

**LETTERS**

**Apolipoprotein E and neurocognitive outcome from coronary artery surgery**

The apolipoprotein E (apoE) gene (APOE) is polymorphic with three alleles, ε2, ε3, and ε4, which give rise to three isoforms, E2, E3 and E4. Many reports have now described a strong association between the ε4 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.<sup>1</sup> The APOE ε4 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 ε4 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<sup>2</sup> found that the APOE ε4 allele was associated with greater risk of cognitive impairment, especially in those patients with lower educational levels. More recently, Steed and colleagues<sup>3</sup> were unable to replicate the findings in a larger study. However, both of these studies had low incidences of APOE ε4 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 cognition after CABG surgery.<sup>4</sup> Here we report the effect of the APOE ε4 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 ε4 negative and 34 were APOE ε4 positive. The allele frequencies for APOE ε2, APOE ε3, and APOE ε4 were 0.07 (12/172), 0.72 (123/172), and 0.21 (37/172) respectively. The incidence of palpable aortic atheroma ( $\chi^2=0.536$ ,  $p=0.464$ ) and preoperative ( $\chi^2=0.124$ ,  $p=0.724$ ) and postoperative ( $\chi^2=2.44$ ,  $p=0.118$ ) neurological deficits were not significantly affected by the APOE ε4 allele.

We tested the hypothesis that people with one or more APOE ε4 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 ε4 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 ε4 positive and APOE ε4 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 ε4 allele ( $F=6.31$ ,  $p=0.014$ ). However, possession of the APOE ε4 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 ε4 and general cognitive or neurological change after CABG surgery. Verbal fluency was adversely affected by the presence of the APOE ε4 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.<sup>2,3</sup> Reasons that may account for these contrasting findings are as follows.

The younger mean age of our study population (59 compared with 61<sup>2</sup> and 64<sup>3</sup> years) may limit the expression of APOE ε4 and cognitive change but heighten the association of APOE ε4 with coronary artery disease. This may account for our greater APOE ε4 allele frequency (0.21 compared with 0.13<sup>2</sup> and 0.17<sup>3</sup>) 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.<sup>5</sup> 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.<sup>2,3</sup> The longer follow up time may unmask the interaction of APOE ε4 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 ε4 on general cognitive performance.

We found no association between APOE genotype and cognitive scores before surgery, which is in agreement with previous studies.<sup>2,3</sup> 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 ε4 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**

This work was supported by Wellcome Trust Grant 050190.

**M J A Robson**

Department of Anaesthesia, St Vincent's Hospital, Melbourne, Australia

**Table 1** Influence of APOE ε4 on individual cognitive tests

Test	Pre-score mean (SD)	Post-score mean (SD)	Mean difference (95% CI) ε4 (-) - ε4(+)	F	p
AVLT					
ε4 (-)	74 (11)	79 (9)	0.71 (-2.7 to 4.1)	0.176	0.676
ε4 (+)	73 (14)	78 (13)			
PASAT					
ε4 (-)	80 (20)	86 (18)	0.78 (-3.3 to 4.8)	0.147	0.703
ε4 (+)	78 (18)	83 (16)			
Trail making					
ε4 (-)	126 (52)	123 (43)	0.73 (-18.1 to 19.6)	0.001	0.938
ε4 (+)	127 (56)	123 (66)			
Verbal fluency					
ε4 (-)	55 (14)	55 (15)	5.2 (1.1 to 9.4)	6.310	0.014
ε4 (+)	58 (15)	52 (11)			
Pegboard					
ε4 (-)	170 (32)	171 (35)	6.9 (-5.5 to 19.1)	1.270	0.262
ε4 (+)	178 (60)	169 (47)			
WAIS					
ε4 (-)	112 (20)	117 (21)	-0.393 (-4.7 to 3.9)	0.032	0.857
ε4 (+)	108 (20)	113 (23)			

APOE ε4 (+), Apolipoprotein epsilon 4 allele present; APOE ε4 (-), 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, Weschler adult intelligence scale revised.

