LETTERS TO THE EDITOR

No association between the APOE ϵ 4 allele and outcome and susceptibility in primary progressive multiple sclerosis

Recent reports, primarily in patients with secondary progressive and relapsing-remitting multiple sclerosis have suggested that the apolipoprotein (APOE) ϵ 4 allele may be associated with a worse prognosis.¹⁻³ The ϵ class of APOE is involved in lipid transport and plays a part in brain development, synapse repair, and response to neuronal injury. It has been postulated that patients possessing the ϵ 4 allele might have a reduced capacity for neuronal remodelling after multiple sclerosis relapses.³

There is general agreement that patients with primary progressive multiple sclerosis have a worse outcome both in relation to development of disability over time and in mortality. Such patients do not have a relapsing course. Moreover, there are pathological and imaging differences between primary progressive and secondary progressive multiple sclerosis suggesting that primary progressive disease may be a less inflammatory form of the disease.⁴ The relation between APOE and outcome has not been specifically considered in patients with primary progressive multiple sclerosis, although 11 patients with primary progressive disease were included in one previous study.³

A possible role for the ϵ 4 allele in primary progressive multiple sclerosis was therefore studied in a well characterised cohort of 50 patients with primary progressive disease (32 men, 18 women), all of whom were under the care of the National Hospital for Neurology and Neurosurgery and had been seen from their initial presentation. The mean age of onset was 40.3 (range 18-63) years, mean disease duration 8.7 (range 2-26) years, and the mean Kurtzke expanded disability status scale (EDSS) was 5.5 (range 2-8.5). All were white northern Europeans, recruited after local ethics committee approval. No patient had received disease modifying therapy at the time of recruitment. Disability was measured using the EDSS. In addition, age of onset, sex, and disease duration were noted. One hundred and fifty nine randomly selected healthy white subjects served as controls (60% women, 40% men, mean age 45.6 (SD 12.8) years).

DNA was isolated from leucocytes using a standard phenol/chloroform extraction method. APOE genotypes were determined after polymerase chain reaction (PCR) amplification and *Hha*I restriction digestion. Fragments from PCR were separated on an 8% polyacrylamide gel.

Associations between the ϵ 4 allele and disease outcome were investigated using two

previously described stratifications of disability: firstly EDSS 0-5.5 v 6-10. An EDSS score of 6 (need for unilateral support) is clinically important and a clearly defined division. It may therefore be subject to less interrater variability than other points on the EDSS. As long term prognosis may be more clearly established in patients with a greater disease duration,⁵ patients with a disease duration of either ≥ 5 years or ≥ 9 years disease duration were included. For the purposes of comparison with previous data we also used a second method of stratification (EDSS score divided by disease duration to give a "severity score"). Patients were divided into those with "mild" and those with "aggressive" disease using the median "severity score" as the threshold.³

The Pearson χ^2 test was used to compare the ϵ 4 allele frequency between cases and controls and between outcome groups. The influence of the ϵ 4 allele on outcome was also studied by logistic regression analysis (Stata statistical package version 5.0, Stata Corp, Texas, USA). This allowed correction for sex, disease duration, and age of onset, as each has previously been shown to influence outcome.³

Genotype distribution did not significantly differ between the sexes ($p=0.21$). There was no significant difference in ϵ 4 allele frequency between cases and controls ($p=0.95$). Furthermore, using t test analysis, possession of the ϵ 4 allele did not significantly influence the age of onset ($p=0.78$).

Outcome was not significantly influenced by ϵ 4 allele possession (for EDSS ≥ 6 , $p=0.71$, $n=34$ at ≥ 5 year disease duration, and $p=0.59$, $n=23$ at ≥ 9 year disease duration, and for the "severity score" $p=0.76$, $n=50$). The table illustrates the frequency of allele ϵ 4 possession in patients stratified according to outcome. Using logistic regression to correct for potential confounding factors (sex, age of onset, and disease duration), no significant effect of the ϵ 4 allele was found on the likelihood of having an EDSS of ≥ 6 at ≥ 5 or ≥ 9 years (OR=1.09, $p=0.92$, $n=34$; OR= 0.67, $p=0.69$, $n=23$ respectively) or having a "severity score" greater than the median value (OR=1.24, $p=0.74$, $n=50$).

The results of this investigation in patients with primary progressive disease suggest that the ϵ 4 allele does not influence prognosis in this group. When considered together with our findings in a large cohort of 370 patients with relapsing-remitting and secondary progressive disease which also showed no evidence of an association between allelic variation of APOE and disability,⁶ we suggest it is unlikely that the ϵ 4 allele when considered alone significantly influences prognosis in multiple sclerosis.

