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 E4 isoform binding to β-amyloid protein and accelerating the deposition of amyloid, which is the main constituent of senile plaques.1 The APOE e4 allele also appears to be associated with deposition of β-amyloid after traumatic brain injury, which is also accompanied by 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, Cardiff 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 their role remains equivocal.

Previously, we have reported that palpable aortic atheroma and a preoperative neurological deficit are risk factors for a decline in cognition after CABG surgery. Here we report the effect of the APOE e4 allele in 86 patients who formed a subgroup in that study.

The day before and three months after CABG surgery, a battery of cognitive tests and a structured neurological examination were completed. Factor analysis of the 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), 0.53 (90/172), and 0.40 (69/172) respectively. The incidence of palpable aortic atheroma (χ²=0.536, p=0.464) and preoperative (χ²=0.124, p=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, using 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: 81% at SD difference of 0.9; 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 on 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 change 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 I statistical error. Our findings neither fully support nor refute earlier reports.1 Reasons that may account for these contrasting findings are as follows.

The younger mean age of our study population (39 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.1 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.1 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.1 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.

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M J A Robson
Department of Anaesthesia, St Vincent’s Hospital, Melbourne, Australia
Interferon β-1a treatment of corticosteroid sensitive polymyositis

Inflammatory myopathies may occur with malignancies or collagenosis (lupus erythematosus, rheumatoid arthritis, overlap syndrome, or mixed connective tissue disease) or be associated with retroviral disease. Idiopathic inflammatory myopathies may present as dermatomyositis, inclusion body myositis, or polymyositis.

Most patients with polymyositis respond well to pulse treatment with corticosteroids. However, this treatment is usually restricted to short periods of time in an effort to contain disease activity and to taper corticosteroids below the cushing level. When the patient developed spontaneous fractures, all treatment was halted; however, the patient continued to deteriorate clinically. Thus, cyclophosphamide pulse therapy in combination with corticosteroid treatment was initiated. Although each pulse reduced the serum 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. Both biopsies confirmed the diagnosis of polymyositis that showed a mixed lymphocytic, monocytic, and mononuclear infiltrate. No sign of a storage disease or inclusion body myositis could be detected. At the age of 32 years, 17 years after the onset of symptoms, she was referred to our hospital.

On admission the patient was able to walk a maximum of 50 m with the help of aids, climb two steps, and stand with straightened knees. Longer distances required the use of a wheelchair. Physical examination showed proximal accentuated weakness of the limbs with predominant involvement of both legs. The deep tendon reflexes were reduced in the upper extremities and absent in the lower ones. The remaining physical examination was unremarkable. The patient refused additional diagnostic procedures including a rebiopsy and electromyography.

The patient was administered 22 μg of interferon β-1a subcutaneously (RebiFix®, Se- rono, Geneva, Switzerland) every other day. She tolerated the treatment well and steroid treatment was stopped permanently. After three and a half years of follow up with interferon β-1a treatment, CK concentration has stabilised at 600–1000 U/l and her severe symptoms have abated substantially. At her last visit, the patient was no longer confined to a wheelchair, walked inside her apartment without aids, and could climb one set of stairs. For longer distances she was still dependent on two walking aids.

This is, to the best of our knowledge, the first report of interferon β-1a treatment in polymyositis. Interferon β-1a treatment was initiated because it was a course of action that had not been tested before and other conventional immunosuppressive treatments proved ineffective or caused unacceptable side effects in this patient. Steroid treatment could be discontinued shortly after treatment with interferon β-1a was started. Moreover, disease activity was controlled for three years without requiring concomitant immunosuppressive drugs, suggesting that beta interferons have utility in patients who require long term treatment of the disease. Since the interferon β-1a treatment has never been stopped, we can not formally exclude the possibility that the improvement reflects the natural history of the disease. However, we believe this to be highly unlikely given the longstanding history of the disease in this patient. Controlled clinical trials are necessary to fully test the efficacy of interferon β-1a in the treatment of inflammatory myopathies. Indeed, one multicentre trial with interferon β-1a is underway. This study thus suggests that interferon β-1a may be a new therapeutic option in autoimmune diseases beyond multiple sclerosis, particularly in cases where established steroid regimens fail.
between clinical phenotypes and genotypes in FHM has been discussed in recent reports.4 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 50, she had an episode of unconsciousness for three days. She had suffered from reversible hemiparesis followed by throbbling migraine headaches lasting for several hours since she was 47. The hemiplegic episodes occurred 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 atactic, 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 vermal 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 throbbling migraine attack followed by the sudden onset of numbness and dysaesthesia of the left upper limb were recorded.

Case 2
A 63 year old woman, a younger sister of case 1, had slight difficulty in speaking since the age of 36. Dysarthria, truncal ataxia, limb incoordination, and gaze nystagmus were noted by a neurologist at that time, and she was diagnosed as having spinocerebellar degeneration (autosomal dominant spinocerebellar ataxia presenting with pure cerebellar ataxia). At the age of 40, she had an episode of unconsciousness lasting two days (details unknown). She began to show a staggering gait at the same age. She had been suffering from reversible hemiparesis followed by throbbling migraine headaches since the age of 55. Neurological examination revealed horizontal gaze nystagmus, mild dysarthria, and mild truncal and limb incoordination, similar to those of her elder sister. The presence of cerebellar atrophy was confirmed by MRI (data not shown).