**R P Alston, P J D Andrews**

Anaesthesia, Critical Care and Pain Medicine  
Section, Department of Clinical and Surgical  
Sciences, University of Edinburgh, Edinburgh,  
Scotland, UK

**P R Wenham**

Department of Clinical Biochemistry, Western  
General Hospital

**M J Souter**

Department of Anesthesiology, Harborview Medical  
Centre, Seattle, WA, USA

**I J Deary**

Department of Psychology, University of Edinburgh

Correspondence to: Professor Deary, Department of  
Psychology, University of Edinburgh, 7 George  
Square, Edinburgh EH8 9JZ, Scotland, UK;  
I.Deary@ed.ac.uk

**References**

- 1 **Saunders AM**, Strittmatter WJ, Schmechel D, *et al.* Association of apolipoprotein E allele  $\epsilon 4$  with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;**43**:1467-72.
- 2 **Tardiff BE**, Newman MK, Saunders AM, *et al.* Preliminary report of a genetic basis for cognitive decline after cardiac operations. *Ann Thorac Surg* 1997;**64**:715-20.
- 3 **Steed L**, Kong R, Stygal J, *et al.* The role of apolipoprotein E in cognitive decline after cardiac operation. *Ann Thorac Surg* 2001;**71**:823-6.
- 4 **Robson MJ**, Alston RP, Deary IJ, *et al.* Jugular bulb oxyhemoglobin desaturation, S100 $\beta$ , and neurologic and cognitive outcomes after coronary artery surgery. *Anesth Analg* 2001;**93**:839-45.
- 5 **Grafman J**, Litvan I. Importance of deficits in executive functions. *Lancet* 1999;**354**:1921-

## Interferon $\beta$ -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.<sup>1</sup> 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 severe bouts of the disease. A more chronic term of corticosteroid treatment is often desirable but this approach is complicated by untoward side effects and by the tolerability of the patient. Most authors recommend a combination of azathioprine and low doses of corticosteroids. If this regimen fails, cyclosporin A, immunoglobulins, or cyclophosphamide is recommended.<sup>2</sup>  $\beta$  Interferons are a new group of immunomodulatory drugs widely used for treatment of patients with multiple sclerosis, a disease of probable autoimmune origin.<sup>3</sup> However, no data are available on the efficacy of  $\beta$  interferons in the treatment of other autoimmune diseases.

Here we report the results of treatment of a patient with a longstanding history of polymyositis with interferon  $\beta$ -1a.

At the age of 15 years, the female patient noticed leg weakness associated with muscular pain in her calves during physical exercise. Laboratory investigation found a serum creatine kinase (CK) concentration of 9000 U/l. Necrotising myositis was diagnosed based on muscle biopsy and corticosteroid treatment

was initiated. This treatment was initially well tolerated and the symptoms resolved. Attempts to discontinue the corticosteroid treatment led to recurrent exacerbations of the disease. Treatment was therefore initiated with second and third line immunosuppressant and immunomodulatory drugs (azathioprine, cyclosporin A, intravenous immunoglobulins, methotrexate) in an attempt 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 re-biopsy and electromyography.

The patient was administered 22  $\mu$ g of interferon  $\beta$ -1a subcutaneously (Rebif®, Serono, 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  $\beta$ -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 aid, 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  $\beta$ -1a treatment in polymyositis. Interferon  $\beta$ -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  $\beta$ -1a was started. Moreover, disease activity was controlled for three years without requiring corticosteroid treatment, suggesting that beta interferons have utility in patients who require long term treatment of the disease. Since the interferon  $\beta$ -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  $\beta$ -1a in the treatment of inflammatory myopathies. Indeed, one multicentre trial with interferon  $\beta$ -1a is underway.<sup>2</sup> This case study thus suggests that interferon  $\beta$ -1a may be a new therapeutic option in autoimmune

diseases beyond multiple sclerosis, particularly in cases where established steroid regimens fail.

**Acknowledgement**

We thank Dr. Bogumil for helpful discussion of the manuscript.

Competing interests: AD and WB have both received support for attending conferences and organising education; in addition, AD has received speaker fees and holds a research grant from Serono. Similar support has been given to both authors by Schering and Biogen as well as Teva (AD) and Aventis (WB), companies manufacturing immunomodulatory drugs for the treatment of multiple sclerosis. No support has been granted for the treatment of the patient described here.

