admitted to our hospital in 1995 for evaluation of cerebellar ataxia. She was born to first cousin parents. At age 30, she had an episode of unconsciousness for three days. She had suffered from reversible hemiparesis followed by throbbing migraine headaches lasting for several hours since she was 47. The hemiplegic episodes recurred often until the age of 52 years but gradually improved in frequency and severity without any treatment. She had begun to experience difficulty in walking since the age of about 62 years, and her gait difficulty had gradually progressed.

On neurological examination at the age of 67 years, she had horizontal gaze nystagmus and mild dysarthria. Her gait was ataxic, and she could stand on one foot only for a few seconds. Her tandem gait was unstable. Mild limb ataxia was also noted. Her muscle power was normal. No abnormal findings were noted in her sensory or autonomic nervous system. Her complete blood count, electrolytes, serum creatinine, and glucose levels were normal. Cerebrospinal fluid protein and sugar levels were normal. Brain magnetic resonance imaging (MRI) showed marked cerebellar vermian atrophy, but no areas of abnormal intensity were detected (fig 1). Single photon emission computed tomography (SPECT) showed low perfusion of the cerebellum. During her hospital admission, a throbbing migraine attack (SPECT) showed low perfusion of the cerebellum. During her hospital admission, a throbbing migraine attack followed by the sudden onset of numbness and dysesthesia of the left upper limb were recorded.

Case 2
A 63 year old man, a son of case 2, had had migraine and mild truncal and limb incoordination, and mild dysarthria. His gait was ataxic, and he could stand on one foot only for a few seconds. His tandem gait was unstable. Mild limb ataxia was also noted. Her muscle power was normal. No abnormal findings were noted in her sensory or autonomic nervous system. Her complete blood count, electrolytes, serum creatinine, and glucose levels were normal. Cerebrospinal fluid protein and sugar levels were normal. Brain magnetic resonance imaging (MRI) showed marked cerebellar vermian atrophy, but no areas of abnormal intensity were detected (fig 1). Single photon emission computed tomography (SPECT) showed low perfusion of the cerebellum. During her hospital admission, a throbbing migraine attack followed by the sudden onset of numbness and dysesthesia of the left upper limb were recorded.

References

Cellular schwannoma of the posterior fossa
Schwannomas are slowly growing, non-invasive neoplasms derived from Schwann cells and usually arise from peripheral nerves. They may also arise from cranial nerves, most commonly the vestibulocochlear nerve (VIIIth nerve). In this situation, they are sometimes associated with neurofibromatosis type 2 (NF2). The cellular variety of schwannoma has been described as a distinct “pseudosarcomatous” entity, composed of hypercellular areas of spindle shaped cells that can easily be mistaken for a malignant tumour. There are fewer than 60 reported cases of intraparenchymal schwannoma in which the tumour is not associated with any cranial or peripheral nerves. In 1991, a 37 year old woman presented with left sided facial pain and numbness of several weeks’ duration, accompanied by blurring of vision in her left eye. Computed tomography revealed a left trigeminal schwannoma. This was resected and, macroscopically, the tumour appeared to have been completely removed. Histology showed a schwannoma of normal cellularity with some areas composed of compact spindle cells arranged in short bundles and other areas with cells set in a loosely textured matrix containing some large, irregular vessels. There were only occasional mitotic figures and the tumour showed diffuse positivity for S100. She developed a recurrence in 1994 and underwent further treatment, with no residual tumour growth and no unusual clinical or radiological abnormalities. She was reviewed annually from 1995 and treated with stereotactic radiosurgery. She was followed up with regular cranial magnetic resonance (MR) scanning and a scan in March 1998 appeared satisfactory, with minimal further tumour growth and no unusual clinical or radiological abnormalities.
A more rapid clinical course, with marked neurological deficits.\(^5\) Comparison between the two MR scans (fig 1A and B) shows that the cellular schwannoma had grown to 20 mm diameter in eight months (that is, a growth rate of 30 mm a year). This is faster than in any previously published report.