Case 3
A 37 year old man, a son of case 2, had had progressive gait and speech disturbances since childhood. He had never had migraine headache episodes. Neurological examination showed limb and truncal ataxia, nystagmus, scanning speech, hyperreflexia, and neck dystonia. MRI revealed cerebellar atrophy, particularly in the vermis.

Genetic features
Mutational analyses of the CACNA1A gene were performed in cases 1 and 2 by direct nucleotide sequence analysis of exons 4, 16, 17, and 36, in which the first four missense mutations—namely, R192Q, T666M, V714A and I1181L—were reported.5,6 The analysis was performed using an ABI377 automated sequencer with cycle sequencing. A C→T transition (T666M) in the CACNA1A gene was identified in both case 1 and case 2. The number of CAG repeat units of the CACNA1A gene of case 1 was 11/11. As molecular diagnosis was performed only in cases 1 and 2, there remains the possibility of a phenocopy in case 3.

Comment
Although FHM cases confirmed by DNA analyses have been reported in the USA, the United Kingdom, Italy, France, Netherlands, and Denmark, this is the first report confirming the mutation in the CACNA1A gene in FHM cases in Japan. Compared with other FHM cases associated with cerebellar ataxia, characteristic clinical features of the cases of the two sisters are that migraine attacks began in their fifth decade, and that the younger sister had shown only cerebellar ataxia for more than 10 years before her first migraine attack.

The findings in our patients emphasise that the clinical presentation of FHM/PCA is more varied than previously described and that even the same mutation can lead to considerably different clinical presentations, suggesting that other genetic or environmental factors may modify the phenotype.

T Takahashi, S Igarashi, T Kimura, I Hozumi, I Kawachi, O Onodera, H Takano, M Saito, S Tsuji
Department of Neurology, Brain Research Institute, Niigata University, 1-757 Asahimachi, Niigata 951-8585, Japan
Correspondence to: Professor Tsuji; tsuji@cc.niigata-u.ac.jp

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Cellular schwannoma of the posterior fossa
Schwannomas are slowly growing, non-invasive neoplasms derived from Schwann cells and usually arise from peripheral nerves.7 They may also arise from cranial nerves, most commonly the vestibular part of the 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.8 There are fewer than 60 reported cases of intraparenchymal schwannoma9 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 a further, presumed complete, resection. However, a remnant was discovered in 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 tumour elsewhere in her brain (fig 1A).

She presented eight months later (now aged 44 years) with a two month history of increasing posterior and right sided neck pain. She also complained of headaches but had no other features of raised intracranial pressure. Examination was unremarkable except for the longstanding left trigeminal

Figure 1 T1 weighted magnetic resonance imaging showing marked atrophy of the cerebellar vermis.
nerve palsy. A further MR scan was obtained and this revealed a 20 mm diameter tumour behind the brain stem, which was extending through the foramen magnum to the posterior arch of C1 (fig 1B).

The tumour was removed using a posterior approach. Macroscopically it originated from the posterior surface of the brain stem and was remote from any peripheral nerve. Histology showed tumour composed exclusively of compact spindle cells arranged in short bundles and with focal nuclear palisading. It was more cellular than previously and showed moderate nuclear polymorphism and slightly more frequent mitotic figures than the previous specimens. There was a large central area of necrosis and it was diffusely positive for S100. The appearance was that of a cellular schwannoma. The proliferative index was measured (two years later) using MB1 (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, following which she developed pseudomonas meningitis. This led to the development of hydrocephalus, which required external ventricular drainage. An MR scan two months after the operation showed several lesions in the mid-thoracic spinal cord, which were suggestive of metastases (unfortunately these were not sectioned at necropsy), the possibility that the original foramen magnum tumour was 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. In our patient, genetic studies showed no alteration in the NF2 gene (although these are only 60–70% sensitive). Also, she had a trigeminal rather than a vestibular schwannoma. These two factors suggest that NF2 is less likely but not impossible. Schwannomatosis is characterised by multiple non-vestibular schwannomas, in the absence of meningiomas, intraspinal ependymomas, and other clinical signs of NF2. Although this is consistent with our case, the aggressive behaviour of the tumour, as well as the histological findings (in particular, a lack of Verocay bodies, which are common in schwannomatosis), 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.