**A Dressel**

Klinik und Poliklinik für Neurologie, Universität  
Greifswald, Greifswald, Germany

**W Beuche**

Klinik für Neurologie, Städtisches Klinikum  
St Georg, Leipzig, Germany

Correspondence to: Dr Dressel, Neurologische  
Klinik, Universität Greifswald, Ellernholzstraße 1/2,  
17487 Greifswald, Germany;  
alexander.dressel@neurologie.uni-greifswald.de

**References**

- 1 **Mantegazza R**, Bernasconi P, Confalonieri P, *et al.* Inflammatory myopathies and systemic disorders: a review of immunopathogenetic mechanisms and clinical features. *J Neurol* 1997;**244**:277-87.
- 2 **Mastaglia FL**. Treatment of autoimmune inflammatory myopathies. *Curr Opin Neurol* 2000;**13**:507-9.
- 3 Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (prevention of relapses and disability by interferon beta-1a subcutaneously in multiple sclerosis) Study Group. *Lancet* 1998;**352**:1498-504.

## 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 19p13 by linkage analysis,<sup>1</sup> and the causative gene was subsequently identified as the CACNA1A gene, encoding a P/Q-type calcium channel  $\alpha 1A$  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 only in cases carrying CACNA1A mutations. Other clinical phenotypes associated with ataxia may also be caused by mutations in the CACNA1A gene, which include 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 carboxyl 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.<sup>2-5</sup> 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 headache followed by the sudden onset of numbness and dysaesthesia of the left upper limb were recorded.

### Case 2

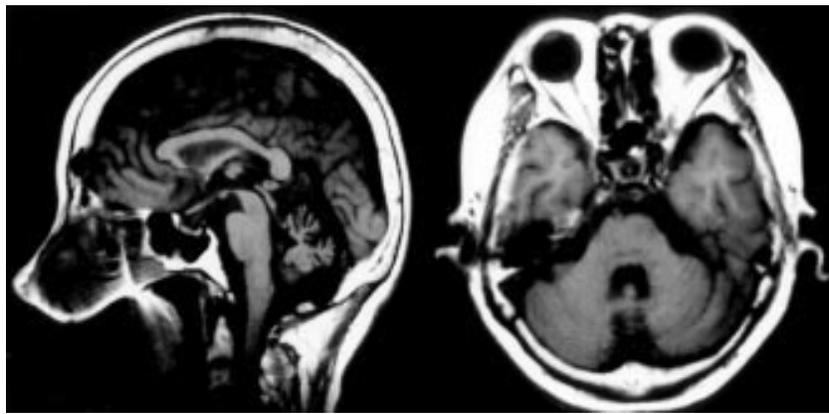
A 63 year old woman, a younger sister of case 1, had slight difficulty in speaking since the age of 36. Dysarthria, truncal ataxia, limb incoordination, and gaze nystagmus were noted by a neurologist at that time, and she was diagnosed as having spinocerebellar degeneration (autosomal dominant spinocerebellar 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 throbbing 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 vermian.

### 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 I1811L—were reported.<sup>6</sup> The analysis was



**Figure 1** T1 weighted magnetic resonance imaging showing marked atrophy of the cerebellar vermis.

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

### References

- 1 Joutel A, Bousser MG, Biouesse V, et al. A gene for familial hemiplegic migraine maps to chromosome 19. *Nat Genet* 1993;5:40-5.
- 2 Terwindt GM, Ophoff RA, Haan J, et al. Variable clinical expression in the P/Q-type calcium channel gene in familial hemiplegic migraine: Dutch Migraine Genetics Research Group. *Neurology* 1998;50:1105-10.
- 3 Ducros A, Denier C, Joutel A, et al. Recurrence of the T666M calcium channel CACNA1A gene mutation in familial hemiplegic migraine with progressive cerebellar ataxia. *Am J Hum Genet* 1999;64:89-98.
- 4 Battistini S, Stenirri S, Piatti M, et al. A new CACNA1A gene mutation in acetazolamide-responsive familial hemiplegic migraine and ataxia: *Neurology* 1999;53:38-43.

5 Ducros A, Denier C, Joutel A, et al. The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. *N Engl J Med* 2001;345:17-24.

