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.

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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

high voltage D180 stimulator (Digitimer Ltd, Welwyn Garden City, England).

Plasmapheresis was carried out by a standard polypropylene filter P2S (Fresenius, Germany) with a maximum pore diameter of 0.5 μ m. This filter separates immunoglobulins. Three litres were exchanged against human albumin (5% on each of 3 consecutive days (12, 13, 14 November 1998)).

The patient had given fully informed consent for both nerve conduction studies and treatment.

The male patient was born in 1931. In 1979 distal atrophic weakness developed in his right shoulder and hand muscles. There were no sensory symptoms. His CSF and neuroradiology were normal; electromyography showed a chronic neurogenic lesion. Vasculitis had been excluded by sural nerve biopsy. The diagnosis of spinal muscular atrophy was made. In 1993, when the patient was first seen here, he had complete paresis of his right arm, paretic left hip flexion (MRC 4), and peroneal weakness in his left leg with slightly impaired position sense in the toes. No weakness was found in the left arm and right leg. Muscle stretch reflexes were absent in the right arm and both legs. There were no central signs. In 1993 GM1 antibodies were positive (serum titre 1/200) and remained positive until 1998 (December 1998, GM1-antibodies 29 U/ml, limit of normal 25 U/ml). In 1993 muscle sum score was 34 and conduction block was seen in the proximal right ulnar nerve between Erb's and axilla

and in both proximal sciatic nerves between L1 and the sciatic notch. His CSF was normal again. Multifocal motor neuropathy was diagnosed, and the patient was put on intravenous immunoglobulin (IVIg) with 180 g Sandoglobin[®] initially—followed by 100 g IVIg every fortnight. Within two weeks muscle strength improved. The patient was able to use his right arm, strength in his left leg improved, and position sense became normal (muscle sum score 42 in 1996). Intermittent deterioration was treated with oral methylprednisolone (1994-6 (4 mg a day); 1996-8 (2 mg a day)) which had a subjective effect on muscle strength. Additional cyclophosphamide had to be withdrawn because it was not tolerated very well. In 1998 muscle strength gradually deteriorated under 100 g IVIg every 2 weeks. Muscle weakness became more pronounced in the proximal right arm (MRC 2-3) and left foot dorsiflexion (MRC 1); sum score was 36 in August 1998. Therefore, it was decided to give three courses of plasmapheresis. Before plasmapheresis muscle sum score was 36 and the patient was able to walk. Plasmapheresis was performed on 12-14 November 1998. On 14 November muscle strength started to deteriorate. On 17 November the patient became tetraplegic with a disability sum score of 19. His left arm and right leg, which had not been weak before, were paretic with shoulder abduction MRC 4, hip flexion MRC 2. There was proximal conduction block in both ulnar and sciatic nerves

(figure). The patient received 120 g IVIg immediately (17-19 November) and 60 g IVIg on 24-25 November. Muscle strength improved gradually. On 30 November he was able to stand. On 11 December—after another three courses of 50 mg IVIg—he could walk with a stick, but he was still unable to use his right hand and to climb stairs. Treatment was continued with 50 g IVIg a week and 50 mg cyclophosphamide a day. By the end of January 1999 the patient had regained his former muscle strength. He was able to walk without a walking aid, to climb stairs, and he could use his right hand (sum score 36). Increasing CMAPs after proximal nerve stimulation (figure) paralleled clinical improvement.

This follow up study illustrates that deterioration can be seen under continuing treatment with IVIg. Additionally, plasmapheresis may stimulate antibody rebound, and cause substantial deterioration in multifocal motor neuropathy. It is assumed that it is not only antibodies which are responsible for conduction block and muscle weakness that are washed out by plasmapheresis but also those which act at the lesion site by blocking the pathogenic agent. In this patient, before plasmapheresis, serum gammaglobulin was increased at 2.32 g/dl (12 November); thereafter it was 0.7g/dl (18 November), and recovered to 1.79 g/dl (24 November).

It has been shown that serum of patients with multifocal motor neuropathy can block stimulus conduction in distal motor nerves.⁴

Recording of CMAPs from right and left hypothenar after ulnar nerve stimulation at wrist, distal and proximal elbow, axilla, Erb's point, and C7 vertebra. Before plasmapheresis no muscle weakness had been seen in the left arm and no conduction block in the left ulnar nerve. After plasmapheresis a pronounced conduction block was seen in the right ulnar nerve, and proximal conduction block developed in the left ulnar nerve. After IVIg treatment muscle strength recovered and stimulus conduction improved (MRC sum score indicated in lower trace).

This could be due to an effect on sodium channel function in the distal motor nerve. Furthermore, the rapid clinical improvement after IVIg could be due to an interference of IVIg with the blocking effect of antibodies on the sodium channels at the motor nerve endings.⁵ It is unlikely that plasmapheresis caused acute demyelination in our patient. In plasmapheresis, antibodies, complement, and cytokines are removed; therefore, this case supports the hypothesis⁴ of a complement independent effect of antibodies on sodium channel function in the distal motor nerve.

Even with good clinical results the pathogenic process of multifocal motor neuropathy may remain active under the treatment with IVIg for many years. Therefore, muscle weakness develops if immunoglobulins are washed out by plasmapheresis.

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Ethambutol related headache in HIV infection: sensitisation to normal CSF pressure? A case report

It is well recognised that headache can be a key symptom in intracranial hypertension, often accompanied by lesions of the optic and other cranial nerves. Typical characteristics of this headache are postural dependence, worsening during exercise, Valsalva's manoeuvre, and relief of headache after lumbar puncture.