S J M WEATHERBY
C L A MANN
A A FRYER
R C STRANGE
C P HAWKINS

Centre for Cell and Molecular Medicine, Postgraduate Medical School, Keele University, North Staffordshire Hospitals, Stoke-on-Trent ST4 7LN, UK

V L STEVENSON
S M LEARY
A J THOMPSON

University Department of Clinical Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

Correspondence to: Dr S J M Weatherby, Department of Neurology and Neurophysiology, School of Postgraduate Medicine, Keele University, North Staffordshire Hospitals, Princes Road, Stoke-on-Trent ST4 7LN, UK
med13@keele.ac.uk

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Transverse myelopathy, a rare complication of mixed connective tissue disease: comparison with SLE related transverse myelopathy

Transverse myelopathy is a rare complication of mixed connective tissue disease (MCTD). To date there have been relatively few reports, all in females.¹⁻⁶ We describe a case of transverse myelopathy in a man with MCTD and review the previous cases, comparing them with transverse myelopathy related to systemic lupus erythematosus (SLE).

A 46 year old man with a history of a squamous cell carcinoma of his right upper lobe bronchus and a 2 year history of MCTD was admitted to hospital with a 3 month history of subacute progressive lower limb weakness, sensory loss, and sphincter disturbance. He had been diagnosed with MCTD on the basis of Raynaud's phenomenon, polyarthralgia, synovitis, acrosclerosis, raised muscle enzymes, biopsy established myositis, dysphagia for solids, positive test for antinuclear factor (ANF) (speckled 1/2560), negative DNA binding, and high titre antiribonuclear protein (anti-RNP). His bronchial carcinoma had been treated surgically with a right pneumonectomy and radiotherapy to the bronchial stump at a low dose of 3000 cgrad over 10 days. No lymph node involvement was identified either at operation or on CT. He had recently been prescribed a reducing course of prednisolone for active myositis. There was no history of recent infections.

On examination he was systemically well. There was no clinical evidence of tumour recurrence. He had an asymmetric spastic paraparesis (power of 4-4+ MRC grading) with a sensory level at D10. The remainder of the neurological examination was normal. Brain and spinal cord MRI with gadolinium enhancement showed mild atrophy of the cord at D9/D10 but was otherwise normal. Routine haematology (full blood count, vitamin B12, and folate), inflammatory markers,

The effect of ϵ 4 allele possession on outcome (EDSS 0-5.5 v 6-10 at ≥ 5 years, and "severity score" <median v "severity score" >median value) (percentages)

	EDSS 0-5.5 ≥ 5 years disease duration	EDSS 6-10 ≥ 5 years disease duration	Total number of patients	"Severity score" <median value "Mild" disease	"Severity score" >median value "Aggressive" disease	Total number of patients
ϵ 4 Allele positive	6 (54.6)	5 (45.4)	11 (100)	7 (46.7)	8 (53.3)	15 (100)
ϵ 4 Allele negative	11 (47.8)	12 (52.2)	23 (100)	18 (51.4)	17 (48.6)	35 (100)

Features of MCTD associated transverse myelopathy

Report 1st author	Duration of MCTD (y)	Age	Sex	Onset	Site	Treatment	Neurological outcome	Imaging
Current	2	46	M	Progressive over 3 months	Thoracic	Pred/Aza	No change	Spinal MRI cord atrophy
Mok ¹	2	46	F	Progressive	Thoracic	Pred/Aza/ Anticoagulation	Improved. Power increased from 3-4 over 4 months	Spinal MRI normal
Flehtner ²	5	19	F	Progressive with a subsequent relapsing course	Thoracic and Cervical	Pred/Aza/ Plasmapheresis	Each "relapse" resolved. Sequelae: mild sensory disturbances	Spinal MRI high signal intramedullary lesion
*Obara ³	n/k	42	F	Progressive	Thoracic	Pred/Aza	Resolved. Sequelae: painful tonic spasm	Spinal MRI abnormal
*Yamaguchi ⁴	n/k	53	F	Progressive	Thoracic	Pred	Improved	n/k
Pedersen ⁵	2	16	F	Progressive over less than 1 week	Thoracic	Pred/Aza	Resolved. Sequelae: urge incontinence	CT brain normal. No spinal CT
Weiss ⁶	1	24	F	Progressive over 4 weeks	Thoracic	Pred/Aza	No change	n/k

(Pred=Prednisolone; Aza=azathioprine; n/k=not known); *Japanese journal, English abstract only.

and biochemistry were normal. ANF remained at high titre with anti-RNP antibody positivity. All other autoimmune markers and serum angiotensin converting enzyme were normal. A thrombophilia screen (protein C, protein S, and antithrombin III, lupus anticoagulant, and anticardiolipin) was unremarkable. Complement, creatinine phosphokinase, and immunoglobulins were normal, and a venereal disease research laboratory test was negative. Examination of CSF excluded infection and standard indices were normal. Oligoclonal bands were negative and visual evoked potentials were normal.