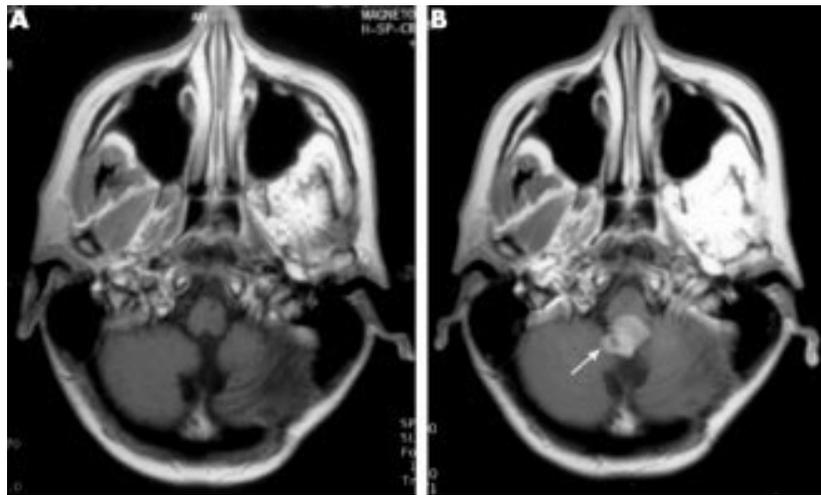
6 Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca<sup>2+</sup> channel gene CACNA1A4. *Cell* 1996;87:543-52.

### Cellular schwannoma of the posterior fossa

Schwannomas are slowly growing, non-invasive neoplasms derived from Schwann cells and usually arise from peripheral nerves.<sup>1</sup> 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.<sup>2</sup> There are fewer than 60 reported cases of intraparenchymal schwannoma<sup>3</sup> 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** (A) Axial T1 weighted magnetic resonance imaging (MRI) (without contrast), eight months before discovery of a cervicomedullary lesion, showing no evidence of tumour. (B) Axial T1 weighted MRI (without contrast) at presentation showing a large tumour at the level of the foramen magnum.

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 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, 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. There was also dural thickening at the level of S2 downwards. These findings suggested extensive meningeal spread of the disease. She died soon afterwards from aspiration pneumonia.

In this patient, the cervicomedullary schwannoma arose from the pia of the brainstem, and was well away from the lower cranial or upper cervical nerves. These intraparenchymal schwannomas are generally indolent in nature and present in a variety of ways. Younger patients tend to present with a longer duration of illness (often seizures or headaches), whereas older patients tend to have a

more rapid clinical course, with marked neurological deficits.<sup>3</sup> 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.<sup>4</sup> As our patient developed spinal lesions that 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.<sup>5</sup> 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.<sup>5</sup> 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<sup>3</sup>), 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

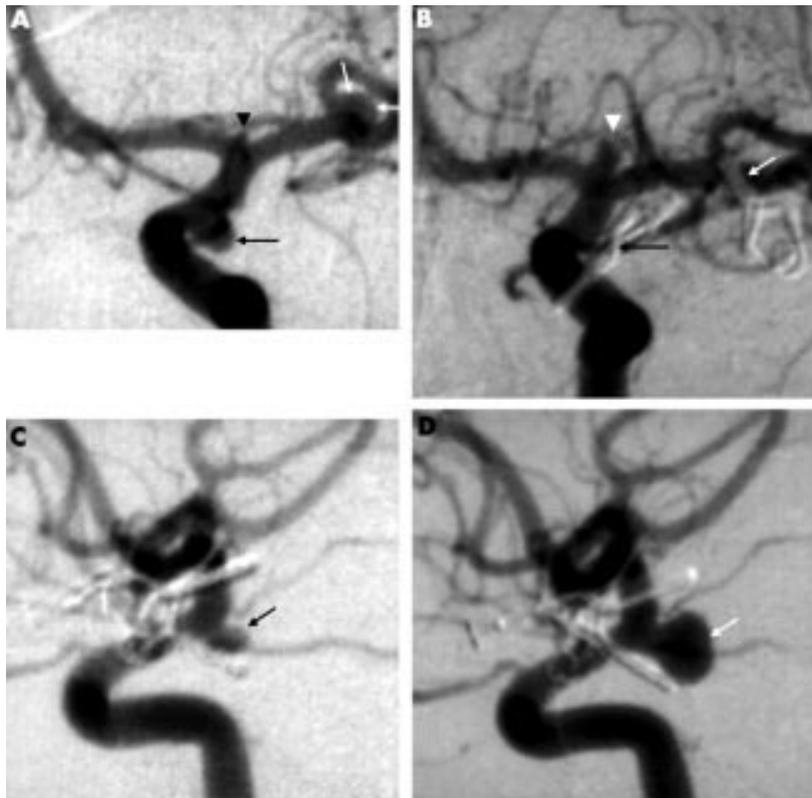
- 1 **Crockard A**, Hayward R, Hoff JT. Neurosurgery. *The scientific basis of clinical practice*. Boston: Blackwell Scientific Publications, 1992.
- 2 **Fletcher CDM**, Davies SE, McKee PH. Cellular schwannoma: a distinct pseudosarcomatous entity. *Histopathology* 1987;11:21–35.
- 3 **Casadei GP**, Komoro T, Scheithauer BW, et al. Intracranial parenchymal schwannoma. A clinicopathological neuroimaging study of nine cases. *J Neurosurg* 1993;79:217–22.
- 4 **Salmon I**, Kiss R. Relationship between proliferative activity and ploidy level in a series of 530 astrocytomas, meningiomas, schwannomas, and metastases. *Hum Pathol* 1993;24:329–35.
- 5 **Seppala MT**, Sainio MA, Haltia MJ, et al. Multiple schwannomas: schwannomatosis or neurofibromatosis type 2? *J Neurosurg* 1998;89:36–41.