However, it is possible that the cervicomedullary tumour was a metastasis from the previous trigeminal schwannoma. This cervicomedullary tumour was originally considered to be benign on the basis of the histological findings, but was later found to have a proliferation index of 22%—surprisingly high considering the relative sparsity of identifiable mitotic figures.\(^4\) As our patient developed spinal lesions that were suggestive of metastases (unfortunately these were not sectioned at necropsy), the possibility of the original foramen magnum tumour being a metastasis from the previous trigeminal schwannoma is more likely. The difficulty in determining whether or not these lesions are malignant has important implications for the surgeon when considering how aggressive to be with treatment.

Another possibility is that our patient may have had NF2 or schwannomatosis. Tumours in both of these conditions behave differently from solitary cases, with faster growth rates and a more fulminant clinical course.\(^7\) In our patient, genetic studies showed no alteration in the NF2 gene (although these are only moderately polymorphic and slightly more frequent mitotic figures than the previous specimens. There was a large central area of necrosis and it was diffusely positive for p100. The appearance was that of a cellular schwannoma. The proliferative index was measured (two years later) using MIB1 (Ki67) antibody and counting automatically using the Kontron 3000 system. The result, counting 1000 nuclei, was 22%.

In early 2000, the patient underwent genetic testing which revealed no alterations in the NF2 gene.

In March 2000 she presented again with neck pain and headaches. An MR scan showed recurrence of the tumour at the foramen magnum. This was resected, and the histology indicated recurrences of the cellular schwannoma. Her postoperative recovery was complicated by a breakdown of her wound, which revealed a 20 mm diameter tumour through the foramen magnum to the posterior arch of C1 (fig 1B).

In summary, our unusual case of a cellular schwannoma of the posterior fossa underlines the difficulty in determining the exact nature of these lesions, both histologically and clinically. Despite benign histological appearances, there was an aggressive clinical course. The aggressive behaviour of the tumour, as well as the histological findings (in particular, a lack of Verocay bodies, which are common in schwannomatosis\(^7\)), suggest that this diagnosis was unlikely.

In summary, our unusual case of a cellular schwannoma of the posterior fossa underlines the difficulty in determining the exact nature of these lesions, both histologically and clinically. Despite benign histological appearances, this posterior fossa tumour behaved as a malignant peripheral nerve sheath tumour (MPNST). This is the first time that growth rate has been reported for this particular type of tumour.

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References

Multiple cerebral aneurysms and the Diamond-Blackfan syndrome

A 17 month old girl presented with pallor, lethargy, and tiredness. She had an uncompli- cated birth and no delays in attaining her developmental milestones. There was no family history of either neurological, haemato- logical, or connective tissue disorders. There was no preterm exposure to noxious sub- stances. On examination physical features were within normal limits. She was noted to have a squint in the left eye but no other craniofacial or musculoskeletal abnormalities. Investigations revealed a macrocytic anaemia (Hb 3.9 g/dl, MCV 105 fl) and on haemoglobin electrophoresis there was a raised level of HBF. Bone marrow examination showed erythrocyte adenine deaminase (ADA) levels that were elevated and a diagnosis of Diamond-Blackfan anaemia was made.

Three months after presentation there was no change in red cell indices, and treatment with high dose prednisolone (2 mg/kg) was begun. There was marked symptomatic improvement within four weeks, without the need for blood transfusion. Maintenance prednisolone (1 mg/kg) was discontinued at the age of four years, by which stage her Hb had normalised while the MCV remained raised (100 fl). There were no relapses follow- ing cessation of steroids.

At the age of nine years, she suffered recurrent small pneumothoraces. By the age of 16 she had become a heavy smoker and pre- sented with a sudden onset of frontal headache with signs of meningism, but no other abnormalities. Cranial computed tomography showed diffuse subarachnoid haemorrhage in the right perimesencephalic region extending into the right Sylvian fissure, as well as early hydrocephalus. Subsequent cerebral angiography revealed multiple aneurysms: a right internal carotid artery aneurysm, a left middle cerebral artery aneurysm, a left posterior communicating artery aneurysm, and a small right middle cerebral artery aneurysm (fig 1A).
cerebral aneurysms in a patient with this condition is likely to represent an incidental but novel finding. However, if subtle vascular abnormalities are an inherent feature of Diamond-Blackfan anaemia, the possibility is raised that the development of the cerebral aneurysms in this patient may have been accelerated by steroid treatment. As this is the first reported case of cerebral aneurysms in a patient with Diamond-Blackfan anaemia, this seems unlikely as there are many patients with this disease in whom prolonged courses of high dose steroids have not resulted in intracranial vascular anomalies. Similarly, although superficial vascular fragility is a recognised manifestation of steroid treatment, there are no reports of ruptured cerebral aneurysms in association with prolonged high dose steroids.