He received high dose steroid therapy (1g/day intravenous prednisolone for 3 days followed by an oral reducing dose) and was started on 125 mg azathioprine. There was no further deterioration in his condition and at 6 year follow up his neurological condition remains stable. No recurrence of carcinoma was detected over the same time period and we think that a paraneoplastic cause can be excluded. Similarly, radiation myelopathy is unlikely, as no vertebral abnormalities were seen on MRI and the patient had only a small radiation dose to a localised field.

Transverse myelopathy is a rare complication of MCTD and has not been previously reported in a male. Postulated mechanisms include vasculitis of small arachnoid arteries of the cord and arterial thrombosis causing microinfarction of the spinal cord because of necrotising vasculitis or the presence of a circulating antiphospholipid antibody. The patient presented after an interval of several months from onset of symptoms. It is possible that the initial pathology was related to a vasculitis that had resolved by the time of presentation. Magnetic resonance findings in transverse myelopathy depend on the timing of the examination and the stage of disease. In this case the delay to presentation may explain the fact that MRI demonstrated atrophy of the cord only.

The table shows features of this patient, and of other reports of transverse myelopathy related to MCTD. Transverse myelopathy was noted to occur relatively early in the evolution of MCTD, although in no patient was it a presenting feature. By contrast, retrospective studies of patients with SLE and transverse myelopathy found that transverse myelopathy was a presenting feature in 50%.^{7,8} All cases of MCTD related transverse myelopathy involved the thoracic region. One patient also had a cervical myelopathy. In SLE, a retrospective analysis⁷ found the cervical cord to be the most commonly affected site (50%). The onset was reported

as progressive in all cases with MCTD, although the duration of symptom onset was not precisely identified in every report. By contrast, however, a review of 20 cases of transverse myelopathy related to SLE,⁹ showed that 50% evolved over less than a day. Neurological improvement or resolution with only mild sequelae followed treatment with high dose prednisolone and azathioprine in five of the seven cases of transverse myelopathy related to MCTD. In this case and one other in which there was a delay in presentation of over 4 weeks, neurological features were stabilised but did not improve. The clinical course of transverse myelopathy related to SLE is variable, although historically prognosis is relatively poor. In one series in which 70% of patients received steroid treatment, 50% died in less than 6 weeks, 35% had permanent neurological deficits, and 15% had a near normal recovery.⁹ Another study⁸ described seven patients with transverse myelopathy and SLE. Four died and one remained wheelchair bound. In SLE, early aggressive therapy with high dose steroids and cytotoxic agents has been associated with a satisfactory outcome.^{7,8,10}

Considering this patient together with previous reports suggests that, by contrast with SLE, transverse myelopathy is unlikely to be a presenting feature of MCTD. Onset is progressive rather than acute, and cervical areas are less often involved. Transverse myelopathy associated with MCTD would seem intrinsically to have a better prognosis, as improvement or resolution occurred in 70% of cases treated with prednisolone and azathioprine. In this and one other patient there was a delay to presentation of over 4 weeks and no neurological improvement was noted. We therefore suggest that whereas high dose prednisolone and azathioprine generally seems sufficient to treat MCTD associated transverse myelopathy, if there is a delay to presentation more aggressive immunosuppression may be appropriate.

S J M WEATHERBY
M B DAVIES
C P HAWKINS

Department of Neurology, Royal Infirmary,
Stoke-on-Trent, UK

N HAQ
Department of Neuroradiology

P DAWES
Department of Rheumatology, Hayward Hospital,
Stoke-on-Trent, UK

Correspondence to: Dr S J M Weatherby, Research Office, Department of Neurology, Royal Infirmary, Princes Road, Stoke-on-Trent. ST4 7LN, UK
med13@keele.ac.uk

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Plasmapheresis in multifocal motor neuropathy: a case report

Plasmapheresis is a well established therapy in immunogenic peripheral neuropathies.¹ However, patients with multifocal motor neuropathy do not respond very well to prednisone or plasmapheresis.² This case report illustrates that plasmapheresis may even be disadvantageous in multifocal motor neuropathy.

Muscle strength was assessed (MRC scale) and a sum score was calculated from 10 sites (bilateral shoulder abduction, extension of hands and fingers, hip flexion, dorsal flexion of feet); full muscle strength meaning a sum score of 50.

Nerve conduction studies were carried out according to the method described elsewhere.³ Compound muscle action potentials (CMAPs) were recorded from abductor digiti minimi and tibialis anterior bilaterally by surface electrodes. Ulnar nerves were stimulated supramaximally with surface electrodes at the wrist, distal elbow, proximal elbow, axilla, Erb's point, C7 vertebra; peroneal and sciatic nerve at head of fibula, sciatic notch, and L1 vertebra by a Digitimer