## 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 family 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 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 erythroblast hypoplasia only. Erythrocyte adenosine deaminase (ADA) levels were moderately raised 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 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).



**Figure 1** (A) Frontal digital subtraction cerebral angiography following selective injection into the left internal carotid artery showing a left posterior communicating artery region aneurysm (black arrow). A left middle cerebral artery aneurysm is also seen (white arrows), as well as a suggestion of a terminal left internal carotid artery aneurysm (arrowhead). (B) Surveillance digital subtraction cerebral angiography in a frontal projection at two years showing the left posterior communicating artery aneurysm clip (black arrow), the left middle cerebral artery aneurysm clip (white arrow), and growth of the terminal left internal carotid artery aneurysms (white arrowhead). (C) A lateral projection showing residual filling of the left posterior communicating artery region aneurysm at two years (white arrow). (D) Further surveillance cerebral angiography in a lateral projection demonstrating significant growth of the left posterior communicating artery region aneurysm (white arrow).

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 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.

### Comment

We report a previously undescribed case of rapidly growing multiple cerebral aneurysms in a young woman diagnosed as having Diamond-Blackfan anaemia. We offer a possible explanation for the aetiology of cerebral 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.<sup>1</sup>

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.<sup>2</sup> The gene encodes a ribosomal protein (RPS19) which is ubiquitously expressed in both haematopoietic and non-haematopoietic tissues,<sup>3</sup> 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-predisposed person is also rare. Diamond-Blackfan anaemia is not known to predispose to either aneurysm formation or connective tissue disease. Thus the finding of multiple

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.<sup>4</sup>

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.<sup>5</sup> 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 Neurosurgery, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

**J H Gillard**

University Department of Radiology, Addenbrooke's Hospital

Correspondence to: Mr Kirkpatrick; pjkt21@medscl.cam.ac.uk

### References

- 1 **Ball SE, McGuckin CP, Jenkins G, et al.** Diamond-Blackfan anaemia in the UK: analysis of 80 cases from a 20 year birth cohort. *Br J Haematol* 1996;**94**:645-53.
- 2 **Willig TN, Draptchinskaia N, Dianzani I, et al.** Mutations in ribosomal protein S19 gene and Diamond-Blackfan anaemia: wide variations in phenotypic expression. *Blood* 1999;**94**:4294-306.
- 3 **Draptchinskaia N, Gustavsson P, Andersson B, et al.** The gene encoding ribosomal protein S19 is mutated in Diamond-Blackfan anaemia. *Nat Genet* 1999;**21**:169-75.
- 4 **Willig TN, Gazda H, Sieff CA.** Diamond-Blackfan anaemia. *Curr Opin Haematol* 2000;**7**:85-94.
- 5 **International Study Investigators.** The International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms-risk of rupture and risks of surgical intervention. *N Engl J Med* 1998;**339**:1725-33.