It has been suggested that mutations in the ribosomal protein encoding gene (RPS19) on chromosome 19, occurring at critical points in embryonal development, may account for features of this syndrome.

Whatever the aetiology of the aneurysms, their management continues to be based on clinical and angiographic findings following subarachnoid haemorrhage, and favourable cases occlusion of the aneurysm is indicated. Management of unruptured incidental aneurysms remains difficult. Current scientific evidence suggests that the risk of spontaneous rupture of incidental cerebral aneurysms is less than 0.05% a year, and following a subarachnoid haemorrhage it increases to approximately 0.5% a year. This is independent of underlying predisposing conditions, but is influenced by the size and location of the aneurysm. In addition, very little is known about the factors that affect the rate of growth of cerebral aneurysms in patients with predisposing conditions, and it is unknown whether incidental aneurysms progress to spontaneous rupture. In the case we describe, we have adopted a pessimistic view because of the preceding appearances and an apparently rapid rate of aneurysm growth.

In view of the distribution of blood products, the right internal carotid aneurysm was thought to have ruptured, and three days after admission it was successfully clipped. Surgical appearances were of very thin walled aneurysms, unlike the usual appearance of degenerate aneurysms. Four weeks later, both the left middle cerebral and the left posterior communicating artery aneurysms were occluded in a similar fashion, again without complication. Twenty two months after the subarachnoid haemorrhage, a terminal left middle cerebral artery aneurysm was clearly demonstrated on surveillance angiography (fig 1B). With hindsight this probably started as an infundibulum of the terminal left internal carotid artery (fig 1A). At this stage a conservative course was adopted. However, repeat angiography 12 months later showed enlargement of the clipped left posterior communicating artery aneurysm (fig 1C). Two years later, surveillance angiography demonstrated a significant increase in the size of the left posterior communicating artery aneurysm (fig 1D) and she subsequently underwent a further clipping of this aneurysm. During the surveillance period, follow up by a specialist geneticist excluded other predisposing conditions, including autosomal dominant polycystic kidney disease and Ehlers-Danlos syndrome type IV.

References
Plasmapheresis and Miller Fisher syndrome: analysis of 50 consecutive cases

Miller Fisher syndrome (MFS), characterised by the clinical triad of ataxia, ophthalmoplegia, and areflexia, is considered to be a variant form of Guillain-Barré syndrome (GBS). Large studies have shown that plasmapheresis and immunoglobulin treatment are beneficial for treating GBS. Because of the close relation between GBS and MFS, plasmapheresis may prove efficacious for treating MFS and has actually been tried in some cases. Moreover, because antibody to GQ1b is often present in serum from patients with MFS and is suggested to have a role in the pathophysiology of MFS, removing this antibody through plasmapheresis should have beneficial effects on patients with this syndrome. Although several reports have described possible plasmapheresis benefits for treating MFS, no one has compared its clinical effects in patients treated and not treated with plasmapheresis. We conducted a retrospective analysis of 50 consecutive patients with MFS to clarify whether plasmapheresis enhanced the speed of recovery.

Medical records of 53 patients with MFS seen at Chiba University Hospital or its affiliated hospitals between 1979 and 1999 were reviewed. These patients were described in our previous investigation of the natural course of MFS. Criteria for inclusion in the study were the clinical triad of MFS (ataxia, ophthalmoplegia, and areflexia) and MFS onset without major limb weakness or other signs suggestive of central nervous system involvement. Of the 53 patients who initially had the typical clinical triad of MFS laid down by Fujise, 11 had profound limb weakness and a GBS was diagnosed. Clinical data for the remaining 50 patients were therefore analysed. Twenty-two patients with MFS underwent plasmapheresis with a second filter (Tryptophan-immobilized column adsorbs immunoglobulin G anti-GQ1b antibody from Fisher’s syndrome: a new approach to treatment. Neurology 1996;46:1644–5).

References


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