A L Green, J S Yeh, H L Brydon
Department of Neurosurgery, North Staffordshire Royal Infirmary, Stoke on Trent ST4 6TA, UK
M P Carey
Queen Elizabeth Hospital, Birmingham, UK
Correspondence to: Mr Green; a.l.green@virgin.net

References

Multiple cerebral aneurysms and the Diamond-Blackfan syndrome

A 17 month old girl presented with pallor, lethargy, and tiredness. She had an uncomplicated birth and no delays in attaining her developmental milestones. There was no familiar history of either neurological, haematological, or connective tissue disorders. There was no preterm exposure to noxious substances. On examination physical features were within normal limits. She was noted to have a splint 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 erythroblast hypoplasia only. Erythrocyte adenosine deaminase (ADA) levels were normal and the patient had normalisation of Hb while on high dose prednisolone (2 mg/kg) was begun. This was marked asymptomatic 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 following 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 presented 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).
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 in this condition and consider the presence of coexisting conditions such as type III Ehlers-Danlos syndrome.

Diamond-Blackfan anaemia results from a maturation abnormality in the bone marrow erythroid series, and is usually associated with other anomalies including craniofacial dysmorphism and musculoskeletal defects, particularly abnormalities of the thumb. Genetic advances in the last few years have linked the Diamond-Blackfan (DBA) phenotype to a locus on chromosome 19 in approximately 25% of familial and sporadic cases of Diamond-Blackfan anaemia. The gene encodes a ribosomal protein (RPS19) which is ubiquitously expressed in both haematopoietic and non-haematopoietic tissues, though its precise role is not known.

The incidence of Diamond-Blackfan anaemia is low, and the finding of multiple cerebral aneurysms in a young non-anaemic patient is an extremely rare occurrence. We report the first case of multiple cerebral aneurysms in a young woman diagnosed as having Diamond-Blackfan anaemia.

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 internal carotid 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 conservatively indicated approach was adopted. However, repeat angiography 12 months later showed enlargement of the clipped left posterior communicating artery aneurysm (Fig 1D). Two years later, surveillance angiography demonstrated a significant increase in the size of the left posterior communicating artery aneurysm (Fig 1D) and the patient 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.

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 the clinical and angiographic findings following subarachnoid haemorrhage, and in 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 unproven whether incidental aneurysms progress to spontaneous rupture. In the case we describe, we have adopted a pessimistic view because of the operative appearances and an apparently rapid rate of aneurysm growth.

R A Trivedi, C Watts, P J Kirkpatrick
University Department of Neuroradiology, Addenbrooke’s Hospital, Cambridge CB2 2QQ, UK
J H Gillard
University Department of Radiology, Addenbrooke’s Hospital
Correspondence to: Mr Kirkpatrick; pkj21@medschl.cam.ac.uk

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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 plasmapheresis1 and immunoglobulin treatment2 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 in both MFS and Miller Fisher syndrome. Although several reports have suggested the possible efficacy of plasmapheresis treatment for MFS,3,4 it has not been independently confirmed. Our previous investigation of the natural course of MFS5 revealed that, for patients with typical MFS, plasmapheresis has been established to be an efficacious treatment for GBS.6 Such patients would require immunotherapy. We found that, for patients with typical MFS, plasmapheresis had no effect on recovery speed.

There could be a number of limitations in our study. Firstly, it is a retrospective one and did not involve a large enough number of patients to reach a firm conclusion. Secondly, our plasmapheresis method based on the use of a second filter may have affected the results. In Japan, second filters are often used to reduce the loss of albumin. As a consequence, fewer immunoglobulins would be removed in our method than in simple plasma exchange. Six months after onset, almost all the patients with MFS were symptom free, indicating the naturally good course of the disorder, as described elsewhere.7 Lack of a significant difference in the speeds of recovery of the two patient groups is probably due to the small number of patients in each subgroup of patients who had severe disability (inability to walk because of ataxia or complete total ophthalmoplegia) and those with bulbar palsy, the time required to resolve the ataxia and ophthalmoplegia did not differ significantly between those who received plasmapheresis (all underwent plasmapheresis more than four times) and those who did not. Nor did the interval from onset to the start of plasmapheresis affect the speed of the clinical recovery from ataxia and ophthalmoplegia of the patients with MFS. Six months after the onset of neurological symptoms, except for areflexia, almost all the patients with MFS were symptom free, irrespective of whether they received plasmapheresis.

Our findings failed to show that plasmapheresis hastens the amelioration of ataxia and ophthalmoplegia in patients with MFS, whereas some reports have suggested the possible efficacy of plasmapheresis treatment for MFS.4 Because MFS is a self-limiting disease and recovery is spontaneous, a case-control study is needed to evaluate the effects of plasmapheresis treatment. Our findings do not completely negate the efficacy of plasmapheresis in every instance of MFS. On the basis of two cases, Yeh et al.8 reported that plasmapheresis is indicated for the treatment of complicated MFS in which there is profound ataxia, severe bulbar palsy, and respiratory and motor involvement. Although our study excluded patients with MFS who had prominent muscle weakness (Miller-Fisher-Guillain-Barré overlap syndrome), plasmapheresis has been established to be an efficacious treatment for GBS.9 Such patients would require immunotherapy. We found that, for patients with typical MFS, plasmapheresis had no effect on recovery speed.

Figure 1. Cumulative probabilities of recovery from ataxia (A) and ophthalmoplegia (B) in patients with Miller Fisher syndrome based on Kaplan-Meier curves.

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