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

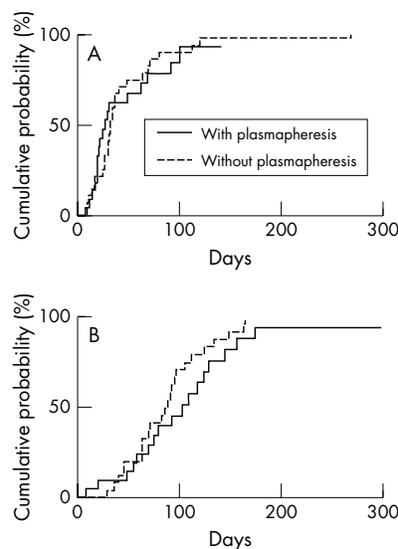
Miller Fisher syndrome (MFS), characterised by the clinical triad of ataxia, ophthalmoplegia, and areflexia, is considered to be a variant form of Guillain-Barré syndrome (GBS). Large studies have shown that plasmapheresis<sup>1</sup> and immunoglobulin treatment<sup>2</sup> are beneficial for treating 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 treating MFS,<sup>3,4</sup> none 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.<sup>5</sup> Criteria for inclusion in the study were the clinical triad of MFS (ataxia, ophthalmoplegia, and areflexia) and acute onset without major limb weakness or other signs suggestive of central nervous system involvement. Three of the 53 patients who initially had the typical clinical triad of MFS later developed profound limb weakness, and GBS was diagnosed. Clinical data for the remaining 50 patients were therefore analysed. Twenty two patients with MFS underwent plasmapheresis with a second filter (Evaflex 3A (Kurare Co Ltd, Kurashiki, Japan) or Immusorber TR-350 (Asahi Medical Co Ltd, Tokyo, Japan)). They received plasmapheresis every other day two to six times (mean 4.1 times). All had given informed consent to receive the treatments. The other 28 patients did not receive plasmapheresis or an intravenous immunoglobulin infusion. The clinical course was charted monthly until the disappearance of symptoms and signs, with focus on the amelioration of ataxia and ophthalmoplegia. The severity of ataxia was evaluated on the Hughes functional grading scale (0, no ataxia; 1, able to run; 2, able to walk 5 m without assistance; 3, able to walk 5 m with assistance; 4, chair bound or bed bound). The two tailed  $\chi^2$  or Fisher's exact test was used to test the significance of differences in percentage. The Mann-Whitney U test was used to test the differences in medians. Recoveries were assessed from Kaplan-Meier curves.

At entry, there were no significant differences in age, sex, antecedent events, the frequency of bulbar palsy, inability to walk,

total ophthalmoplegia, the Hughes grade, and speed of progression (interval between neurological onset and nadir) between the two patient groups. Whether patients were allocated to plasmapheresis or not depended on the different practice of different neurologists and the different time of diagnosis of MFS. Some patients did not receive plasmapheresis because it was not widely used in the early 1980s.<sup>1</sup> The time required to resolve ataxia and ophthalmoplegia did not differ significantly for the patient groups with or without plasmapheresis. The chance of recovery from ataxia and ophthalmoplegia on the Kaplan-Meier curve was not affected by whether or not plasmapheresis was received (fig 1). Of the 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 free from symptoms and signs, 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



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

for MFS.<sup>3,4</sup> 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*<sup>6</sup> reported that plasmapheresis is indicated for the treatment of complicated MFS in which there is profound ataxia, severe bulbar palsy, and respiratory and motor impairment. 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.<sup>1</sup> 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.<sup>5</sup> Lack of a significant difference in the speeds of recovery of the two patient groups is probably due mainly to good spontaneous recovery from MFS symptoms. Our findings suggest that the indication for the use of immunotherapy may be limited to an MFS subpopulation (those cases overlapped by GBS).

M Mori, S Kuwabara, T Fukutake, T Hattori

Department of Neurology, Chiba University School of Medicine 1-8-1, Inohana, Chuo-ku, Chiba, 260-8670 Japan;

Correspondence to: Dr Mori, morim@olive.ocn.ne.jp

## References

- 1 French Cooperative Group on Plasma Exchanges in Guillain-Barré syndrome. Efficiency of plasma exchange in Guillain-Barré syndrome: role of replacement fluids. *Ann Neurol* 1987;**22**:753-61.
- 2 van der Meché FGA, Schmitz PIM, The Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. *N Engl J Med* 1992;**326**:1123-9.
- 3 Yuki N. Tryptophan-immobilized column adsorbs immunoglobulin G anti-GQ1b antibody from Fisher's syndrome: a new approach to treatment. *Neurology* 1996;**46**:1644-51.
- 4 Yeh JH, Chen WH, Chen JR, *et al*. Miller Fisher syndrome with central involvement: successful treatment with plasmapheresis. *Therapeutic Apheresis* 1999;**3**:69-71.
- 5 Mori M, Kuwabara S, Fukutake T, *et al*. Clinical features and prognosis of Miller Fisher syndrome. *Neurology* 2001;**56**:1104-6.