Here, we report on a patient with a headache that bears all of the above symptoms including relief after lumbar puncture but with normal CSF opening pressures.

A 48 year old white man with a long history of HIV infection (first diagnosis 1991, actual staging CDC/WHO C3, CD4 79/ml, CD8 179/ml, CD4/CD8 0.4) was referred to the neurological department because of new onset progressive intractable headache that had started 3 months previously. The headache was described as generalised but with highest intensity retro-orbitally and of a constricting and pulsating character. Further characteristics were a pronounced aggravation when resting supine that forced the patient to sit upright at night and extreme exacerbations during coughing or sneezing. The patient complained of photophobia

associated with severe headaches, but nausea and vomiting were absent.

In the previous weeks he had received several unsuccessful treatments including high doses of intravenous acetylsalicylic acid (1000-3000 mg daily), other non-steroidal anti-inflammatory drugs such as ibuprofen and naproxen, metamizol, and tramadol, and short term treatment with prednisolone over 1 week. Concomitant medication related to HIV infection consisted of antiviral triple therapy with lamivudin, stavudin, and nelfinavir for 2 months. Other medication included foscavir and ganciclovir for previous cytomegalovirus retinitis, pentamidine for sustained pneumocystic pneumonia prevention, and pyrimethamine/sulfadoxine for previous cerebral toxoplasmosis for 12 months. Six months previously he also had been started on ethambutol when atypical mycobacteria were detected during bronchial lavage although without clinical manifestation.

On neurological examination there was mild meningism but no papilloedema. Vision was permanently impaired bilaterally after cytomegalovirus retinitis 3 years previously and fundoscopy showed only old lesions and no florid inflammatory signs. Proximal reflexes were normal but were reduced peripherally due to HIV and medication related sensorimotor neuropathy.

On admission cranial CT and MRI (including contrast enhancement) showed no signs of local or generalised oedema. Ventricle size and configuration was normal and identical with previous scans. Neuroimaging showed no evidence of intracerebral tumours nor opportunistic CNS infection. White blood cell count was 2100/ml; routine blood chemistry including antinuclear antibody screening was normal.

Diagnostic lumbar puncture showed normal CSF opening pressure (16 cm H₂O), cell count, and protein. Extended CSF analysis was normal including microbiology, antigen screening for HIV, cytomegalovirus, and polymerase chain reaction for mycobacteria. However, within minutes after the lumbar puncture the patient reported substantial relief from his headache and meningism disappeared. Two days after the lumbar puncture the headache worsened again and the procedure was repeated on day 5. Because of the lack of response to any analgesic medication the procedure had to be repeated every 4 to 5 days for 3 weeks. The CSF opening pressure was always in the range 10-18 cm H₂O. Altogether, six lumbar punctures were performed and the headache resolved each time.

To exclude a placebo effect of the lumbar puncture the patient gave consent to a blinded protocol under continuous monitoring of pressure via a three way connector. Lumbar puncture without withdrawal of CSF had no beneficial effect on the headache. Two withdrawals of 10 cm³ CSF resulted in a significant decrease of the headache when the pressure changed from 12 (10) to 4 (4) cm H₂O. By contrast, a slow intrathecal injection of sterile saline increasing the pressure to 16 cm H₂O produced an immediate exacerbation of the headache. The treatment option of lumboperitoneal shunting was denied by the local neurosurgeons because of lack of objective signs of increased intracranial pressure.

Eventually, ethambutol was stopped because of its general neurotoxicity and the headaches stopped 5 days afterwards without further need for lumbar puncture.

Postural headaches that are worse in the supine position can be a diagnostic challenge. They may be present in Chiari-type I malformation, as a symptom of intracranial hypertension with or without papilloedema and with papilloedema but without increased intracranial pressure.¹⁻³

However, to our knowledge this is the first case report of a secondary headache syndrome without papilloedema but with strong dependence on intracranial pressure with relief after lumbar puncture although intracranial pressure was within normal limits. Under normal circumstances the trigeminal intracranial sensory system is insensitive to small changes in intracranial pressure and even high pressures may not result in headache. The nociceptive sensory threshold for pressure differences can be lowered by inflammatory processes as seen in meningitis, after histamine administration, and during acute migraine attacks.⁴ In our patient none of these conditions were met.

It has been demonstrated in experimental animals that trigeminal sensory fibres can change their transduction and transmission properties due to their chemosensitivity and lead to sensitisation inducing increased mechanical intracranial hypersensitivity.⁵ This lowered threshold for the activation of nociceptive trigeminal fibres may have been the case in our patient. From the clinical presentation during the detailed lumbar puncture it seemed evident that a drop in pressure was beneficial, whereas an increase was barely tolerable; pressures below 6 cm H₂O produced no headache, whereas pressures above 10 cm H₂O did.

On ethical grounds the patient was not re-exposed to ethambutol. Therefore, despite the temporal link between the ethambutol treatment and the new onset headache no further evidence for a causative relation could be established. Because of the many other drugs coadministered with ethambutol a noxious direct drug synergism or accumulation of metabolites cannot be excluded. It also remains unclear to what extent an HIV or cytomegalovirus related change of the cranial sensory nociceptive system may have contributed to the described headache. Ethambutol, apart from its known neurotoxicity particularly involving the optic nerve, can cause headaches as an adverse event.⁶ How ethambutol may cause headache is not known but induction of trigeminal sensitisation seems a plausible explanation. A postural headache after ethambutol has not been described previously.

In conclusion a clearly postural headache clinically suggestive of intracranial hypertension can occur with normal intracranial pressure.

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